SECOND EDITION

TEXTBOOK OF TRAUMATIC BRAIN INJURY



Jonathan M. Silver, M.D.
Thomas W. McAllister, M.D.
Stuart C. Yudofsky, M.D.

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Note: The authors have worked to ensure that all information in this book is accurate at the time of publication and consistent with general psychiatric and medical standards and that information concerning drug dosages, schedules, and routes of administration is accurate at the time of publication and consistent with standards set by the U.S. Food and Drug Administration and the general medical community. As medical research and practice continue to advance, however, therapeutic standards may change. Moreover, specific situations may require a specific therapeutic response not included in this book. For these reasons and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of physicians directly involved in their care or the care of a member of their family.

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To the members of the United States Armed Forces and American war veterans who have suffered traumatic brain injuries in the defense of our freedom.

May your sacrifices inspire our efforts and those of other physicians and health care professionals who read this book.

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Foreword

IN 2006, OUR WORLD WAS MOVING FORWARD as most people's do. Bob was traveling overseas for his job, Lee had work deadlines, kids to get to school, the stuff of everyday life.

And then, as happens to so many others who experience a traumatic event, life changed in an instant. For some, it is an unexpected fall or sports injury, a car or bicycle accident; for others, an act of violence. For our family, it was a bomb in the middle of an Iraqi war zone.

Bob had newly been named the co-anchor of ABC's *World News* after the untimely death of Peter Jennings. He was in Iraq to report on the progress of the coalition forces.

The 155-mm shell exploded about 20 feet from the armored personnel carrier when Bob was filming above the hatch. Hundreds of rocks packed around the shell blasted into his face, neck, and back, and the power of the explosion shattered his skull. The prognosis was grim, and as is often the case with a traumatic brain injury (TBI), the extent of the concussive effects of the injury, the shearing of neurons within the brain, and how that would affect Bob was impossible to know initially.

Our family began to travel on the rollercoaster that too many others know so well, experiencing the many octaves of pain, suffering, grief, frustration, expectation, disappointment and, on good days, small blessings. We learned to hold hope for ourselves on the days when the medical community wouldn't or couldn't offer it. We adjusted to life in "the new normal."

Most people with TBI would tell you that the injury or the accident is the easy part. After five weeks in a medically induced coma, Bob did wake up, and he began the most difficult portion of his journey—the journey to return to himself through recovery. This involved an excellent medical and rehabilitation staff, including cognitive work with a neuropsychologist. Through a combination of determination, sheer will, repetition, rest, focus, the love and support of family and friends, and the sheer power of the human spirit, Bob drove his recovery.

Each year, 1.5 million Americans receive a brain injury, and 5.4 million live with this injury every day of their lives. These are often the people whom one doctor referred to as "the folks that live in the back of the house." They are often mistaken for the mentally impaired, socially unacceptable, inebriated, or simply inappropriate and "off." TBI can result in a range of emotional, behavioral, and/or cognitive impairments, among them a quickness to anger, loss of executive function, depression, emotional highs and lows, inappropriate behaviors, or colorful language when the filter is gone from the impact. These differences often lead to vast changes in relationships; one statistic places the divorce rate after TBI at more than 80%.

In the past few years, with the wars in Iraq and Afghanistan, the number of TBIs has risen dramatically, making it the signature injury of this war. In previous wars, soldiers did not survive the more severe kinds of head wounds. Those who did were diagnosed with "shell shock" with little or no treatment prescribed. Medical technology and intervention, as well as better body armor, have increased survival rates. In the sixth year of the war, a new study confirmed that at least 325,000 of U.S. returning troops have some form of a brain injury with or without concomitant posttraumatic stress disorder, combat stress, and/or personality disorder.

Severe TBI is often obvious. The person may live for months, before the cranioplasty, with part of their skull missing, or the resulting scars may be visible. But many brain injuries are hidden. Once the person heals on the outside, the damage remains on the inside, which is why the brain injured are often referred to as the "walking wounded."

Sadly, we are welcoming home a new generation of wounded with our returning veterans. This has placed TBI somewhat more prominently in the public's eye. But there is so much more work to do in the areas of public awareness and education, scientific research, long-term rehabilitation, and insurance reimbursement.

The good news is that the war is rewriting what we know about TBI in many ways. It used to be believed that after almost two years a person was mostly finished healing. Now, with a better understanding of the power of cognitive rehabilitation and the brain's keen abilities to rewire itself, we are seeing progress in ways that could only have been hoped for decades ago.

It is critical that TBI be recognized as a major health problem, and resources must be devoted to educate psychiatrists, rehab specialists, and other mental health professionals about all the various aspects of this serious and life-changing epidemic.

We were honored to write the foreword for the *Textbook of Traumatic Brain Injury* because information is the key to understanding TBI and bringing about the critical support that millions of families need. It is our hope that this text will aid in understanding the very complex and individual nature of TBI and help to educate and inform professionals who are often not trained in this critical area. The authors are well known in the field, and the variety of topics provides a comprehensive resource housed in one volume.

This second edition of the *Textbook of Traumatic Brain Injury,* published by American Psychiatric Publishing, Inc., is a comprehensive, up-to-date book co-edited by three neuropsychiatrists with extensive academic and clinical expertise in the assessment and treatment of people with brain injury. It comprises 39 chapters that are divided into five sections that cover, comprehensively, the assessment, pathophysiology, signs, symptoms, and treatment of those who with TBI. This is a lively, practical, and interesting book that will be of vital help to professionals of almost every medical specialty, as well as the full range of mental health professionals who care for those among us who have suffered from this disabling condition. We who know, first hand, the painful and disabling effects of TBI derive hope from the science and treatments described in this book and are grateful to Professors Jonathan M. Silver, M.D., Thomas W. McAllister, M.D., and Stuart C. Yudofsky, M.D., for editing and organizing this remarkable text.

Bob and Lee Woodruff

Preface

EACH YEAR IN THE UNITED STATES, MORE THAN 3 million people sustain traumatic brain injury (TBI). In this population, the psychosocial deficits are, most frequently, the major source of disability to the patient and of stress to the family. Patients may have difficulties in many vital areas of functioning, including family, interpersonal, vocational, educational, and recreational. Many people who have suffered TBI also exhibit extreme personality changes. Because of the focus of most medical specialists on the sensory and motor deficits and dysfunctions associated with TBI, the psychiatric impairments often go unrecognized. Education of most mental health professionals regarding the psychosocial sequelae of TBI is vastly insufficient. The cognitive, emotional, and behavioral consequences of TBI range from the dramatic to the subtle; consequently, clinicians without the requisite training and experience may not look for or recognize these symptoms or may attribute impairments to other conditions such as major depression or dementia. The net result is often delayed diagnosis or failure to diagnose neuropsychiatric aspects of TBI, which, of course, leads to inadequate or deficient treatment.

Our initial book on this topic, *Neuropsychiatry of Traumatic Brain Injury*, was published in 1994. This book was the first comprehensive, data-based text on the subject and was crafted to serve as a clinically relevant and practical guide to the neuropsychiatric assessment and treatment of patients with TBI. In 2005, we followed and expanded the original book with the publication of the first edition of *Textbook of Traumatic Brain Injury.* That book included comprehensive reviews of the current literature on the topic and expanded discussions of pathophysiology, evaluation, and treatment. Since 2005, there has been a remarkable and exponential increase in both interest and research in TBI, fueled by the recognition of TBI as the "signature injury" in our returning soldiers from Iraq and Afghanistan. In addition, there recently has been increased awareness of the devastating role of TBI in association with sports such as football, ice hockey, boxing and other types of competitive pugilism, skiing, bicycle racing, horseback riding, and many more. Finally, with the growing access of American youths to automobiles, snowmobiles, jet skis, and all-terrain vehicles; with the enhanced recognition by pediatricians of child abuse; and with the aging of the U.S. population leading to increased falls and other types of accidents among the elderly, clinicians are increasingly recognizing that they are treating patients who have suffered neuropsychiatric concomitants of TBI. The second edition of the *Textbook of Traumatic Brain Injury* was written to address these emerging and enlarging issues.

All chapters in this textbook have been revised. We have endeavored to assemble a group of authors who are authoritative and renowned in their areas and to use a prominent multinational, interdisciplinary editorial board to guide the book's conceptualization and review its ultimate content for accuracy and relevance. To address specific issues of the care of our returning soldiers, a chapter on TBI in the military has been added to this edition of the textbook. We have also added a chapter on posttraumatic stress disorder (PTSD) to emphasize the common cooccurrence of TBI and PTSD. We have made every effort to buttress all chapters with evidence based on the most recent and best-conducted research in the field. Finally, we conclude each chapter with essential points and key references.

We hope that this book will be used by psychiatrists, neuropsychiatrists, neuropsychologists, clinical psychologists, physiatrists, neurologists, and other medical and mental health professionals, including residents and trainees involved in brain injury rehabilitation. We also realize that a number of our patients who have sustained TBI find themselves entangled in prolonged and complicated legal, financial, and insurance-based struggles; we hope that this text provides an unbiased and sound source of information for fair adjudications of such.

Few people read a textbook of this length from cover to cover. Most read only one or two chapters during any particular period of time—often as a reference to guide the treatment of a specific patient. Consequently, we have endeavored to ensure that each chapter would be complete, readable, and relevant in itself. As a result, there is some unavoidable overlap among chapters, but we have judged that this was necessary from an information-retrieving standpoint and to prevent readers from having to jump from section to section while reading about a particular subject.

This book would not have been possible without the help and support of many people. First, we thank the chapter authors who labored diligently to produce contributions that we consider unique, scholarly, and enjoyable to read. We also thank the members of our editorial board who provided their informed perspectives on these chapters. We greatly appreciate the efforts of the outstanding staff at American Psychiatric Publishing, Inc., and especially those of Tina Coltri-Marshall, who served as our coordinator for the myriad details—major and minor—inherent in writing a book of this size and complexity.

Expert and indefatigable in this Herculean task, Tina has been a joy to work with.

Last, and most important, we thank our patients with TBI and their families, who have been our greatest source of inspiration to further our knowledge on the presentation, pathophysiology, assessment, and effective treatment of the psychiatric symptoms and syndromes of people who have experienced TBI—and to pass this knowledge on to others. We hope that the efforts of all who have participated in this book will result in reducing your suffering, enhancing your recovery, and achieving fully your potentials.

Jonathan M. Silver, M.D.
Thomas C. McAllister, M.D.
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Part I

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

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CHAPTER 1

Epidemiology

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TRAUMATIC BRAIN INJURY (TBI) IS AMONG THE MOST disabling of injuries. Concern about TBIs related to the Iraq and Afghanistan conflicts has led to increased interest in the epidemiology of TBI among service members and veterans as well as civilians. The purpose of this chapter is to describe the epidemiology of TBI in terms of frequency, severity, outcomes, and cost, focusing primarily on the most recent population-based data for the United States, including military as well as civilian data when available, and highlighting issues that affect the accuracy, completeness, and interpretation of epidemiological data for TBI.

Definitions and Related Issues

Traumatic Brain Injury

Definitions of TBI, including those for concussion or mild TBI (mTBI), vary across studies, making it difficult to compare findings. Definitions in use include those from the Centers for Disease Control and Prevention (Marr and Coronado 2004) and the Department of Veterans Affairs and Department of Defense (VA/DoD 2009). Because the Va/DoD clinical definition is among the most recently developed and addresses issues specific to TBI among service members, veterans, and civilians, it is summarized here:

TBI is defined (VA/DoD 2009) as a traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset of at least one of the following clinical signs, immediately following the event:

- Any period of loss of or a decreased level of consciousness;
- Any loss of memory for events immediately before or after the injury;
- Any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc., also known as alteration of consciousness [AOC]);
- Neurological deficits (weakness, loss of balance, change in vision, praxis, paresis/paraplegia, sensory loss, aphasia, etc.) that may or may not be transient;
- Intracranial lesion.

Notably, although skull fracture is included in some surveillance definitions as an indicator of possible TBI, skull fracture by itself is not a TBI.

External forces may include any of the following events: the head being struck by an object, the head striking an object, the brain undergoing an acceleration/deceleration movement without direct external trauma to the head, a foreign body penetrating the brain, forces generated from events such as a blast or explosion, or other force yet to be defined.

It is important to note that the above criteria define the "event" of a TBI. Not all individuals exposed to an external force will sustain a TBI, but any person who has a history of such an event with manifestations of any of the above signs and symptoms, most often occurring immediately or within a short time after the event, can be said to have had a TBI.

Disclaimer: The views expressed in this chapter are those of the authors and do not reflect the official policy or position of the Department of Veterans Affairs or the U.S. Government.

TABLE 1–1. Glasgow Coma Scale scores

Type of response		Score	Description/significance
Eye opening	Spontaneous	4	Eyes are open, but this does not imply intact awareness; indicates active arousal mechanisms in the brain stem.
	To speech	3	Nonspecific response to speech or shout; does not imply patient obeys commands to open eyes; indicates functional cerebral cortex in processing information.
	To pain	2	Pain stimulus is applied to chest or limbs; suggests functioning of the lower levels of the brain.
	None	1	No response to speech or pain (not attributable to ocular swelling).
Motor	Obeys commands	6	Can process instructions and respond by obeying a command (Fischer and Mathieson 2001).
	Localizes pain	5	Pain stimulus is applied to supraocular region or fingertip; patient makes an attempt to remove the source of the pain stimulus.
	Withdrawal	4	Normal flexor response; patient withdraws from painful stimulus with abduction of the shoulder.
	Abnormal flexion	3	Abnormal responses to pain stimulus; includes flexion or extension of upper extremities; indicates more severe brain dysfunction. Decortication is manifested by adduction of the upper extremities with flexion of the arms, wrists, and fingers; the lower extremities extend and rotate internally with plantar flexion of the feet; suggests lesions in the cerebral hemispheres or internal capsule.
	Extension	2	Decerebrate responses to pain stimulus manifested by adduction and hyperpronation of the upper extremities; the legs are extended with plantar flexion of the feet; includes opisthotonos, a backward extension of the head and arching of the back, indicating damage extending from the midbrain to the upper pontine.
	No response	1	Flaccid, fails to respond to a painful stimulus.
Verbal	Oriented	5	Oriented to person (knows identity); place (knows where he/she is); and time (knows the current year, season, and month).
	Confused	4	Responds to questions in a conversational manner, but responses indicate disorientation/confusion.
	Inappropriate	3	Intelligible speech (e.g., shouting or swearing), but no sustained or coherent conversation.
	Incomprehensible	2	Moaning and groaning; no recognizable words.
	No response	1	No verbal response.

Note. Overall score=sum of all scores.
Source. Adapted from Institute of Medicine 2009, pp. 42, 43; Teasdale and Jennett 1974.

Severity

Length of loss of consciousness (LOC) and posttraumatic amnesia (PTA) are the most common clinical indicators used to assess acute brain injury severity, and the most widely used tool for assessing level of consciousness is the Glasgow Coma Scale (GCS) (Teasdale and Jennett 1974) (Table 1–1). Although the use of the Glasgow Coma Scale–Extended has shown some utility in differentiating patients with mild TBI (Drake et al. 2006; Nell et al. 2000), the usefulness of the GCS in predicting severity is greater for moderate and severe TBI because the vast majority of mTBI patients have normal or near-normal GCS scores within hours after the injury. Mild TBI can also be diagnosed if there is transient alteration in consciousness without LOC or PTA, although the use of this criterion alone for diagnosing mTBI, especially in postinjury screening or surveillance, has been questioned (Hoge et al. 2009). TBI can be further categorized as mild, moderate, or severe based on the length of AOC, LOC, or PTA. Acute injury severity is best determined at the time of the injury (VA/DoD 2009). Criteria for determining acute severity are summarized in Table 1–2.

Concussion

The terms *concussion* and *mild traumatic brain injury* have been used interchangeably. *Concussion* is preferred, however, because it refers to a specific injury *event* that may or may not be associated with persisting symptoms. Moreover, the term *concussion* conveys more positive expectations for recovery than the term *traumatic brain injury*, which is important because positive expectations have been strongly correlated with recovery (Ponsford et al. 2002; Suhr and Gunstad 2002). Also, concussion does not convey conflicting implications regarding outcome—that is, that people should consider themselves "brain injured" if they have a concussion, or conversely that mild TBIs by definition are always mild. Because both are used in the literature cited here, the term *concussion/mTBI* is used in the remainder of this chapter.

TABLE 1–2. Severity of brain injury stratification

Criteria	Mild/concussion	Moderate	Severe
Structural imaging	Normal[a]	Normal or abnormal	Normal or abnormal
Loss of consciousness (LOC)	0–30 minutes	>30 minutes and <24 hours	>24 hours
Alteration of consciousness/mental state (AOC)[b]	A moment up to 24 hours	>24 hours	Severity based on other criteria
Posttraumatic amnesia (PTA)	≤1 day	>1 and <7 days	>7 days
Glasgow Coma Scale (best available score in first 24 hours)[c]	13–15	9–12	3–8

[a]Minor abnormalities possibly not related to the brain injury may be present on structural imaging in the absence of LOC, AOC, and PTA.

[b]Alteration of mental status must be immediately related to trauma to the head. Typical symptoms would be looking and feeling dazed and uncertain of what is happening, confusion, difficulty thinking clearly or responding appropriately to mental status questions, and being unable to describe events immediately before or after the trauma event.

[c]Some studies report the best available Glasgow Coma Scale score within the first 6 hours or some other time period.

Source. Adapted from VA/DoD (2009) Clinical Practice Guideline.

In the United States, the most widely accepted criteria for concussion/mTBI are those proposed by the American Congress of Rehabilitation Medicine (1993) for mild traumatic brain injury:

> a physiological disruption of brain function as a result of a traumatic event as manifested by at least one of the following: alteration of mental state, LOC, loss of memory or focal neurological deficit, that may or may not be transient; but where the severity of the injury does not exceed the following: PTA for greater than 24 hours, after the first 30 minutes GCS score is 13–15, and LOC is less than 30 minutes.

Criteria used by other groups include the Centers for Disease Control and Prevention (CDC 2003) and the World Health Organization (Carroll et al. 2004) definitions. However, most agree that the common criteria include GCS scores of 13–15, brief LOC, brief PTA, and negative head computed tomography scan (VA/DoD 2009).

Various efforts have focused on better characterization of the severity of concussion based on the presence or absence of LOC and/or length of PTA (American Academy of Neurology 1997; Cantu 1986). Most clinicians would agree that a concussion/mTBI at the extremes of the AOC or LOC ranges specified in the guidelines, for example involving 20 minutes of LOC or 23 hours of PTA, would likely carry a higher risk than a concussion/mTBI involving only transient alteration in consciousness (American Academy of Neurology 1997). However, these classification efforts have not had strong clinical validation. A likely reason is that many studies and surveillance reports have focused on concussion/mTBI with a level of severity high enough to warrant emergency department care or hospitalization. As a result, these research and surveillance efforts tend to overrepresent the more severe concussion/mTBI cases involving LOC or PTA and fail to include the milder cases involving only AOC or brief LOC/PTA, resulting in an underestimate of the true incidence of concussion/mTBI.

On the basis of currently accepted definitions and neurophysiological studies, TBI is considered to exist on a continuum of injury from mild to severe. However, some experts have pointed out problems with the continuum perspective based on the distinct clinical features and epidemiology of concussion/mTBI compared with moderate and severe TBI (Hoge et al. 2009; McCrea 2008). The natural history, risk factors for injury sequelae, expectation of full recovery, and treatment approaches differ substantially between concussion/mTBI and moderate/severe TBI (Table 1–3). Studies that fail to adequately distinguish between concussion/mTBI and moderate/severe TBI complicate interpretation of available clinical studies and natural history or epidemiological data.

Notably, the case definition for concussion/mTBI (VA/DoD 2009), which is designed for the acute injury period, lacks essential criteria for retrospective assessment of concussion/mTBI history, including the lack of specific symptoms, time course, and functional impairment (Hoge et al. 2009). Thus, when the case definition is used to assess concussion/mTBI weeks or months after the injury on the basis of self-report, as is done in some health screening programs, these limitations can lead to subjective attribution of non-mTBI-related symptoms to concussion/mTBI. Misattribution of nonspecific symptoms such as headache, which may be due to other causes and not the injury event, can result in inflated estimates of the true numbers of cases of concussion/mTBI.

Although accurate diagnosis of concussion/mTBI remains challenging because of the limitations of sign- and symptom-based diagnosis, recent studies suggest that structural abnormalities identified using advanced neuroimaging techniques (diffusion tensor imaging) can serve as quantitative biomarkers for concussion/m TBI (Niogi et al. 2008a, 2008b; Wilde et al. 2008). Improvements in TBI diagnosis based on neuropathology will lead to an improved classification system for all levels of TBI severity, not only for clinical research (Saatman et al. 2008) but also for epidemiological studies.

Because there is no single system that comprehensively tracks the occurrence of TBI and includes the full range of severity, data representing the true incidence are lacking, especially for large, defined populations such as the U.S. population. Typically surveillance is used to estimate the number of TBIs that occur nationally. Public health surveillance is defined as "the ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health" (CDC 2001).

TABLE 1–3. Comparison of mild TBI with moderate and severe TBI

Variable	Mild TBI (concussion)	Moderate and severe TBI
Clinical definition	<30 minutes loss of consciousness, any alteration in consciousness, or posttraumatic amnesia lasting <24 hours. Some definitions include Glasgow Coma Scale score of 13–15.	Loss of consciousness ≥30 minutes up to prolonged coma. Posttraumatic amnesia ≥24 hours up to permanent. Glasgow Coma Scale score as low as 3.
Focal neurological signs	Generally none or transient.	Frequently present.
Computed tomography or magnetic resonance imaging	Usually negative or very minor.	Diagnostic.
Natural history	Usually leads to full recovery. There is lack of consensus on the natural history of postconcussive symptoms or syndrome; some evidence of possible prolonged sequelae.	Natural history and recovery are directly related to severity of injury and functional neuroanatomy.
Case definitions and specificity of injury sequelae	Case definitions of postconcussion syndrome have low reliability and validity and show poor correlation with each other. There are high rates of these symptoms in healthy populations, and high rates of "postconcussion syndrome" after nonhead injuries.	Injury sequelae are not debated.
Predictors of persistent symptoms or disability (predictors or risk factors should be consistent in use)	Risk factors that have most consistently been shown to be associated with persistent symptoms include psychological factors (e.g., depression, anxiety, or posttraumatic stress disorder), compensation and litigation, and negative expectations and beliefs.	Directly related to injury characteristics.
Neurocognitive testing	Often inconclusive beyond acute injury period.	Essential and valuable component of ongoing clinical care.
Neuronal cell damage	Metabolic and ionic processes caused by axonal twisting or stretching can lead to secondary disconnection.	Combination of cellular disruption directly related to injury and metabolic and ionic processes.
Epidemiological evidence of causation between injury and sequelae	Inconsistent. Debated.	Not debated.

Note. TBI=traumatic brain injury.
Source. Adapted from Hoge et al. 2009.

The CDC conducts surveillance of TBI in the United States by routinely analyzing data from the National Center for Health Statistics regarding TBI deaths, hospital discharges, and emergency department visits using an established case definition (Marr and Coronado 2004). Data for hospital discharges and emergency department visits are based on data from a representative sample of hospitals (Faul et al. 2010). Thus the resulting numbers are estimates. Because the CDC routinely publishes population-based estimates of the frequency of TBI, it is the primary source for the civilian incidence data reported here.

TBI Among the Civilian U.S. Population

Incidence

Incidence refers to the number of new TBI events that occur each year in a specific population or geographic region. It represents the number of people who *had* a TBI event whether or not they experienced related symptoms or problems after the acute phase of the injury. It is important to note that these numbers include people who experienced a TBI and appear to have recovered from the injury.

According to the most recent data from the CDC, on average an estimated 1,691,481 TBIs (576.8 per 100,000) occurred in the United States each year during the years 2002 through 2006, including 1,364,797 emergency department visits (465.4 per 100,000), 275,146 hospitalizations (93.8 per 100,000), and 51,538 deaths (17.6 per 100,000) (Faul et al. 2010) (Table 1–4).

Previous national incidence estimates varied depending on the data source(s) and year(s). Using self-report data from the National Center for Health Statistics' National Health Interview Survey, Sosin et al. (1996) estimated that the annual incidence of TBI was 1.5 million for the year 1991. Langlois et al. (2004), using combined emergency department, hospitalization, and death data from the National Center for Health Statistics, reported an average annual incidence of TBI of 1.4 million per year for the years 1995 through 2001. Rutland-Brown et al. (2006), using the same methods, reported an estimated 1.6 million TBIs for the year 2003. Using data from multiple sources for deaths, hospitalizations, emergency department visits, and office-based and/or outpatient visits, Finkelstein et al. (2006) reported an estimated 1.4 million TBIs occurred in the United States in the year 2000. Variations in the incidence estimates reported were likely due in part to variations in the data sources and methods used.

TABLE 1–4. Estimated average annual numbers, rates, and percentages of traumatic brain injury–related emergency department visits, hospitalizations, and deaths, by age group, United States, 2002–2006

	Disposition										
	Emergency department visits[a]			Hospitalizations[b]			Deaths			Total	
Age (years)	Number	Rate[c]	Row %	Number	Rate[c]	Row %	Number	Rate[c]	Row %	Number	Rate[c]
0–4	251,546	1,256.2	93.9	15,239	76.1	5.7	998	5.0	0.4	267,783	1,337.3
5–9	105,015	532.9	91.9	8,799	44.7	7.7	450	2.3	0.4	114,264	579.9
10–14	117,387	559.8	90.8	11,098	52.9	8.6	726	3.5	0.6	129,211	616.2
15–19	157,198	757.0	84.5	24,896	119.9	13.4	3,995	19.2	2.1	186,089	896.2
20–24	136,079	655.8	84.1	20,683	99.7	12.8	5,048	24.3	3.1	161,810	779.8
25–34	174,811	438.3	83.0	28,953	72.6	13.7	6,826	17.1	3.2	210,591	528.0
35–44	123,436	279.9	75.8	32,310	73.3	19.9	6,995	15.9	4.3	162,741	369.1
45–54	99,715	239.7	73.4	29,068	69.9	21.4	7,125	17.1	5.2	135,908	326.7
55–64	57,612	198.2	67.6	22,600	77.7	26.5	5,028	17.3	5.9	85,240	293.2
65–74	46,365	250.2	64.7	20,990	113.3	29.3	4,252	22.9	5.9	71,607	386.4
75	95,633	536.2	57.5	60,510	339.3	36.4	10,095	56.6	6.1	166,237	932.0
Total	1,364,797	465.4	80.7	275,146	93.8	16.3	51,538	17.6	3.0	1,691,481	576.8
Adjusted[d]		468.0			93.6			17.4			579.0

Note. Numbers subject to rounding error.

[a]Persons who were hospitalized, died, or transferred to another facility were excluded.

[b]In-hospital deaths and patients who transferred from another hospital were excluded.

[c]Average annual rate per 100,000 population.

[d]Age-adjusted to the 2000 U.S. standard population.

Source. Faul et al. 2010.

Routinely reported U.S. national data underestimate the true incidence of TBI for several reasons. First, these data do not include persons treated for TBI in other civilian health care settings such as hospital outpatient clinics or physicians' offices (Schootman and Fuortes 2000). Second, TBIs treated in military facilities in the United States and abroad are not included (see section below regarding TBI among service members and veterans). Third, the number of persons who receive medical care but whose TBI is not diagnosed is not counted. Patients with concussion/mTBI who did not lose consciousness are among those most likely to be missed (Powell et al. 2008). Finally, those who sustain TBI, particularly concussion/mTBI, but do not seek care also are not counted. This last number is probably considerable. Civilians who had a TBI may be less likely to seek medical care if they are older, sustained a concussion/mTBI, or were injured in the home (Setnick and Bazarian 2007).

Incidence by Age Group

TBI rates for emergency department visits, hospitalizations, and deaths combined are highest among young children ages 0–4 years (1,337.3 per 100,000), followed by adolescents and young adults ages 15–19 years (896.2 per 100,000); however, when emergency department visits are excluded, TBI hospitalization and death rates are highest among older adults age 75 years or older (339.3 per 100,000 and 56.6 per 100,000, respectively) (Faul et al. 2010) (Table 1–4). In every age group, TBI rates are higher for males than for females (Faul et al. 2010).

Trends

The average annual age-adjusted incidence rates for TBI-related emergency department visits and hospitalizations during 2002–2006 (468.0 and 93.6 per 100,000, respectively) (Faul et al. 2010) were higher than for the previous period 1995–2001 (401.2 and 85.5 per 100,000, respectively) (Langlois et al. 2004); however, the TBI-related death rate for 2002–2006 (17.4 per 100,000) (Faul et al. 2010) was lower than for 1995–2001 (Langlois et al. 2004). Although Faul et al. noted differences in the incidence of TBI for the two time periods, they did not indicate whether these differences were statistically significant.

Severity

More than 85% of the medically treated TBIs that occur in the United States annually are considered "mild" (Bazarian et al. 2005). However, because many mild TBIs go untreated, the proportion of TBIs that are mild is likely to be considerably higher. Among hospitalized TBI patients, a minority of total TBI cases, approximately 20% of TBIs are in the severe range (Institute of Medicine 2009). Although they comprise a relatively small proportion of all TBIs, the resulting burden associated with severe TBI on the injured persons, their families, and society is much greater than for less severe injuries.

External Causes

When emergency department visits, hospitalizations, and deaths were combined, falls were the leading cause of TBI (35.2%), followed by motor vehicle/traffic crashes (17.3%), being "struck by/against" (16.5%), and assaults (10%), on average, during the years 2002–2006 (Faul et al. 2010). The remaining 21% had some other external cause or the cause was unknown. "Struck by/against" injuries involve striking against or being struck accidentally by objects or persons. Although not specified in the report by Faul et al. (2010), non–motor vehicle pedal cycle–related injuries accounted for 3% and suicide or suicide attempts accounted for 1%, on average, during the years 1995 through 2001 (Langlois et al. 2004).

When individual medical care settings were considered, falls were the leading cause of TBI-related emergency department visits (30.1%), and motor vehicle/traffic crashes were the leading cause of hospitalizations (25%) (Langlois et al. 2004). For TBI-related deaths, firearm-related injury was the leading cause, accounting for 40% (Adekoya et al. 2002).

Because they are not routinely coded in the national data sets used for surveillance, sports and recreation activities are frequently underestimated as a cause of TBI, especially concussion/mTBI. A previous CDC study estimated that 300,000 concussions/mTBIs occur each year (Thurman et al. 1998). This estimate included only TBIs for which the injured person reported an LOC. Other studies indicate that injuries involving LOC may be associated with only between 8% (Schultz et al. 2004) and 19.2% (Collins et al. 2003) of sports-related TBIs. Taking these data into account, a more accurate estimate may be that 1.6 million to 3.8 million sports-related TBIs occur each year in the United States, including those for which no medical care is sought (Langlois et al. 2006). This estimate may still be low because many concussions/mTBIs go unrecognized and as a result remain uncounted.

TBIs associated with violence are also underreported. The number of cases of TBI due to intimate partner violence or domestic violence is not known. According to CDC estimates, at least 156,000 TBI-related deaths, hospitalizations, and emergency department visits in the United States each year are associated with all types of assaults (Langlois et al. 2004). However, strangulation or blows to the head occur in 50%–90% of intimate partner physical assaults against women (Greenfield and Rand 1998; Wolfe et al. 1997), and U.S. women experience about 4.8 million intimate partner–related physical assaults annually (Tjaden and Thoennes 2000). Thus, the true number of TBIs related to intimate partner violence likely is much higher than the CDC estimate. Abusive head trauma, also known as inflicted TBI, shaken baby syndrome, or shaken impact syndrome, is a leading cause of death from TBI in infants and young children (Duhaime et al. 1998; Keenan et al. 2003). A population-based study of children ages 2 years or younger who were admitted to a North Carolina pediatric intensive care unit or who died with a TBI revealed an incidence rate of inflicted TBI of 17.0 per 100,000 person-years (Keenan et al. 2003). Accurate diagnosis of abusive head trauma is challenging because the caregivers of abused children often give a history of *no* trauma having occurred (Ettaro et al. 2004; O'Neill et al. 1973), children may present with nonspecific symptoms such as fussiness or vomiting (Duhaime and Partington 2002; Jenny et al. 1999), and results of the physical examination may be normal (Haviland and Russell 1997; Morris et al. 2000). Thus, reported rates of abusive head trauma likely represent underestimates.

Selected Risk Factors

Alcohol Consumption

It is well known that the risk of a TBI associated with all types of exposure, including motor vehicle crashes, increases with increased blood alcohol concentration (BAC) (Modell and Mountz 1990; Waller et al. 1986). Rimel (1981) showed that 72% of newly admitted patients identified in a central Virginia TBI data bank had positive BAC, and 55% were legally intoxicated (BAC of 0.10% or higher). Langlois et al. (2003) reported on alcohol use and TBI hospitalization from a 14-state CDC TBI surveillance system. Among motor vehicle occupants in that study, approximately 21% had documented alcohol use of any level, 12% had documented BACs of 0.10 gram per deciliter or higher (i.e., above the legal limit for intoxication for motor vehicle drivers), and 19% of motorcyclists had BACs at this level. Notably, among those with TBI due to assaults, 41% had documented alcohol use of any level and 23% had BACs above the legal limit.

In addition to increasing the risk of injury, alcohol use among TBI patients can complicate diagnosis in the emergency department by depressing the level of consciousness and thereby affecting the accuracy of initial assessment of TBI severity using GCS. In one study, this effect appeared to be independent of the severity of the injury (Jagger et al. 1984). However, findings from more recent studies showed that alcohol intoxication generally did not result in a clinically relevant reduction in GCS in trauma patients with TBI (Stuke et al. 2007) except in those with the most severe injuries (Sperry et al. 2006) and those with very high blood alcohol levels (200 mg./dL or higher) who also had intracranial abnormalities detected on CT scan (Lange et al. 2010). Inaccurate assessment of individuals with TBI, especially concussion/mTBI, in the emergency department can contribute to missed diagnosis (Powell et al. 2008) and underestimates of the incidence of medically treated TBI.

Recurrent TBI

Recurrent TBI, including concussion/mTBI, is associated with prolonged recovery (Guskiewicz et al. 2003) and increased risk of a catastrophic outcome such as second-impact syndrome (CDC 1997). In one of the first population-based studies of recurrent TBI involving review of medical record data for a 10-year period, Annegers et al. (1980) reported that 7.1% of males and 3.0% of females experienced a second head injury; of those with a second head injury, 14.6% of males and 6.2% of females experienced at least a third head injury. In this study, males who had an initial head injury were 2.8 times as likely and females were 3.0 times as likely to have had a second head

injury; males who had a second head injury were 7.8 times as likely and females 9.3 times as likely to have had at least a third head injury. In a more recent population-based study, Saunders et al. (2009) reported that 7% of those hospitalized with a TBI had a least one recurrent TBI during the follow-up period, which varied by participant from 2.5 to 7 years posthospitalization.

Ruff et al. (1990), Kreutzer et al. (1990), and Corrigan (1995), who reviewed the literature on this topic, concluded that recurrent TBI was strongly associated with alcohol abuse. This was also confirmed in a more recent population-based longitudinal study from Finland in which persons with an alcohol-related first injury were 4.4 times as likely (95% confidence interval [CI] 1.5–12.7) to have a recurrent TBI (Winqvist et al. 2008). In sports in which the high incidence of concussion/mTBI is well documented and alcohol is less likely to be a factor, recurrent concussion/mTBI is also a problem. In a prospective study of collegiate football players, those reporting a history of three or more previous concussions were 3.0 (95% CI 1.6–5.6) times more likely to have an incident concussion than those with no concussion history (Guskiewicz et al. 2003).

Lifetime Prevalence of a History of TBI

Lifetime prevalence of TBI refers to the number or percentage of individuals who have "ever" experienced a TBI, whether or not they continue to have persisting symptoms or related disability.

General Population

In a population-based study of TBI among U.S. adults age 18 years or older, the prevalence of a self-reported history of a severe head injury that was associated with a loss of consciousness or confusion was 8.5% (Silver et al. 2001). Because this study was retrospective, the findings are limited by potential recall bias and likely represent an underestimate. More recent prospective studies support this notion. Specifically, a birth cohort study in Finland reported the prevalence of a history of confirmed TBI, including concussion/mTBI in persons admitted to a hospital or seen in an outpatient clinic, to be 2.9% among males and 1.9% among females up to age 15 years (Timonen et al. 2002). A birth cohort study in New Zealand in which TBI diagnosis was determined on the basis of the child's history of medical attendances, including general practitioner, specialist, and hospital, found that approximately 38% of males and 24% of females experienced at least one TBI up to the age of 25 years (McKinlay et al. 2008). Thus, although the exact lifetime prevalence is unknown, the findings from these prospective studies of the history of TBI through youth and young adulthood suggest that the true lifetime prevalence of a history of TBI for adults is likely much higher than suggested by the previous retrospective self-report finding (Silver et al. 2001).

Incarcerated Persons

A history of TBI is common among inmates. According to several studies, an estimated 25%–87% of the jail and prison population reported having experienced one or more TBIs (Morrell et al. 1998; Schofield et al. 2006; Slaughter et al. 2003). In a survey of male prisoners in Minnesota, 82.8% reported having had one or more head injuries during their lifetime (Wald et al. 2008). This finding is consistent with the prevalence reported in a previous study (Slaughter et al. 2003). In the Minnesota study, the majority of TBIs were reportedly caused by assaults (37%), followed by auto crashes (25%), sports (11%), and falls (11%) (Wald et al. 2008). In a large study of delinquent youth (mean age 15.5 years), most of whom were male, 18.3% reported a lifetime history of TBI, defined as ever having had a head injury causing unconsciousness for more than 20 minutes (Perron and Howard 2008). Although previous studies have focused primarily on male inmates, preliminary results suggest that the prevalence of a history of TBI may also be high among female offenders (Diamond et al. 2007). Challenges in obtaining accurate estimates of the prevalence of TBI among incarcerated persons include obtaining data that are population based versus facility based, inaccuracy due to problems with recall, and the potential for overreporting associated with inmates' perception of possible gain.

Homeless Persons

Studies from England, the United States, and Canada reported that 46% (Bremner et al. 1996), 48% (Solliday-McRoy et al. 2004), and 58% (Hwang et al. 2008) of homeless men, respectively, and 42% of homeless women (Hwang et al. 2008) had a lifetime history of head injury or TBI involving LOC. Accurate determination of rates of TBI among homeless persons are also challenging because they rely on self-report, which may be inaccurate.

Outcomes

Long-Term Adverse Health Outcomes

Of particular concern after TBI are adverse outcomes that affect health and the ability to function in society. The Institute of Medicine (2009) Committee on Gulf War and Health recently conducted a large-scale and detailed systematic review of the literature to answer the question, "What are the long-term outcomes associated with sustaining TBI?" The committee reported significant limitations in many of the existing studies, including reliance on self-report, small sample sizes, lack of uniformity in defining TBI severity, and inadequate comparison groups. However, they also found evidence in the literature of a range of adverse long-term health outcomes (lasting greater than 6 months) associated with moderate and severe TBI and mild TBI with LOC. The committee's main findings for the studies that could be categorized by TBI severity are summarized in Table 1–5. According to the committee, evidence of long-term adverse health effects was strongest for moderate, severe, and penetrating TBI and limited or inadequate for concussion/mTBI. The evidence of an association between concussion/mTBI alone and long-term neurocognitive deficits (defined as performance on tests of sensory integrity, motor speed and coordination, attention, processing, and executive functions) was found to be insufficient/inadequate based on the published literature

to date. The committee also found insufficient/inadequate evidence for the association between concussion/mTBI and long-term social and occupational dysfunction. Although they concluded on the basis of combined results from studies of a range of TBI severity that there is sufficient evidence of an association between sustaining a TBI and development of postconcussive symptoms (such as memory problems, dizziness, and irritability), this finding is problematic. Specifically, there was no adequate evaluation of the association of concussion/mTBI alone with postconcussive symptoms because in some studies, data were not analyzed separately for concussion/mTBI and moderate/severe TBI, or postconcussion-symptom inventories were used to assess symptoms in persons who had moderate to severe TBI. The failure to separate concussion/mTBI from moderate/severe TBI in the evaluation of postconcussive symptoms is a problem in some natural history studies of TBI.

Protective Factors

Little is known about factors that may protect against adverse outcomes or promote recovery after TBI, such as a healthy lifestyle. For instance, it is not clear from the available literature whether physical fitness preinjury facilitates recovery post-TBI. However, physical exercise has been shown to enhance cognition, counteract age-related memory decline, delay the onset of neurodegenerative diseases, and promote recovery after brain injury (van Praag 2008). The timing of exercise and degree of exertion are important factors. For example, laboratory studies suggest that voluntary exercise may enhance neuroplasticity after TBI, but only when it is delayed; when exercise is administered too soon after injury, recovery may be adversely affected (Griesbach et al. 2004a, 2004b). The level of exertion is also important. In a study of athletes, a high activity level after concussion resulted in worse neurocognitive performance, whereas those engaging in moderate activity demonstrated the best performance (Majerske et al. 2008). However, results of a preliminary study of subsymptom threshold exercise training showed that treatment with controlled exercise was safe and appeared to reduce persistent postconcussion symptoms when compared with no-treatment baseline measurements (Leddy et al. 2010). Other lifestyle factors may interact with exercise to influence recovery. For example, the results of one laboratory study suggest that a high saturated fat diet may dampen the positive effects of exercise on neuroplasticity after TBI (Wu et al. 2003), reinforcing the potential importance of good nutrition on recovery post-TBI.

Postconcussion Symptoms Following Concussion/mTBI

It has been well described that acute symptoms occurring in association with concussion/mTBI, such as headaches, irritability, concentration/memory problems, sleep disturbance, dizziness, or fatigue, can sometimes persist and become chronic and debilitating. Numerous reviews and research studies have reported on the incidence/prevalence of persistent postconcussion symptoms, or postconcussion syndrome, following concussion/mTBI. However, the lack of a valid and consistently used case definition has limited the ability to interpret the available clinical and epidemiological data. Two widely used definitions for postconcussion symptoms, the DSM-IV-TR (American Psychiatric Association 2000) research definition and the International Classification of Diseases–10 (World Health Organization 1992) definition, have shown poor correlation with each other (kappa 0.14) (Boake et al. 2004), and the prevalence of postconcussion symptoms has been shown to be similar following injuries not involving the head compared with the prevalence following concussions/mTBIs (Meares et al. 2008). Postconcussion symptoms have also been shown to be very nonspecific and to occur with high rates in healthy individuals (Iverson and Lange 2003), including university students (Wang et al. 2006), as well as in persons with depression and various other chronic diseases (Iverson et al. 2007). Risk factors shown to be strong predictors of persistent postconcussion symptoms after concussion include mental disorders (depression, anxiety), litigation/compensation, and negative illness expectations (McCrea 2008).

Despite these problems with the postconcussion symptoms construct, it has been widely reported that 10%–20% of individuals continue to experience postconcussive symptoms for months or years after injury (Alexander 1995; Alves et al. 1993; Ruff et al. 1996). Recent analysis of the biases inherent in these estimates, including the nonrepresentativeness of study samples, suggests a much lower estimate of the prevalence of persistent postconcussive symptoms, perhaps as low as <5% (Iverson 2005). Even this figure, however, is speculative because of the lack of a valid case definition and the absence of well-controlled prospective natural history studies.

Disability

Incidence of TBI-related disability refers to the number of people in a defined geographic region who have had a TBI and are expected to have long-term or lifelong disability. An estimated 43.3% of hospitalized TBI survivors in the United States in 2003 experienced a TBI with related long-term disability (Selassie et al. 2008). Disability was defined broadly and was inferred from self-reports of inability or a lot of difficulty performing activities of daily living, having postinjury symptoms that prevented people from doing things they wanted to do, and poor cognitive and mental health scores on standard measures based on findings from a previous population-based study (Selassie et al. 2008). Overall, the probability of TBI-related long-term disability increased with age and was significantly higher among women (49.5%) than among men (39.9%) (Selassie et al. 2008). TBIs associated with falls (58.4%) and firearm injuries (49.9%) were the most likely to be associated with long-term disability. It should be noted that these figures are likely underestimates because they are based on hospitalizations only and exclude TBIs treated in other settings or for which treatment was not sought.

Prevalence of TBI-related disability refers to the number of people in a defined geographic region, such as the United States, who have ever had a TBI and are living with symptoms or problems related to the TBI. This excludes people who had a TBI and recovered from it. The most re-

TABLE 1–5. Institute of Medicine summary of long-term (lasting more than 6 months) health effects of TBI by severity and strength of evidence

	Strength of evidence			
TBI severity	Sufficient evidence of causality	Sufficient evidence of an association	Limited/ suggestive evidence of an association	Inadequate/insufficient evidence of an association
Mild			Unprovoked seizures (with LOC or amnesia) Ocular and visual motor deterioration Alzheimer's dementia (with LOC) Parkinsonism (with LOC) Posttraumatic stress disorder (military populations)	Neurocognitive deficits[a] Alzheimer's dementia (without LOC) Posttraumatic stress disorder (civilian populations) Long-term adverse social functioning[b]
Moderate	Unprovoked seizures	Growth hormone insufficiency Alzheimer's dementia Endocrine dysfunction[c] Parkinsonism Long-term adverse social functioning[d] Premature mortality[e]	Neurocognitive deficits Diabetes insipidus Psychosis[g]	Brain tumor
Severe	Unprovoked seizures	Neurocognitive deficits Growth hormone insufficiency Endocrine dysfunction[c] Alzheimer's dementia Parkinsonism Long-term adverse social functioning[d] Premature mortality[e]	Diabetes insipidus Psychosis[g]	Brain tumor
Penetrating	Unprovoked seizures Premature mortality	Neurocognitive decline[f] Long-term unemployment		

Note. TBI=traumatic brain injury; LOC=loss of consciousness.

[a]Compared with preinjury levels in the 1- to 3-year period post-TBI.

[b]Including unemployment, diminished social relationships, and decrease in the ability to live independently.

[c]Primarily hypopituitarism.

[d]Particularly unemployment and diminished social relationships.

[e]Subset of patients admitted into or discharged from rehabilitation centers or receive disability services.

[f]Associated with the affected region of the brain and the volume of tissue lost.

[g]In the 2- to 3-year period post-TBI.

Source. Adapted from Institute of Medicine 2009.

cent estimate of the prevalence of Americans living with disability related to a TBI hospitalization is 3.2 million (Zaloshnja et al. 2008). The previous estimate was 5.3 million Americans living with disability after being hospitalized with a TBI (Thurman et al. 1999). The seeming decrease is related to the different methods and data used. In the most recent estimate, the numbers of people with TBI expected to have died were accounted for more completely than in the previous estimate.

The estimates for the incidence and prevalence of TBI-related disability are based on hospital discharges only. They do not include persons treated and released from emergency departments or who received no medical care. Service members injured outside of the United States and those treated in military health care facilities within the United States also are not included. This is in part because data for TBI incidence and for mortality over an extended period of time (e.g.,70 years) are needed and are not readily available for these groups. Available data only allow for meaningful estimates of the risk of disability after moderate and severe TBI. Because a large percentage of concussions/mTBIs do not result in medical treatment, there are inadequate data to evaluate the risk of disability after concussions/mTBIs.

Disorders of Consciousness

Among the most severely disabling outcomes of TBI are disorders of consciousness, including coma, the vegetative state, and the minimally conscious state. These disorders are characterized by severe alteration of the awareness of self and the environment.

Coma is a transitory state of unconsciousness in which the eyes remain continuously closed and there is no behavioral evidence of an awareness of self or the environment. Individuals in the vegetative state maintain wakefulness but show no evidence of the capacity to interact with the environment. They do, however, exhibit periods of eye

opening that occur either spontaneously or in response to sensory stimulation, but show no signs of purposeful behavior. In contrast, the minimally conscious state is a condition of severely altered consciousness in which minimal but definite behavioral evidence of awareness of self or the environment is demonstrated (Bérubé et al. 2006).

It is estimated that at least 4,200 new individuals in the vegetative state, including those in a vegetative state due to TBI, are diagnosed each year in the United States (Jennett 2002). The frequency of new cases of the minimally conscious state, including the number who transition from the vegetative to the minimally conscious state, has not yet been determined. Published estimates suggest that as many as 315,000 Americans, including those with TBI, are living with a disorder of consciousness, including 35,000 in the vegetative state (Multi-Society Task Force 1994) and 280,000 in the minimally conscious state (Strauss et al. 2000), but the proportion of the total due to TBI is not known. An estimated 40% of individuals with disorders of consciousness are children (Strauss et al. 2000). These figures most likely underestimate the frequency of the vegetative and minimally conscious states because of the lack of surveillance in subacute care settings in which most of these individuals reside. Detailed information about persons in vegetative states and minimally conscious states by age, sex, and cause of the disorder has not been reported, nor have the numbers of service members and veterans in the vegetative and minimally conscious states.

With regard to outcomes for people in a vegetative state, based on a comprehensive review of the world literature (Multi-Society Task Force 1994), it was reported that 52% of adults and 62% of children in a vegetative state 1 month after TBI recovered consciousness within 1 year postinjury. Good recovery of function was uncommon. Among adults, at 1 year postinjury, 28% had severe disability, 17% had moderate disability, and 7% had a good recovery according to the Glasgow Outcome Scale. Among children, recovery of function was comparable with that in the adults. At 1 year, 35% of the children had severe disability, 16% had moderate disability, and 11% had made a good recovery (Multi-Society Task Force 1994).

Mortality

In a study of a representative sample of persons age 15 years and older hospitalized with TBI in South Carolina in which mortality was ascertained from statewide multiple cause-of-death data, the mortality rate was 8.4% by 15 months posthospital discharge (Selassie et al. 2005). Increased risk of death was strongly associated with older age and was seven times the rate for the general population (Selassie et al. 2005). Similarly, a 7.4% mortality rate 1 year post-TBI was reported in the National Institute on Disability and Rehabilitation Research TBI model systems population (Harrison-Felix et al. 2004). Among this study population of adults who received acute inpatient rehabilitation, persons with TBI were twice as likely to die as the general population, and older age was also a risk factor. Although these findings suggest an increased likelihood of premature death among persons hospitalized with TBI, additional studies are needed to confirm this (Institute of Medicine 2009).

Economic Cost

The total lifetime comprehensive costs of fatal, hospitalized, and nonhospitalized TBI among civilians who were medically treated in the year 2000 were estimated, in 2009 dollars, to total more than $221 billion, including $14.6 billion for medical costs, $69.2 billion for work loss costs, and $137 billion for the value of lost quality of life (Table 1–6). By age and sex, both the total lifetime comprehensive costs and the per TBI patient (unit) total comprehensive lifetime costs were highest for males ages 25–44 years ($62.1 billion and $431,755, respectively) (Tables 1–7 and 1–8). Notably, nonhospitalized TBI included those presenting for emergency department, office-based, or hospital outpatient visits. These cost estimates do not adequately account for the costs of extended rehabilitation, services, and supports, such as informal caregiving, needed by those with long-term or lifelong disability, or the value of lost quality of life or productivity losses for parents or other caregivers. Conversely, these estimates only represent TBIs associated with medical treatment, and it is likely that the per person costs associated with most concussion/mTBIs are substantially less than this.

Costs provide a way to weight the severity of injuries in different settings. By mechanism, Table 1–9 shows the contrasting patterns in the incidence of medically treated TBIs in 2000 and their combined medical and work loss cost. Here the number of TBIs includes those treated only in physicians' offices as well as hospital-treated cases and deaths. From an incidence viewpoint, falls, struck by/against injuries, and injuries in motor vehicle crashes each accounted for 24%–29% of the cases. But motor vehicle crashes and firearms caused much more severe TBIs than other mechanisms. Consequently, motor vehicle crashes accounted for almost 40% of the costs and firearms for almost 30%, with falls accounting for 15% and struck by/against incidents for just 6%.

TBI Among Military Service Members and Veterans

Interest in war-related TBIs has increased in response to concern about TBIs, especially from blasts, among U.S. service members deployed to the conflicts in Iraq (Operation Iraqi Freedom [OIF]) and Afghanistan (Operation Enduring Freedom [OEF]). However, because military personnel routinely engage in risky activities, non-combat-related TBIs are also common and thus of concern.

The diagnosis of moderate and severe TBI among service members is relatively straightforward even in the war theater because the clinical signs and symptoms, neuroimaging abnormalities, and functional deficits tend to be readily apparent. However, the accurate identification of concussion/mTBIs can be very challenging for several reasons: first, the signs associated with the injury are more subtle than for moderate/severe injuries; second, structural abnormalities are not always identified on neuroimaging; third, there are limited diagnostic tools with known sensitivity and specificity that can be administered in the combat environment; and fourth, concussion/mTBI symp-

TABLE 1–6. Total lifetime comprehensive costs of traumatic brain injury by level of treatment, 2000 (million 2009$)

Level of treatment	Incidence	Medical cost (millions)	Work loss cost (millions)	Quality of life loss (millions)	Total cost (millions)	% of total
Fatal	40,148	585	53,329	93,345	147,260	66.9
Hospitalized	155,587	11,613	12,568	31,086	55,267	25.0
Nonhospitalized	1,147,486	2,407	3,287	12,962	18,657	8.4
Total	1,343,221	14,605	69,185	137,393	221,183	100.0
% of total		6.6	31.3	62.1	100.0	

Source. Derived from unpublished tables supporting Finkelstein et al. 2006.

TABLE 1–7. Total lifetime comprehensive costs of traumatic brain injury by sex and age, 2000 (million 2009$)

Age (years)	Fatal	Hospitalized	Nonhospitalized	Total
All	144,651	57,803	18,729	221,183
0–4	4,394	4,315	3,161	11,869
5–14	6,095	5,733	6,925	18,753
15–24	41,242	14,157	1,381	56,780
25–44	55,721	17,706	4,453	77,881
45–64	26,519	9,068	2,338	37,925
65–74	5,194	2,502	169	7,865
75+	5,487	4,322	301	10,111
Males	113,147	41,035	11,876	166,057
0–4	2,646	2,577	1,429	6,652
5–14	3,983	4,087	5,284	13,354
15–24	33,297	10,999	774	45,071
25–44	45,303	13,696	3,130	62,129
45–64	21,038	6,460	1,078	28,575
65–74	3,667	1,413	94	5,174
75+	3,212	1,802	88	5,103
Females	31,504	16,769	6,853	55,126
0–4	1,748	1,738	1,732	5,218
5–14	2,111	1,646	1,642	5,399
15–24	7,945	3,157	607	11,709
25–44	10,418	4,011	1,324	15,752
45–64	5,481	2,608	1,260	9,349
65–74	1,528	1,088	75	2,691
75+	2,274	2,520	214	5,008

Source. Derived from unpublished tables supporting Finkelstein et al. 2006.

toms overlap with those of other conditions such as acute stress reaction and posttraumatic stress disorder (Iverson et al. 2009)

Population-based estimates of the numbers of service members and veterans who sustain a TBI at any level of severity are available through several sources. The DoD (2009b) has routinely reported surveillance data for persons with medically treated TBI. The DoD, VA, and individual investigators have also reported data based on screening, which has been used to retrospectively identify service members who experienced concussion/mTBI based on self-report. Selected findings from these sources are summarized in this section. Because the availability of TBI-related mortality data are limited by concerns for operational security, information regarding TBI-related morbidity only is presented here.

Surveillance

Surveillance can be used to estimate the number of TBIs among members of the military. Two primary sources routinely report surveillance data for TBI among service members. The first source, the DoD TBI numbers website, reports the numbers of service members with TBI diagnosed by a medical provider (DoD 2009b). Cases are reportedly ascertained from electronic records of service

TABLE 1–8. Unit lifetime comprehensive costs of traumatic brain injury by sex and age, 2000 (2009$)

Age (years)	Fatal	Hospitalized	Nonhospitalized	Total
All	3,602,901	371,518	16,322	164,666
0–4	5,050,354	464,758	21,223	74,608
5–14	5,213,794	464,426	24,500	63,318
15–24	5,369,199	515,669	7,030	245,155
25–44	4,766,926	479,288	16,727	247,338
45–64	3,192,815	355,677	18,354	235,314
65–74	1,576,560	204,669	6,850	195,625
75+	768,604	135,740	2,980	72,163
Males	3,791,387	419,877	22,312	251,662
0–4	5,225,409	479,782	21,144	90,548
5–14	5,392,840	475,878	29,757	71,456
15–24	5,489,843	537,342	8,735	391,255
25–44	4,884,279	505,311	29,110	431,755
45–64	3,232,235	380,111	17,243	332,271
65–74	1,521,141	213,342	8,704	260,980
75+	740,493	143,305	4,965	147,543
Females	3,057,068	289,831	11,139	80,666
0–4	4,806,583	444,136	21,288	60,933
5–14	4,906,421	438,248	15,619	49,402
15–24	4,916,379	452,140	5,628	100,582
25–44	4,315,974	407,604	8,339	92,128
45–64	3,050,035	306,826	19,425	124,380
65–74	1,727,643	194,403	5,411	132,045
75+	812,149	130,801	2,559	47,459

Source. Derived from unpublished tables supporting Finkelstein et al. 2006.

TABLE 1–9. Incidence and lifetime medical and work loss costs of traumatic brain injury by mechanism, 2000 (2009$)

Cause	Incidence	% of incidents	Medical and work loss cost (in millions of 2009$)	% of costs	Comprehensive cost (in millions of 2009$)
Total	1,343,000	100.0	83,790	100.0	221,183
Motor vehicle occupants/ other road users	323,000	24.1	33,382	39.8	85,584
Falls	398,000	29.6	12,143	14.5	33,484
Struck by/against	337,000	25.1	5,274	6.3	13,555
Cut/pierce	7,000	0.5	248	0.3	595
Fire/burn	1,000	0.1	27	0.0	72
Machinery/tools	1,000	0.1	288	0.3	731
Firearm/gunshot	17,000	1.3	23,911	28.5	64,545
Other/unknown	259,000	19.3	8,518	10.2	22,616

Source. Derived from unpublished tables supporting Finkelstein et al. 2006.

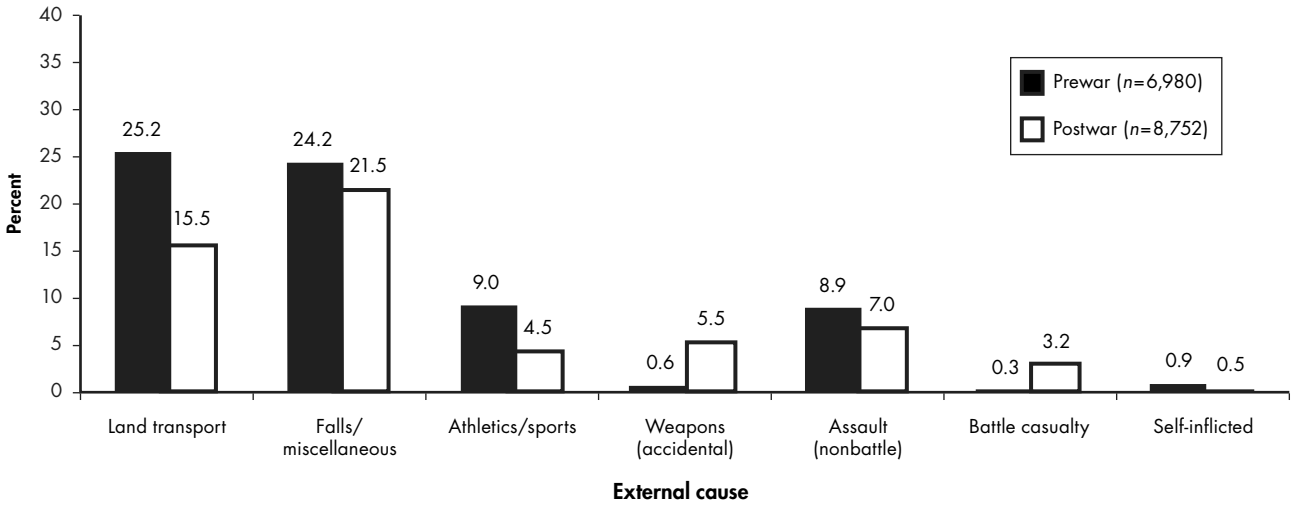


FIGURE 1–1. Percentage of traumatic brain injury hospitalizations pre- and postwar, by selected external causes, U.S. Armed Forces, 1997–2006.

Excludes other causes (prewar: 5.5%; postwar: 4.1%) and missing/invalid code (prewar: 25.3%; postwar: 38.1%). Prewar=January 1, 1997, to August 31, 2001; postwar=September 1, 2001, to December 31, 2006.

Source. Armed Forces Health Surveillance Center 2007.

members diagnosed "anywhere in the world," but no further detail about the data sources is provided. The second source, the Armed Forces Health Surveillance Center (AFHSC) TBI surveillance, has routinely published population-based estimates of the frequency of TBI in greater detail than the DoD TBI numbers website and reports monthly updates on the number of TBIs (AFHSC 2010). In the reports cited here, the AFHSC analyzed TBI morbidity data from the Defense Medical Surveillance System, including information about battle- and non-battle-related hospitalizations and ambulatory medical treatment encounters. A standard DoD case definition for TBI surveillance, published in October 2008 (AFHSC 2008, 2009), is now used for both the TBI numbers website and AFHSC TBI surveillance reports. AFHSC reports published prior to October 2008 used an older surveillance case definition (AFHSC 2008). Both the new and old DoD case definitions are similar, but not directly comparable, to that recommended by the CDC (Marr and Coronado 2004).

Selected data from both the TBI numbers website and a previous AFHSC (2007) report are summarized here. To highlight changes in TBI-related rates associated with initiation of the OEF/OIF conflicts, we report the AFHSC data separately for two surveillance periods: prewar as indicated by the beginning of the war in Afghanistan (prior to 2001) and postwar.

Incidence

According to the DoD TBI numbers website (DoD 2009b), 10,963 incident TBI diagnoses were identified for the year 2000 (prewar). From 2001 through 2005 (i.e., the first few years postwar), the annual number of incident TBI diagnoses remained relatively stable, averaging 12,496 per year, an increase of approximately 14% compared with the prewar number. However, from 2006 to 2009 the numbers increased substantially, averaging 24,074 per year, more than 2 times the prewar number. On the basis of numbers updated as of December 31, 2009, the greatest number of incident TBI diagnoses in a single year was 28,557 in 2008. For 2009, the most recent year for which data for the full year were reported, the website reported that of the 27,862 incident TBIs, 21,859 (78.4%) were mild, 3,059 (11.0%) were moderate, 258 (0.9%) were severe, 404 (1.4%) were penetrating, and 2,282 (8.2%) were unclassifiable. According to a more recent AFHSC TBI surveillance report, the average monthly number of TBIs for January through May 2010 (302.2/month) was substantially lower than the average monthly number for 2009 (482.1/month) (AFHSC 2010). Notably, although anecdotal reports of multiple concussions/mTBIs are common, the number of service members who have experienced them is not reported.

External Causes

For U.S. military populations, external cause information is routinely available only for hospitalizations from AFHSC surveillance reports (AFHSC 2007). During the prewar period, land transport (25.2%), falls/miscellaneous (24.2%), athletics/sports (9.0%), and nonbattle assault (8.9%) were the leading causes of TBI hospitalizations among active duty service members (Figure 1–1). In the postwar period, falls/miscellaneous (21.5%) was the leading cause, followed by land transport (15.5%) and nonbattle assault (7.0%). The percentages of TBI hospitalizations postwar were higher than prewar for accidental weapons injuries (5.5% vs. 0.6%; 9:1 ratio postwar vs. prewar) and battle casualty injuries (3.2% vs. 0.3%: 10:1 ratio postwar vs. prewar). Battle casualty–related TBIs accounted for a very small proportion of all TBI-related hospitalizations both prewar and postwar (AFHSC 2007). It is important to note that external cause information was missing/invalid for 25.3% of prewar TBI-related hospitalizations and 38.1% of those occurring postwar.

War-related TBIs are often associated with mechanisms not specified in routine surveillance reports, including explosions or blasts. The most likely mechanism for blast-related TBIs is impact from debris propelled into the individual or the impact of the individual being thrown against a hard object. Emerging evidence, including from animal studies, suggests a possible effect of nonimpact blasts on the brain (DoD 2009a), but this topic remains controversial. Wilk et al. (2010) reported that among soldiers who reported LOC, blast mechanism was significantly associated with headaches and tinnitus 3–6 months postdeployment compared with a nonblast mechanism, but among the larger group of soldiers reporting concussions without LOC, blast was not associated with adverse health outcomes.

Estimates of the proportion of TBIs associated with blasts vary depending on the study population and the method of ascertainment. For example, with regard to severe injury, in a retrospective medical study of all neurosurgical consults involving OIF patients at the two primary U.S. military medical facilities treating serious central nervous system trauma, 228 of the 408 patients with head injury presented with a penetrating brain injury. The leading cause was explosive blast injuries (56%) followed by high-caliber gunshot wounds (14.2%) (Bell et al. 2009). With regard to concussion/mTBI, the percentages associated with blast/explosions, based on self-report, were 72.2% (Wilk et al. 2010), 72.7% (Hoge et al. 2008), and 88% (Terrio et al. 2009). One study reported that self-reported blast-related concussions/mTBIs were more than twice as likely to occur in conjunction with other mechanisms, such as falls or motor vehicle crashes, than as the sole reported injury (Schneiderman et al. 2008).

Surveillance data for TBIs among active duty service members are limited for several reasons. First, although the DoD TBI numbers website has more complete case ascertainment, data for some key variables, including external cause of injury, are lacking. Conversely, the AFHSC TBI surveillance reports include only data from medical encounters in "fixed," not deployed, medical facilities, but they include some important information about external cause of injury (such as fall, motor vehicle crash) and context (such as battle or nonbattle related). Second, as for civilians, the number of service members who receive medical care but the TBI is not diagnosed, or who sustain a TBI but do not seek care, is not known. Finally, because denominator data (i.e., the total number of service members at risk of a TBI) are not routinely provided, TBI rates cannot be calculated, limiting the potential for meaningful interpretation and comparison with data from other sources.

Despite heightened concern about war-related injuries, these data suggest that TBI is an important health problem among service members in general and that the TBIs sustained during service in Iraq and Afghanistan represent a substantial proportion but not a majority of the medically treated TBIs that occur each year.

Screening

Because of concern that some TBIs, especially concussions/mTBIs occurring in the war theater, may not be identified through surveillance of medical encounters, service members returning from Iraq and Afghanistan have been administered "postdeployment screening" measures intended to specifically assess for a self-reported history of concussion/mTBI. These measures have been implemented by the DoD, VA, and independent researchers (Schneiderman et al. 2008; Schwab et al. 2007; Tanielian and Jaycox 2008). The current DoD and VA screening measure consists of four questions (see Chapter 26, Figure 26–1). Notably, DoD researchers reported that a variation of these questions received "preliminary validation" based on a study in which individuals who screened positive were then interviewed to determine whether their histories were consistent with concussion/mTBI (Schwab et al. 2007). However, this study did not include a negative comparison group or blind evaluation, which are necessary for true validation.

Department of Defense

Results of recent studies using available screening methods suggest that between 11.2% and 22.8% of deployed service members report a possible concussion/mTBI (Hoge et al. 2008; Mental Health Advisory Team-V 2008; Schneiderman et al. 2008; Tanielian and Jaycox 2008; Terrio et al. 2009). Based on extrapolation of these findings, it has been widely reported that of the 1.6 million service members up to that time who had been deployed to Iraq or Afghanistan, an estimated 320,000 had experienced a probable concussion/mTBI (Tanielian and Jaycox 2008). However, limitations in the screening methodology suggest that such an extrapolation may not be valid for several reasons. First, the majority of service members who screened positive for a possible concussion/mTBI likely did so because they answered "yes" only to the question regarding AOC (dazed, confused, or saw stars) (Hoge et al. 2008); they did not report either LOC or PTA. AOCs occurring in combat may result not only from concussion/mTBI but also from normal responses to injury, acute stress, dissociation, sleep deprivation, syncope, or confusion of war (Hoge et al. 2009). One study (Terrio et al. 2009) reported that clinicians confirmed the screening results through in-depth interview. Although self-report elicited by structured or in-depth interview is considered the current gold standard for determining prior TBI (Corrigan and Bogner 2007), the lack of a validated tool to retrospectively assess AOC limits the potential of such interviews to accurately assess prior TBI. Second, variability in exposure to combat and related risk of sustaining a concussion/mTBI limits the applicability of the findings from specific screening studies to the total population of deployed service members. Finally, two studies involving OIF/OEF veterans (Hoge et al. 2008; Schneiderman et al. 2008) have demonstrated that postconcussion symptoms are more strongly associated with posttraumatic stress disorder than with concussion/mTBI, and one study (Hoge et al. 2008) has shown that concussion/mTBI incurred in combat was not associated with postdeployment postconcussion symptoms in soldiers who reported an injury with AOC but without LOC. In contrast, one study reported that in soldiers with histories of physical injury, concussion/mTBI and posttraumatic stress disorder were independently associated with postconcussion symptom reporting (Brenner et al. 2009). Thus, estimates of the incidence of concussion/mTBI based on available screening data must be interpreted with caution.

Department of Veterans Affairs

Using the same questions as the DoD, the VA has been screening all OEF/OIF veterans who come to VA for care. They also follow up with all veterans identified by this process to ensure that any health problems they may have, whether or not they are found to be related to possible TBI, are appropriately evaluated and treated. From April 2007 through December 2009, VA screened 383,054 OEF/OIF veterans for possible TBI. Of those, 77,069 (18.5%) screened positive (i.e., they reported having had a concussion and current symptoms) and were referred for a comprehensive evaluation (VA Patient Care Services, unpublished data, 2009). Of note, only approximately 40% of service members deployed to Iraq and Afghanistan who have separated from the military have enrolled with VA (VA Patient Care Services, unpublished data, 2009), and thus this 20% prevalence figure, which reflects the prevalence in a health-care-seeking population, probably is higher than the prevalence in the total deploying population.

Prevalence of Concussion/mTBI-Related Symptoms

Among all returning OEF/OIF service members screened by the DoD, the number who report persisting concussion/TBI-related symptoms is not known. For the subset of service members who have separated from the military and enrolled with VA, based on data for the 51,416 veterans who initially screened positive and received comprehensive evaluations (through February 10, 2010), the estimated prevalence of a history of TBI with persisting symptoms among all veterans who presented for care (N=383,054) was 10.1% (n=27,287 who screened positive and had a TBI diagnosis confirmed through comprehensive evaluation). Notably, an additional 11,448 veterans (3%) with a self-reported previous diagnosis of TBI were not screened and are not included in this estimate (VA Patient Care Services, unpublished data, 2010). However, because not all those who initially screened positive have received comprehensive evaluations, this estimate must be interpreted with caution. It is also important to note that some researchers have suggested that the screening process itself may contribute to misdiagnosis and overattribution of unrelated symptoms to concussion (Hoge et al. 2009; Iverson et al. 2009), leading to potential overestimates of the numbers of service members who have persisting symptoms associated with concussion/mTBI.

Conclusion

Although TBI surveillance methodology in the United States continues to improve, the information on TBI among civilians must be interpreted with caution because of differences in case definitions, limitations in the available population-based data sources, and the specific data used in each analysis. The epidemiology of concussion/mTBI is particularly confusing and easily misunderstood because of the challenges associated with retrospective identification and the failure of some studies to distinguish concussion/mTBI from moderate and severe TBI. Notably, the impact of the wars in Iraq and Afghanistan now necessitates the inclusion of data for service members and veterans injured in combat or non-combat situations in any comprehensive reports of the epidemiology of TBI. Although military TBI surveillance efforts have also improved, detailed information regarding TBI among military personnel and veterans with TBI, including concussion/mTBI, remains limited.

Despite these limitations, some useful estimates provide an overview of the public health impact of TBI. Specifically, an estimated 1.7 million TBI-related emergency department visits, hospitalizations, and deaths occur each year among civilians in the United States, excluding those treated in doctors' offices and those for which no medical care is sought. An estimated 3.2 million civilians hospitalized with TBI in the United States are living with long-term or lifelong TBI-related disability, and the economic cost of TBI occurring among civilians in the year 2000 has been estimated to be $60 billion. Among service members, 27,862 incident medically diagnosed TBIs, including battle- and non-battle-related injuries, were reported during 2009, based on numbers updated as of December 31, 2009. Among service members who separated from the military and enrolled with the VA, the estimated prevalence of a history of TBI with persisting symptoms among those who presented for care was 7.1%.

Definitions and screening tools that are clinically meaningful and valid need to be established and used consistently for concussion/mTBI. High-quality prospective and well-controlled natural history studies are needed. Improvements in TBI diagnosis based on neuropathology will lead to an improved classification system for all levels of TBI severity, not only for clinical research (Saatman et al. 2008) but also for epidemiological studies. Further studies of the role of lifestyle factors such as exercise and nutrition in protecting against adverse outcomes and promoting recovery from TBI are also needed.

KEY CLINICAL POINTS

- Although traumatic brain injury (TBI) surveillance methodology in the United States continues to improve, the information on TBI among civilians must be interpreted with caution because of differences in case definitions, limitations in the available population-based data sources, and the specific data used in each analysis.

- TBI is a traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset of at least one of a specified set of clinical signs, immediately following or shortly after the event (as defined by the Department of Veterans Affairs and Department of Defense).

- Concussion/mild TBI (mTBI) is "a physiological disruption of brain function as a result of a traumatic event as manifested by at least one of the following: alteration of mental state, loss of consciousness, loss of memory or focal neurological deficit, that may or may not be transient; but where the severity of the injury does not exceed the following: posttraumatic amnesia for greater than 24 hours, after the first 30 minutes Glasgow Coma Scale score is 13–15, and loss of consciousness is less than 30 minutes" (as defined by The American Congress of Rehabilitation Medicine).

- The Centers for Disease Control and Prevention estimated that 1.7 million TBIs occurred on average each year in the United States during 2002 through 2006, including 1,365,000 emergency department visits, 275,000 hospitalizations, and 52,000 deaths.

- When emergency department visits, hospitalizations, and deaths are combined, falls are the leading cause of civilian TBI (35%), followed by motor vehicle/traffic crashes (17%), being "struck by/against" (16%), and assaults (10%).

- According to a systematic review of the published literature, evidence of long-term adverse health effects associated with TBI was strongest for moderate, severe, and penetrating TBI and limited or inadequate for concussion/mTBI.

- An estimated 43.3% of hospitalized TBI survivors in the United States in 2003 experienced a TBI with related long-term disability.

- The most recent estimate of the prevalence of Americans living with disability related to a TBI hospitalization is 3.2 million.

- In 2009 dollars, the economic costs of TBI among civilians occurring in the year 2000 were estimated to be more than $221 billion, including $14.6 billion for medical costs, $69.2 billion for work loss costs, and $137 billion for the value of lost quality of life.

- Although military TBI surveillance efforts have also improved, detailed information regarding TBI among military personnel and veterans with TBI, including concussion/mTBI, remains limited.

- Among service members, 27,862 incident medically diagnosed TBIs, including battle- and non-battle-related injuries, were reported during 2009 (Department of Defense 2009b).

- Among service members who separated from the military and enrolled with the Department of Veterans Affairs (VA), the estimated prevalence of a history of TBI with persisting symptoms among those who presented for care was 7.1%.

- Definitions and screening tools that are clinically meaningful and valid need to be established and used consistently for concussion/mTBI, and high-quality prospective and well-controlled natural history studies are needed.

Recommended Readings

Department of Veterans Affairs, Department of Defense (VA/DoD). VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury (mTBI), Version 1.0. 2009. Available at: http://www.healthquality.va.gov/mtbi/concussion_mtbi_ full_1_0.pdf. Accessed August 4, 2009.

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CHAPTER 2

Neuropathology

Colin Smith, M.D.

TRAUMATIC BRAIN INJURY (TBI) REMAINS A MAJOR cause of morbidity and mortality throughout the world, affecting young and old alike. Pathological data have been developed through observations of human autopsies and developing animal models to investigate its mechanisms. One always has to be aware of the limitations of both these approaches: autopsies, in most cases, provide information relating to the most severe end of the clinical spectrum of TBI, fatal outcome; animal models do not represent the polypathology of human brain injury; and there are likely to be significant differences in the anatomical basis of injury and cellular responses between species.

Classification of Traumatic Brain Injury

No single classification of TBI exists that encompasses all the clinical, pathological, and cellular/molecular features of this complex process. In 2007 a workshop convened by the National Institute of Neurological Disorders and Stroke, supported by the Brain Injury Association of America, the Defense and Veterans Brain Injury Center, and the National Institute of Disability and Rehabilitation Research, reviewed the current status of classification systems and arrived at recommendations for classifications to support translational and targeted therapies (Saatman et al. 2008). Classification systems can be pathological, clinical, or mechanistic. Pathological classifications can be anatomical, describing injuries as focal or diffuse, or pathophysiological, based on primary and secondary injuries. A number of clinical classifications have been developed over the years, with the Glasgow Coma Scale (GCS) being the most widely used, although this scale is less useful in pediatric assessment and is a poor discriminator of mild head injury. In general, mild head injury is a GCS score of 13–15, moderate head injury a score of 9–12, and severe head injury a score of 8 or less.

Mechanistic classifications of TBI describe impact, inertial loading, penetrating, and blast injuries (Table 2–1). Impact injuries require the head to make contact with an object, with the forces being transmitted to the brain. Experimental studies in nonhuman primates have demonstrated that, biomechanically, acute subdural hemorrhages secondary to torn bridging veins are produced by a rapid acceleration (or deceleration) (Gennarelli and Thibault, 1982). These biomechanical findings account for the association between subdural hemorrhage and falls or assaults, both being situations in which there is a rapid acceleration or deceleration. Inertial forces do not require contact, but rather the brain moves within the cranial cavity. Penetrating injuries produce damage when an object passes through the protective covering of the skull resulting in direct parenchymal damage (Figure 2–1); in the case of firearm injuries there is also a significant element of tissue damage caused by the pressure cavities produced by the projectile passing through brain tissue. Blast injuries are the least well described and are seen in military or terrorist situations; the shock waves from an explosive device can result in injuries to the brain parenchyma.

In this chapter I follow the standard outline for the neuropathological description of TBI focal and diffuse injuries (Table 2–2) and discuss penetrating and blast injuries as well as specific pediatric issues and long-term problems associated with TBI.

TABLE 2–1. Mechanisms of traumatic brain injury

Mechanism	Main pathology
Impact	Vascular (hemorrhages)
	Traumatic axonal injury
Inertial loading	Traumatic axonal injury
Penetrating	Local tissue necrosis
Blast	Brain swelling

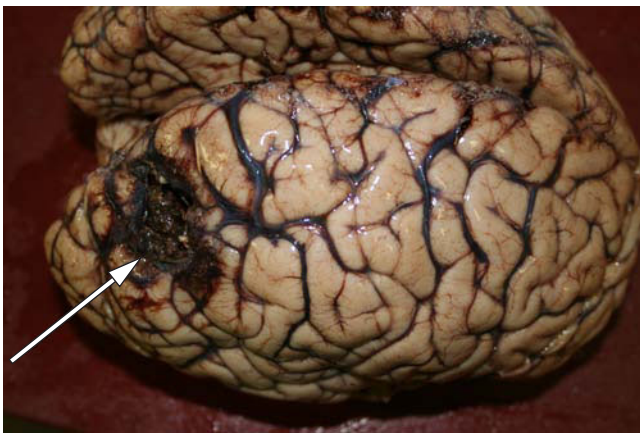


FIGURE 2–1. An area of cortical laceration secondary to a penetrating head injury.

In this case the penetrating injury was a metal rod that entered the brain in the occipital region (arrow) and extended through the brain, exiting in the inferior frontal region.

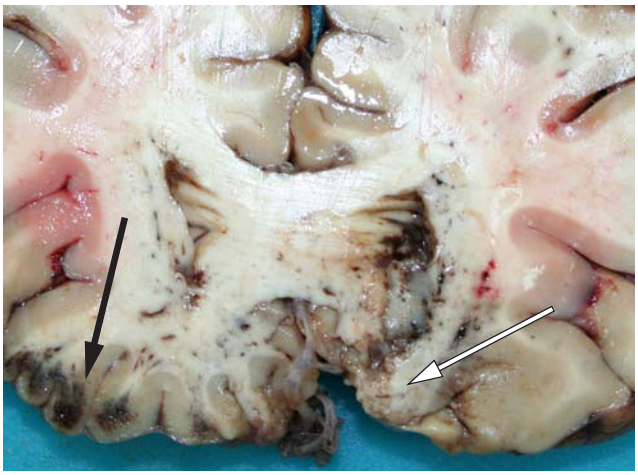


FIGURE 2–2. Acute cortical contusions involving the inferior frontal lobes.

On the left side, the contusions involve the full thickness of the cortex (black arrow), extending into underlying white matter. On the right side, there is more extensive tissue damage resulting in a laceration (white arrow).

TABLE 2–2. Classification of traumatic brain injury

Focal	Diffuse
Scalp lacerations	Global ischemic injury
Skull fractures	Traumatic axonal injury/diffuse vascular injury
Contusions/lacerations	Brain swelling
Intracranial hemorrhage	
Focal lesions secondary to raised intracranial pressure	

Pathology Associated With Fatal Head Injury

Blunt Force Head Injury: Focal and Diffuse Injuries

Scalp and Skull Lesions

The scalp and skull may be injured by contact injury. The presence of scalp bruising is indicative of contact injury and in some situations may provide clues to the possible intracranial pathology. Occipital bruising is typically associated with a backward fall and contrecoup contusions involving the frontal and temporal tips. Incised wounds are usually insignificant and easily managed in the emergency room, but in some cases they may be associated with blood loss, hypotension, and associated brain injury.

The incidence of skull fractures is associated with the severity of the head injury. In one series (Adams et al. 1980), the incidence of skull fractures was 80% in fatal head injury; in clinical practice skull fractures have been recorded with an incidence of 3% in mild head injury presenting to the emergency room, rising to 65% in those requiring neurosurgical admission. There is no direct correlation with the presence or absence of a skull fracture and underlying parenchymal brain injury, unless the fracture is depressed and makes direct contact with the underlying tissue. However, as discussed later in this chapter, there is a correlation between skull fractures and intracranial hemorrhages.

Skull fractures include linear, depressed, and hinge fractures. In children, growing fractures may be seen where soft tissue becomes trapped between the edges of the fracture, preventing healing.

Contusions and Lacerations

In simple terms, contusions represent bruising of the surface of the brain (Figure 2–2). By definition the pia mater is intact overlying contusions but torn in lacerations. They typically involve the frontal poles, the inferior frontal lobe including the gyrus rectus, and medial and lateral orbital gyri; the temporal poles and lateral and inferior aspects of the temporal lobes; and the cortex above and below the Sylvian fissure. Fractures and contusions may be seen at atypical sites in direct relationship to a skull fracture. Contusions typically involve the crests of gyri and are often superficial, involving the gray matter only. However, they may extend into underlying white matter and form a hematoma. In severe cases extensive laceration injury with underlying parenchymal hemorrhage may be associated with subdural hemorrhage, forming a so-called burst lobe. This type of injury is most often seen involving the temporal lobes.

The pattern of contusions may be coup, following a fall forward; contrecoup, following a backward fall; or underlying fractures. In coup contusions scalp bruising is over the forehead, with the contusions involving frontal and temporal lobes. In contrecoup contusions the same pattern of contusional injury is associated with bruising in the oc-

cipital scalp. Contusions involving the occipital lobes and cerebellum are rare due to the smooth inner surface of the posterior fossa of the skull (compared with the bony ridges of the anterior and middle fossae); when seen they are usually associated with an adjacent skull fracture.

Contusions may extend some hours after the initial head injury. This delayed traumatic intracerebral hemorrhage usually becomes apparent within 48 hours after the head injury. The precise mechanism of this delayed injury is uncertain but is thought to reflect increased blood flow or pressure through a vascular capillary network that is focally damaged, compounded possibly by posttraumatic coagulopathy.

At autopsy, in the acute phase contusions are hemorrhagic and often associated with focal swelling. In time the contusions shrink and take on a golden brown color secondary to hemosiderin deposition (Figure 2–3). Old contusions are a not infrequent incidental autopsy finding, particularly when at-risk groups, such as individuals with chronic alcoholism, are included.

A method for assessing the extent of contusions was developed by Adams et al. (1980) and subsequently modified. This assesses the extent (score range, 0–3) and depth (score range, 0–4) of contusions in a variety of anatomical locators, producing a numerical score for each hemisphere which is then combined and interpreted as absent, mild, moderate, or severe. The anatomical locators are the frontal, temporal, parietal, and occipital lobes; the cortex above and below the Sylvian fissure; and the cerebellum. The maximum score for an anatomical locator is 12 (4×3=12), and the total contusion index (TCI) has a maximum value of 144 (each side 6×12=72, 2×72=144). In assessment of the severity of the contusional injury, mild is considered to be a TCI less than 20, moderate a TCI between 20 and 37, and severe a TCI greater than 37. A similar index, although more detailed and not limited to assessment of contusions, has also been proposed (Ryan et al. 1994).

Intracranial Hemorrhages

Intracranial hemorrhages are classified by anatomical location as extradural (also known as epidural), subdural, subarachnoid, or intracerebral. They are the most common causes of clinical deterioration in patients who experience a lucid interval, "talk and die," or "talk and deteriorate after injury" (Bullock and Teasdale 1990). The clinical complications associated with a hematoma are related to the size/volume of the lesion, the anatomical location, and the rapidity with which the hematoma develops. The complications associated with a mass lesion are described later in this chapter.

Extradural (epidural) hematoma. The incidence of extradural hemorrhage has been reported in several large clinical and autopsy studies of head injury. Clinical studies report an incidence of between about 0.2% and 4% in all head injuries. Autopsy studies have reported an incidence of between 5% and 22% the incidence being highest in fatal cases with a fracture of the skull (Freytag 1963), although an extradural hemorrhage may occur in the absence of a fracture, especially in children.

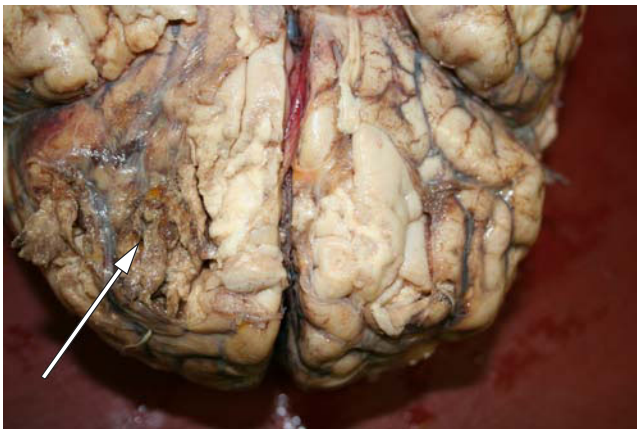


FIGURE 2–3. Old cortical contusions involving the inferior aspect of the frontal lobes.

The pathology is most obvious on the left-hand side of this image; the discoloration (arrow) is secondary to hemosiderin accumulation.



FIGURE 2–4. An acute extradural hematoma, revealed by removing the skull cap.

The hematoma lies on the surface of the dura and is well circumscribed.

Extradural hemorrhages are most frequently seen overlying the convexity in relation to the temporoparietal region, although 20%–30% may occur in frontal and occipital regions. Extradural hemorrhages in the posterior fossa are rare, accounting for approximately 3% of all extradural hemorrhages seen at autopsy. Extradural hemorrhage is most commonly (approximately 50%) associated with fracture of the squamous temporal bone resulting in damage to the underlying middle meningeal artery or vein. Bleeding will strip the dura (periosteum) from the inner table of the skull forming a circumscribed ovoid blood clot (Figure 2–4) that progressively indents and flattens the adjacent brain. There may be little discernible naked-eye damage to the underlying brain, although microscopic examination frequently demonstrates at least focal ischemic injury.

TABLE 2–3. Causes of subdural hematoma (SDH)

Causes	Comment
Trauma	Blunt force head injury, either accidental or inflicted, can cause SDH.
Neurosurgical complication	Neurosurgical management of hydrocephalus may be associated with SDH.
Perinatal	SDH is well recognized following labor but rarely clinically significant.
Vascular	Aneurysms are a rare childhood cause of SDH.
Coagulation and other hematological disorders	Both inherited and acquired coagulation disorders and hematological malignancies can cause SDH.
Metabolic disorders	Glutaric aciduria, Menkes disease, and galactosemia can cause SDH.
Hypernatremia	Elevated sodium levels are often associated with intracerebral hemorrhages including SDH.
Infection	SDH can rarely be seen in cases of meningitis.
Raised central venous pressure	Intradural bleeding may lead to subdural collections.

Subdural hematoma. Subdural hematomas are most commonly seen after head injury but can also develop secondary to a number of nontraumatic causes (Table 2–3). Subdural hematoma has been reported in 5% of all head injuries. The frequency increases with the severity of the head injury, and in autopsy studies acute subdural hematomas are seen in 20%–63% of cases (Adams et al. 1980; Freytag 1963). Acute subdural hematomas may be due to either rupture of a bridging vein (cortical vein passing from cortical surface to dural sinus), the so-called pure subdural hematoma, or secondary to contusions with damage to cortical veins or arteries and overlying leptomeninges. Posterior fossa subdural hematoma is rare and is thought to be due to damage to the vein of Galen or a tear in the straight sinus.

Acute subdural hematomas are liquid and can spread in the subdural space (Figure 2–5). They produce an accentuation of the gyral pattern on the affected side, with flattening of the gyri on the opposite side. Like extradural hematomas, they are mass lesions producing secondary effects.

Chronic subdural hematoma may follow an episode of relatively trivial head injury, although in 25%–50% of cases there is no history of trauma. Alcohol abuse is common in chronic subdural hematoma cases: the individual may be unable to remember the incident, or the subdural hematoma may be a consequence of an increased bleeding diathesis associated with liver disease and thrombocytopenia. Although an episode of acute hemorrhage is clearly needed to initiate the lesion, imaging studies have demonstrated that most acute subdural hematomas resolve without the formation of a chronic subdural hemorrhage. In those cases that progress to a chronic subdural hemorrhage, the mechanism of enlargement is uncertain, although current evidence suggests that fragile new blood vessels within the evolving hematoma are susceptible to bleeding, resulting in repeated episodes of hemorrhage enlarging the overall lesion (Yamashima and Yamamoto 1984).

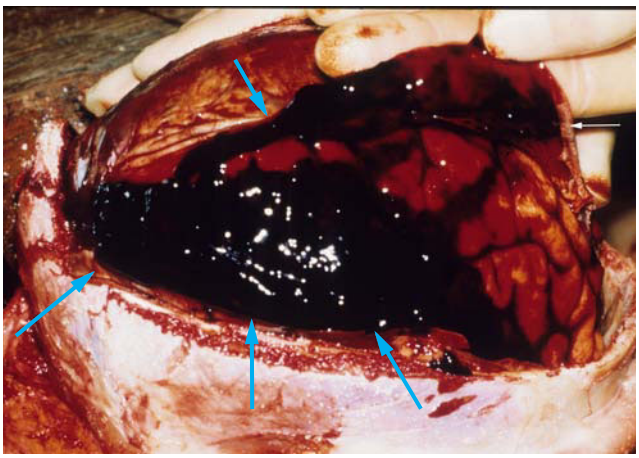


FIGURE 2–5. An acute subdural hematoma.
The dura has been incised and reflected upward, revealing diffuse bleeding between the dura and the brain. The cut edges of the dura are highlighted by arrows.

Subarachnoid hemorrhage. Subarachnoid hemorrhage (SAH) is common in traumatic brain injury, but rarely significant. An exception is the situation of primary traumatic SAH usually due to rupture of the vertebral or basilar arteries. A commonly encountered scenario is a sudden collapse after a single punch, usually just under the mandible. Primary traumatic SAH has a high mortality, and the SAH has a predominantly basal distribution.

Intracerebral hemorrhage. Intracerebral hemorrhages are seen most frequently in the frontal and temporal lobes. In one series (Freytag 1963), intracerebral hemorrhages were described in 15% of fatal head injuries. When superficially located, they are most likely related to extensive contusional injury; more deeply seated hematomas are seen in impacts of greater force, such as road traffic accidents, and occur in regions of maximal acceleration-induced brain injury. In some situations a deeply seated basal ganglia hematoma needs to be differentiated from a hypertensive hematoma: was the hematoma caused by the head injury, or did the hematoma cause the head injury? Often this differentiation is very difficult, but histological evidence of preexisting small vessel disease may be helpful.

Brain Injury Secondary to Raised Intracranial Pressure

As soon as the cranial sutures fuse, the skull is effectively a solid bony box. While this arrangement is of great value in protecting the soft parenchyma of the brain from injury, the design allows little opportunity to accommodate in-

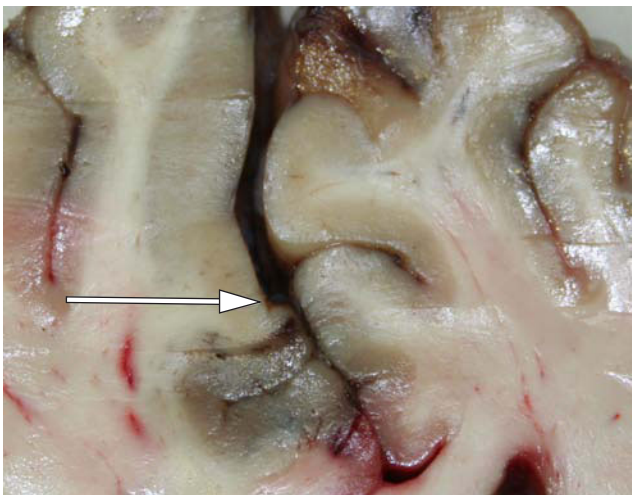


FIGURE 2–6. Subfalcine herniation.
The cingulate gyrus has been forced below the free edge of the falx cerebri, producing a notch (arrow). The herniated tissue shows the dusky discoloration of infarction.

creasing mass lesions, such as expanding hematomas, within the cranial cavity. The increasing volume may be secondary to a diffuse process, such as brain swelling, or may be secondary to a unilateral expanding mass lesion, such as a hematoma.

Normal intracranial pressure (ICP) is in the range of 0–10 mmHg. Pressures greater than 20 mmHg are abnormal, greater than 40 mmHg are associated with neurological dysfunction and compromised cerebral circulation, and beyond 60 mmHg are invariably fatal. In diffuse brain swelling, the systemic blood pressure (SBP) increases in an attempt to maintain the cerebral perfusion pressure (CPP) in the face of an increasing ICP (CPP = SBP − ICP). A point is reached whereby the CPP drops to such a degree that global brain ischemia develops. The process of brain ischemia is described later in this chapter.

With a unilateral mass lesion there will be displacement of fluid, such as cerebrospinal fluid and venous blood, in an attempt to compensate for some increase mass; however, ultimately the brain tissue itself will herniate. Brain herniation may extend under the falx cerebri (Figure 2–6) damaging the cingulate gyrus (subfalcine or supracallosal hernia), under the tentorium cerebelli damaging the parahippocampal gyrus/medial temporal lobe (tentorial or uncal hernia), and through the foramen magnum damaging the tonsil of the cerebellum (tonsillar hernia).

A supracallosal hernia may obstruct flow within the pericallosal artery (anterior cerebral circulation), resulting in infarction within the corpus callosum and cingulate gyrus. A tentorial hernia may obstruct flow within the posterior cerebral artery resulting in medial occipital cortical infarction. Caudal displacement and elongation of the rostral brain stem may result in brainstem hemorrhage and infarction (Figure 2–7), a common terminal event in raised ICP, seen in up to 75% of brain-injured patients who die (Graham et al. 1987). Clinically, a tentorial hernia may produce an ipsilateral fixed dilated pupil due to ipsilateral oculomotor nerve damage and ipsilateral weakness due to contralateral cerebral peduncle compression (Kernohan lesion–false localizing sign). Medial occipital cortical infarction may develop secondary to pressure on the posterior cerebral artery from a tentorial hernia (Figure 2–8). A wedge of necrosis in the parahippocampal gyrus provides good evidence of raised ICP during life (Figure 2–9).



FIGURE 2–7. Sections from different levels of the pons showing extensive hemorrhagic infarction within the brain stem secondary to axial displacement.
This is commonly seen as a terminal event secondary to mass lesions, particularly extradural and subdural hematomas.

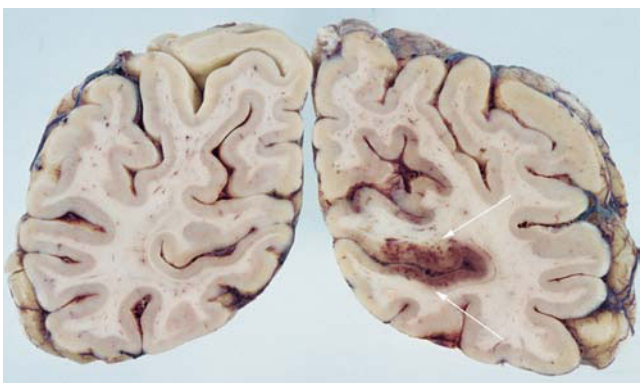


FIGURE 2–8. Medial occipital cortical infarction secondary to a tentorial hernia compressing the posterior cerebral artery.
The right medial occipital cortex, involving the primary visual cortex, shows dusky discoloration. The area of infarction is outlined by arrows.

Ischemia

Ischemic brain injury is a common pathology seen in autopsy series of fatal TBI, being seen in 91% of cases in one study (Graham et al. 1978). Early stabilization of patients reduces the incidence of hypotensive brain injury but not of diffuse ischemic injury. Diffuse ischemic injury can develop as a consequence of increasing cerebral swelling, secondary to cardiorespiratory arrest, or as a consequence of profound hypotension as a result of other injuries, particularly long bone fractures.

Physiologically, ischemia refers to reduced blood flow. In the brain, neurons are particularly sensitive to reduced

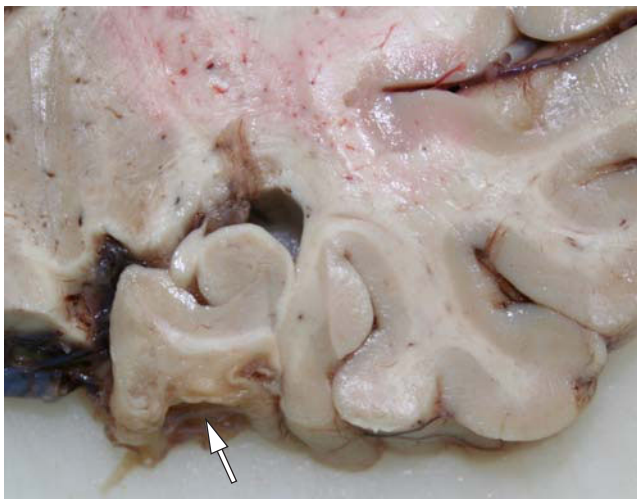


FIGURE 2–9. A wedge-shaped area of infarction involving the parahippocampal gyrus (arrow) is indicative of a previous episode of tentorial herniation.

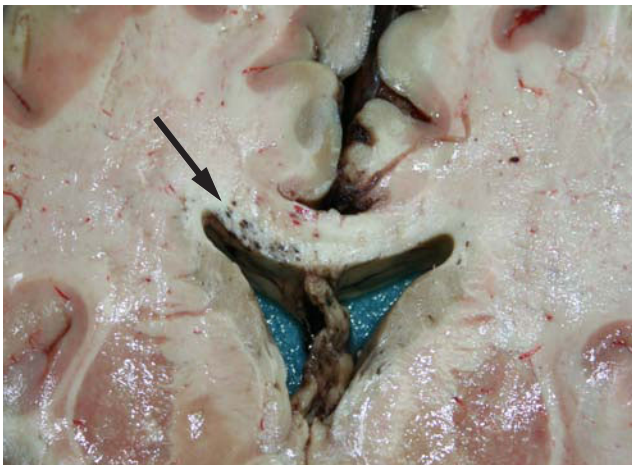


FIGURE 2–10. In diffuse traumatic axonal injury, corpus callosal hemorrhage typically extends to involve the lateral white matter bundles (arrow).

Hemorrhage secondary to infarction in cases with subfalcine herniation is more typically limited to the midline.

blood flow and are the first cell type to be injured (selective neuronal necrosis). Different neuronal populations show different thresholds when exposed to ischemic injury (selective vulnerability); neurons of the hippocampal sector CA1 are particularly vulnerable to ischemic injury, whereas the adjacent population (sector CA2) are resistant, requiring prolonged ischemia before they suffer irreversible injury. If the ischemia is prolonged, then other cell types are also damaged (glial cells, endothelial cells, smooth muscle cells, etc.), resulting in pan-necrosis, also known as infarction.

Histologically, neuronal ischemic injury is easily identified using a simple hematoxylin and eosin stain; the neuronal nucleus is shrunken and the cytoplasm undergoes eosinophilic change, appearing red. Incrustations, conclusive histological evidence of irreversible neuronal injury, are best seen using a cresyl violet stain; incrustations represent the blebbing of the neuronal cytoplasm prior to breakup of the cell. Physiologically, it is not hypoxia that underlies the cellular damage, but rather the buildup of tissue lactate secondary to the absence of blood flow. Lactate is produced as a consequence of cellular metabolism and is normally removed by local blood flow. Lactate accumulation results in local tissue acidosis and cellular injury.

Diffuse Traumatic Axonal Injury

Diffuse traumatic axonal injury is important because it contributes to at least 35% of the mortality and morbidity of TBI cases without space-occupying lesions, and it is also related to the mortality and morbidity attributable to focal brain injuries. In addition, traumatic axonal injury is considered to be an important cause of severe disability and vegetative state, along with diffuse ischemic injury, in survivors of head injury (Graham et al. 2005).

The term *diffuse axonal injury* is now reserved for the clinical syndrome with supporting neuroradiological changes. The term used for the pathological demonstration of damaged axons in a pattern supporting a traumatic etiology is traumatic axonal injury.

Originally, trauma-induced axonal injury was thought to be the result of axons being disconnected at the time of the impact (primary axotomy) leading to axonal retraction and axoplasmic pooling. However, current opinion based on many experimental studies offers an alternative view (Farkas and Povlishock 2007): the forces modify focal axonal sections, resulting in mechanoporation with calcium influx and microtubule disruption causing local axonal transport impairment and axonal swelling, followed by detachment over a period of time after injury.

The typical pattern of traumatic axonal injury includes axonal injury in the corpus callosum, dorsolateral segments of the rostral brain stem adjoining the cerebellar peduncles, and the internal capsule, and in some cases hemorrhagic lesions are seen in the corpus callosum (Figure 2–10) and dorsolateral quadrant. There are three degrees of traumatic axonal injury: mild, moderate, and severe. In grade 1 there are microscopic changes in the white matter of cerebral cortex, corpus callosum, brain stem, and cerebellum; grade 2 is distinguished by grossly obvious focal lesions isolated to the corpus callosum; in grade 3 additional focal lesions are seen in the dorsolateral quadrants of the rostral brain stem. Studies have demonstrated axonal pathology after mild head injury in patients who have died from unrelated causes (Blumbergs et al. 1994).

Several techniques have been used to identify damaged axons. They can be seen as eosinophilic swellings on hematoxylin and eosin stained sections (Figure 2–11) and can be detected by silver stains, although a survival of 15–18 hours is required before they can be identified using this technique.

Immunohistochemistry is the most sensitive technique, and currently immunostaining for beta-amyloid precursor protein (β-APP) is the most widely used method, detecting axonal flow disruption (Sherriff et al. 1994). β-APP is a membrane-spanning glycoprotein and a nor-

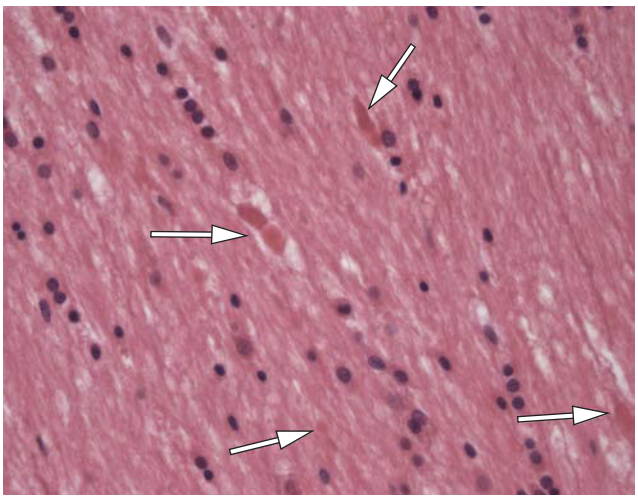


FIGURE 2–11. Eosinophilic axonal spheroids indicating axonal degeneration (arrows).

Presence is not indicative of trauma as spheroids will also be seen secondary to a number of other pathologies, particularly ischemia (hematoxylin and eosin stain×40).

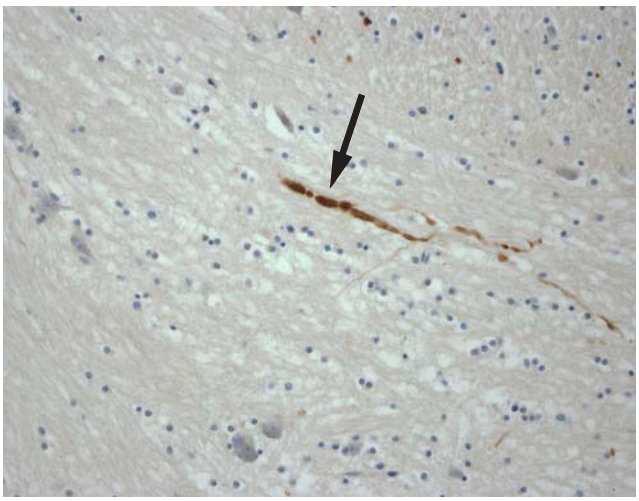


FIGURE 2–12. Degenerating axon (arrow) identified with beta-amyloid precursor protein (β-APP) immunohistochemistry.

The beaded appearance is typical in degenerating axons (β-APP immunohistochemistry×40).

mal component of neuronal cells which is transported along axons by fast transport mechanisms. When there is axonal transport interruption, β-APP has been shown to accumulate, indicative of dysfunction or possibly ultimate detachment of the axon (Figure 2–12). β-APP accumulation has been described with survival times as short as 35 minutes (Hortobágyi et al. 2007). β-APP accumulation is not specific to traumatic axonal injury and may be seen in any cause of axonal disruption, such as ischemia (Dolinak et al. 2000a) and hypoglycemia (Dolinak et al. 2000b), although specific patterns of immunohistochemical staining for trauma have been described (Reichard et al. 2005).

Brain Swelling

Brain swelling is a common pathology in cases of fatal TBI and may be focal or diffuse. The swelling may be congestive, secondary to an increase in the cerebral blood volume, or due to edema, an increase in the water content of the brain tissue. Current understanding of the mechanisms underlying brain swelling is incomplete, although progress has been made from the study of molecules such as aquaporin 4.

In the setting of TBI, the swelling may be focal in relation to contusions, diffuse within one cerebral hemisphere or diffuse in both cerebral hemispheres. The majority of edema in trauma is cytotoxic, with only a small component of swelling due to vasogenic edema, most of this being seen in relation to focal swelling adjacent to contusions. Adjacent to contusions there is physical disruption of the tissues, including the blood-brain barrier, and loss of the normal autoregulation within the local vasculature.

Diffuse swelling of one cerebral hemisphere. This situation is most typically associated with an adjacent subdural hematoma. If this is removed surgically, the hemisphere may swell. The reasons for this are not entirely understood, but the mechanism is likely a combination of a nonreactive vascular bed and local ischemic injury.

Diffuse swelling of both cerebral hemispheres. This is common in fatal TBI and is due to global ischemic injury. There is loss of normal physiological cellular activity, which ultimately results in a breakdown of the blood-brain barrier. However, in children a specific type of "malignant" brain swelling may be seen in the absence of significant ischemic injury; this is discussed in more detail later in the chapter. The concept of malignant edema being a childhood entity has been challenged. A computed tomography–based study (Lang et al. 1994) found that diffuse swelling of both cerebral hemispheres was associated equally with pediatric and adult head injury and had a more aggressive course in adults.

Penetrating Injuries

In strict terms, a penetrating injury is one in which the object/missile enters the cranial cavity but does not exit, whereas a perforating injury is one in which the missile also exits. The pathology produced is very much determined by the nature of the missile. Sharp objects, such as knives, long nails, or metal poles, may pierce the skull and extend into the underlying brain parenchyma causing local damage. They produce a hemorrhagic tract through the regions of parenchyma into which the missile extends (Figure 2–13). High-velocity missiles such as bullets cause considerably more damage, and the extent of the damage is related to the velocity of the missile; high-velocity military weapons will produce greater tissue damage than small firearms. As the missile travels through the parenchyma, it will produce pressure cavities that can lead to tissue damage. Studies from animal models have indicated that a penetrating ballistic injury will cause local tissue damage,

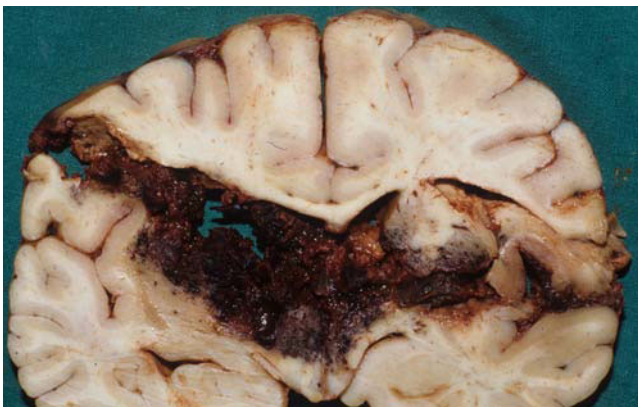


FIGURE 2–13. Hemorrhagic infarction in relation to the tract of a penetrating head injury.

including hemorrhage and necrosis, and will initiate a biphasic inflammatory response: in the acute phase there is cytokine expression and neutrophilic infiltration; the delayed response involves white matter degeneration seen distant from the site of direct tissue injury and develops some days after the injury (Williams et al. 2006).

Blast Injuries

Traditionally, the study of blast injuries has focused on the damage caused by blast waves to air-filled viscera such as the lungs in the thoracic cavity. However, increasingly, and particularly in relation to the recent conflicts in Iraq and Afghanistan, attention has been focused on possible injuries to solid viscera, and the brain in particular. The abrupt pressure changes associated with a blast can lead to a mild head injury and, in particular, concussion. Long-term sequelae in the form of impaired concentration and memory problems have been described with a greater frequency when compared with other nonblast TBIs.

The cellular basis of this injury is to date poorly defined, although there is considerable research activity in this field. The cellular responses produced by blast injuries, including microglial and astrocytic activation, are reviewed by Leung et al. (2008). The presence or absence of white matter injury in the form of traumatic axonal injury is controversial. Saljo et al. (2000) described redistribution of phosphorylated neurofilaments from the axon to the neuronal cell body in an animal model of blast injury. A possible explanation as to why damage to axonal transport mechanisms have not been convincingly demonstrated in blast-injury models, as demonstrated in both blunt force and penetrating head injuries, may be either that a different white matter degenerative process occurs or that the current methods used to identify axonal damage are not sensitive enough to identify thinner nonmyelinated axons (Svetlov et al. 2009).

Pediatric Head Injury

Although head injury is relatively common in the pediatric population, the vast majority of cases are mild with little acute clinical concerns. As with adult head injury, the outcome in children is partly determined by the force of the injury and whether the injury is contact or noncontact. Head injury in childhood may be due to a variety of causes, including road traffic accidents, falls, injuries sustained in recreational and competitive activities, and assault. Unlike adult head injury, the severity of the injury and outcome in pediatric head injury is modified by the maturation of the developing skull and nervous system. The brain lies within the cranial cavity surrounded by cerebrospinal fluid and the relative protection of the bony skull. Pediatric head injury, while sharing some similarities with adult injuries, differs with respect to the immaturity of many of the components of the developing nervous system. At birth the bones of the cranial vault lack diploë, and ossification is incomplete, with bony elements being joined by fibrous or cartilaginous tissue. The cranial vault grows rapidly during the first year and continues to grow until approximately the seventh year by which time the vault has achieved adult dimensions. Myelination of the human brain begins in utero and continues into early adult life. Myelination is particularly active in the first 2 years of life. As a result of these ongoing processes of maturation, the child's brain responds differently than an adult brain for a given force.

The age at which the head injury is sustained has been demonstrated to be important in determining the vulnerability to and recovery from a focal injury in a piglet model. Piglets of different ages were injured using a scaled cortical impact model and then sacrificed at 7 days postinjury. Assessment of the brains demonstrated smaller lesions in the younger animals despite comparable injury inputs (Duhaime et al. 2000). The authors concluded that vulnerability to mechanical trauma increased progressively during maturation. Magnetic resonance imaging assessment of similar animals over a longer time period (24 hours, 1 week, and 1 month postinjury) showed that in the younger animals the lesions reached maximal volumes earlier and resolved more quickly (Duhaime et al. 2003).

The largest pathological study of fatal human pediatric TBI looked at patients between the ages of 2 and 15 years (Graham et al. 1989), and the results are referred to in the following discussion. Skull fractures were recorded in 72% of the cases, with the majority being linear. It is important not to confuse a linear skull fracture with sutures or Wormian bones, and the pathologist should be aware of this potential pitfall. Depressed fractures are usually associated with high-velocity impacts, such as is seen in road traffic accidents. Diastatic fractures are traumatic separations of bones of the vault at sites of sutures and are normally only seen in the first few years of life. Growing fractures can develop if intracranial tissue herniates through the fracture defect.

Traumatic intracranial hematomas in children under the age of 5 years are less commonly seen than in adults, although the main indicators of risks for developing an intracranial hematoma are similar, most notably the presence of a skull fracture and a reduced conscious level. Extradural hematomas are seen in some 3% of patients. In infants venous bleeding from bone is seen more frequently as the cause of extradural hematoma, unlike the situation in adults in which most are arterial. Pure subdural hemor-

rhages (hemorrhages not associated with underlying intracerebral hemorrhage) are seen in 6% of patients. Although subdural hemorrhage is most commonly seen in relation to trauma, and in infants it often raises the possibility of nonaccidental injury, in pediatric cases particularly a number of alternative causes need to be considered (Kemp 2002) (see Table 2–3). Intracerebral lesions were seen in 17% of fatal pediatric patients, with burst lobes being seen in 8% of patients.

Contusions are seen in approximately 90% of fatal cases of TBI in children, similar to the figure seen in adults. A type of contusional injury associated with very young children (under approximately 6 months of age) is the gliding contusion, a parasagittal white matter injury often associated with focal hemorrhage (Figure 2–14).

In children diffuse brain swelling is encountered with no underlying cause, being present in 21% of patients in one study (Graham et al. 1989). In these patients the swelling is considered to be secondary to hyperemia, although other studies have suggested the degree of hyperemia is insufficient to cause cerebral swelling. The response of the cerebral circulation in childhood after TBI has been reviewed (Zwienenberg and Muizelaar 1999). Numerous animal models have been used to assess the response of cerebral circulation after TBI. Using a scaled cortical impact piglet model, Durham et al. (2000) demonstrated that very young animals have increased cerebral blood flow after an episode of focal injury, a response not seen in older animals. However, the relationship of this response to cerebral ischemia remains uncertain, and it has been suggested that this hyperemic response may be protective against ischemic lesions. The incidence of this type of injury may be modified in light of recent improvements in acute management of acute TBI in children.

Pathological studies of nonaccidental injuries are limited and are complicated by case selection bias. Geddes et al. (2001a, 2001b) published detailed macroscopic and microscopic data from 53 cases of nonaccidental injuries, of which 37 were infants (age < 1 year) and 13 were children (age ≥ 1 year), and challenged many of the preconceived ideas relating to the neuropathology of nonaccidental injuries. They demonstrated that the injuries sustained by the child were influenced by the age of the child. Infants appeared to be susceptible to localized axonal injury at the cervicomedullary junction, a feature not seen in any of the older children. In both groups, global cerebral ischemia with associated cerebral swelling and raised ICP was a common finding. Acute subdural bleeding and retinal hemorrhages were common and were seen in 72% and 71% of cases, respectively. The authors found that infants, and particularly infants under the age of 2–3 months, presented with sudden collapse and apnea and that this was associated with skull fracture, thin film subdural hemorrhages, and axonal injury at the cervicomedullary junction. Extracranial injuries were not a feature. In contrast, children tended to have more significant extracranial injuries and larger subdural hematomas; where axonal injury was present, it had a pattern more consistent with traumatic axonal injury seen in adults. The authors proposed that in infants damage to the cervicomedullary region resulted in cardiorespiratory arrest and subsequent global cerebral ischemia and swelling. Diffusion-weighted imaging has detected early infarction in cases of nonaccidental injuries, and this can be used to identify children at high risk for a poor outcome.

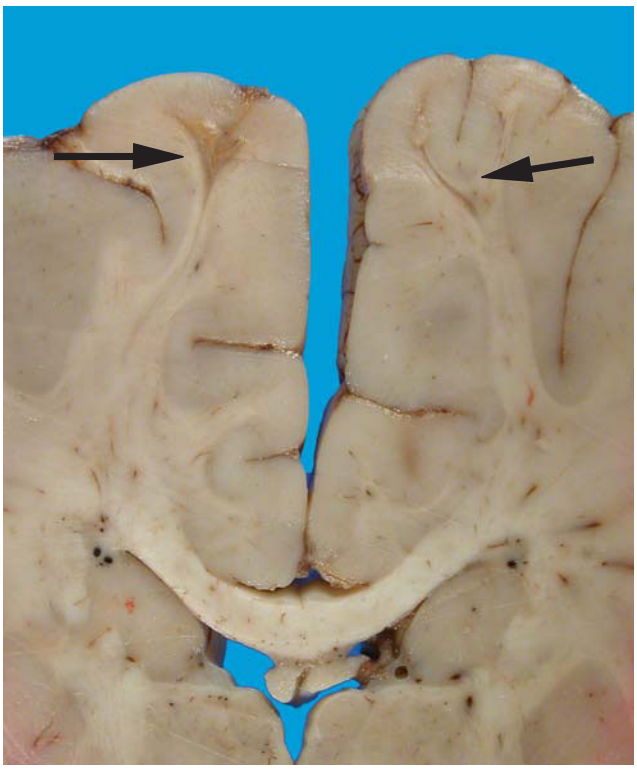


FIGURE 2–14. Gliding contusions in a child's brain, with a survival of approximately 2 years after a period of traumatic brain injury.

The contusions lie in the parasagittal white matter and are often, as in this case, bilateral (arrows).

Long-Term Sequelae of Brain Injury

Vegetative State

Concussion refers to an immediate, usually reversible episode of brain dysfunction after TBI. A clinical spectrum is recognized ranging from mild concussion, in which consciousness is often preserved, to severe diffuse traumatic axonal injury resulting in the vegetative state (Gennarelli 1993). The anatomical basis of concussion syndromes is currently considered to be traumatic axonal pathology and, in particular, axonal disruption resulting in disconnection between areas involved in consciousness: cerebral cortex, brainstem reticular activating areas, thalamus, and hypothalamus. Patients *in a vegetative state* refers to patients who have loss of meaningful cognitive function and awareness but retain spontaneous breathing and periods of wakefulness. The neuropathological basis of the vegetative state has been explored in a study that examined 49 patients in a vegetative state, 35 of whom had experienced TBI (Adams et al. 2000). In the trauma-related cases, diffuse traumatic

axonal injury of grade 2 or 3 was found in 71% of cases, and thalamic pathology was found in 80% of cases. In cases with minimal brainstem and cerebral cortical pathology, thalamic pathology was always present. Therefore, damage to the thalamic nuclei and/or the afferent and efferent white matter pathways of the thalamus appear to play a major role in the genesis of the vegetative state after head injury. The thalamic nuclei showed differing degrees of loss, with cognitive and executive function nuclei being most severely affected (Maxwell et al. 2006). White matter (Wallerian) degeneration is a consequence of severe diffuse traumatic axonal injury. The axonal loss results in gliosis and macrophage activation, which may be under genetic control, as discussed later. In contrast, the structural basis of moderate disability after TBI is more likely to be a focal lesion rather than diffuse brain pathology, usually an evacuated intracranial hematoma (Adams et al. 2001). In a study of 30 patients with severe disability, 50% had focal brain pathology only. Some severely disabled patients did show diffuse brain pathology similar to vegetative state patients, and it may be that there is a greater quantitative amount of damage in the vegetative cases. In assessment of the pathology of moderate and severe disability, case selection may be important, and it must be remembered that autopsy-based studies may not be a true reflection of the clinical spectrum associated with both moderate and severe disability.

Long-Term Cognitive Problems

There is a considerable retrospective epidemiological literature suggesting that TBI is associated with an increased risk of developing Alzheimer's disease in later life, although not all studies have confirmed this association. Data from prospective studies have also reported conflicting data, with some studies showing an association and others showing no association. A meta-analysis of 7 case-control studies (Mortimer et al. 1985) calculated a relative risk of developing Alzheimer's disease of 1.82 for head injury with loss of consciousness, only reaching statistical significance for males. Fleminger et al. (2003) studied 15 case-control studies and calculated an odds ratio (OR) of 1.58. Again, however, this study showed that the association between head injury and Alzheimer's disease was only statistically significant for males (males OR 2.26, females OR 0.92), who form the majority of the head-injured population.

Follow-up of patients 10–20 years after admission to the hospital with TBI provided further evidence of neurodegeneration at a late stage (Millar et al. 2003). However, even mild head injury (acute GCS score 13–15) is associated with a higher-than-expected incidence of disability (GCS outcome score: moderate or severe disability) at 1 year postinjury (Thornhill et al. 2000).

There is increasing evidence at a cellular and molecular level that there are similarities between the long-term responses to TBI and Alzheimer's disease. Neuropathologically, Alzheimer's disease is characterized by the deposition of β-amyloid (Aβ) plaques and the accumulation of tau neurofibrillary tangles and neuritic threads. Studies have focused attention on neuroinflammation in the form of microglial activation as a mechanism of potential relevance to neurodegeneration both in Alzheimer's disease and in the response to brain injury (Griffin et al. 1998). Microglia are the principal cellular mediators of inflammatory processes in the central nervous system and have a variety of functions, including antigen presentation, synthesis, and secretion of cytokines and phagocytosis. These cells are a source of several of the proteins upregulated both in Alzheimer's disease and after TBI, including apolipoprotein E, amyloid precursor protein, and proinflammatory cytokines such as interleukin 1 (IL-1). This raises the question that patients who sustain a head injury may have a microglial response that plays a role both in influencing their outcome following injury and in their increased susceptibility to Alzheimer's disease later in life.

After brain injury, cytokines are released and microglia are activated, with the degree of activation reflecting the severity of the injury. Microglial activation will lead to further cytokine release, including IL-1, possibly secondary to elevated levels of adenosine triphosphate released from damaged cells, with activation of purinergic P2X7 receptors on microglia. IL-1 is expressed in increased quantities in the cerebral cortex within hours of TBI, and chronic overexpression of IL-1 is found in Alzheimer's disease. Griffin et al. (1998) proposed a "cytokine cycle" in which TBI or other forms of brain injury can, in susceptible individuals, initiate an overexuberant sustained inflammatory response that can result in neurodegeneration. IL-1 positive microglial cells lie in close relation to β-APP positive neurons and dystrophic neurites in the brains of head-injured patients and are also found in close apposition to neurofibrillary tangle–containing neurons in Alzheimer's disease. β-APP is upregulated in response to increased IL-1 levels and is known to be upregulated in Alzheimer's disease (Griffin et al. 1998). Not only is β-APP upregulated in acute TBI, but there is increased intraneuronal processing of the molecule potentially resulting in Aβ production and deposition. Diffuse Aβ plaques have been identified in approximately 30% of individuals who die shortly after a single episode of severe TBI (Roberts et al. 1991), a higher proportion than in control subjects with no head injuries. Most of the deposits consist of Aβ42, which is believed to be of pathological significance in Alzheimer's disease. Aβ accumulation has been demonstrated within damaged axons in human brains after a single episode of fatal TBI. The authors postulated that damaged axons can act as a reservoir of Aβ, which may then be involved in plaque formation.

Experimental studies suggest that the cellular pathology initiated by an episode of acute TBI may indeed be progressive, and the role of programmed cell death after TBI has been reviewed by Raghupathi et al. (2000). Rats subjected to severe lateral fluid-percussion brain injury were studied for up to 12 months and showed long-term cognitive and neurological motor dysfunction. Studies have demonstrated cell loss from the neocortex, thalamus, and hippocampus with associated gliosis and ventriculomegaly in rats after fluid-percussion-induced injury that continues for up to 12 months. Studies in human cases have found TUNEL assay–positive cells up to 12 months after TBI (Williams et al. 2001). The majority of the cells were present in the white matter and were considered to be closely associated with Wallerian degeneration. Long-term DNA fragmentation therefore appears to be a feature of TBI in humans.

Repetitive head injury has been linked with neurodegeneration for many years. The largest pathological assess-

TABLE 2–4. Main neuropathological features associated with boxing

Pathological feature	Comments
Abnormalities of the septum pellucidum	A fenestrated cavum septum pellucidum was seen in 77% of boxers but only 3% of nonboxing aged-matched control subjects.
Cerebellar damage	Ataxia is common in ex-boxers, and gliosis is seen on the inferior aspects of the cerebellar hemispheres.
Degeneration of the substantia nigra	Parkinsonism is common in ex-boxers and substantia nigra degeneration is seen, although typically with neurofibrillary tangles rather than Lewy bodies.
Cerebral cortex pathology	Diffuse neurofibrillary tangles are seen in dementia pugilistica.

ment of dementia pugilistica was the examination of the brains of 15 boxers, 11 of whom were diagnosed with dementia pugilistica in life (Corsellis et al. 1973). This study reported four principal features of the brain in dementia pugilistica (Table 2–4). Extensive immunoreactive plaquelike structures were seen in most cases of dementia pugilistica, although the neuritic plaques characteristic of Alzheimer's disease were absent. Geddes et al. (1999) examined the brains of four young individuals (age range 23–28 years) with a history of repetitive head injury (two boxers, one footballer, and one mentally subnormal patient with a history of self-inflicted head banging) and a frontal lobectomy specimen from an individual with intractable complex partial seizures with recurrent minor head injury. They identified widespread neocortical neurofibrillary tangles and neuropil threads not seen in age-matched control subjects, in areas that showed a perivascular distribution. They concluded that neurofibrillary tangle formation in the absence of Aβ deposition is an early consequence of repetitive head injury and that, because of the striking perivascular distribution, neurofibrillary tangle formation may be related to damage to blood vessels. The molecular profiles of the neurofibrillary tangles in dementia pugilistica and Alzheimer's disease show a common tau isoform profile and phosphorylation state, suggesting that the mechanisms underlying both these conditions might be similar.

Experimental Models

Animal models of TBI are essential to advance the study of the cellular and molecular responses to TBI. Animal models allow an opportunity to control the physiological parameters of the model and to focus specifically on a single focal or diffuse injury. Human tissue typically shows polypathology, and many of the cellular and molecular responses are due to secondary injuries, such as ischemia, rather than reflecting the primary tissue response, such as axonal mechanoporation. However, it is important not to overinterpret the data from animal models, and a number of clinical trials of promising pharmacological therapies have failed because of a failure to recognize the polypathology in human brain injury.

Models of Focal TBI

The three main animal models used for focal injury are weight drop, controlled cortical impact, and fluid percussion (Morales et al. 2005). The weight drop model is a rodent model that uses a weight falling freely under gravity to produce a focal impact. The skull is not opened, and fractures are common. The controlled cortical impact method in rodents uses a rigid impactor directly onto the exposed dura, causing an underlying contusion. Midline fluid percussion injury requires the skull to be opened by trephination over the sagittal suture. A fluid bolus is accelerated onto the dural surface, the force being modified by variation of height from which the pendulum used to accelerate the bolus is released. These models are useful for modeling focal lesions such as contusions and hematomas. Rodents are most frequently used with these models, although the models can be modified for larger animals.

Diffuse Brain Injury Models

Models to study diffuse traumatic axonal injury have been developed for rodents and larger animals. Much of the initial work on diffuse axonal injury was done using nonhuman primates and the inertial acceleration brain injury model (Gennarelli et al. 1982); this method has recently been used extensively in swine models (Friess et al. 2007).

Much of the work relating to the basic science of axonal injury has been undertaken on the optic nerve stretch model. This model, developed in guinea pigs and modified to rodents, produces pure white matter injury that can be studied at different stages postinjury.

Mixed Focal and Diffuse Brain Injury Models

The most widely used animal model for producing a mixed brain injury is the lateral fluid percussion model (McIntosh et al. 1989). In this model the craniotomy is moved from the sagittal suture (midline fluid percussion model) to a lateral position. Although the injury is unilateral, the pathology produced is bilateral.

Models of Penetrating Brain Injury

Historically, there have been a number of animal models used to study ballistic brain injury, including nonhuman primates, although such studies are no longer undertaken. Most penetrating ballistic brain injury work in animals currently undertaken uses a rodent model (Williams et al. 2005). This model does not use a fired projectile but rather an inflatable penetrating probe that can simulate a cavity produced by a missile. The probe extends into brain parenchyma in a controlled fashion from a stereotaxic frame.

Models of Blast Injury

Of all the animal models used to investigate TBI, the models for blast injury are the least well reported and characterized. Most of the current animal models of blast injury use pressure generators such that the blast wave can be, to a degree, controlled and scaled (Elder and Cristian 2009), and these can be used with larger and smaller animals.

KEY CLINICAL POINTS

- Traumatic brain injury may be produced by blunt force head injury, either contact or noncontact, penetrating injuries, or blast injuries. The forces associated with each are different, and the range of pathologies seen is correspondingly different.
- Traumatic brain injury can result in either focal or diffuse pathology, or in many cases a combination of both. These pathologies are not static but may evolve with time, being modified by other pathophysiological parameters, and therefore windows of therapeutic intervention may be achievable.
- Childhood brain injury is not the same as adult head injury, and the effects may be different. The anatomy and physiology of the child, particularly the very young child, are different from those of the adult, and thus the tissue responses are often different.
- In some cases the effects of a mild head injury may lead to long-term problems. Long-term neurodegeneration is more frequent after traumatic brain injury, but to date we do not know how to identify patients at risk and the underlying pathological processes.
- Animal models are important in advancing our understanding of the mechanisms of brain injury associated with trauma, and only through work with animal models and translation to the human setting will we extend our knowledge base.

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CHAPTER 3

Genetic Factors

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Outcome after a traumatic brain injury (TBI) is quite variable and difficult to predict. For example, in clinical practice one can see very different cognitive and functional outcomes in individuals with similar preinjury intellectual and educational backgrounds and seemingly similar degrees of injury. This variability suggests that factors other than injury severity play important roles in outcome. Host genotype might be one such factor.

Advances in molecular biology have made it possible to sequence animal and human genomes and have facilitated understanding of genetic variation in a number of neurological conditions (Pulst 2003; Wright 2005). Since the 1970s the field has progressed from counting the number of chromosomes or identifying structural deficits in specific chromosomes to looking at the functional significance of single nucleotide base pair substitutions in specific genes (Hirschhorn and Daly 2005).

In this chapter I review key concepts important to understanding genetic influences on the response to and recovery from TBI. The Appendix provides brief definitions of key terms and concepts with which it is helpful to be familiar in considering this topic. Individuals less familiar with this area may find it useful to review the Appendix first. For additional details the reader is referred to texts such as *Human Molecular Genetics* (Strachan and Read 2004). Genetics is a rapidly changing field, and the intent in this chapter is not to provide an exhaustive list of potential candidate genes and alleles (see Jordan 2007 for review), but rather to illustrate the various ways that genetic differences influence response to trauma and provide illustrative examples of mechanisms that may inform treatment in the future.

Genetic Response to Neurotrauma

An array of genetic responses is triggered by neurotrauma both acutely and over time (DeKosky et al. 1998; Dutcher and Michael 2001; McIntosh et al. 1998; Michael et al. 2005). Initial responses include activation of genes involved in expression of stress proteins (e.g., heat shock proteins, ubiquitin), nerve growth factors (brain-derived neurotrophic factor [BDNF], glial cell-derived neurotrophic factor, insulin-like growth factor), and immediate early genes (thought to play a role in promoting transcription of other genes that in turn facilitate initiation of excitotoxic cascades) (Dutcher and Michael 2001; Michael et al. 2005). This makes the task of sorting out genetic contributions to this process complex. As a starting point it is useful to consider four broad categories in which genotype could play an important role in outcome after trauma: 1) modulation of injury extent, 2) response to/repair/recovery from injury, 3) preinjury traits and cognitive capacities, 4) links to neurobehavioral disorders (see Figure 3–1). Each of these four broad categories involve multiple steps (and hence multiple genes) and thus are under complex polygenic control. For example approximately 75–100 genes have been identified as candidates for affecting human cognition (Morley and Montgomery 2001). Even in conditions in which significant associations have been found between the condition or trait and a given gene or allele, the effect size is typically small, accounting for 1%–5% of the variance (Comings 1998). Although the individual contribution of a given allele might be small, the effects of multiple alleles could be quite significant. This suggests that "good cognitive out-

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come," or good functional outcome following TBI, is viewed best as a complex polygenic phenotype.

Genetic Influence on Extent of Injury

Full discussion of the neuropathology of TBI can be found elsewhere (see Gennarelli and Graham 2005; Raghupathi 2004; and Chapter 2, Neuropathology, in this volume). However, processes that amplify or diminish cellular responses to trauma are under genetic control, and thus functional polymorphic alleles in genes that play key roles in the cellular response to trauma could account for some of the variance in injury burden. Broadly speaking, these cellular injury mechanisms can be categorized as resulting from excitotoxicity, protease activation, and inflammation.

Excitotoxicity

TBI is accompanied by a dramatic and rapid release of the excitatory amino acids glutamine and aspartate. Excessive release of these compounds has been associated with neuronal death (see DeKosky et al. 1998; Gennarelli and Graham 2005; Laurer and McIntosh 2001; see also Chapter 2 of this book). The glutamatergic system is the major excitatory neurotransmitter system in the central nervous system (CNS). Glutamatergic transmission occurs through two broad classes of receptor families: ionotropic and metabotropic. Polymorphism induced altered glutamate receptor kinetics could affect associated injury cascades, and several such polymorphisms have been shown to modulate cognition, epilepsy, hypoxic injury, and neurodegenerative disorders (Lipsky and Goldman 2003), but to date there is no literature on these polymorphisms in TBI.

Protease Activation

Two major categories of proteases are involved in cell death: calpains and caspases. Both play important roles in mediating excitotoxic and inflammatory cell damage (Friedlander 2003). Caspases are cysteine-dependent proteases that play a role in apoptotic cell death through fragmentation of or interference with repair of cellular DNA (DeKosky et al. 1998; Friedlander 2003). Calpains are also cysteine-dependent proteases that degrade elements of the cytoskeleton such as microfilaments and microtubules (Friedlander 2003). Surprisingly, relatively little is known about functional polymorphisms in the genes that code for steps in the necrotic or apoptotic pathways and cascades. Thus, although caspase- and calpain-related genes may well be targets in the future, there are no known likely candidates at this time.

There are initial reports of three genes that may play a role in TBI outcome but whose mechanisms are unclear that are included in this section.

Human p53 Tumor Suppressor Gene

Originally identified as a tumor suppressor protein, the human p53 tumor suppressor gene *TP53* (formerly known as p53) is also felt to play a facilitating role in orchestrating both cell growth arrest and the onset of apoptosis (Fisher 2001). Of interest is a functional nonsynonymous coding polymorphism at codon 72 of *TP53,* where a change from guanine to cytosine results in a change from arginine to proline (Ara et al. 1990). The arginine protein is significantly more effective at initiating apoptosis (Dumont et al. 2003). Martinez-Lucas et al. (2005) assessed 90 patients with severe TBI with the Glasgow Outcome Scale (Jennett et al. 1981) at discharge from the intensive care unit and 6 months after injury. Poor outcome in this sample was associated with a higher percentage of individuals homozygous for the Arg allele.

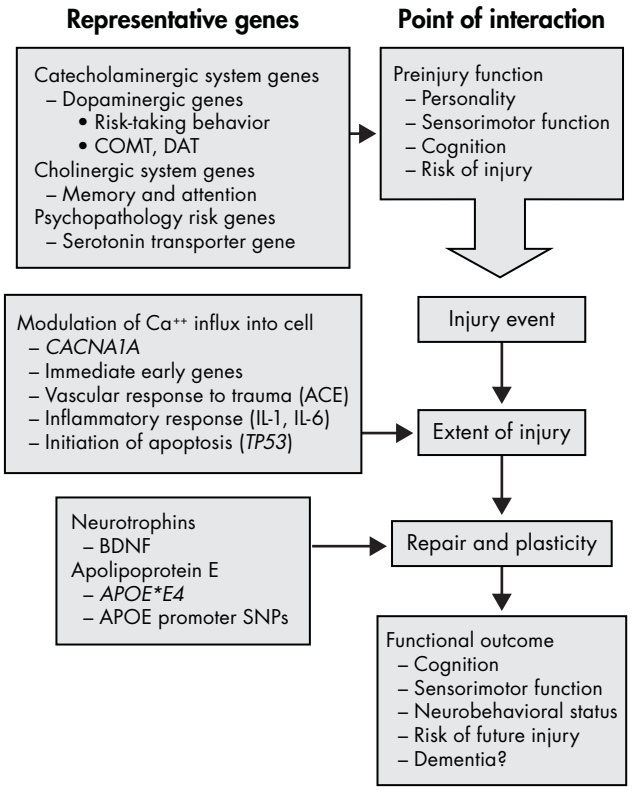


FIGURE 3–1. Scheme of potential mechanisms for genetic modulation of outcome after traumatic brain injury.

ACE=angiotension-converting enzyme; BDNF=brain-derived neurotrophic factor; COMT=catechol O-methyltransferase; DAT=dopamine transporter; IL=interleukin; SNP=single-nucleotide polymorphism; TP=tumor suppressor.

Angiotensin Converting Enzyme

Angiotensin converting enzyme (ACE) plays a central role in the regulation of blood pressure through the conversion of angiotensin I to angiotensin II. The gene *ACE* is located on chromosome 17 and has a common insertion/deletion mutation in intron 16 that may be associated with higher levels of circulating ACE (Tiret et al. 1992). Some reports have linked one of the alleles (the insertion or I allele) with increased risk of Alzheimer's disease, whereas others have reported an association between the deletion (D) allele and

cognitive impairment (Amouyel et al. 1996; Richard et al. 2001). Ariza et al. (2006) found that the D allele was associated with poorer cognitive performance in a cohort of 73 patients with moderate and severe TBI studied shortly after resolution of posttraumatic amnesia. The mechanism underlying this effect was unknown, although the authors speculated that the increased ACE activity associated with the D allele might result in vasospasm and cerebral compromise, thus adding to TBI related injury, and others have reported that ACE may interact with amyloid-beta aggregation (Hu et al. 2001).

Calcium Channel Subunit Gene

The calcium channel subunit gene (*CACNA1A*) codes for the alpha1 subunit (pore forming component) of the neuronal calcium channel. Thus functional polymorphisms in this gene might alter the downstream effects of the influx of calcium into the neuron that is triggered at the time of injury. Kors et al. (2001) published a small case series (N=3) on the association between delayed cerebral edema after mild brain injury and a novel cytosine to thyronine substitution resulting in a switch from serine (hydrophilic) to leucine (hydrophobic) at codon 218. This group recently reported an additional two patients with this same mutation (leucine allele) who had early seizures after very mild TBI (Stam et al. 2009).

Inflammation

Inflammation is associated with the biomechanical disruption of brain tissue, alterations in the blood-brain barrier, and the injury cascades that occur in TBI. Cytokines are a diverse group of soluble proteins and peptides that modulate the inflammatory response (Ibelgaufts 2010). They may be proinflammatory or anti-inflammatory, and they play a role in normal function and pathology in the CNS (Quan and Herkenham 2002). They are activated through interaction with the caspases and related proteases, thus it is important to consider the interaction of these two systems in considering response to trauma. Animal models and some human data (Holmin et al. 1998) suggest that TBI is associated with disruption of the blood-brain barrier and access of proinflammatory cells to brain parenchyma (Ray et al. 2002). In animal models, TBI is associated with upregulation of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (Ray et al. 2002). Preliminary data suggest that polymorphisms in several cytokines, including IL-1 and IL-6, may play roles in human TBI outcome.

Interleukin-1 Family

The IL-1 family consists of two proinflammatory interleukins (alpha and beta) and an interleukin receptor antagonist (IL-1RN). Functional polymorphisms exist within this family. Uzan et al. (2005) found higher rates of IL-1beta+3953 allele 2 and the IL-1beta –511 allele 2 in poor outcome (measured by Glasgow Outcome Scale) compared with the good outcome group 6 months after injury. The sample consisted primarily of patients with moderate and severe TBI.

Hadjigeorgiou et al. (2005) reported that those with the IL-1RN allele 2 had more hemorrhagic events after TBI. Tanriverdi et al. (2006) failed to find an association between a polymorphism in the 5′ regulatory region of the IL-1alpha gene and outcome measured by the Glasgow Outcome Scale 6 months after injury in a sample of 71 TBI patients of mixed severity (primarily moderate and severe), although there was a trend for those with the IL-1alpha allele 2 to have a poorer outcome.

Interleukin-6

IL-6 is a proinflammatory cytokine that has been associated with reduced hippocampal neurogenesis. There is a guanine-cytosine single-nucleotide polymorphism (SNP) in the –174 promoter region of the gene that appears to be functional, although the mechanism is not clear. The G allele has been associated with increased production of IL-6, particularly the GG genotype. The latter has been associated with Alzheimer's disease in some (e.g., Pola et al. 2002) but not all studies (Capurso et al. 2004). Our group found an association between the presence of the G allele and reduced temporal lobe gray matter in elderly individuals with memory problems (Saykin et al. 2005). Interestingly, Winter et al. (2004) have reported that elevated levels of IL-6 are associated with improved outcome 6 months after TBI, however Minambres et al. (2003) failed to find an allele effect on TBI outcome for a polymorphism at position –174 of the promoter region.

The above literature suggests that several polymorphisms in genes that determine the brain's response to trauma do play a role in outcome after TBI. Furthermore, there are likely to be others that are identified in the next several years.

Alleles Affecting Repair and Plasticity

Given equivalent amounts of primary and secondary injury, individuals with greater capacity for repair, regeneration, and plasticity may well have better functional and cognitive outcomes. Functional polymorphisms in genes at key nodal points in these processes could account for some of the observed differences in outcome.

Neurogenesis

Generally it is now accepted that neurogenesis occurs in the adult human brain (Kaneko and Sawamoto 2009; Kempermann 2002a; Schaffer and Gage 2004). Although it may occur in other sites, the hippocampus, particularly the dentate gyrus, is the primary site of neurogenesis. Furthermore a variety of mediators of this process have been identified (for reviews, see Kaneko and Sawamoto 2009 and Kempermann 2002a, 2002b). Fibroblast growth factor-2, epidermal growth factor, sonic hedgehog gene, and central serotonergic tone play key roles in facilitating neurogenesis (Kaneko and Sawamoto 2009; Schaffer and Gage 2004). There are few reports of common functional poly-

morphic alleles identified in the genes coding for the component processes of neurogenesis, although this is likely to change in the future. There is, however, an allele of interest in the serotonin transporter that may have an effect on central serotonergic tone and thus indirectly on neurogenesis.

Serotonin Transporter

Serotonin transmission is terminated by sodium- and chloride-dependent transporter molecules that move serotonin from the synapse back into the presynaptic neuron. Of interest is a polymorphic allele located in the promoter region (a 44-bp insertion [the long allele, l] or deletion [the short allele, s]). The short variant of the serotonin transporter–linked polymorphic region has been shown to result in reduced transcriptional efficiency (Blum et al. 1997) and has been associated with major depression (Mann et al. 2000); family history of depression (Joiner et al. 2003); violent suicide attempts (Bellivier et al. 2000); the development of depression, depressive symptoms, and suicidality in response to stressful life events (Caspi et al. 2003); development of depression after stroke (Ramasubbu et al. 2006); and development of posttraumatic stress disorder (PTSD) after exposure to trauma (Xie et al. 2009). Studies testing the association of this polymorphism with depression after TBI are under way.

Adaptive Synaptic Organization

The second major component in repair/regeneration/plasticity is synaptic organization. Neurotrophic factors play a key role in this process. (For full discussion of these critical factors, see reviews by Chao 2003; Lang et al. 2004; Lim et al. 2003; and Skaper 2008). In brief, there are four broad categories of neurotrophins: 1) the nerve growth factor family, 2) the glial-derived factor family, 3) the neurokine family, and 4) the nonneuronal growth factor family (Lang et al. 2004). Neurotrophins play a role in the protection and maintenance of neurons, neurogenesis, and synaptic plasticity (Mufson et al. 1999). Each of the neurotrophin families include factors that in theory could be relevant to the mitigation of and recovery from neurotrauma. The best, albeit limited, evidence suggests roles for several members of the nerve growth factor family and the glial-derived factor family in the response to neurotrauma (Hicks et al. 1997; Kulbatski et al. 2005; Oyesiku et al. 1999; Ray et al. 2002).

Brain-Derived Neurotrophic Factor

BDNF is initially manufactured as a precursor protein (pro BDNF) and then cleaved to BDNF and stored in and released from secretory vesicles in response to neural activity. BDNF facilitates both early and late long-term potentiation, a process critical to the formation and maintenance of episodic and working memory (Egan et al. 2003; Lu and Gottschalk 2000; Poo 2001). BDNF messenger RNA (mRNA) is elevated in hippocampus within one hour of trauma and remains elevated for several days (Hicks et al. 1997, 1998). There is an SNP occurring in the 5′ promoter region in the pro-BDNF sequence, at codon 66, nucleotide 196 involving a change from G to A, with a subsequent change in amino acid from valine to methionine (Egan et al. 2003). Egan et al. (2003) studied the effect of this polymorphism in a sample of 136 healthy control subjects, 106 individuals with schizophrenia spectrum disorders, and 138 unaffected siblings. There was a significant main effect of genotype on Wechsler Memory Scale—Revised scores, with the Met/Met group scoring lower than the Val/Met or Val/Val groups. The Met allele was also associated with abnormal storage and secretion of BDNF in an in vivo cell culture assay. The role of Val66Met polymorphism in response and recovery of human TBI has not been well characterized. In a preliminary study (McAllister et al. 2008b) our group studied 38 healthy subjects and 75 patients with mild TBI approximately 1 month after injury. Participants were given the Wide Range Achievement Test, 3rd Edition, Reading subtest; the Wechsler Adult Intelligence Scale (WAIS)–III Block Design subtest; the California Verbal Learning Test (CVLT); and the Gordon Continuous Performance Test (CPT). There was a significant main effect of 3 of 9 SNPs in the BDNF gene (including Val/Met SNP rs6265) on measures of processing speed (CPT; $P<0.005$) and 2 of the SNPs on a measure of episodic memory (CVLT; $P<0.05$). These results provide support for the hypothesis that polymorphisms in the BDNF gene may influence cognitive performance shortly after mild TBI.

Repair

Apolipoprotein E

Another candidate gene of interest in response and repair processes following TBI is the gene encoding apolipoprotein E (apoE). ApoE is a complex glycolipoprotein that facilitates the uptake, transport, and distribution of lipids. A four-exon gene, *APOE,* codes for apoE on chromosome 19 in humans. The gene for apoE has three major alleles: *APOE*E2, APOE*E3,* and *APOE*E4.* These alleles differ in amino acids at positions 112 and 158: **E2* (cysteine/cysteine), **E3* (cysteine/arginine), and **E4* (arginine/arginine). ApoE appears to play an important role in neuronal repair and plasticity after neurotrauma (Chen et al. 1997). Animal models suggest a link between the **E4* allele and increased mortality, extent of damage, and poor repair following trauma (Chen et al. 1997; Hartman et al. 2002). The human **E4* allele has been associated with a variety of disorders with prominent cognitive dysfunction, including normal subjects with memory complaints (Laws et al. 2002), Alzheimer's disease, and poor outcomes in stroke and TBI (Chen et al. 1997; Nathoo et al. 2003).

Several studies, using a variety of measures, have reported that the **E4* allele of *APOE* is associated with poor outcomes following TBI (Chiang et al. 2003; Nathoo et al. 2003). Teasdale and Engberg (1997) prospectively studied individuals with TBI and found that persons with the **E4* allele had a significantly worse outcome 6 months after brain injury when compared with individuals with similar demographic and brain injury variables but without *APOE*E4.* In this study, worse outcome meant being in a vegetative state, being severely disabled based on the Glasgow Outcome Score, or death. Crawford et al. (2002) found poorer memory performance in their sample of 30 individ-

uals with TBI with at least one **E4* allele compared with 80 TBI patients without an **E4* allele. Lichtman et al. (2000) found lower total functional independence measure scores in 7 patients with TBI with the **E4* allele compared with 24 individuals with TBI but without an **E4* allele. Friedman et al. (1999) found a significantly higher percentage of poor outcome indicators both acutely (prolonged loss of consciousness) and at 6–8 months after injury (significant dysarthria, global functional outcome rating) in 27 individuals with TBI and the **E4* allele compared to 42 individuals with TBI but without an **E4* allele. Liberman et al. (2002) found lower cognitive performance on several cognitive measures at 3 weeks but not at 6 weeks after injury in the patients with the **E4* allele. Notably, not all studies have found an association between the **E4* allele and poor outcome. Recently, Willemse-van Son et al. (2008) found better outcomes on the Glasgow Outcome Scale was associated with the **E4* allele in their cohort of 79 individuals with moderate-severe TBI followed up to 3 years after injury.

The mechanism by which the **E4* allele exerts an effect is unclear. *APOE*E4* shows an increased affinity for amyloid beta and thus an increased propensity to promote amyloid beta aggregation (Friedman et al. 1999). Rather than an active detrimental effect, it may be that *APOE*E4* is less effective than *APOE*E3* in promoting neuronal repair and neuritic growth and branching. There may be a cholinergic link between apoE and cognitive impairment (Parasuraman and Greenwood 2002). In Alzheimer's disease, the degree of reduction of choline acetyl transferase, one of the markers for the disease, is correlated with the "dose" of **E4* (Chen et al. 1997). Parasuraman and Greenwood (2002) have argued based on accumulated neuropsychological, electrophysiological, and neuroimaging evidence that the cognitive effects of the **E4* allele are mediated through reduced cholinergic input to posterior parietal systems regulating selective attention.

In addition to the effects of apoE genotype on outcome after TBI, there is a concern that apoE genotype may interact with TBI to increase risk of developing neurodegenerative disorders such as Alzheimer's disease later in life (e.g., see Van Den Heuvel et al. 2007). After initial observations of progressive dementia in boxers with repetitive brain injury (Martland 1928), neuropathological studies showed prominent neurofibrillary tangles and subsequently amyloid plaques similar to those found in Alzheimer's disease and other neurodegenerative disorders (Roberts and Bruton 1990). Furthermore, TBI-associated disruption of axonal transport results in the rapid accumulation of amyloid precursor protein (APP) in both animals (Van Den Heuvel et al. 1999, 2007) and humans (Blumbergs et al. 1995; Graham et al. 1995). Current evidence suggests that APP, amyloid beta, and other proteins associated with Alzheimer's disease and other neurodegenerative disorders accumulate quite rapidly after a TBI (Chen et al. 2009; Uryu et al. 2004, 2007) and that in some but not all individuals these abnormal deposits can be chronic. Such differences have led investigators to question whether genetic factors play a role. For example, Mayeux et al. (1995) retrospectively studied 113 older adults with Alzheimer's disease, comparing them with a control group of 123 healthy older individuals. They found that the combination of the **E4* allele and a history of TBI increased the risk of Alzheimer's disease by a factor of 10. Not all studies agree that TBI increases the risk of developing Alzheimer's disease in people with the **E4* allele. A large, prospective population-based study of 6,645 individuals ages 55 years and older and free of dementia at baseline found that mild brain trauma was not a major risk factor for the development of Alzheimer's disease. Moreover, brain trauma did not appear to increase the risk of developing Alzheimer's disease in people carrying the *APOE*E4* (Mehta et al. 1999). Thus the relationship between TBI and dementia needs further study.

APOE Promoter Polymorphisms

There are also several polymorphisms in the promoter region of the *APOE* gene (Artiga et al. 1998). Two common SNPs in the promoter region, one at site 219, the other at 491, appear to influence promoter activity and thus presumably *APOE* expression (Artiga et al. 1998). Lendon et al. (2003) studied the effects of genotype at both SNPs on 6-month outcome in 92 individuals hospitalized at a trauma center with TBI. In this sample, being homozygous for the T allele at site G-219T (associated with decreased promoter activity) was associated with poorer outcome as measured by the Glasgow Outcome Scale. No allele effect on outcome was found for the A-491T polymorphism.

Pre- and Postinjury Cognitive Capacity and Reserve

As noted previously, genes that effect cognitive capacity and reserve play a role in cognitive outcome after TBI. A large number of factors determine cognitive performance, including genetic factors (Deary et al. 2009; Morley and Montgomery 2001; Savitz et al. 2006). Because the effect of a single allele on cognitive performance may be small, it may be overwhelmed by other factors such as educational opportunity, parental education and expectations, nutrition, and other health factors. However, it may be the case that the effects of different "cognitive alleles" are additive and that in combination they might have measurable effects on outcome. In addition, such "adverse alleles" might not be noticeable until an individual's cognitive reserve is depleted by an injury. Much of the work to date focuses on genes that play a role in catecholaminergic and cholinergic function because of the central role that these neurotransmitters play in cognition. Several representative examples are presented below.

Dopamine Receptor Gene Polymorphisms

Dopamine plays an important role in the regulation and modulation of mood, cognition (particularly memory, attention, and executive functions), reward functions, endocrine systems, and motor function. Thus dopaminergic system genes are ideal candidates to probe for roles in neuropsychiatric disorders. To date most of the attention has

focused on polymorphisms in genes coding for dopamine receptor subtypes, dopamine reuptake (the dopamine transporter [DAT]), and dopamine metabolism (catechol O-methyltransferase [COMT]).

Dopamine D_2 Receptor

DRD2, the gene for the dopamine D_2 receptor, is located on chromosome 11. There are a dozen or more polymorphisms described for this gene, three that result in amino acid substitutions, and two that reduce the expression of dopamine D_2 receptors. Most work has focused on the three restriction fragment length polymorphisms known as *Taq*I A, B, and C. A large body of work suggests that a *Taq*I A polymorphism plays a role in modulation of the reward system and to lesser extents movement disorders and psychosis. Originally thought to be in the gene *DRD2,* this polymorphism (rs1800497) is actually in an adjacent gene—*ANKK1.* Autopsy studies have found reduced dopamine D_2 receptor binding in the striatum of individuals with the T allele (Ritchie and Noble 2003; Thompson et al. 1997). This appears to be a reduction in the number of dopamine D_2 receptors rather than a change in receptor affinity. Polymorphisms in this region appear to play a role in cognitive outcome after mild TBI. Our group reported an association between the *Taq*I A allele and response latency after mild TBI (McAllister et al. 2005). We studied a second cohort of 54 patients with TBI and 21 comparison subjects genotyped for rs1800497 (McAllister et al. 2008a). Ninety-three patients with TBI and 48 comparison subjects were genotyped for 31 additional neighboring polymorphisms in *NCAM, ANKK1,* and *DRD2.* Once again the T allele (rs1800497) was associated with poorer performance on the CVLT, and there was a significant diagnosis-by-allele interaction on the CPT, largely driven by slower performance in the TBI participants with the T allele. A haploblock of three SNPs in *ANKK1* showed the greatest association with cognitive outcome measures.

DRD2 alleles also may be associated with certain personality styles or traits (see Ebstein et al. 2000 for review) and thus with risk for sustaining a TBI. Most of these studies use self-report questionnaires or personality inventories to classify personality styles or traits along a limited number of domains such as "novelty seeking," "harm avoidance," and "reward dependence." These dimensions generally are considered to be constructs representing exploratory behavior, inhibition of approach behaviors, and attachment or persistence of intermittently reinforced behaviors, respectively (Ebstein et al. 2000). Associations have been reported between the *Taq*I A1 allele and schizoid/avoidant behavior (Blum et al. 1997) and impulsive/addictive behavior such as pathological gambling (Comings et al. 1996). Several reports have linked the *D4.7* allele (part of the D_2 family) to increased novelty seeking (Ebstein et al. 2000; Wong et al. 2000) in adults, neonates (Ebstein et al. 1998), and D_4 receptor knockout mice (Dulawa et al. 1999).

Polymorphisms of Monoamine Transporters

After their release into the synapse, dopamine, serotonin, and norepinephrine bind to presynaptic membrane proteins known as *transporters* and are taken back into the presynaptic neuron. The activity of these transporters plays a major role in the regulation of neurotransmitter tone. Thus polymorphisms in the genes coding for these transporters could play important roles in the etiology of neuropsychiatric disorders, and medications modulating the activity of these transporters could and in fact already do play important therapeutic roles (i.e., serotonin reuptake inhibitors).

Dopamine Transporter

The gene for the DAT is located on the short arm of chromosome 5. Blockade of DAT is thought to be the mechanism of action for a variety of different drugs, including cocaine, amphetamine, phencyclidine, methylphenidate, and bupropion, among others. In the 3′-untranslated region, this gene contains a region with a 40 base-pair variable number of tandem repeats. There are at least 10 different alleles known, corresponding to a range of 3–13 repeat sequences. Furthermore, these variations in the number of tandem repeats appear to have an effect on the expression of DAT (Miller and Madras 2002). The 10-repeat allele has received the most attention and several studies have linked this allele to attention-deficit/hyperactivity disorder (ADHD). Cook et al. (1995) showed an association between ADHD and the 10/10 homozygous genotype. This finding was confirmed by Waldman et al. (1998) and Daly et al. (1999).

Serotonin Transporter

The gene for the serotonin transporter is located on the long arm of chromosome 17 and was mentioned earlier with respect to potential effects on neurogenesis as well as links to gene/environment interactions and risk for depression and PTSD.

Norepinephrine Transporter Gene

Similar to the other monoamine transporters, the norepinephrine transporter (NET) gene plays a crucial role in the modulation of brain noradrenergic tone. A variety of polymorphisms in various regions of the gene have been described, although there is little information on the functional significance of these alleles and no data to date regarding TBI.

Polymorphisms of Enzymes Involved in Catecholamine Synthesis and Metabolism

Dopamine Beta Hydroxylase

The gene for dopamine beta hydroxylase (DBH) is located on the long arm of chromosome 9. DBH catalyzes the conversion of dopamine to norepinephrine and plays an important role in the modulation of dopaminergic and noradrenergic tone. Inhibition of DBH results in a reduction of norepinephrine. Under ordinary circumstances norepinephrine exerts an inhibitory effect on tyrosine hydroxy-

lase and thus the conversion of tyrosine to dopamine and subsequently norepinephrine. DBH inhibition and the subsequent reduction in norepinephrine can therefore result in an increase of dopamine (Comings et al. 1996). Changes in DBH activity have been linked to conduct disorder and a variety of personality traits in several studies (Comings et al. 1996). There is a functional polymorphism of *DBH* (*Taq*B), occurring in approximately 50% of non-Hispanic Caucasians that does appear to effect transcription of the gene product. Our group reported preliminary findings suggesting that *DBH* allele status was related to several measures of cognitive function in a cohort of 100 individuals with mild-moderate TBI studied approximately 1 month after injury (McAllister et al. 2009).

Catechol O-Methyltransferase

COMT catalyzes the metabolic breakdown of catecholamines through the methylation of dopamine and norepinephrine. The gene for COMT is located on the long arm of chromosome 22. There is a common functional polymorphism of this gene characterized by a single nucleotide change from G to A at position 472. This switch results in a code change to methionine instead of valine. The effect of this amino acid substitution is a significant change in the efficiency of the enzymatic activity at normal body temperatures (Weinberger et al. 2001). The valine version (Val allele) is almost four times as active as the methionine version of the gene (Met allele). Thus individuals homozygous for the Val allele presumably metabolize dopamine much more rapidly than those with the Met allele. This is of particular importance in the frontal cortex, where DAT shows relatively less expression compared with striatal regions. In frontal cortex COMT becomes a major modulator of dopaminergic tone, accounting for approximately 60% of the metabolic degradation of dopamine (Malhotra et al. 2002). Although COMT also catalyzes the methylation of NET, the regional brain differences in transporter density/expression are not found with NET; thus the Val/Met polymorphism appears to have a relatively specific effect on frontal dopaminergic tone (Weinberger et al. 2001).

Changes in COMT activity alter frontal dopaminergic activity and cognitive capacity in both animals and humans. *COMT* knockout mice show reduced frontal but not striatal dopamine relative to wild-type mice (Gogos et al. 1998). COMT inhibitors given to rats (Liljequist et al. 1997) and humans (Apud et al. 2007) have been shown to improve memory. Egan et al. (2001) found that the Val allele was associated with poorer performance (more perseverative errors) and that there was an allelic load effect (i.e., Val/Val homozygotes did worse than Val/Met heterozygotes) in healthy control subjects and individuals with schizophrenia and their siblings. Lipsky et al. (2002) studied 113 individuals with TBI with a battery of frontal-executive tests. Analysis of variance showed significant between group differences, with the Val/Val group making the most perseverative errors on the Wisconsin Card Sorting Test, the Met/Met group making the least number of errors, and the Val/Met group making an intermediate number of errors. Thus, the weight of evidence suggests that the Val158Met polymorphism affects frontal dopaminergic tone and that this change in tone is reflected in altered performance of some measures of frontal-executive cognitive function.

Polymorphisms Relevant to the Cholinergic System

Several genetic variations exist that affect CNS cholinergic function and play a role in certain neuropsychiatric conditions. Surprisingly very little work has been done on these alleles in patients with TBI.

Cholinergic Receptors

The two broad categories of cholinergic receptors are the muscarinic and nicotinic types, based on receptor responses to muscarine or nicotine. The focus in this section will be on the nicotinic receptor system. Nicotinic receptors are part of the superfamily of ligand-gated ion channels. Binding of an agonist to the receptor results in a conformational change, allowing cations to flow across the membrane. Nicotinic receptors are made up of different combinations of five subunits (designated alpha and beta). Each subunit has four transmembrane components and the N-terminal region that is located extracellularly (Mihailescu and Drucker-Colin 2000; Weiland et al. 2000). The eight different alpha subunits (α2–α9) and three beta subunits (β2–β4) are all coded for by different genes, many of which have potentially significant polymorphisms. Thus, there are a large number of neuronal nicotinic receptors, characterized by the different arrays of subunits that comprise the specific receptor. The most common neuronal nicotinic receptor is composed of the α4β2 subunits, accounting for almost 90% of brain nicotinic receptors (Mihailescu and Drucker-Colin 2000; Weiland et al. 2000).

Attempts have been made to link some of the subunit polymorphisms to a variety of neuropsychiatric disorders. For example, deficits in sensory gating as manifested by abnormalities in the P50 auditory evoked response are very common in individuals with schizophrenia, as well as individuals with TBI and persistent postconcussive complaints (Arciniegas et al. 2000), and have been linked to a dinucleotide repeat polymorphism in the gene coding for the α7 subunit on the long arm of chromosome 15 (Weiland et al. 2000). Of interest is that the P50 deficit can be attenuated with the use of nicotine (Adler et al. 1992, 1993, 1998; Weiland et al. 2000).

Conclusion

The study of genetic determinants of outcome after TBI is at a very early stage. The complex series of events that are set in motion by a TBI suggests that functional polymorphisms in genes that regulate the brain's response to neurotrauma, repair processes after injury, and neural plasticity play a role in determining outcome (Table 3–1). Currently there is reasonable evidence that *APOE* allele type affects outcome, although the mechanism is not clear. It also appears that polymorphisms in nerve growth factors and the inflammatory cascades, particularly in genes for IL-1 and IL-6 are promising candidates. To date, these

TABLE 3–1. Polymorphisms affecting outcome after traumatic brain injury (TBI)

Domain affected	Gene	Polymorphism	Functional mechanism	Comments
Response to neurotrauma				
Initiation of apoptosis	Human p53 tumor suppressor	G/C (arginine to proline) at codon 72	Arg allele more efficient initiator of apoptosis	Arg homozygosity associated with lower Glasgow Outcome Scale in one study (Martinez-Lucas et al. 2005)
Effect on vascular response to trauma?	Angiotensin converting enzyme gene	Insertion/deletion in intron 16	Alters circulating levels of angiotensin converting enzyme (higher in D/D)	D allele associated with poorer cognitive performance in moderate/severe TBI (Ariza et al. 2006)
Calcium influx into cell	Calcium channel subunit gene (*CACNA1A*)	C/T substitution at codon 218 (serine to leucine switch)	Alters configuration of Ca^{++} pore forming component	Small case series associated L allele with cerebral edema and seizures after mild TBI (Kors et al. 2001; Stam et al. 2009)
Inflammatory response	Interleukin-1 beta (proinflammatory cytokine)	Restriction site at position +3953 exon 5	Not known; presumed effect on degree of inflammatory response	Poor 6-month outcome associated with allele 2 after moderate to severe TBI (Uzan et al. 2005)
Inflammatory response	Interleukin-6 (IL-6) (proinflammatory cytokine)	G/C single-nucleotide polymorphism (SNP) in promoter region (position –174)	G allele associated with increased production of IL-6	Conflicting results on association of G allele with TBI outcome (Minambres et al. 2003; Winter et al. 2004)
Repair and plasticity				
Repair and plasticity	Brain-derived neurotrophic factor (*BDNF*)	G/A SNP in promoter region (codon 66); results in Val to Met switch	Met allele associated with abnormal storage and secretion of BDNF	Preliminary study shows association with Met allele and lower memory and attention scores 1 month after mild TBI (McAllister et al. 2008b)
Repair	Apolipoprotein E (*APOE*)	Three major alleles: **E2, *E3,* and **E4,* differ in amino acids at positions 112 and 158; also several polymorphisms in the promoter region	Mechanism of allele effect for this gene is not known	*APOE*E4* allele associated with poor outcome in several studies of TBI (e.g., see Alexander et al. 2007); T allele at the G-219T site in promoter region associated with poor outcome (Lendon et al. 2003)
Pre- and postinjury cognitive capacity and reserve				
Catecholamine receptors	Dopamine D_2 receptor region *DRD2* and *ANKK1*	Numerous polymorphisms in this region; unclear how many are functional	rs1800497 associated with reduced expression of D_2 receptors in striatum	rs1800497 associated with measures of memory and attention 1 month after mild TBI (McAllister et al. 2005, 2008a)
Catecholamine transporters	Dopamine transporter (*DAT*)	40 base pair variable number tandem repeat (VNTR)	Different alleles affect expression of *DAT*	Preliminary data suggest association of 10 allele with measures of memory and attention 1 month after mild TBI (McAllister et al. 2009)
Catecholamine metabolism	Catechol O-methyltransferase (*COMT*)	G/A SNP (val158met) resulting in Met/Val switch at position 472	Met allele less efficient in metabolizing dopamine	Met allele associated with reduced performance on some frontal-executive tasks after TBI (Lipsky et al. 2002; McAllister et al. 2009)
Catecholamine synthesis	Dopamine beta-hydroxylase (*DBH*)	Functional polymorphism affects gene transcription	Not known	5 SNPs in DBH gene associated with memory and attention measures 1 month after mild TBI (McAllister et al. 2009)

preliminary studies confirm the "proof of concept." What is less clear is how the different "adverse" alleles interact with each other. Largely unexplored are the questions of genetic contributors to the increased burden of psychiatric disorders associated with TBI and whether there are certain candidate genes/alleles that put an individual at increased risk of sustaining a TBI. Such questions will have to be addressed by careful large multicenter studies because minor allele frequencies are often in the range of 10%–20%, thus limiting cohort sizes.

KEY CLINICAL POINTS

- Genetic polymorphisms in genes that modulate response to trauma, neural repair/plasticity, and cognitive reserve/capacity influence outcome after TBI. These genetic polymorphisms may contribute to some of the observed clinical variation that is seen after seemingly similar injuries.
- Although there is no clear role for genetic testing at this time in TBI survivors, further clarification of the role of specific alleles in the modulation of neural trauma may lead to targeted interventions to mitigate secondary injury and prevent neuropsychiatric sequelae after TBI in the future.

Recommended Readings

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Appendix 3–1

A BRIEF REVIEW OF KEY CONCEPTS AND TERMS follows in order to help orient those who are new to this area. For additional details the reader is referred to texts such as Strachan and Read (2004).

The Genome

The *genome* refers to the sum total of genetic material that defines an organism. The human genome consists of approximately 3 billion base pairs of DNA, containing approximately 30,000 genes by current estimates (Strachan and Read 2004) (see Figure 3–2).

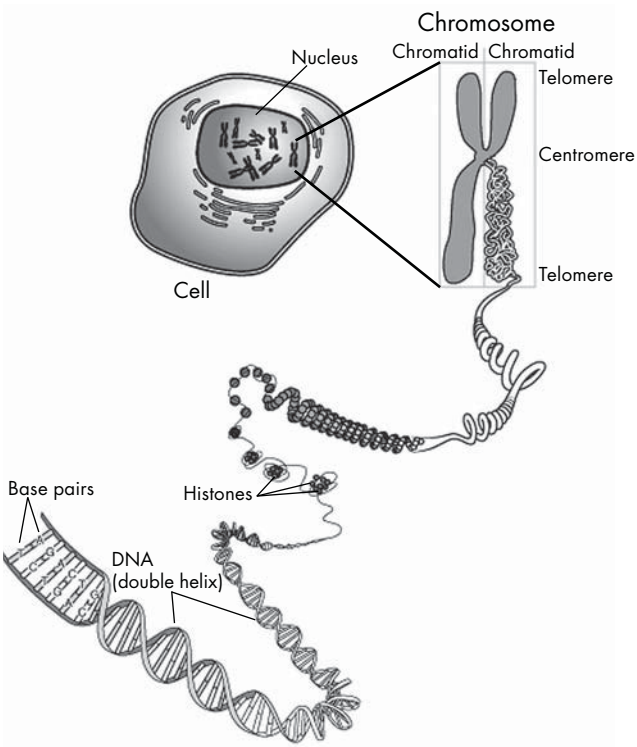


FIGURE 3–2. Organization and location of genetic material in the cell.

Source. Reprinted from American Mathematical Society: Molecular Biology and Genetics Primer for Mathematicians. Available at: http://www.ams.org/featurecolumn/archive/primer1.html. Accessed April 10, 2010.

Chromosomes

Human genetic material is organized into 46 (23 pairs) components known as *chromosomes* (see Figures 3–3 and 3–4). One member of each pair of chromosomes is inherited from each parent. Using proper staining techniques, chromosomes in actively dividing cells can be seen to have several identifiable regions and subregions, or bands. Locations of a specific gene usually are given as the chromosome number (e.g., 22), short arm (p) or long arm (q), region number, and then band number (Horwitz 2000). For example, 22q11.2 microdeletion syndrome (also known as DiGeorge syndrome) (Bearden et al. 2001) signifies that there is a microdeletion in chromosome 22, the long arm, region 11, band 2.

Chromatin

Chromatin consists of the DNA and protein that make up chromosomes. When the cell is not dividing, chromatin is not condensed into easily identifiable chromosomes but rather as less condensed strings. Chromatin is organized into nucleosomes consisting of 147 base pairs of DNA wrapped around four pairs of proteins, known as *histones* (MacDonald and Roskams 2009). Alterations in the structure of these histone proteins, either through changes in methylation or acetylation, can have important effects on the expression of neighboring genes. Methylation and acetylation status are tightly regulated (see MacDonald and Roskams 2009). The alteration of these factors, with subsequent effect on cell differentiation and gene expression are known as *epigenetic factors* (see below). By altering gene transcription and expression, such factors play a major role in individual differences among cells (i.e., cell differentiation through development) as well as phenotypic differences between organisms with identical genetic material.

Genotype

The term *genotype* refers to the particular array of genetic material of an individual or organism. The term can be used to describe the entire genetic array of a given organism or to the particular variant of a gene of interest that an individual has.

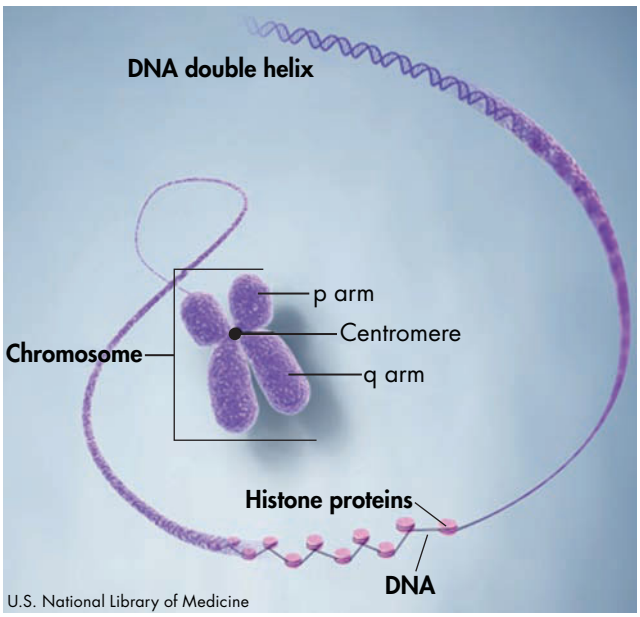


FIGURE 3–3. Diagram of a chromosome.

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Phenotype

The term *phenotype* refers to the manifestation or expression of an underlying genotype. For example, one might refer to an individual's genotype for eye color (the particular array of genes he or she carries for eye color), and the phenotype would be the actual observable color (e.g., blue eyes).

Gene Components

Genes generally have several identifiable structural components, including binding sites for RNA polymerase and other transcription factors, promoter and enhancer regions, a ribosome-binding site that permits cytoplasmic ribosomes to recognize mRNA, and the coding sequence for the gene's protein product (see Figures 3–5 and 3–6). Most genes also contain regions known as *introns* that do not code for gene-specific information and must be "edited" out prior to export of the gene product to the cytoplasm. Translation of the sequence of nucleotides to a specific protein occurs through a *code,* in which the building blocks of proteins (amino acids) are specified through trinucleotide sequences or codons (see Figure 3–7). Locations of markers within a gene are sometimes specified by the nucleotide sequence number and sometimes by the codon sequence number. The end of the coding sequence is signaled by a *termination codon* (TAA, TAG, or TGA), and the gene ends with a variable number of adenine residues referred to as the polyadenylation signal (Horwitz 2000).

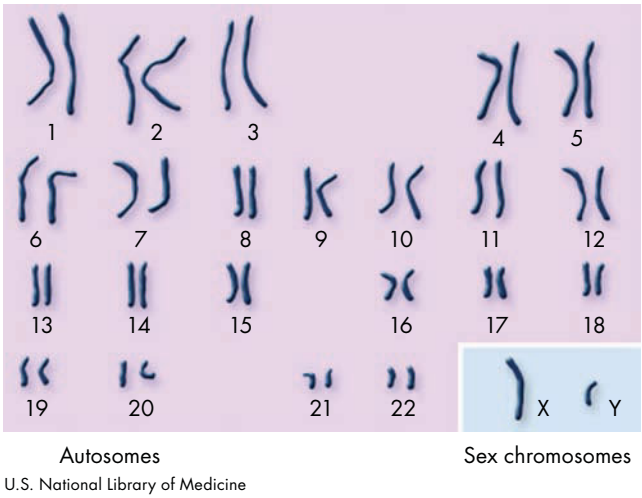


FIGURE 3–4. Picture of human chromosomes (karyotype).

Source. Reprinted from Genetics Home Reference: Handbook: Help Me Understand Genetics. Available at: http://ghr.nlm.nih.gov/handbook/illustrations/chromosomes. Accessed April 10, 2010. Used with permission.

Alleles

Within a given population, there may be several versions of a gene known as *alleles.* When more than one version of a gene is present in a population the gene is said to be *polymorphic.* A gene can contain more than one polymorphism, each with two or more alleles at that site. These different versions (alleles) arise via several different mechanisms. Some alleles are produced by deletion, substitution, or insertion of single nucleotide bases at a point in the DNA sequence—a so-called point mutation. Single-nucleotide polymorphisms (SNPs) are point mutations resulting from a change in a single base pair. Other alleles come from the deletion of a variable numbers of base pairs or differences in the number of times a given base pair sequence is repeated in a specific region of the gene (variable number of tandem repeats).

Functional Polymorphisms

Allelic variations can result in functional or nonfunctional change. For example, if a point mutation occurs in the section of the gene coding for the protein product, this can result in a frame shift in which the downstream sequences are now shifted one base. This may lead to a different amino acid coding or the premature occurrence of a termination code resulting in a truncated polypeptide or protein. Alternatively, if the sequence change is not in the coding section of the gene where the protein is made (for example, is located in an intron), then the protein product may not be altered, and there may be no pathological significance to the change. This is also true for point mutations that do not actually change the amino acid called for, which can happen because there is more than one triplet

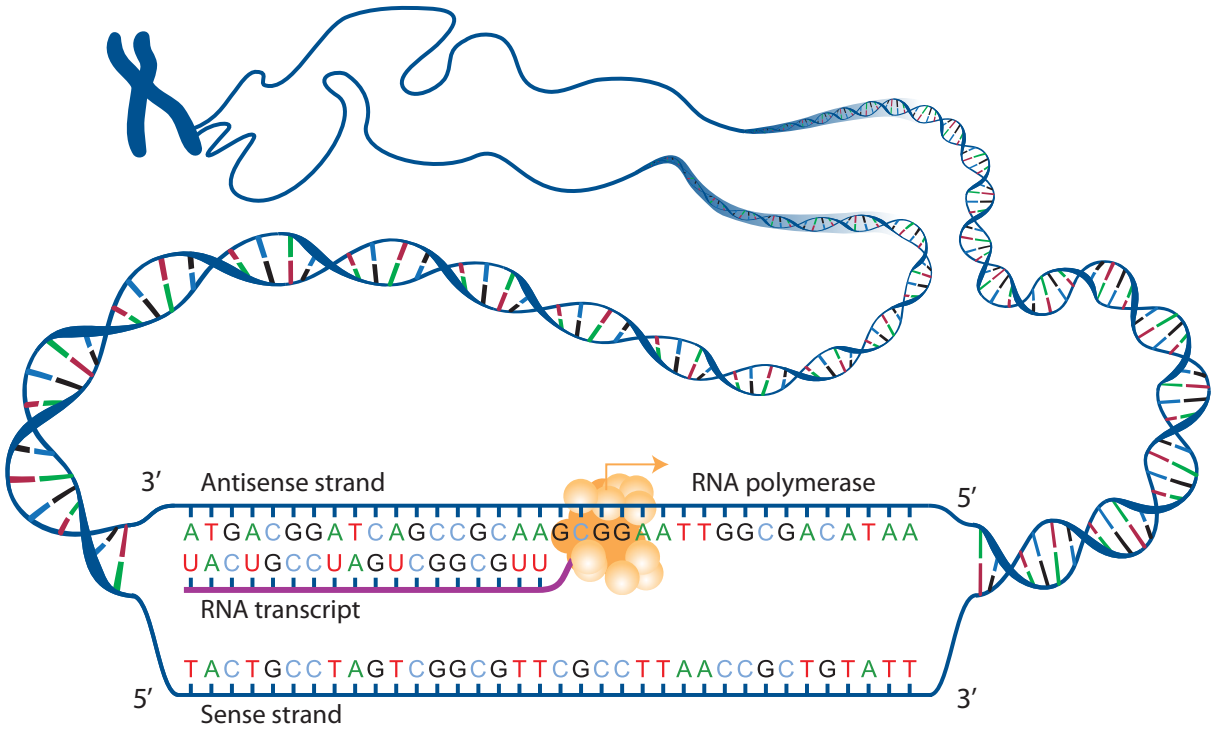


FIGURE 3–5. Transcription process. RNA polymerase promotes formation of messenger RNA transcript of DNA.

Source. Reprinted from National Human Genome Research Institute: Talking glossary of genetic terms. Available at: http://genome.gov/Glossary/index.cfm?id=197. Accessed April 10, 2010.

code for some of the amino acids. Alterations in the coding region that do not result in a change in the amino acid sequence are referred to as *synonymous.* Many polymorphisms do not result in illness, but some changes in DNA sequence can have profound pathologic consequences.

Epigenetic Factors

Although much of our understanding of individual differences has focused on changes in the genetic code itself, other factors play a role. As noted previously, epigenetic factors are inheritable changes in gene expression that are often caused by DNA methylation or changes in chromatin structure. Although it is possible to inherit these changes, the changes are potentially reversible. This can result in a situation in which two genotypes may be identical in content but be associated with different phenotypes because of alterations in the expression of the gene in question in one of the individuals.

Genetic Testing

The ability to detect polymorphisms, a necessary element of both linkage studies and genetic testing, is dependent on the sensitivity of the methods used to sequence and detect DNA. Direct testing of DNA base pair sequences is the most accurate method of gene sequencing and has become increasingly accessible through the use of polymerase chain reaction or Southern blot techniques (Micklos and Freyer 2003).

Linkage Studies and Linkage Disequilibrium

As the name implies, *linkage studies* seek to establish whether there is a connection or link between a particular identifiable marker (a polymorphic site for example) and a particular phenotype (e.g., development of a disease). Such studies rely on the physical proximity of known polymorphisms to unknown sequences that may contain disease genes. The closer together two loci are on a chromosome, the smaller the odds that recombination will occur between the sites. When there is essentially no distance between the two loci, they are always linked and crossover never occurs, a state known as *linkage disequilibrium.* It should be emphasized that the marker gene does not need to be the site of the functional change resulting in disease, although it can be. More importantly, the marker should be an identifiable polymorphism of DNA, which can be used to identify an individual's allelic inheritance and link it to a disease phenotype (Horwitz 2000; Micklos and Freyer 2003).

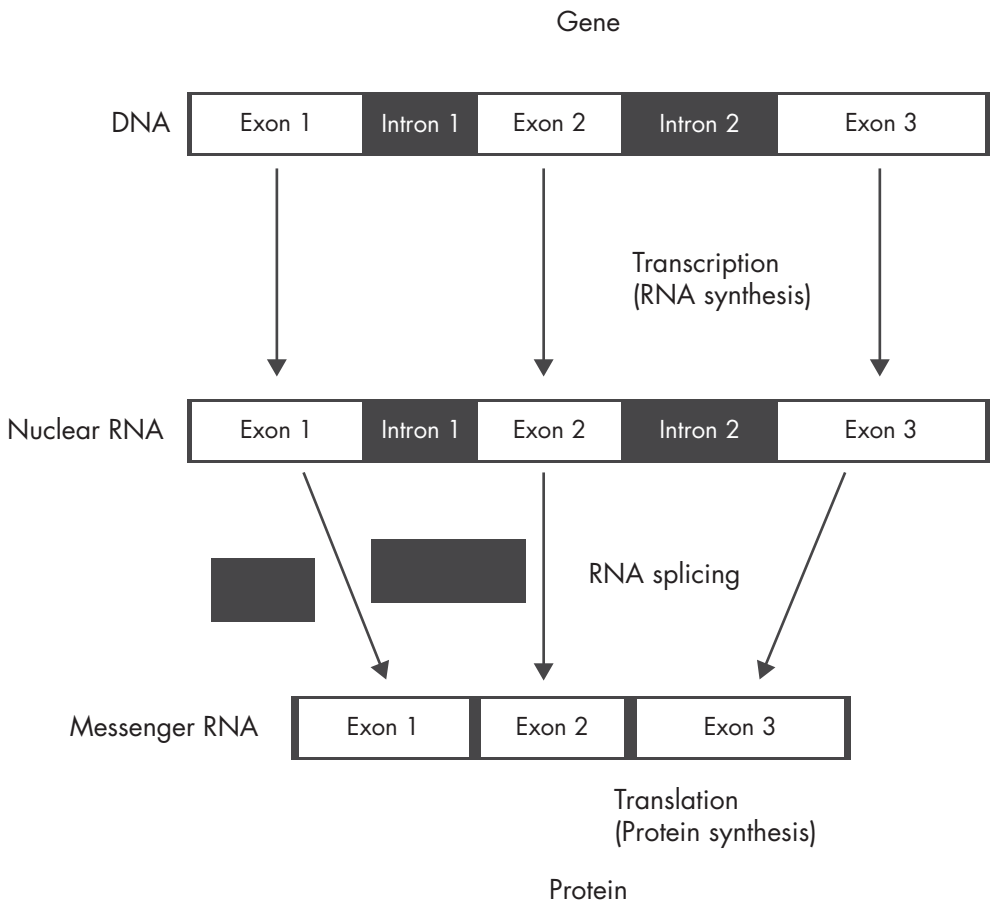


FIGURE 3–6. Diagram of a gene and the process of transcribing the gene into protein.

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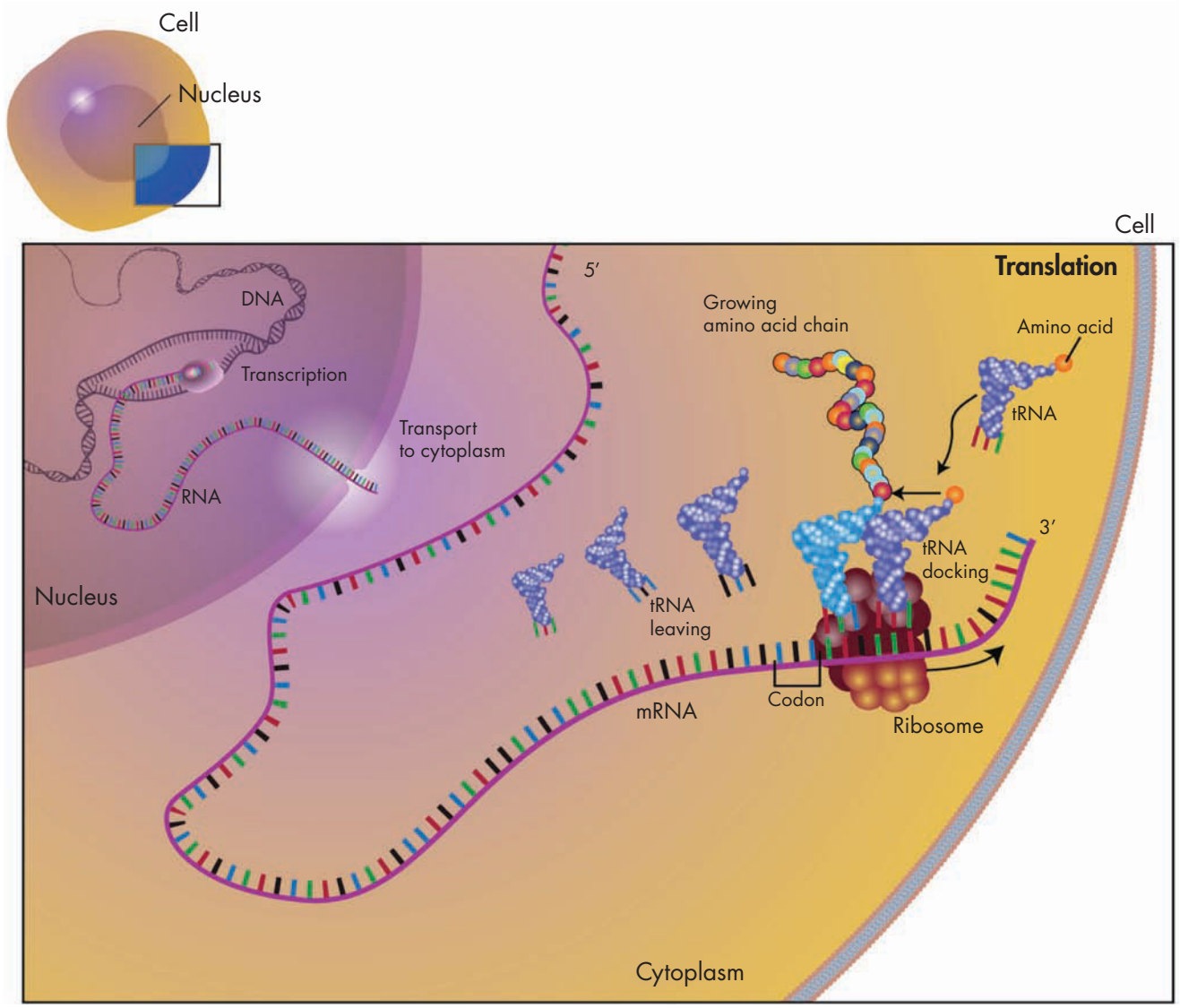


FIGURE 3–7. Translation of mRNA to protein.

Source. Reprinted from National Human Genome Research Institute: Talking glossary of genetic terms. Available at: http://genome.gov/Glossary/index.cfm?id=200. Accessed April 10, 2010.

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CHAPTER 4

Neuropsychiatric Assessment

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A TRAUMATIC BRAIN INJURY (TBI) IS A SIGNIFICANT event that may result in dramatic alterations in an individual's cognition, behavior, and emotions. The neuropsychiatric manifestations of such an injury depend on several factors: 1) preexisting variables such as the patient's personality and temperament before the injury, family psychiatric history, and previous psychiatric, medical, and neurological history; 2) the patient's psychosocial, economic, and vocational status at the time of injury; 3) the type, location, and severity of the brain injury; 4) the emotional and psychological responses of the individual to the TBI-mediated disturbances in cognition and behavior; 5) the impact of such changes on personal and professional roles and relationships, especially those involving the family; and 6) the interplay between TBI-related impairments and community barriers and supports. The multiple variables that result in neurobehavioral disturbances subsequent to TBI require a comprehensive and integrated approach to data collection, diagnostic formulation, and treatment planning.

Clinical Assessment: The Biopsychosocial Approach

A useful conceptual framework for a comprehensive neuropsychiatric assessment is the biopsychosocial model. The biopsychosocial model integrates clinical data from three interrelated domains: 1) biological disturbances in brain function; 2) emotional and psychological reactions to impairments in cognition and disturbances of behavior; and 3) disruptions of interpersonal relationships, family interactions, work capacities, and community participation. A comprehensive, integrated clinical assessment based on such a framework leads to the identification of specific problem areas, a multidimensional formulation of etiology, and development of specific treatment approaches.

History Related to the Brain Injury and Recovery Period

In their article "The Enigma of 'Hidden' Traumatic Brain Injury," Gordon et al. (1998) noted that TBI may be hidden in three senses: 1) the diffuse axonal injury of mild TBI is rarely detected by standard brain imaging techniques, 2) the effects of TBI are usually not obviously physical, and 3) individuals with TBI are often unaware that significant problems have occurred as a result of the injury. Because TBI is often "the invisible injury," the history of TBI may elude both the examiner and the patient; therefore, the clinician must specifically inquire about events that may be associated with TBI, such as motor vehicle accidents, falls, assaults, sports or recreational injuries, and blast injuries. With the advent of improvised explosive devices commonly used in contemporary warfare, TBI has become one of the most common injuries in wounded soldiers (see Chapter 26, Traumatic Brain Injury in the Context of War). Questions relevant to the neuropsychiatric assessment of the patient with TBI are shown in Table 4–1.

Once a history of TBI is obtained, it is useful to delineate the type, severity, and location of the injury and when it occurred. Several parameters are commonly used to ascertain the severity of injury, including the Glasgow Coma Scale (GCS), duration of loss of consciousness (LOC), and posttraumatic amnesia (PTA) (Table 4–2). Because the survivor of a TBI may not be able to reliably report whether he or she was rendered unconscious by the trauma, it is important to verify LOC with a witness or through medical record review, if possible. The survivor may believe that LOC occurred when, in actuality, he or she was conscious but in a state of PTA. Introduced by Teasdale and Jennett (1974), the GCS (see Table 1–1 in Chapter 1, Epidemiology) has become the most widely used measure of TBI severity. Estimating the severity of an acute TBI guides the

TABLE 4–1. Sample questions for traumatic brain injury (TBI) assessment

Questions	Rationale
Have you ever hit your head? Have you ever been in an accident? Have you ever been in or near an explosion?	Probe for car/motorcycle/bicycle/other motor vehicle accidents, falls, assaults, sports or recreational injuries, blast injuries
(If so) Did you black out, pass out, or lose consciousness?	Establish LOC (verify LOC with witness, if possible)
What is the last thing you remember before the injury?	Establish extent of retrograde amnesia
What is the first thing you recall after the injury?	Estimate duration of LOC and/or PTA (must ask when contiguous memory function returned to define PTA interval)
(If no known LOC) At the time of the injury, did you experience any change in your thinking or feel "dazed" or "confused"?	Establish change in mentation or level of consciousness
Did you suffer any other injuries during the incident?	Identify related injuries that may contribute to symptom presentation
What problems did you have after the injury?	Delineate post-TBI symptoms (see Table 4–5)
Has anyone told you that you're different since the injury? If so, how have you changed?	Detect problems outside survivor's awareness or those he or she may be minimizing
Did anyone witness or observe your injury?	Identify source of collateral history
Many people who have injured their head had been drinking or using drugs; how about you?	Offer survivor greater "permission" to admit substance use and determine if substances contributed to the altered mental status at the time of injury
Have you had any other injuries to your head or brain?	Identify previous TBIs that may increase morbidity from current injury

Note. LOC=loss of consciousness; PTA=posttraumatic amnesia.

clinician in quantifying the signs and symptoms associated with mild, moderate, or severe TBI as well as the patient's likely prognosis. According to Asikainen et al. (1998), the GCS score and duration of LOC and PTA all have strong predictive value in assessing functional or occupational outcome for TBI patients. Lovell et al. (1999) questioned the predictive value of LOC following mild TBI based on the lack of statistical correlation between LOC and neuropsychological functioning in a large sample of patients with mild head trauma. Sherer et al. (2008) described many of the strengths and limitations of GCS, LOC, and PTA with regard to predicting prognosis, recovery, and functional outcomes.

Establishing a history of moderate to severe TBI is relatively straightforward because lengthy periods of LOC and PTA are likely documented in medical records or can be reasonably ascertained from the report of the patient or family members. The immediate neurological impact of mild TBI, however, is frequently transient in nature. Alterations in mental status and clear neurological signs may be resolved by the time a patient is evaluated by emergency medical providers, thus resulting in the likely underidentification of mild TBI in health care settings. A history of mild TBI may also be easily overlooked when more overt medical problems (e.g., lacerations, musculoskeletal injuries) require immediate attention. In a study of emergency room diagnoses of mild TBI, Powell et al. (2008) found that research staff identified twice as many cases of likely mild TBI compared with medical providers. This discrepancy was attributed to the medical providers' apparent focus on ruling out more significant brain injuries and their reliance on computed tomography (CT) scan results. Research staff were instead trained to identify evidence of altered mental status through review of medical records and interviews with patients and bystanders.

Due to multiple factors that may confound the GCS, duration of LOC, and PTA (e.g., intoxication, hypovolemic shock, sedation, intubation, and facial injuries), other systems of classification are evolving. The Mayo classification system for traumatic brain injury severity, shown in Table 4–3 (Malec et al. 2007), strives to classify TBI using positive evidence available in the medical record rather than relying on potentially unreliable indicators and struggling with the meaning of missing documentation (i.e., if LOC was not documented, did it occur?). Malec and colleagues identified 1,678 TBI events in a sample of 1,501 residents in Olmsted County, Minnesota, between 1985 and 1999. GCS was not rated in 74%; LOC and PTA were either not present or not recorded in 70.2% and 58.1%, respectively. Head CT was not done in 49.3%. When comparing the Mayo system with single-indicator systems, GCS classified 433, PTA 704, and LOC 500 of the 1,678 confirmed cases, all of which were classified by the Mayo system. Thus, advantages of the Mayo system include classifying a larger number of TBI cases due to less reliance on documentation of GCS, PTA, and LOC and differentiating probable versus possible TBI among milder cases—an important distinction given that the vast majority of TBIs are mild and "postconcussive" symptoms are not specific to TBI. Unlike the GCS, PTA, and LOC, the Mayo system has yet to be evaluated for predicting outcomes after TBI.

Recognizing the importance of creating a classification system that links patterns of brain and neurovascular injury with appropriate therapeutic interventions, the National Institute of Neurological Disorders and Stroke, with support from the Brain Injury Association of America, the Defense and Veterans Brain Injury Center, and the National Institute of Disability and Rehabilitation Research, convened a workshop in October 2007 to outline the steps needed to accomplish this task (Saatman et al. 2008). Par-

TABLE 4–2. Classification of traumatic brain injury (TBI)

Type of TBI	Glasgow Coma Scale	Loss of consciousness	Posttraumatic amnesia
Mild	13–15	30 minutes or less (or none)	< 1 hour
Moderate	9–12	30 minutes to 24 hours	1–24 hours
Severe	≤8	> 24 hours	> 24 hours

Source. Rao and Lyketsos 2000.

TABLE 4–3. Mayo Traumatic Brain Injury (TBI) Severity Classification System

A. Classify as moderate-severe (definite) TBI if one or more of the following criteria apply:
   1. Death due to this TBI
   2. Loss of consciousness of 30 minutes or more
   3. Posttraumatic anterograde amnesia of 24 hours or more
   4. Worst Glasgow Coma Scale full score in first 24 hours <13 (unless invalidated upon review, e.g., attributable to intoxication, sedation, systemic shock)
   5. One or more of the following present:
      - Intracerebral hematoma
      - Subdural hematoma
      - Epidural hematoma
      - Cerebral contusion
      - Hemorrhagic contusion
      - Penetrating TBI (dura penetrated)
      - Subarachnoid hemorrhage
      - Brainstem injury

B. If none of Criteria A apply, classify as mild (probable) TBI if one or more of the following criteria apply:
   1. Loss of consciousness of momentary to less than 30 minutes
   2. Posttraumatic anterograde amnesia of momentary to less than 24 hours
   3. Depressed, basilar, or linear skull fracture (dura intact)

C. If none of Criteria A or B apply, classify as symptomatic (possible) TBI if one or more of the following symptoms are present:
   - Blurred vision
   - Confusion (mental state changes)
   - Dazed
   - Dizziness
   - Focal neurologic symptoms
   - Headache
   - Nausea

Source. Reprinted from Malec JF, Brown AW, Leibson CL, et al.: "The Mayo Classification System for Traumatic Brain Injury Severity." *Journal of Neurotrauma* 24:1417–1424, 2007. Used with permission.

ticipants agreed that preclinical models were vital in establishing pathophysiological mechanisms relevant to specific pathoanatomical types of TBI and verifying that a given therapeutic approach improves outcomes in these targeted TBI types.

A temporal relationship should be established between the onset of current signs and symptoms and the occurrence of the TBI. This information helps to differentiate the premorbid personality characteristics and psychiatric and behavioral symptoms from those arising after the brain injury. In cases of milder injuries, establishing a temporal relationship between the TBI and the onset or increase in severity of symptoms is especially important given the high base rates of many postconcussion symptoms (e.g., headaches, forgetfulness) in healthy individuals (Chan 2001; Lees-Haley and Brown 1993; Wong et al. 1994). Any number of emotional and behavioral difficulties that existed in milder form before the brain injury can be accentuated after it. Careful consideration of temporal relationships also must address the phase of recovery and associated behavioral changes, because improvement after TBI tends to occur along a continuum, with certain sequelae generally resolving before others (e.g., confusion and disorientation generally resolve before short-term memory impairment). The clinician should also focus attention on the patient's psychological reactions and adjustment to injury-induced cognitive and emotional changes, as well as their impact on interpersonal relationships, family dynamics, and employment status.

In assessing TBI, it is helpful to categorize observed signs and symptoms into the broad domains of cognition, emotion, behavior, and physical symptoms (Table 4–4). This permits more precise diagnosis of the patient's problems and assists in formulating an optimal treatment plan.

Importance of Collateral History

Because insight into disturbances of cognition, behavior, and emotional state is often compromised in patients with brain injury (Sherer et al. 1998), it is incumbent on the clinician to verify from collateral sources the accuracy of the patient's account of his or her history and symptomatology. In cases of severe TBI, patients rarely recall the incidents surrounding the injury. This disturbance in recall of the incident itself, in conjunction with the patient's decreased awareness of his or her deficits, makes accessing collateral information essential. Collateral history may be obtained from a variety of sources (Table 4–5), including family and friends who can describe changes in behavior, cognition, personality, and general level of functioning since the brain injury.

Collateral history is also pivotal because survivors of TBI and their families and friends see the injuries through different lenses. For example, Sbordone et al. (1998) found that patients with TBI generally underreported cognitive, behavioral, and emotional symptoms as compared with those reported by significant others, regardless of the severity of injury. For example, 58.8% of significant others in the study noted emotional lability or mood swings in the patients with TBI, whereas only 5.9% of the patients reported such difficulties. Circumstantiality was observed by 29.4% of significant others, but none of the patients reported such problems. In those with severe TBI, none of the patients recognized problems with judgment, whereas 45% of their significant others identified this problem.

TABLE 4–4. Traumatic brain injury symptom checklist

Cognitive	Emotional	Behavioral	Physical
Level of consciousness	Mood swings/lability	Impulsivity	Fatigue
Sensorium	Depression	Disinhibition	Weight change
Attention/concentration	Hypomania/mania	Anger dyscontrol	Sleep disturbance
Short-term memory	Anxiety	Inappropriate sexual behavior	Headache
Processing speed	Anger/irritability	Lack of initiative	Visual problems
Executive function (planning, abstract reasoning, problem solving, information processing, ability to attend to multiple stimuli, insight, judgment, etc.)	Apathy	Change in personality	Balance difficulties
Thought processes			Dizziness
			Coldness
			Change in hair/skin
			Seizures
			Spasticity
			Loss of urinary control
			Arthritic complaints

Source. Hibbard et al. 1998b.

TABLE 4–5. Sources of collateral history

People	Documents
Family	Police reports
Friends	Emergency medical service reports
Coworkers	Medical records
Witnesses to injury	Education history
Medical staff	Driving record
Allied health professionals (occupational, physical, and speech therapists, etc.)	

Hospital records related to the acute treatment of a TBI provide invaluable information about the traumatic event. This information includes the nature of the trauma (e.g., motor vehicle accident, fall, or blunt trauma); severity (GCS, period of unconsciousness, presence of traumatically related seizures, duration of retrograde amnesia and PTA, medical complications, and course of recovery); the types and dosages of medications administered immediately postinjury that may have affected the recovery course; the time of onset and types of neurobehavioral changes that occurred during the acute and postacute phases of recovery; and results of neuroimaging, electrophysiological, and neuropsychological testing delineating the location and extent of injury and pattern of cognitive and memory impairment associated with it. Medical and psychiatric records for the period before the trauma are also helpful in relating current signs and symptoms to past psychiatric disturbances and premorbid personality and can assist in ascertaining the relative contributions of antecedent variables, the brain injury itself, and current psychosocial parameters to observed neurobehavioral changes.

If available, posttrauma psychiatric and/or rehabilitation records help delineate the course of the patient's recovery, including the acute versus chronic nature of presenting psychiatric complaints, and provide a source of additional behavioral observations. Relevant posttrauma records also should be reviewed for the emergence of subsequent medical problems, results of neurodiagnostic studies, and indications of the efficacy and adverse effects of various treatment interventions the patient may have received. Additional sources of collateral information that may prove helpful include police reports and emergency medical service records (to provide information about the accident and condition of the patient at the scene), education records, and driving record (to provide a history of prior motor vehicle accidents).

Current Neuropsychiatric Symptoms

Within days of a mild to moderate TBI, the vast majority of patients experience headaches, fatigue, dizziness, decreased attention, memory disturbance, slowed speed of information processing, and distractibility (Levin et al. 1987; McLean et al. 1983). Other symptoms that frequently occur within the first few days after such an injury include hypersensitivity to noise and light, irritability, easy loss of temper, sleep disturbances, and anxiety (Binder 1986). These symptoms, which are often referred to as postconcussive symptoms, are described in more detail in Chapter 15, Mild Brain Injury.

Although there are some discrepancies in the results of available follow-up outcome studies, it is apparent that most patients experience substantial resolution of cognitive, somatic, and emotional symptoms within 1–6 months after a mild brain injury (Barth et al. 1983; Rimel et al. 1981). However, there is a significant subgroup of patients who continue to experience difficulties with reasoning, information processing, memory, vigilance, attention, depression, and anxiety (see Chapter 17, Cognitive Changes).

The symptom profile with moderate TBI is generally similar to that seen with mild TBI, but the frequency of

TABLE 4–6. Rancho Los Amigos Cognitive Scale

I	No response: Unresponsive to any stimulus
II	Generalized response: Limited, inconsistent, and nonpurposeful responses, often to pain only
III	Localized response: Purposeful responses; may follow simple commands; may focus on presented object
IV	Confused, agitated: Heightened state of activity; confusion and disorientation; aggressive behavior; unable to perform self-care; unaware of present events; agitation appears related to internal confusion
V	Confused, inappropriate: Nonagitated; appears alert; responds to commands; distractible; does not concentrate on task; agitated responses to external stimuli; verbally inappropriate; does not learn new information
VI	Confused, appropriate: Goal-directed behavior, needs cuing; can relearn old skills such as activities of daily living; severe memory problems, some awareness of self and others
VII	Automatic, appropriate: Appears appropriately oriented; frequently robotlike in daily routine; minimal or absent confusion; shallow recall; increased awareness of self and interaction in environment; lacks insight into condition; decreased judgment and problem solving; lacks realistic planning for future
VIII	Purposeful, appropriate: Alert and oriented; recalls and integrates past events; learns new activities and can continue without supervision; independent in home and living skills; capable of driving; defects in stress tolerance, judgment, and abstract reasoning persist; may function at reduced levels in society

Source. Reprinted, with slight modifications, from the Adult Brain Injury Service of the Rancho Los Amigos Medical Center, Downey, California. Used with permission.

symptoms is greater, and the symptoms tend to be more severe (Rimel et al. 1981). Severe TBI is associated with a large number of chronic neurobehavioral changes, acute as well as delayed in onset. Recovery from severe TBI is typically marked by a number of stages that can be documented using the Rancho Los Amigos Cognitive Scale (Table 4–6).

Severe TBI

A common sequence of stages has been identified in the recovery from severe TBI. It is important to note that not everyone follows this sequence. For example, one may reach a particular stage and fail to progress further, or one may demonstrate features of different stages simultaneously.

The first stage of recovery after a severe TBI is coma, which is characterized by LOC and unresponsiveness to the environment. A simple but useful measure of the depth of coma is the GCS. On emerging from deep coma, the patient enters the second stage of recovery, a state of unresponsive vigilance, marked by apparent gross wakefulness with eye tracking but without purposeful responsiveness to the environment. The third stage of recovery is characterized by mute responsiveness, in which there are no vocalizations but the patient responds to commands. Identification of this stage depends on demonstrating the patient's capacity to carry out simple commands that will not be confused with reflex activity and do not depend on intact language function, because the patient may have an aphasia or apraxia. Requesting that the patient carry out various eye movements is often the best task to use, and the movements can range from simple to complex (Alexander 1982). The next phase of recovery is characterized by the return of speech and language function. During this stage, the patient begins to demonstrate a confusional state akin to delirium, as indicated by fluctuating attention and concentration and an incoherent stream of thought (see Chapter 9, Delirium and Posttraumatic Confusion). The confused or delirious patient usually displays distractibility, perseveration, and a disturbance in the usual sleep-wake cycle. Such patients may become agitated and demonstrate increased psychomotor activity. This stage is also frequently associated with sensory misperceptions, hallucinations, confabulation, and denial of illness (Alexander 1982).

During the stage of confusion, the patient is not able to form new memories in a normal fashion and is disoriented. This stage is the period when posttraumatic anterograde amnesia is prominent. PTA is considered to be present until the patient is consistently oriented and can recall particulars of his or her environment in a consistent manner. Emergence from PTA may be erroneously assumed when the patient first begins to recall one or two very salient or recurrent recent events. Evidence that the patient is continuously encoding new episodic memories, however, is the hallmark in determining the resolution of PTA. The duration of PTA can be assessed with the Galveston Orientation and Amnesia Test (GOAT) (Levin et al. 1979a, 1979b) (see Figure 8–1 in Chapter 8, Neuropsychological Assessment), which monitors both the degree of orientation and recall of newly learned material. The length of PTA is one of the best indicators of the severity of injury and is a clinically useful predictor of outcome. Furthermore, the length of PTA may correlate with the occurrence of psychiatric and behavioral sequelae.

When the stage characterized by PTA resolves, attention and concentration improve, confabulation lessens, and the sleep-wake cycle normalizes, although problems often persist with daytime fatigue and insomnia. These changes mark a major transition from the acute to the subacute and chronic phases of recovery. This transition phase is characterized by persistent, though less severe, disturbances in attention, concentration, memory impairments, and limited awareness of the presence of other disturbances of cognitive function. Some patients also experience retrograde amnesia, which shrinks rapidly and is usually relatively short in duration.

As the chronic phase of recovery unfolds, changes in personality, behavior, and emotions may emerge and be superimposed on the cognitive disturbances. Many patients with severe TBI complain of forgetfulness, irritability, slowness, poor concentration, fatigue, and dizziness, in addition to headache, mood lability, apathy, depressed mood, and anxiety (Hinkeldey and Corrigan 1990; Thomsen 1984; Van Zomeren and Van Den Burg 1985).

TABLE 4–7. Traumatic brain injury (TBI)–related DSM-IV-TR disorders

TBI sequelae	DSM-IV-TR disorders
Posttraumatic amnesia	Delirium due to TBI (293.0)
Persistent global cognitive impairments in context of intact sensorium (after resolution of posttraumatic amnesia)	Dementia due to TBI, with or without behavioral disturbance (294.11 and 294.10, respectively)
"Postconcussive" syndrome	Cognitive disorder not otherwise specified (294.9) (research criteria specific for "postconcussional disorder" in Appendix B)
Isolated impairment of memory	Amnestic disorder due to head trauma (294.0)
Changes in personality	Personality change (apathetic, disinhibited, labile, aggressive, paranoid, other, combined, unspecified) due to TBI (310.1)
Persistent hallucinations, delusions	Psychotic disorder (with delusions or hallucinations) due to TBI (293.81 and 293.82, respectively)
Persistent depression, mania	Mood disorder (with depressive, major depressive-like, manic, or mixed features) due to TBI (293.83)
Persistent anxiety symptoms	Anxiety disorder (with generalized anxiety, panic attacks, or obsessive-compulsive symptoms) due to TBI (293.84)
Impaired libido, arousal, erectile dysfunction, anorgasmia, etc.	Sexual dysfunction due to TBI: female or male hypoactive sexual desire (625.8 and 608.89, respectively); male erectile disorder (607.84); other female or male sexual dysfunction (625.8 and 608.89, respectively)
Insomnia, reversal of sleep-wake cycle, daytime fatigue, etc.	Sleep disorder due to TBI (780.xx): insomnia type (.52); hypersomnia type (.54); parasomnia type (.59); mixed type (.59)

Source. American Psychiatric Association 2000.

Signs and Symptoms After TBI

The patterns of signs and symptoms that may occur after a TBI of any severity are, in part, related to the type of neurological injury (diffuse or focal) and its anatomical location. Recent literature suggests that diffuse axonal injury produces impairments in multiple cognitive domains (e.g., memory, executive function, attention, and psychomotor speed) and that the integrity of white matter, rather than the total burden of white matter lesions, accounts for the overall degree of neuropsychological impairment. In a study of severely injured patients with magnetic resonance imaging lesion patterns indicative of diffuse axonal injury, Scheid et al. (2006) found persistent global cognitive impairment but failed to identify a clear association between total white matter lesions and degree of cognitive impairment. Application of a relatively new magnetic resonance technique, diffusion tensor imaging, has helped to clarify this apparent inconsistency through measurement of axonal integrity. Kraus et al. (2007) demonstrated the strength of this imaging tool in predicting the positive correlation between the amount of cognitive impairment and degree of white matter integrity.

Symptoms after TBI are often linked to lobar or regional areas of the brain (frontal lobe syndromes or temporal lobe syndromes). Although such models lend convenience and order to the understanding of the sequelae of TBI, they may be too simplistic because individuals often present with symptoms from several regions. Neuropsychiatric symptoms may be more closely linked to circuits that connect a number of lobes and regions involved in similar functions. See Chapter 17, Cognitive Changes, for a more detailed discussion of various brain-behavior relationships.

Some of the signs and symptoms of TBI result from the patient's emotional and psychological responses to having experienced a TBI and having to deal with its negative interpersonal and social consequences. Patients with TBI may experience frustration, anxiety, anger, depression, irritability, isolation, withdrawal, and denial in response to the losses they have experienced. The array of psychiatric and behavioral symptoms demonstrated by patients with TBI do not always cluster in a syndromically defined fashion, nor do they always allow for a specific diagnosis based on DSM-IV-TR criteria (American Psychiatric Association 2000). Table 4–7 shows common DSM-IV-TR diagnoses used in TBI-related neuropsychiatric sequelae.

According to several studies, TBI appears to be a risk factor for a number of psychiatric disorders, including major depression, dysthymia, obsessive-compulsive disorder, phobias, panic disorder, alcohol or substance abuse/dependence, bipolar disorder, schizophrenia, and personality disorders (Hibbard et al. 1998a, 2000; Jorge et al. 2004; Koponen et al. 2002; Ponsford et al. 2007; Silver et al. 2001), although the incidence of bipolar disorder and schizophrenia after TBI is much less frequent than depression and certain anxiety disorders. Given the significant burden of both Axis I and II pathology, it is not surprising that those patients with TBI have a greater lifetime prevalence of suicide attempts (nearly four times that of individuals without a history of TBI) and poorer quality of life, according to Silver et al. (2001). For more detailed information about psychiatric disorders commonly seen after TBI, see Chapters 9–16 in this volume.

Neurological Symptoms

Brain injuries cause a number of subtle as well as gross neurological disturbances, including visual and sensory

TABLE 4–8. Neurological examination after traumatic brain injury: key areas of assessment

Sensory	Motor	Other
Vision (look for field cuts)	Strength, tone, gait (rule out ataxia)	Aphasia, confabulation, perseveration
Smell (rule out anosmia)	Fine motor movements, speed, coordination (observe for tremor)	Seizures
Recognition (rule out agnosia)	Motor imitation (rule out apraxia)	Frontal release signs
	Reflexes	

TABLE 4–9. Common endocrine disturbances after traumatic brain injury

Hypo/hyperthyroidism
Impaired growth hormone release
Impaired adrenal cortical function
Hypopituitarism
Hypothalamic hypogonadism
Precocious puberty
Hyperphagia
Temperature dysregulation
Syndrome of inappropriate antidiuretic hormone
Diabetes insipidus
Menstrual irregularities
Changes in sexual function

disturbances, motor dysfunction, ataxias, tremor, aphasias, apraxias, and seizures. Inquiring about neurological symptoms and performing a careful neurological examination may shed light on the nature and extent of brain injury and associated focal neurological dysfunction. However, it is important to note that the neurological examination may be entirely normal despite the presence of a TBI because the examination focuses primarily on sensorimotor function.

The neurological examination (Table 4–8) should assess various aspects of motor function, such as strength, tone, gait, cerebellar function (ataxia), fine motor movements (speed and coordination), motor imitation, and reflexes. Vision should be tested to identify any field cuts or diminished acuity. Sensory function, including the sense of smell, should also be examined. Although infrequently detected, anosmia (the impairment of the sense of smell) is a common sequela of TBI often associated with negative functional outcomes related to orbitofrontal damage and executive function deficits (Callahan and Hinkebein 1999). Because the olfactory nerves are located in close proximity to the orbitofrontal cortex, anosmia may serve as a marker for frontal lobe deficits. Frontal lobe damage or dysfunction may also be indicated by the presence of frontal release signs, including the grasp reflex, glabellar blink reflex (Meyerson's sign), Hoffmann's sign, palmomental reflex, and suck, snout, and rooting reflexes. For additional information about seizures, headaches, dizziness, and other neurological sequelae of TBI, see Chapters 16, 21, and 22 in this volume.

Endocrine Symptoms

Endocrine disturbances may be seen subsequent to TBI (Table 4–9). According to a review by Rothman et al. (2007), neuroendocrine dysfunction after TBI is underdiagnosed, undertreated, and may adversely affect the rate of recovery. The authors noted that up to two-thirds of persons with TBI incur single or multiple pituitary-target hormone disruption, most commonly affecting the gonadal and growth hormone axes. Regarding the mechanisms of endocrine dysfunction, Rothman and colleagues identified direct mechanical injury (shear-strain damage), cytotoxic processes, or both to the central nervous system (CNS) components of the hypothalamic-pituitary-target organ axes. Compression and occlusion of the hypophysial blood vessels due to brain swelling and edema may also indirectly lead to pituitary lobe infarction (Acerini and Tasker 2008). Abnormalities in gonadotropin, adrenal cortical function, growth hormone, thyroid function, gonadal function, and hyperprolactinemia have all been previously described (for reviews, see Acerini and Tasker 2008; Behan et al. 2008). Complaints of feeling cold, without actual alteration in body temperature, may also be seen (Silver and Anderson 1999). Early hormonal alterations are not generally associated with long-term hypopituitarism, which has been noted frequently only in severe cases of TBI (Klose et al. 2007). However, analysis of a 1994 international survey of 8,500 patients with growth hormone deficiency (GHD) indicated that individuals with TBI were more than 4 cm shorter than controls and experienced significant delays in diagnosis and treatment as well as a reduction in pituitary growth hormone reserve (Casanueva et al. 2005). Because the extent of resolution of endocrine disturbances is highly variable, detection and treatment of hormonal imbalances may have a significant impact on recovery and may ease management of neurobehavioral problems after TBI.

History Before the Injury

Psychiatric Disorders

Although many neurobehavioral disturbances appear to result directly from damage to the brain, the contributions of premorbid personality features, temperament, and antecedent psychiatric disturbances are also important in determining the nature of post-TBI psychiatric and behavioral syndromes, particularly in patients with mild to moderate brain injuries. In a review of mild TBI, Kibby and Long (1996) noted several preinjury factors that influence recovery: alcohol abuse, age, level of education, occupation, personality, emotional adjustment, and neuropsychiatric history (see Table 4–10). Premorbid anxiety, depression, psychosis, personality disorder, attention-deficit/hyperactivity disorder, and alcohol and/or substance abuse may significantly influence recovery from TBI. Individuals with certain personality disorders

(antisocial and obsessive-compulsive) may experience greater post-TBI adjustment issues (Hibbard et al. 2000). Max et al. (1997) found that preinjury psychiatric history along with severity of injury and preinjury family function predicted the development of "novel" psychiatric disorders in children and adolescents during the second year postinjury. The presence of mental retardation or learning disabilities also may influence the presentation of TBI-associated neurobehavioral disturbances.

Neurobehavioral changes after recovery from TBI result from the interplay of temperament, underlying personality traits, premorbid coping mechanisms, TBI-induced alterations in brain function, and injury-related losses and psychosocial stressors. Because all of these factors may influence outcome, all must be carefully assessed in the development of a clinical database. Many recent studies of patients with TBI do not include patients with previous psychiatric disorders or substance abuse. However, clinical experience indicates that premorbid personality traits, whether normal or pathological, are often exaggerated after TBI, possibly due to damage to inhibitory frontal lobe circuits.

TABLE 4–10. Preinjury factors that can influence recovery

Alcohol abuse
Age
Level of education
Occupation
Personality
Emotional adjustment
Psychiatric illness
Learning disability
Mental retardation
Level of family functioning

Source. Kibby and Long 1996; Max et al. 1997.

Drug and Alcohol Abuse

Alcohol use is estimated to be a contributing factor in at least 50% of all TBIs (Sparadeo et al. 1990). Among TBI patients with positive blood alcohol levels at the time of evaluation in the emergency department, 29%–56% were legally intoxicated (Sparadeo et al. 1990; Vickery et al. 2008). Alcohol and some substances may artificially lower GCS scores due to their sedative effects. However, Sperry et al. (2006) suggested that this association of alcohol lowering the GCS scores may not apply in blunt head trauma; thus, caution should be exercised in attributing lowering of GCS scores after blunt trauma to alcohol as this might delay lifesaving monitoring and interventions.

Detecting pre- and postinjury substance use and abuse is important in assessing current levels of functioning, prognosis for recovery, and perhaps most important, treatment planning that addresses the substance abuse problem. The reasons for this are many. First, alcohol use at the time of injury is associated with a more complicated recovery, as indicated by longer hospitalization, longer periods of agitation, and more impaired cognitive function on discharge (Sparadeo et al. 1990). Second, there is evidence that suggests a compounding effect of substance use on neuropsychological outcomes of TBI, with higher blood alcohol levels at the time of injury being associated with poorer verbal learning and memory function, poorer general memory, decreased attention/concentration, poorer delayed recall, and decreased mental processing speed (Bombardier and Thurber 1998; Brooks et al. 1989; Kelly et al. 1997). Third, continued excessive use of alcohol in TBI patients may further compromise their functional capacities, interfere with their rehabilitation, and place them at greater risk for subsequent TBIs (Strauss and Sparadeo 1988).

When screening for substance use in the TBI population, Fuller et al. (1994) found that the CAGE questionnaire and the Brief Michigan Alcohol Screening Test (reproduced as Figures 30–1 and 30–2 in Chapter 30, Alcohol and Drug Disorders) are easy to administer, sensitive, and specific for substance abuse in this population. Although not studied specifically in the TBI population, the Alcohol Use Disorders Identification Test, consumption questions (AUDIT-C), is commonly used to screen for alcohol abuse and is especially effective in detecting binge drinking. Arenth et al. (2001) found that when comparing blood alcohol levels at the time of injury with the Substance Abuse Subtle Screening Inventory–3 (SASSI-3), the two measures showed comparable diagnostic accuracy for alcohol abuse, but blood alcohol level was more specific while the SASSI-3 was more sensitive. Ashman et al. (2004) compared the CAGE questionnaire with the SASSI-3 for the detection of alcohol abuse and suggested the CAGE questionnaire may be preferable for alcohol abuse screening, whereas the SASSI-3 face-valid drug subscale may be preferable for drug abuse screening for individuals with TBI. For more details about substance use and TBI, refer to Chapter 30, Alcohol and Drug Disorders.

Medical History

A thorough medical history and a careful review of systems are important parts of the neuropsychiatric evaluation. Detailed knowledge of prior as well as current medical problems, both related and unrelated to the brain injury, allows the clinician to assess their impact on the patient's overall neurobehavioral status and to take them into account in making recommendations for safe and appropriate treatments. Any history of early childhood illnesses, particularly seizure disorders, previous TBIs, and/or attention-deficit/hyperactivity disorder, should be sought. A history of prior TBIs has been associated with a subsequent increased incidence of moderate TBI (Rimel et al. 1981), a longer duration of postconcussive symptoms (Carlsson et al. 1987), and a poorer overall outcome (Levin 1989). TBI patients who eventually develop dementia are more likely to have had multiple previous brain injuries, alcoholism, and atherosclerosis (Gualtieri 1991). Assessments of developmental milestones and previous levels of cognitive, intellectual, and attentional functioning also provide the clinician with valuable baseline information against which to compare postinjury cognitive capabilities and coping strategies.

A detailed history of preinjury, idiopathic, or posttraumatic seizure disorders and associated treatment is important in understanding the impact of seizures and anticonvulsants on current cognitive and behavioral functioning. Detailed knowledge of seizure disorders and their current treatment is particularly important to the clinician in choosing safe and efficacious psychotropic medications.

Medications

Obtaining a thorough history of past treatment trials with psychotropic drugs, as well as the current types and doses of such medications and their efficacy, is important in establishing the value of previous drug trials, the responsiveness of current neurobehavioral symptoms to medications, and the potential efficacy of pharmacotherapy in maintaining or enhancing current levels of functioning. Psychotropic agents, anticonvulsants, and many other kinds of medication can have important effects on cognition and behavior, and their contributions to the patient's current neurobehavioral status must be ascertained. Benzodiazepines can impair memory and interfere with coordination. Anticholinergic drugs can increase confusion. If a patient is being treated with anticonvulsants, the clinician needs to determine whether this is for prophylaxis (and the patient never had a seizure or had seizures only immediately after the TBI) or for a continuing seizure disorder. Patients treated with anticonvulsants for prophylaxis beyond 1 week may have sedating and cognition-impairing side effects without any actual seizure prophylaxis. A careful review of the patient's medication history should also reveal any drug allergies or drug intolerances.

Family Psychiatric and Medical History

Knowledge of the family psychiatric and medical history can help in differentiating the increased risk of psychiatric disturbance due to genetic predisposition from that due to current psychosocial stressors or the TBI itself. Familiarity with the family history of psychiatric disturbances, medical illness, deaths, and their causes can provide a better understanding of the possible role these factors may be playing in current abnormalities of emotional and psychological functioning in a TBI patient.

Social History

Social history encompasses information about 1) family structure and other support systems; 2) social, school, occupational, and recreational functioning; 3) legal problems; and 4) personal habits. The social history describes the patient's level of current functioning, the nature and severity of psychosocial stressors, characteristic patterns of adaptation to stress, and the adequacy of coping mechanisms and social support systems. Psychopathological reactions may result from severe stresses associated with the losses and disruptions in an individual's life that can be caused by a TBI.

TABLE 4–11. Symptoms reported by family members of patients with severe brain injury

	% Reporting	
Reported symptom	Mother	Wife
Frustration	100	84
Irritability	55	74
Annoyance	55	68
Depression	45	79
Decreased social contact	27	77
Anger	45	63
Financial insecurity	18	58
Guilt	18	47
Feeling trapped	45	42

Source. Mauss-Clum and Ryan 1981.

TBI often has an enormous impact on the patient's family (see Chapter 31, The Family System) (Kreutzer et al. 1994; Mauss-Clum and Ryan 1981; Verhaeghe et al. 2005), as illustrated by the high frequency of psychiatric symptoms reported by family members of patients with TBI (Table 4–11). In turn, there is evidence that unhealthy family functioning can slow progress in recovery following TBI (Sander et al. 2002). The clinician must assess the level of distress experienced by the family in a sensitive manner and should attempt to understand the quality of the relationships between the TBI patient and his or her spouse, children, parents, and siblings. Understanding the nature of the stresses on the family and the family's concerns about the TBI patient enables the clinician to make appropriate referrals for family and/or couples therapy. In addition to the clinical interview, a number of self-report instruments, rater-administered scales, and semistructured interviews have proved effective in monitoring family functions and adaptation over time (Winstanley et al. 2006).

Because of the frequent interruption in social relationships and subsequent loneliness encountered by persons with TBI, it is important to evaluate the patient's level of social integration postinjury. Patients with severe TBI have the greatest difficulty establishing new social contacts and pursuing leisure activities (Morton and Wehman 1995).

School Functioning

Children and adolescents with TBI may experience disturbances in cognition and behavior that interfere with school functioning (see Chapter 28, Children and Adolescents). Formal assessment of cognition, behavior, academic functioning, and interpersonal skills are necessary to facilitate successful reentry into academic setting following TBI. Evaluation should include direct observation and parent-teacher report because office-based data assessment procedures may not elicit important cognitive and behavioral limitations. Periodic reassessments thereafter are helpful in adjusting continuing intervention programs to achieve optimal academic functioning, especially because executive

skills may continue to worsen or new impairments may appear as the child passes through subsequent developmental stages (Fay et al. 2009; Ylvisaker et al. 2005). Any child or adolescent presenting for evaluation of behavioral problems should be queried specifically about previous TBI, particularly when disturbances in attention or memory function, impulsive or aggressive behavior, mood lability, or impaired social skills are evident (Obrzut and Hynd 1987).

Occupational Functioning

TBI often has a significant impact on the ability of a patient to maintain gainful employment. A number of studies have investigated the percentage of TBI patients returning to work, and the reported rates vary from 12% to 87.5% (Shames et al. 2007). These authors suggested that the reasons for this wide degree of variability include the broad range of severity of the TBI patients sampled, the absence of uniform criteria for defining return to work, the lack of verification of actual work performance and occupational status, and the variability in follow-up intervals. The results of a multicenter study including 1,341 patients with moderate to severe TBI also suggest that the rate of successful return to work varies significantly by occupational classification (Walker et al. 2006). Specifically, 56% of patients with professional/managerial positions prior to their injury successfully returned to work 1 year postinjury, whereas only 40% of those with skilled positions and 32% of those with manual labor jobs were successful in their return to work.

According to a review by Kibby and Long (1996), approximately 90% of patients with mild TBI and 80% with moderate TBI return to work by 1 year after the injury. The majority of individuals with mild TBI return to work by 3 months postinjury. Factors possibly adversely affecting return to work include older age, lower levels of motivation to work, lower levels of education, poor social support, or poor coping strategies.

Ben Yishay et al. (1987) cited a study of four comparable groups of 30–50 TBI patients with moderate to severe brain injury who had received extensive rehabilitation and were considered ready for vocational assessment and placement. When followed over time, less than 3% of the patients were able to achieve and maintain competitive employment for as long as 1 year. The high failure rate was attributed to cognitive impairments (deficits in attention, memory, and executive functioning complicated by distractibility and behavioral impersistence), problems with apathy and disinhibition, impaired interpersonal skills, lack of awareness and appreciation of the impact of the injury on functioning, and unrealistic expectations concerning the suitability of various types of employment. Clinicians can target these specific areas in an attempt to facilitate the patient's return to work by using a variety of modalities, including psychotropic medications, supportive psychotherapy, cognitive remediation, and vocational and occupational rehabilitation.

Physical Examination

Although history is the most critical source of information in diagnosing TBI, physical examination is also important, with particular emphasis on the neurological examination. Patients with moderate to severe TBI may have mental status and Mini-Mental State Examination (MMSE) abnormalities as well as focal neurological findings that reflect the location and severity of the injury. However, because the majority of TBIs are mild, the neurological examination is nonfocal and the MMSE normal in most TBI patients. Frontal release signs may be elicited in TBI patients who have no focal findings.

Mental Status Examination and "Bedside" Cognitive Testing

Mental status and MMSE testing should always be carried out as part of a neuropsychiatric evaluation, keeping in mind that both may be relatively normal, particularly when deficits due to the TBI are subtle and involve frontal lobe functions. Although neuropsychological testing provides the most comprehensive "map" of the injury and its sequelae, the clinician may administer a few simple tests in the office or at the beside to evaluate frontal lobe functions (see Table 4–12). The Frontal Assessment Battery, a 10-minute measure of conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy, has also been shown to correlate highly with more extensive measures of cognitive and executive skills (Dubois et al. 2000).

Rating Scales Assessing Cognitive, Emotional, and Behavioral Function

There are numerous rating scales that can be used to quantify various aspects of cognition, memory function, emotion, and behavior (see other chapters for specific scales for depression, mania, aggression, delirium, agitation, and others). Several rating scales have particular utility in evaluating behavior and cognition during the various phases of recovery from TBI.

In the assessment of coma, the GCS described earlier (see Table 1–1 in Chapter 1) is one of the most useful instruments for monitoring changes in levels of consciousness and the patient's emergence from coma. The GCS assesses eye movements, motor coordination, and verbal responses. The GCS severity index scores range from 3 to 15, with scores of 3–8 indicating severe injury, 9–12 moderate injury, and 13–15 mild injury.

Because of the difficulty in assessing severely injured patients as they progress through the early stages of recovery, the Western Neurosensory Stimulation Profile was developed (Ansell and Keenan 1989). The profile assesses arousal/attention, expressive communication, and sensory response to auditory, visual, tactile, and olfactory stimulation. This instrument is particularly useful for monitoring and predicting change in slow-to-recover patients who remain at Rancho levels II and III for extended periods of time.

TABLE 4–12. "Bedside" evaluation of frontal lobe function

Test	Description	Frequent findings
Clock drawing test	Instruct the patient to draw a clock, including all of the numbers, setting the time at 10 past 11 (provide all instructions first, and then allow the patient to begin)	Poor planning (numbers inappropriately positioned; numbers do not fit inside clock; excess space inside clock, perseveration, etc.) Incorrect hand placement: hour and minute hands inappropriately placed; "stimulus-bound" (hands connecting 10 and 11), perseveration, etc.
Verbal fluency	Ask the patient to list number of words that begin with the same letter or number of animals named in 1 minute	Unable to name 10 or more words Perseveration
Set shifts and sequencing (verbal and written)	Verbal: ask the patient to continue the pattern 1A-2B-3C Written: ask the patient to connect numbers and letters in a sequential and alternating manner (1A-2B-3C, etc.)	Perseveration Inability to consistently shift sets (e.g., 1A-2B-3C-4C-5C-6C, etc., or 1A-2B-3C-3D-3E-3F, etc.)
"Fist-palm-side"	Ask the patient to place his or her right fist into left palm, the right palm into left palm, and then right side of hand into left palm in a sequential manner	Perseveration of movement
"Go-No Go" test	Ask the patient to say "two" when one finger is held up; "one" when two fingers are displayed	Inability to inhibit the visual stimulus (says "one" when one finger is displayed)

After emergence from coma, the GOAT (see Figure 8–1 in Chapter 8, Neuropsychological Assessment) can be used to follow the course of improvement in PTA and establish the end of this period (Levin et al. 1979a). The GOAT is a 10-item, rater-administered questionnaire that assesses orientation to person, place, and time and recall of events before and after the injury. The score is calculated by subtracting error points from 100. A score of 65 or less is considered abnormal, whereas borderline abnormal scores range from 65 to 75 (Levin et al. 1979a, 1979b). GOAT scores correlate with the severity of injury, and because this test provides an assessment of the duration of PTA, it is helpful in predicting long-term outcome. The previously mentioned Rancho Los Amigos Cognitive Scale (Table 4–6) is also a useful tool in tracking cognitive and behavioral recovery during PTA. Careful assessment of functional independence in activities of daily living is essential for treatment planning and monitoring progress as patients recover from moderate to severe TBI. The Functional Independence Measure (FIM) is a highly standardized measure of independence in daily living activities that takes into account the impact of both motor and cognitive limitations (Granger 1998). In addition to the usefulness of the FIM in treatment planning, performance on this measure is predictive of many clinically meaningful variables including length of stay and level of functioning at discharge. Attempts to add items to the FIM to reduce ceiling effects (i.e., to make the FIM sensitive to change in functioning after discharge into the community) have met with limited success (Hall et al. 1996).

Although many assessment instruments used in the acute recovery period focus on cognitive impairment, it is also important to assess changes in affect. In a study of 42 moderately to severely brain-injured people, cognitive and affective disturbances were measured during the first 60 days after injury with the Barrow Neurological Institute (BNI) Screen for Higher Cerebral Functions (Borgaro and Prigatano 2002). The BNI screen may be administered in 10–25 minutes. There are seven subtests addressing speech/language, orientation, attention/concentration, visuospatial abilities, learning/memory, affect (expressing happy vs. angry tones of voice, perceiving facial affect, controlling affect, and demonstrating spontaneous affect), and awareness versus performance (the difference between predicted and actual performance on a memory task). The greatest difficulties demonstrated by TBI patients compared with the control group were in memory, awareness, and affect. Teaching patients to improve self-awareness and helping them perceive and generate affect may produce better outcomes than utilizing standard cognitive rehabilitation protocols.

As the period of PTA ends, the patient enters the chronic phase of recovery, in which assessment of TBI-related neurobehavioral and neurocognitive changes becomes especially important. Another comprehensive tool that identifies a broad spectrum of TBI-related symptoms and behaviors is the Neurobehavioral Functioning Inventory (NFI) (Kreutzer et al. 1996). The NFI collects information via self-report from the person with TBI and the family. Because the inventory content is the same for both inquiries, this instrument also permits a comparison of symptom recognition between the injured person and his or her family. The inventory provides information about problems in daily living, such as misplacing things, losing track of time, missing appointments, forgetting phone numbers, and having difficulty with word finding. Emotional and behavioral issues are also assessed, such as breaking or throwing things, feeling hopeless, arguing, and threatening others. The NFI may be completed in 30 minutes or less and assesses 76 items in six scales: depression, somatic, memory/attention, communication, aggression, and motor. It is effective for initial assessment as well as serial evaluations to measure changes over time.

The Mayo Portland Adaptability Inventory–4 (MPAI-4) is similar in design to the NFI in that data can be collected from various sources including the patient, family, and

TABLE 4–13. Mayo Portland Adaptability Inventory–4 (MPAI-4) indexes and item content

Ability Index	Adjustment Index	Participation Index
Mobility	Anxiety	Initiation
Use of hands	Depression	Social contact
Vision	Irritability, anger, aggression	Leisure and recreational activities
Audition	Pain and headache	Self-care
Dizziness	Fatigue	Residence (i.e., homemaking)
Motor speech	Sensitivity to mild symptoms	Transportation
Verbal communication	Inappropriate social interaction	Paid employment
Nonverbal communication	Impaired self-awareness	Other employment
Attention/concentration	Family/significant relationships	Managing money and finances
Memory		
Fund of information		
Novel problem solving		
Visuospatial abilities		

Source. Adapted from Malec JF, Lezak MD: "Manual For Mayo-Portland Adaptability Inventory (MPAI-4) for Adults, Children and Adolescents." http://www.tbims.org/combi/mpai/index.html, 2008.

clinicians (Malec and Lezak 2008). The 35-item MPAI-4 has undergone rigorous psychometric development, and explicit rater instructions are available to help improve ease of administration and rater reliability. This scale was designed specifically to measure outcomes relevant to patients in the postacute stage of recovery following TBI. The MPAI-4 consists of three scales (Ability Index, Adjustment Index, and Participation Index) that capture a range of cognitive, emotional, behavioral, and physical problems (see Table 4–13). Six additional items are included for preexisting and associated conditions used to identify special needs. The 8-item Participation Index may be especially helpful in tracking problems during community reintegration, a stage of recovery often neglected by other rating scales. The scale also offers the option of combining information across raters, which may provide a more meaningful picture of a patient's current level of functioning.

A thorough clinical neuropsychiatric evaluation requires careful assessment of cognitive functioning. The Neurobehavioral Cognitive Status Examination (NCSE), which can be completed in 5–20 minutes, is an extremely useful tool for rapid cognitive screening. Kiernan and colleagues developed the NCSE to assess attention, orientation, language, visuoconstructional skills, memory, calculation, abstract reasoning, and levels of consciousness (Kiernan et al. 1987; Schwamm et al. 1987). Most of the NCSE's assessment categories begin with a screening item that is a relatively demanding test of the skill involved. If the screening item is successfully completed, no further testing in that domain is required. This allows for rapid completion when there is little cognitive impairment. The NCSE generates a performance profile that reflects differentiated functioning and can be compared with group norms for various neuropsychiatric disorders. The NCSE is particularly useful as a screening tool in identifying patients for whom formal neuropsychological testing is indicated and is a valuable adjunct to other clinical neurodiagnostic studies when neuropsychological testing is not readily available.

One of the most important brain functions supporting the ability to live independently is executive function. The Behavior Rating Inventory of Executive Function—Adult Version (BRIEF-A) (Roth et al. 2005) is a standardized measure yielding practical information about the adult patient's executive function in his or her everyday environment. Information is obtained through self-report on two forms, one completed by the TBI survivor and the other by someone who is familiar with the rated individual's everyday functioning. The BRIEF-A measures functioning across nine scales: inhibition, self-monitoring, planning/organizing, shifting sets, initiating, task monitoring, emotional control, working memory, and organization of materials. The Frontal Systems Behavior Scale is another standardized behavior rating scale of executive skills (Grace and Malloy 2001). The 46-item rating scale has forms for both patients and family members. Although a clinician-rated form is not available, the authors indicated that health professionals can use the family form to track changes over time. The scale has two important advantages over many other scales of executive skills: 1) the association between scores on this scale and frontal lobe damage has been empirically demonstrated (Malloy and Grace 2005), and 2) scores on this scale have been validated against other measures of community reintegration (Reid-Arndt et al. 2007).

Due to the often profound and long-lasting disruptions in psychosocial functioning caused by TBI, various outcome scales have been used to capture and quantify psychosocial parameters. Examples include the Community Integration Questionnaire (Willer et al. 1994), the previously mentioned 8-item Participation Index on the MPAI-4 (Malec and Lezak 2008), and the Sydney Psychosocial Reintegration Scale (Tate et al. 1999). The Sydney Psychosocial Reintegration Scale (Table 4–14) is a 12-item questionnaire that measures domains of everyday living often affected by TBI (occupational activities, interpersonal relationships, and independent living skills).

In the case of less severe TBI, changes in cognitive, emotional, or somatic functioning may be too subtle to be detected on the measures discussed above, especially if the patient is evaluated months to years postinjury. In

TABLE 4–14. Items in the Sydney Psychosocial Reintegration Scale

Occupational Activities

1. Current work: Have the hours of work (or study) or the type of work (or study) your relative does changed because of the injury?
2. Work skills: Has your relative's ability to do his or her job (or studies) changed because of the injury?
3. Leisure: Has there been any decrease in the number of leisure activities or a change in the types of leisure activities that your relative does now because of the injury?
4. Organizing activities: Has there been any change in your relative's ability to organize work and leisure activities because of the injury?

Interpersonal Relationships

5. Spouse/partner: Has your relative's relationship with his or her partner changed because of the injury? (If your relative does not have a partner at present, have there been any changes in him or her that would affect such a relationship?)
6. Family: Has your relative's relationships with any other family members (except partner) changed because of the injury?
7. Friends and other people: Has your relative's relationships with other people outside family (such as close friends, workmates, neighbors) changed because of the injury?
8. Communication: Has your relative's ability to communicate with other people (i.e., talk with other people and understand what others say) changed because of the injury?

Independent Living Skills

9. Social skills: Have your relative's social skills and behavior in public changed because of the injury?
10. Personal habits: Have your relative's personal habits (e.g., his or her care in cleanliness, dressing, and tidiness) changed because of the injury?
11. Transport: Has your relative's ability to get about in the community and use transport changed due to the injury?
12. Accommodation: Has your relative's abilities to live independently changed due to the injury?

Source. Reprinted from Tate R, Hodgkinson A, Veerabangsa A, et al.: "Measuring Psychosocial Recovery After Traumatic Brain Injury: Psychometric Properties of a New Scale." *Journal of Head Trauma Rehabilitation* 14:543–557, 1999. Used with permission.

cases such as this, clinicians partially rely on self-report questionnaires, such as the Rivermead Post-Concussion Symptoms Questionnaire, to quantify the subjective change in functioning experienced by some patients (King et al. 1995). Consistent with the literature regarding persistence of self-reported symptoms following mild TBI, Lannsjö et al. (2009) found that 24% of their sample of 2,602 patients reported at least three symptoms 3 months after mild TBI.

Additional Assessment Tools

In addition to history, physical, mental status examination, MMSE (which was developed for assessment of Alzheimer's disease), "bedside" cognitive testing, and behavioral assessment, one may incorporate additional evaluation tools to complete the neuropsychiatric evaluation. These diagnostic tools include neuropsychological testing, structural and/or functional neuroimaging, electroencephalogram, and evoked potentials (see Chapter 5, Structural Imaging; Chapter 6, Functional Imaging; and Chapter 7, Electrophysiological Assessment, for more information). See Table 4–15 for a comprehensive list of tasks and tools used in the neuropsychiatric assessment of TBI.

Computerized Testing

Although no computerized test supersedes traditional neuropsychological testing in obtaining a comprehensive neurocognitive "fingerprint," computerized tests may occupy a unique niche in the assessment process marked by their brevity, interactive design, and financial savings. Three computerized tests have been evaluated in the TBI population: the CNS Vital Signs (CNS VS) (Gualtieri and Johnson 2008), the Automated Neuropsychological Assessment Metrics (ANAM) (Kane et al. 2007), and the Brain Fitness Program (Smith et al. 2009).

The CNS VS battery tests verbal and visual memory, psychomotor speed, complex attention, reaction time, and cognitive flexibility using a Windows-based personal computer. The test is at the fourth-grade reading level, requires manipulation of only a few keys, may be initiated by an office assistant, and takes approximately 30 minutes to complete. The ANAM consists of 31 subtests of processing speed, short-term memory, working memory, and resistance to interference, all of which are delivered entirely through a personal computer. Finally, the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study used the Brain Fitness Program that targets auditory processing skills training, building upon prior work in smaller studies (Mahncke et al. 2006a, 2006b). In the IMPACT study 487 subjects were enrolled, 242 of whom were randomly assigned to the experimental treatment using the Brain Fitness Program and 245 of whom were randomly assigned to an active control arm. Those receiving the auditory processing skills training program showed significant improvement compared with the active control group for the trained auditory memory/attention skills. However, untargeted skills also showed significantly more improvement in the treatment group, including overall memory, digit span backward, letter-number sequencing, total Rey Auditory Verbal Learning Test (RAVLT) scores, and RAVLT delayed recall scores.

Conclusion

Comprehensive neuropsychiatric assessments of patients experiencing neurocognitive and neurobehavioral symptomatology and/or functional disability subsequent to brain injuries due to trauma are essential and should assist the clinician in choosing optimal combinations of pharmacotherapy; individual, group, and family psychotherapy; and rehabilitation, occupational, and resocialization interventions. Such assessments should elicit and integrate clinical data from each of the three major biopsychosocial domains as they apply to patients with TBIs.

TABLE 4–15. Comprehensive assessment of traumatic brain injury

History
Physical examination
Mental status examination
Mini-Mental State Examination
"Bedside" cognitive testing
Neuropsychological testing
Computed tomography of head (acute)
Magnetic resonance imaging
Functional brain imaging (single-photon emission computed tomography, positron emission tomography, functional magnetic resonance imaging)
Electroencephalogram
Evoked potentials

Optimal outcomes from neuropsychiatric treatment depend on careful elicitation of medical, neurological, psychiatric, and substance abuse histories, with special emphasis on premorbid functioning, details of the acute traumatic event, delineation of the nature and time course of development of posttraumatic neurocognitive and neurobehavioral problems, and precise descriptions of the patient's current psychiatric and behavioral symptomatology, functional disabilities, and community supports. In addition to psychotherapeutic, behavioral, and rehabilitative interventions, psychotropic drug treatment is often beneficial if the clinician is aware that the patient may have residual symptoms due to brain trauma and prescribes lower-than-usual doses of psychotropic medications.

The more the neurophysiological effects of various kinds of brain injuries and diseases of the brain are understood, the more commonalities in their underlying pathophysiological mechanisms may be identified. Perhaps individuals who experience poor outcomes from TBI and/or who later develop schizophrenia or dementia are particularly vulnerable to free radicals, the excitotoxic cascade, calcium toxicity, *N*-methyl-D-aspartate activation, cytokines, and other neurocellular apoptotic processes. As future research defines the mechanisms of cellular damage and destruction after brain trauma, it may be discovered that many are identical to those found in a variety of primary neuropsychiatric diseases. Illuminating these shared pathophysiological mechanisms may then focus attention on promising treatments that might be effective in TBI as well as other neuropsychiatric and neurodegenerative disease states.

KEY CLINICAL POINTS

- A biopsychosocial approach is a useful framework in the neuropsychiatric assessment of traumatic brain injury (TBI) given the direct effects of injury on the brain as well as the psychosocial impact of the injury.
- Because most TBIs are invisible, with no external signs of injury, it is important to routinely screen patients for TBI by assessing for any history of head injury resulting in an alteration in mental status and a subsequent change in functioning.
- The most common parameters used in categorizing the severity of TBI are the Glasgow Coma Scale, duration of loss of consciousness, and length of posttraumatic amnesia.
- When assessing symptoms and signs of TBI, it is helpful to categorize them into cognitive, emotional, behavioral, and physical domains, with particular attention to the temporal sequence of symptoms.
- Although a thorough history is key to TBI diagnosis, "bedside" frontal lobe testing and specific rating scales are effective screening and assessment tools.
- Because of the alteration of mental status and poor insight associated with TBI, it is imperative to obtain collateral information regarding the injury and current functioning whenever possible.
- A risk factor for numerous psychiatric disorders and often comorbid with substance abuse, TBI is associated with a greater lifetime prevalence of suicide.
- Consideration of preinjury factors, such as the positive effect of higher education and negative effect of a history of psychiatric illness, is important in estimating prognosis.

- A comprehensive assessment of TBI includes neuropsychological testing, electroencephalogram, and neuroimaging, with promising functional imaging techniques and genetic testing for risk and resilience factors on the horizon.

- The goal of a detailed neuropsychiatric evaluation in TBI is to create a comprehensive treatment plan that will minimize the impact of disability and maximize independence, well-being, social participation, and productivity.

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CHAPTER 5

Structural Imaging

Erin D. Bigler, Ph.D.

STRUCTURAL IMAGING REFERS TO VARIOUS TECHNIQUES that generate static views of the brain, primarily using the methods of computed tomography (CT) and magnetic resonance (MR) imaging (MRI). The brain can be readily compartmentalized into three areas: white matter (WM), gray matter (GM), and cerebral spinal fluid (CSF)–filled spaces or cavities. Brain tissue has its own vasculature and blood vessels that can be separately imaged using structural imaging techniques, but the totality of the brain's vasculature makes up a small percentage of total brain volume. Because of the water content of blood and the makeup of cerebral vessels, most of the cerebral vasculature gets classified within the spectrum of CSF or of the parenchymal tissue where a vessel is embedded using standard imaging sequences. Thus, the microvasculature within GM and WM (unless a disease state exists or a hemorrhage has occurred) becomes classified as the tissue that it is embedded in. From a structural imaging and gross anatomy perspective, this general rule of WM, GM, or CSF classification applies for any region of interest.

Before considering typical structural images associated with traumatic brain injury (TBI), it is essential to comprehend the underlying brain anatomy and functional organization so that the effects of lesions or abnormalities can be understood in the context of their location and potential for disrupting function. Although a TBI-associated lesion may occur anywhere in the brain, lesions often predominantly affect cortical structures, particularly the frontal and temporal lobes and WM pathways. Because of this prevalence, cortical organization will be briefly discussed first, followed by WM organization.

Figure 5–1 diagrams the complex nature of the cerebral cortex, its vascular bed, and neuropil (Logothetis 2008). This complex array of neural circuitry is organized in a modular fashion, in which the basic unit is an excitation-inhibition network (EIN). Within and between each EIN, brain connectivity is mostly bidirectional in what has been referred to as "feedforward" and "feedback" cortical processing (Douglas and Martin 2004, 2007). To best understand how TBI disrupts these networks, the reader may examine Figure 5–1 from the perspective of biomechanical deformation of brain parenchyma in response to trauma and how these delicate neural and vascular fibers are affected when structural damage is detected with structural imaging techniques.

The first formal publications of more than a century ago (A. Miles 1892) recognized that the injurious effects of stretching brain tissue were central to understanding the mechanisms of injury. In the latter half of the twentieth century, the concepts of diffuse axonal injury and diffuse brain injury became the focus of research and clinical understanding, emphasizing the effects of trauma on the axon (Maruichi et al. 2009; Povlishock and Katz 2005). Neuroimaging now has tools to more fully explore in vivo WM integrity and disrupted brain connectivity.

For example, Figure 5–2 shows this neural connectivity of the brain by using MRI diffusion tensor imaging (DTI; discussed below). This is an MRI method that capitalizes on detecting diffusion properties of water molecules; from that information various metrics can be derived that define the health and connectivity of brain microstructure (Mukherjee et al. 2008a, 2008b).

DTI tractography, as illustrated in Figure 5–2, permits the viewing of aggregate bundles of WM tracts in the brain. The normal functioning of the brain depends on the connectivity of disparate brain regions automatically and synchronously integrating information and function (Kumar and Cook 2002). Indeed, the normal functioning of the

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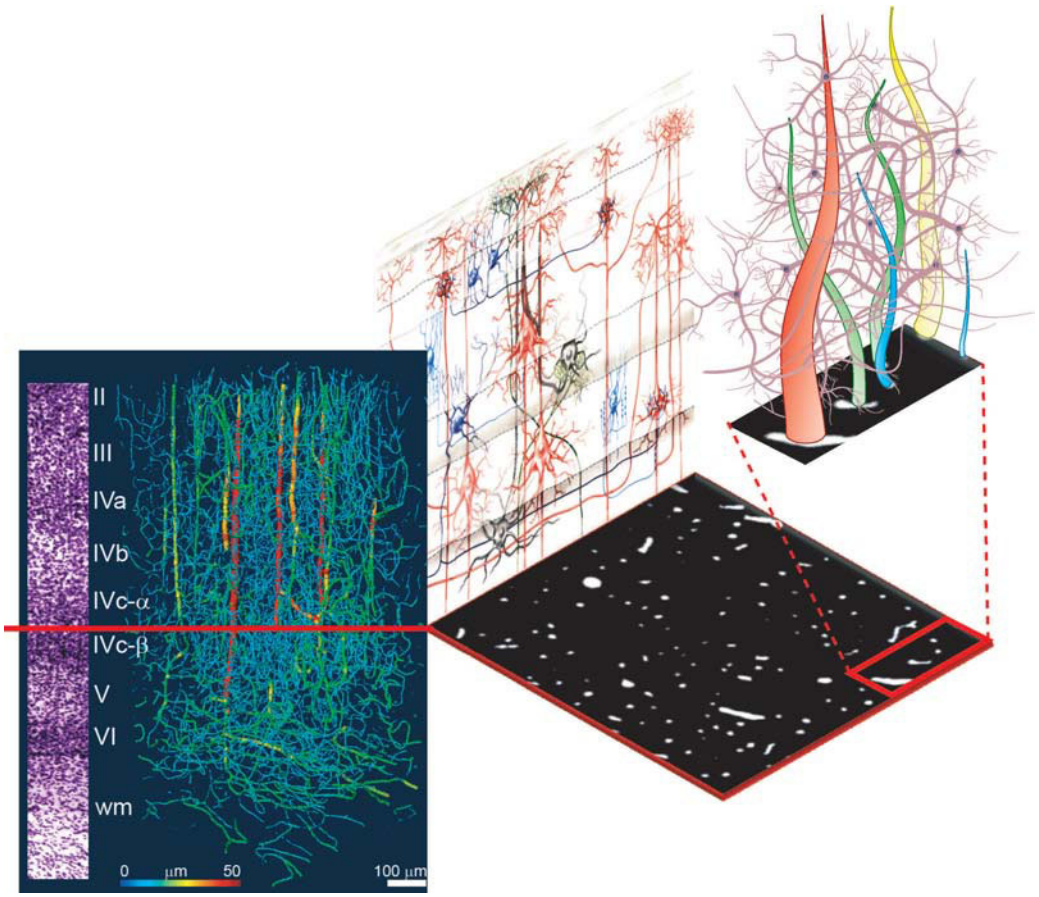


FIGURE 5–1. Relative density of vessels in the visual cortex of monkeys.

The *left panel* demonstrates the relative density of vessels in the visual cortex of monkeys. The dense vascular mesh is displayed by perfusing the tissue with barium sulfate and imaging it with synchrotron-based X-ray microtomography (courtesy B. Weber, Max Planck Institute for Biological Cybernetics). The vessel diameter is color coded. Cortical surface without pial vessels is displayed at the top, white matter (WM) at the bottom. At the left of the panel is a Nissl slice from the same area, showing the neural density for layers II through to the WM. Although the density of the vessels appears to be high in this 3-D representation, it is actually less than 3% (see section at the right; white spots are cross-sections of vessels). The average distance between the small vessels (capillaries) is about 50 μm. This is approximately the distance that oxygen molecules travel by diffusion within the limited transit time of the blood. The dense population of neurons, synapses, and glia occupy the intervascular space, as depicted in the drawing at the *top right*—a hypothetical distribution of vascular and neural elements in a small section (red rectangle). The drawing in the *background* shows some of the typical neuronal types (e.g., red, large pyramidal cell; dark blue, inhibitory basket cells; light blue, chandelier inhibitory neurons; and gray, stellate cells) and their processes. As shown in the left panel, this is approximately the gross resolution of magnetic resonance imaging (i.e., mm^3).

Source. Reprinted from Logothetis NK: "What We Can Do and What We Cannot Do With fMRI." *Nature* 453:869–878, 2008. Copyright © 2008. Used with permission of Macmillan Publishers, Ltd.

neural network is entirely dependent on connectivity through WM pathways. The overall complexity of this system can be seen in Figure 5–2, which shows the totality of DTI-identified WM tracts crossing over the corpus callosum as viewed dorsally in an intact normal adult brain.

This figure is based on the method referred to as tractography, which defines aggregate WM pathways identified by similarity of water diffusion. These images show aggregate WM tracts of the brain (see Hagmann et al. 2007, 2008; Kumar and Cook 2002), which consist of individual axons projecting in short and long coursing fiber tracts in anterior-posterior (green), side-to-side (red-orange), and up-down (blue) trajectories. Again, to best understand how TBI disrupts these fiber tracts, the reader may view the figure from the perspective of mechanical deformation of these tracts/regions during trauma. Myelinated cortical axons range in size from a few to 20–30 microns, which indicates why these delicate fiber tracts can be damaged with mechanical deformation. Although a focal lesion, such as a contusion, may appear as an impressive localized lesion on CT and/or MRI, the true neurobehavioral effect of that region of damage is how it disrupts this network of WM pathways.

Neuroimaging of TBI

In the clinical management of TBI two neuroimaging methods dominate the assessment of the brain-injured individual. Typically, the first imaging procedure is CT,

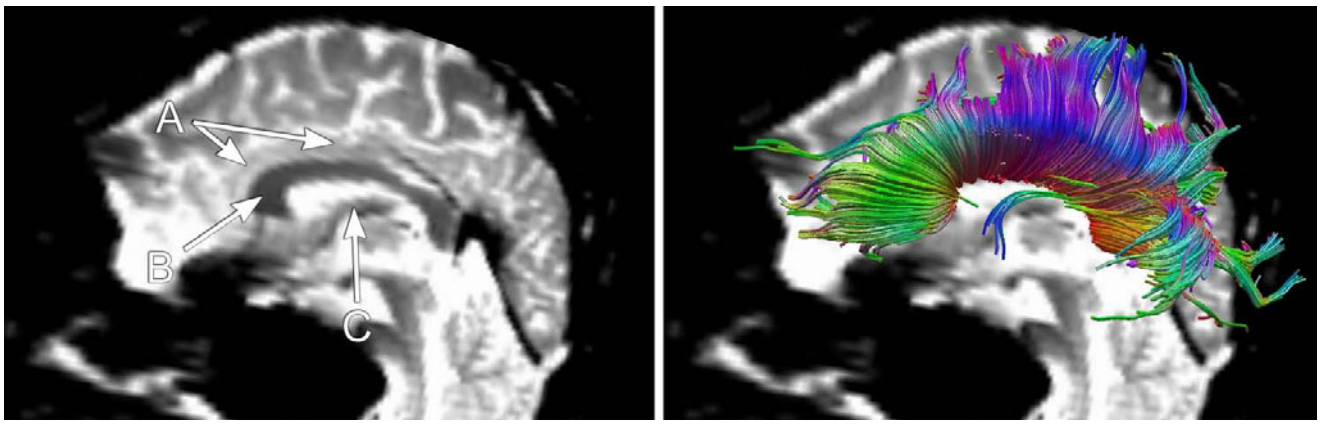


FIGURE 5–2. Diffusion tensor imaging (DTI) of the corpus callosum.

The left panel is a partially rotated left-frontal oblique view of a DTI sequence referred to as B0. DTI sequences have a fuzzy appearance to them and in their unprocessed state lack the anatomical clarity of other magnetic resonance imaging sequences. Major brain landmarks can still be identified, which in this view include the cingulated gyrus (A), corpus callosum (B), and fornix (C). However, from the various DTI sequences, fiber tract directionality can be determined as shown in the panel on the right, which depicts the left hemisphere tracts emanating from the entirety of the length of the corpus callosum. This image is from a normal adult control subject; note the fullness of the projecting tracts. DTI convention depicts anterior-to-posterior projecting tracts as green, vertically oriented tracts as blue, and laterally or back-and-forth projecting tracts as warm colors (red-orange). In this figure only the aggregate fiber tracts of the corpus callosum and fornix are shown, but all regions of the brain and their white matter connections can be shown with DTI.

which offers a gross image of the head and brain and is sensitive enough to detect medically significant acute pathology in TBI. MRI provides more detailed anatomical and pathological information than CT but for a variety of reasons is typically done as a follow-up to the initial CT scan. In this section these neuroimaging procedures and others are more fully discussed.

Computed Tomography (CT)

In the acute management of a brain injury, CT imaging is routinely the first imaging assessment of the patient (Coles 2007; Toyama et al. 2005). CT scans can be performed rapidly; the entire brain is scanned within seconds with no risk factors that are associated with MRI (i.e., the strong magnetic field required for MRI can literally move intracranial or foreign metallic fragments, cannot be done with heart or other life support devices highly susceptible to motion and paramagnetic artifacts, etc.) (Gallagher et al. 2007). CT readily identifies gross brain pathology that is critical to the early medical management of cerebral trauma, as shown in Figure 5–3. Various types of hemorrhages, clinical presentation of cerebral edema, and presence of midline shift are all readily detected by CT imaging. Details on the basis of structural imaging can be found in the first edition of Silver et al. (2005).

Figure 5–4 shows the acute CT imaging from a TBI patient who sustained a severe closed-head injury (there were no open fractures or penetrating injuries). Shearing forces that damage axons also damage and rupture blood vessels (Coles 2007), which can be readily appreciated in the CT images shown, where the hemorrhagic lesions are scattered throughout the brain ranging from small petechial hemorrhages to larger intraparenchymal and intraventricular bleeds. Likewise, mechanical deformation, particularly around bony ridges and protuberances at the base of the skull, results in brain surface contusions (see Bigler 2007). Once blood is out of its naturally bound intravessel state, it immediately begins to coagulate and change in density (see Figure 5–5). Because CT technology is based on reconstructed X-ray density, significant foci of blood can be readily distinguished in brain parenchyma and CSF-filled spaces by their density as shown in Figures 5–3 through 5–5 (see also Toyama et al. 2005). The extent and locale of these hemorrhagic lesions become important for acute medical decision making in the management of the patient and likewise assist in making outcome predictions.

The most widely used day-of-injury (DOI) CT rating system was developed by Marshall et al. (1992) for the Model System TBI database and is reproduced in Table 5–1 (further details in Bigler 2005, p. 81). It is now referred to as the Marshall CT rating system; there are also other CT rating systems similar to this system (see Katz and Alexander 1994; Sherer et al. 2008; Steyerberg et al. 2008; van Baalen et al. 2003).

In a CT study that examined 240 consecutive TBI admissions to an inpatient rehabilitation unit using the Marshall CT rating system, injuries ranged from those with no detectable CT abnormalities to profound, multifocal regions of injury (see Bigler et al. 2006). The diversity of DOI-defined CT abnormalities in this study and others is exemplified by examining DOI injury severity based on length of loss of consciousness (LOC), Glasgow Coma Scale (GCS), and/or duration of posttraumatic amnesia. Regardless of injury severity used, all levels of injury were observed across all Marshall CT severity ratings, although a Level II CT injury (i.e., some swelling and scattered small hemorrhages) was the most common. These studies indicate that patients who meet medical criteria for severe injury (i.e., positive LOC and GCS ≤8) can have a "normal" CT scan whereas those meeting criteria for mild TBI (i.e.,

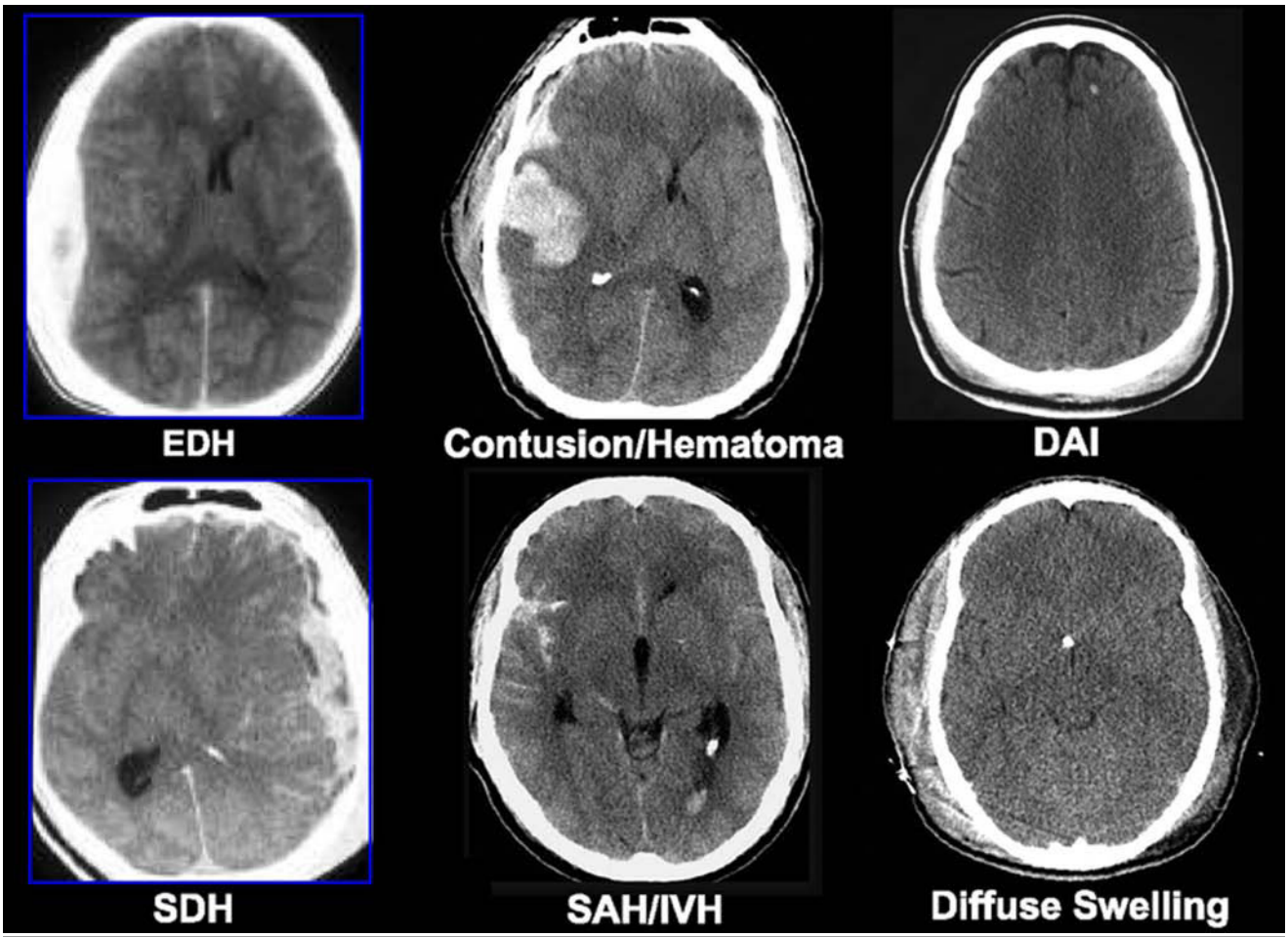


FIGURE 5–3. Heterogeneity of severe traumatic brain injury (TBI) shown by computed tomography (CT) scans of six different patients with severe TBI, defined as a Glasgow Coma Scale score of <8.

Highlighting the significant heterogeneity of pathological findings, CT scans represent patients with epidural hematomas (EDH), contusions and parenchymal hematomas (Contusion/Hematoma), diffuse axonal injury (DAI), subdural hematoma (SDH), subarachnoid hemorrhage and intraventricular hemorrhage (SAH/IVH), and diffuse brain swelling (Diffuse Swelling).

Source. Reprinted from Saatman KE, Duhaime AC, Bullock R, et al: "Classification of Traumatic Brain Injury for Targeted Therapies." *Journal of Neurotrauma* 25:719–738, 2008. Used with permission of Mary Ann Liebert, Inc. Publishers.

no LOC and GCS ≥13) can have distinctly identifiable lesions on CT.

This diversity of CT findings means that from the rehabilitation and neurobehavioral outcome perspective, DOI CT imaging alone is limited in predicting outcome, especially neurobehavioral outcome with one exception: CT-identified brainstem pathology, a Marshall Level VII classification, predicts poor outcome (Bigler et al. 2006; Maas et al. 2005; Steyerberg et al. 2008). Although critical for acute medical management, the DOI CT alone is not consistently predictive of long-term sequelae. As will be discussed later, using CT findings as a baseline and tracking changes over time become predictive of outcome—DOI CT information, in conjunction with other medical and neuropsychological variables, ultimately aides the clinician in understanding the effects of the brain injury.

It is also instructive to know that in prediction modeling for poor outcome from TBI, such models all incorporate DOI CT findings with other variables, and therefore DOI CT observations do have a role in predicting outcome, just not a singular role. In these integrated prediction models, the more CT abnormalities (i.e., Marshall scores ≥2) combined with presence of subarachnoid hemorrhage, subdural hematoma, and/or basal skull fracture become better predictors of poor outcome (see Fabbri et al. 2008; Murray et al. 2007). Although the worst outcome is associated with these types of abnormalities in combination, it should be obvious to the clinician that any of these abnormalities being singularly present carries with it some morbidity with regard to outcome.

CT as a Baseline

CT not only demonstrates the acute injuries but also permits comparison with other imaging modalities obtained during longitudinal follow-up, so that lesions and pathology can be tracked over time. One of the most straightforward comparisons occurs within the ventricular system (see Figures 5–4 and 5–5). The demarcation between brain parenchyma and ventricle is very distinct, regardless of

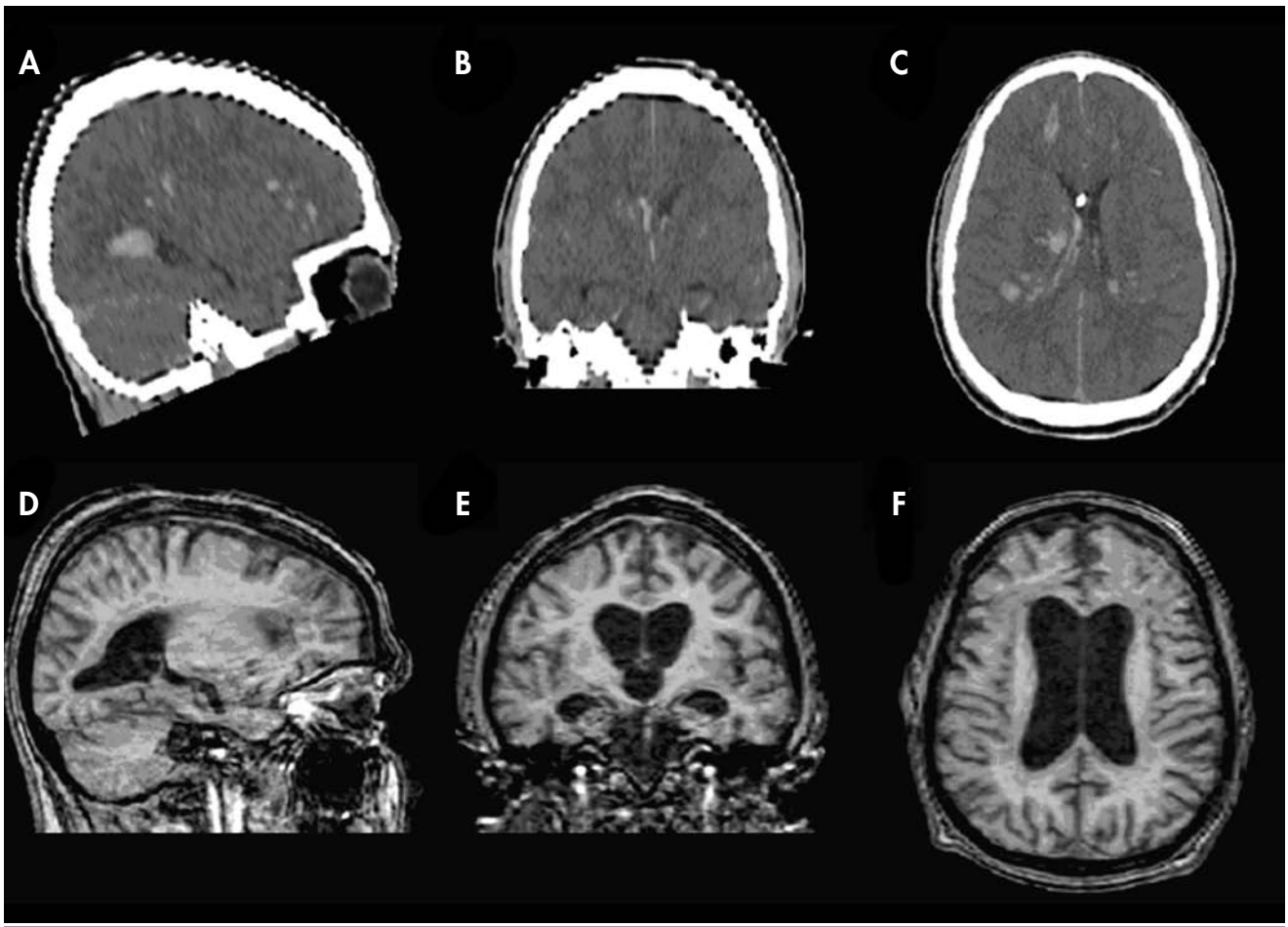


FIGURE 5–4. Day-of-injury computed tomography (CT) compared with follow-up magnetic resonance imaging (MRI).
The day-of-injury CT images (top row) are registered at the same level of the follow-up MR (T1 sequence) images obtained 2 years post-injury (bottom row). The CT demonstrates multiple hemorrhagic lesions scattered throughout the brain but particularly in the fronto-temporal and periventricular regions. Also, note the size of the ventricle on acute imaging. Even though there is effacement of the ventricle because of trauma-induced intracranial edema, the ventricle can be used to estimate original pretrauma size and used to track changes over time. Ventricular dilation is readily apparent on the follow-up MRI, seen below each CT.

TABLE 5–1. Diagnostic categories of abnormalities visualized on CT scanning

Category	Definition
1 Diffuse injury I (no visible pathology)	No visible intracranial pathology seen on CT scan
2 Diffuse injury II	Cisterns present with midline shift 0–5 mm and/or: –lesion densities present –no high- or mixed-density lesion >25 cc –may include bone fragments and foreign bodies
3 Diffuse injury III (swelling)	Cisterns compressed or absent with midline shifts 0–5 mm, no high- or mixed-density lesion > 25 cc
4 Diffuse injury IV (shift)	Midline shift > 5 mm, no high- or mixed-density lesion > 25 cc
5 Evacuated mass lesion V	Any lesion surgically evacuated
6 Nonevacuated mass lesion VI	High- or mixed-density lesion > 25 cc, not surgically evacuated
7 Brainstem injury VII	Focal brainstem lesion, no other lesion present

Note. CT=computed tomography. *Source.* Marshall et al. 1992.

whether CT or MRI is used. Because it takes days to weeks to begin to visualize the extent of pathological changes that will fully emerge 6–18 months postinjury, even with profound pathology as evidenced in Figures 5–4 and 5–5 on the DOI scan, information about the preinjury status of the brain can be gleaned. For example, in Figures 5–4, 5–5, and 5–7, the inferred original (i.e., normal) size of the

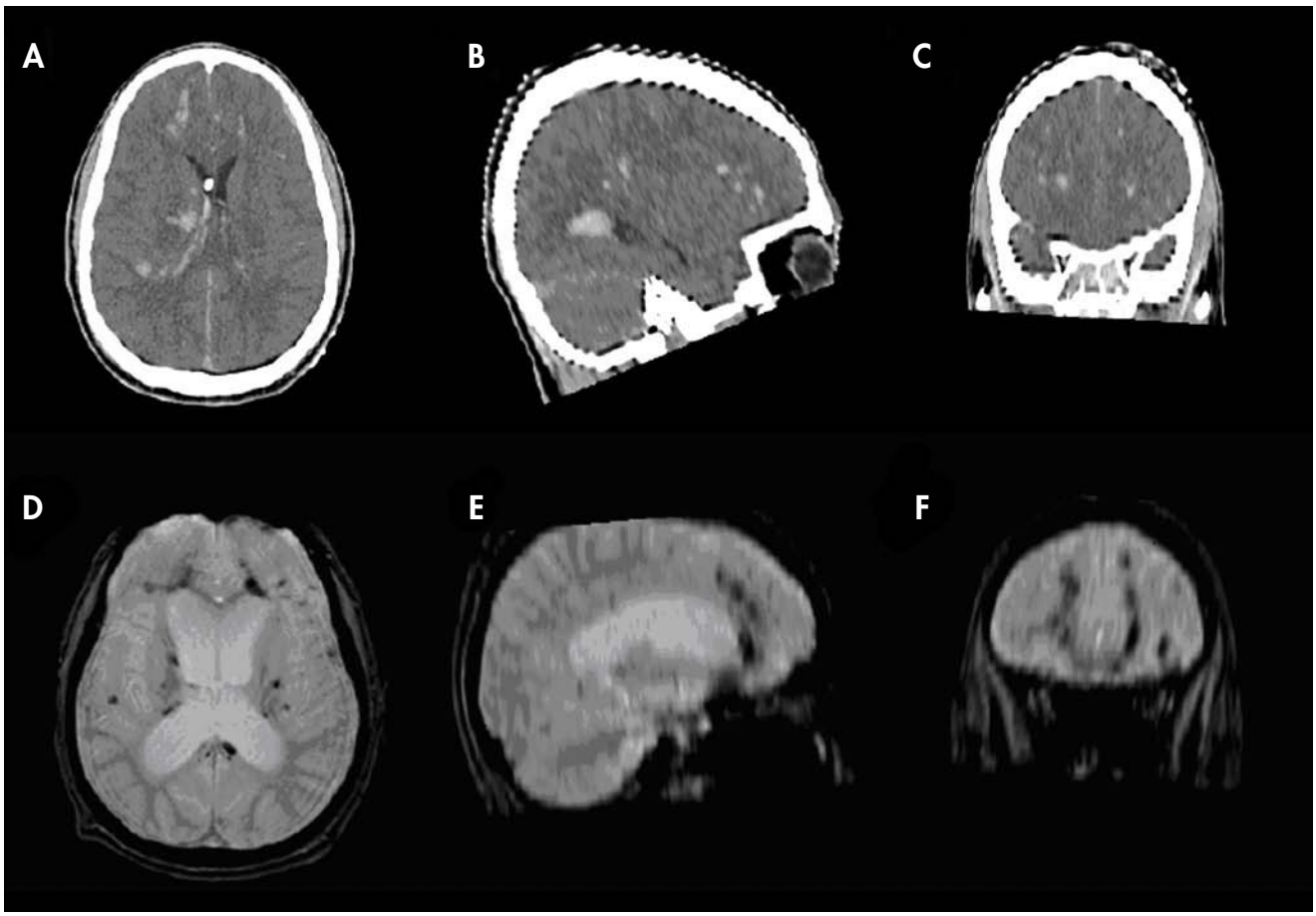


FIGURE 5–5. Computed tomography (CT) imaging from the same case in Figure 5–4, showing the day-of-injury hemorrhagic lesions (top row), compared with the chronic hemosiderin deposits seen on the gradient recalled echo sequence (bottom row) registered in the same orientation as the CT.

ventricular system can be used to estimate its original size to establish its baseline. In the case shown in Figure 5–4, even though intraventricular hemorrhaging has occurred along with effacement of the lateral ventricle secondary to the generalized swelling, its original size can still be estimated. The follow-up MRI distinctly shows ventricular enlargement, and this can be readily appreciated in a 3-D depiction of the ventricular system as shown in Figure 5–6 taken from the DOI CT scan (Figures 5–4 and 5–5) compared with the follow-up MRI (also in Figures 5–4 and 5–5).

The most common cause of chronic ventricular dilation in TBI is hydrocephalus ex vacuo as a result of parenchymal volume loss (Henry-Feugeas et al. 2000). Thus, the regional dilation of the ventricle often signifies surrounding atrophy. This is prominently shown in Figures 5–4 through 5–6. In Figure 5–7 the temporal horns of the lateral ventricle can still be visualized in the DOI CT scan even though there are multiple intraparenchymal hemorrhages and generalized brain swelling, including left temporal lobe hemorrhages. However, by 2 years postinjury there is prominent temporal lobe atrophy, temporal horn dilation noted on all sequences clearly indicating wasting of the hippocampus, and scattered T2 and fluid-attenuated inversion recovery (FLAIR) MR sequence abnormalities. as shown in Figure 5–7. Tracking such changes over time aids the clinician in understanding the full extent of parenchymal damage.

Magnetic Resonance Imaging (MRI)

Typical MRI abnormalities have been introduced in the discussion on CT imaging. The majority of MRI studies are performed during the subacute and chronic stages of recovery from brain injury, with the intention to answer specific neuropsychiatric questions regarding patient status and/or to assist in evaluating outcome (Ashwal et al. 2006; Levine et al. 2006). The sensitivity in detecting TBI-related anatomical abnormalities by MRI depends on the image sequence and methods used. Figure 5–8, from Bigler (2008), shows different image sequences comparing CT and MRI and their sensitivity in detecting hemorrhagic lesions in a case of mild TBI. Because of resolution issues, in terms of current clinical MRI, detection of abnormalities means the abnormality needs to exceed approximately a cubic millimeter. As such, inferences have to be made about the underlying pathology that may be visualized as an abnormality in neuroimaging. Because the shearing forces of TBI affect not only brain parenchyma but also blood vessels, sheared blood vessels will hemorrhage, which shows up as hemosiderin.

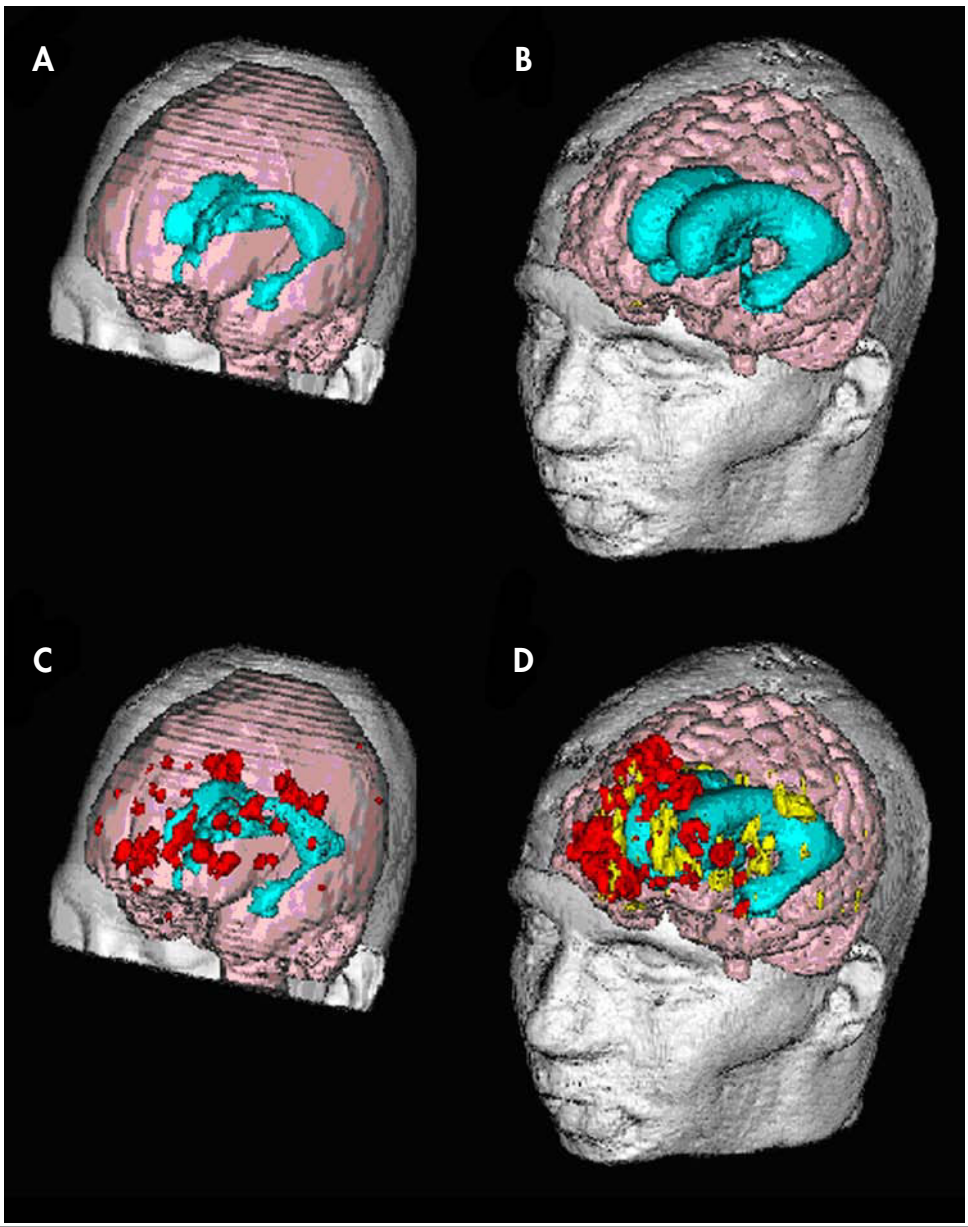


FIGURE 5–6. The day-of-injury (DOI) computed tomography (CT) scans from Figures 5–4 and 5–5 have been analyzed in 3-D space outlining the ventricle (aquamarine color) on the DOI (A, left) compared with the follow-up magnetic resonance imaging (MRI) on the right (B), performed 2 years postinjury.

Note the obvious ventricular dilation, a sign of nonspecific parenchyma volume loss. The bottom left CT scan (C) shows the multiple hemorrhagic lesions in red as occurred on the DOI, identified by points of increased density as shown in Figures 5–4 and 5–5. Note their congregation in the frontotemporal and periventricular regions. Superimposed on the 3-D follow-up MRI (D) is the combination of white matter signal changes (shown in red) revealed on the fluid-attenuated inversion recovery sequence and the regions of hemosiderin deposition identified in the gradient recalled echo sequence (shown in yellow).

In TBI when there is no other known cerebro- or cardiovascular risk factor, the presence of hemosiderin is considered an indicator of diffuse axonal injury (Hahnel et al. 2008; Hou et al. 2007; Levine et al. 2008; Scheid et al. 2007; Tong et al. 2008). As shown by Scheid et al. (2006) the amount and location of hemosiderin relate to neuropsychological outcome, in particular memory and speed-of-processing tasks. More will be reviewed on this below. Often, hemosiderin is not detected, but WM signal hyperintensities are detected on T2 and FLAIR sequences. Presence of WM hyperintense lesions in a TBI patient without other risk factors (e.g., diabetes, hypertension, cardiovascular disease) is likely a reflection of WM injury, and the presence of such deficits relates to neuropsychological outcome (Marquez de la Plata et al. 2007). Traumatic axonal injury is also a term that is used to reflect damaged WM pathways in TBI (Hurley et al. 2004).

Several studies have compared CT with MRI and MRI at different field strengths (Lee et al. 2008; Orrison et al. 2009)

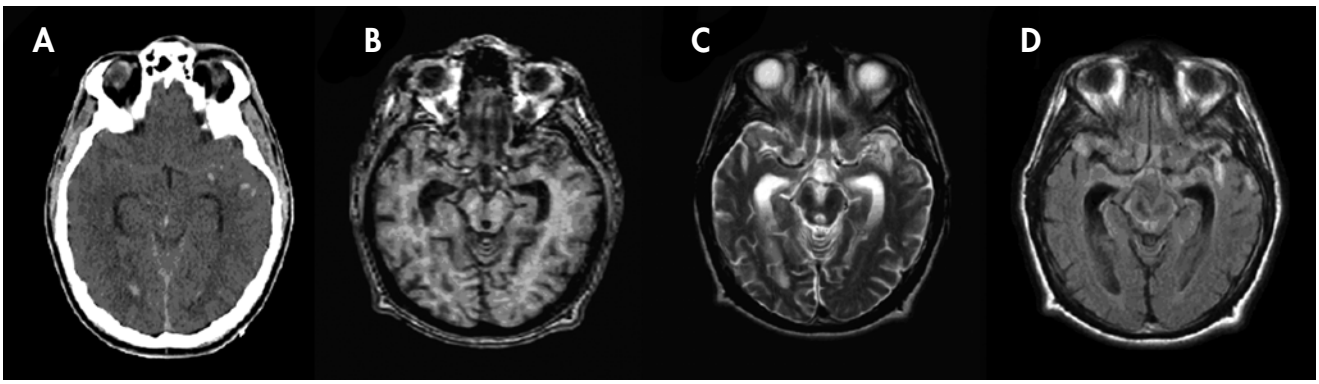


FIGURE 5–7. Sequential changes from traumatic brain injury.

This is the same patient shown in Figures 5–4 through 5–6. (A) Day-of-injury computed tomography (CT), but despite multiple hemorrhagic lesions the temporal horns can still be visualized. In contrast, but 2 years postinjury, prominent temporal horn dilation is evident, with associated hippocampal atrophy as shown in the T1 (B), T2 (C), and fluid-attenuated inversion-recovery (FLAIR) (D) image sequences. The FLAIR sequence (D) also demonstrates signal abnormalities in the left temporal lobe.

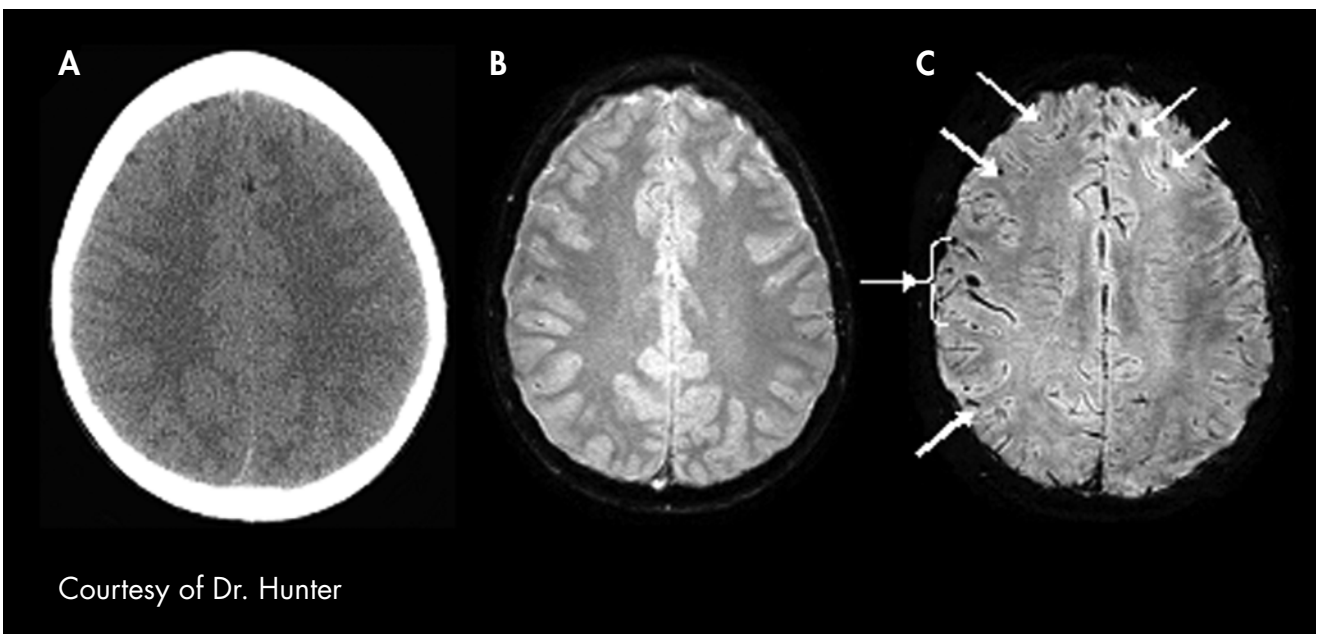


FIGURE 5–8. Detection of microhemorrhage in traumatic brain injury (TBI).

This patient sustained a mild TBI, and the computed tomography on the left (A) was interpreted as within normal limits, as was the standard gradient recalled echo (GRE) sequence magnetic resonance image scan (B) also performed on the day of injury. In contrast, the susceptibility-weighted imaging sequence scan shows multiple hemorrhagic lesions (C, arrows; note, again, the frontal location of the small hemorrhagic lesions). This illustrates the greater sensitivity of the GRE in detecting hemorrhagic abnormalities associated with TBI.

Source. Bigler 2008. Figure courtesy of Dr. J.V. Hunter, Texas Children's Hospital.

in evaluating TBI. MRI is superior to CT in detecting subtle pathology, and 3 Tesla (3T) MRI is superior to lower magnetic field strengths. The typical MRI sequences in evaluating the chronic efforts in TBI patients should include T1, T2, FLAIR, susceptibility-weighted imaging (SWI), and DTI.

Quantitative Neuroimaging of TBI

There are now quantitative neuroimaging databases available for comparison of all major brain structures (Coles 2007; Reddick et al. 2007). A quantitative comparison can be performed on any brain region and compared with a normative sample. These voxel-by-voxel comparisons can be made using conventional structural imaging sequences or DTI. There are also automated methods for examining where atrophic changes occur using voxel-by-voxel or voxel-based morphometry (VBM) and/or standardized template comparisons (Bendlin et al. 2008; Gale et al. 2005; Ghosh et al. 2009; Kim et al. 2008; Kumar et al. 2009; Levine et al. 2008; Mamere et al. 2009). To achieve this cat-

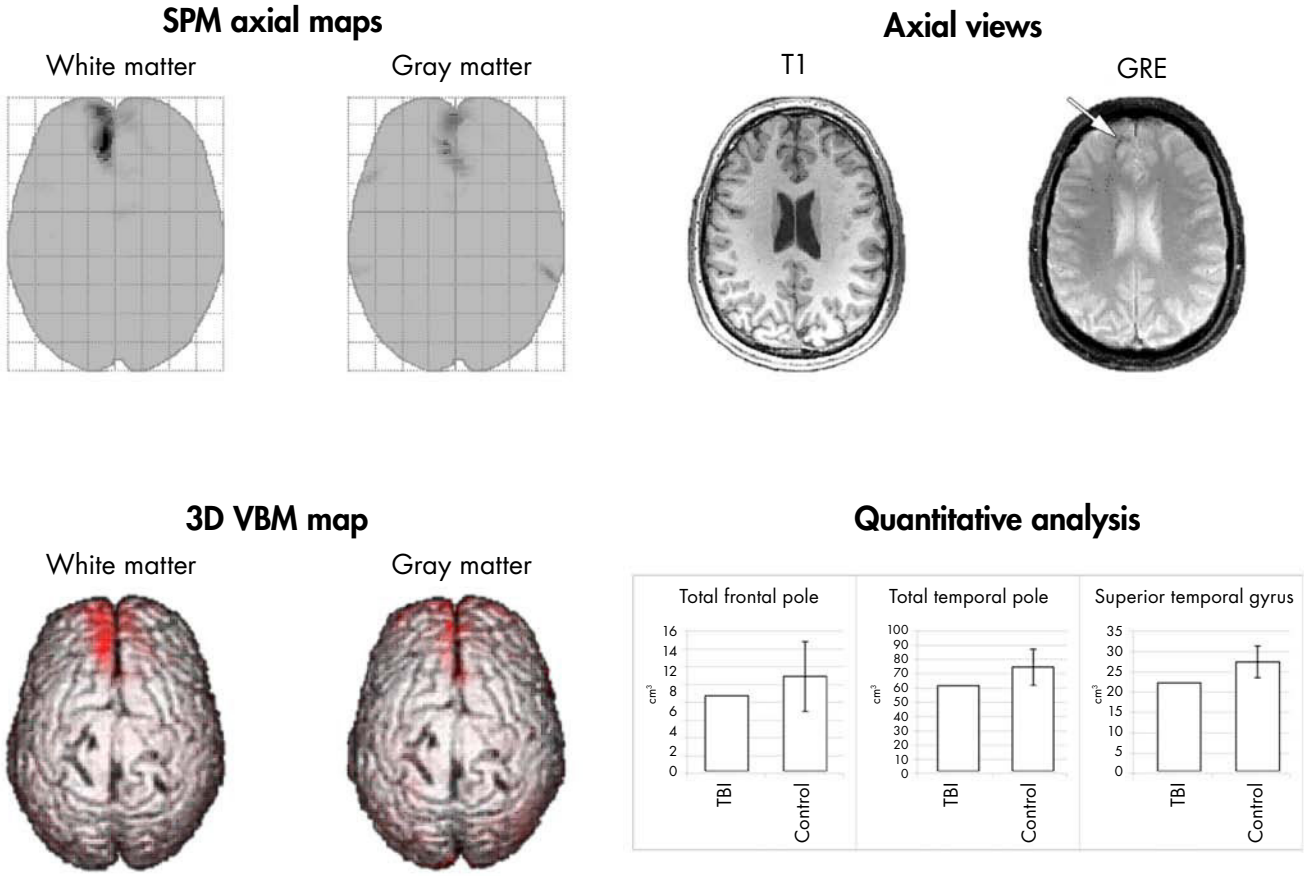


FIGURE 5–9. Methods of quantitative image analysis.

This patient sustained a moderate traumatic brain injury (TBI) in a motor vehicle accident. Axial maps created by statistical parametric mapping (SPM) are shown at top left. As can be readily identified on the gradient recalled echo (GRE) sequence shown at top right, there is hemosiderin in the right frontal region (arrow). The T1 anatomical scan is unimpressive with regard to obvious abnormality, but visually the interhemispheric fissure may be more prominent than what would be expected for a teenager, and likewise some of the frontal sulci are prominent. By applying quantitative analysis (lower right), frontal lobe volume is almost a standard deviation below a control sample of similarly aged individuals, supporting the clinical impression of some frontal atrophy. Voxel-based morphology (VBM) analyses clearly demonstrate that the extent of atrophic change in both white matter (WM) and gray matter (GM) concentration in and around the hemosiderin-defined shear lesion is actually considerably greater than that shown on the GRE sequence where just the hemosiderin deposit can be visualized. The VBM map superimposes the location of the WM and GM abnormalities on a standard 3-D surface magnetic resonance imaging brain reconstruction.

egory of analysis, these types of automated comparisons typically involve methods that modify the individual brain scan so that it conforms to a uniform standard, and in doing so, true volumes of a given structure or region cannot be calculated. However, voxel-by-voxel comparisons permit direct group comparisons between those with TBI and matched controls. These types of group comparison findings clearly demonstrate the diffuseness of TBI, especially involving WM (Kim et al. 2008; Marquez de la Plata et al. 2007).

Volumetric changes can even be demonstrated in mild TBI, particularly in the mild-complicated classification of brain injury (Cohen et al. 2007; MacKenzie et al. 2002). Figure 5–9 demonstrates the integration of such findings using actual volumetric and VBM analyses in a patient who acutely suffered a frontal contusion but conventional structural MRI 2 years postinjury only showed subtle frontal lobe changes on visual inspection. Although hemosiderin could be detected in the frontal region, there were no other specific findings on clinical assessment. However, quantitative analysis demonstrates reduced frontal and temporal pole volumes, consistent with the VBM analyses. It is likely that these automated and quantitative measures will greatly aid in detection of abnormalities associated with brain injury.

Susceptibility-Weighted Imaging (SWI)

As mentioned earlier in this chapter, shear-strain forces sufficient to injure axons are also sufficient to damage blood vessels. Blood by-products of sufficient size can be readily detected by MRI methods (Scheid et al. 2007). Such findings also have modest relationships to neurocognitive outcome (Scheid et al. 2006). Until recently the traditional sequence, the gradient recalled echo, which readily shows hemosiderin as a hypointense signal (see Figures 5–8 and

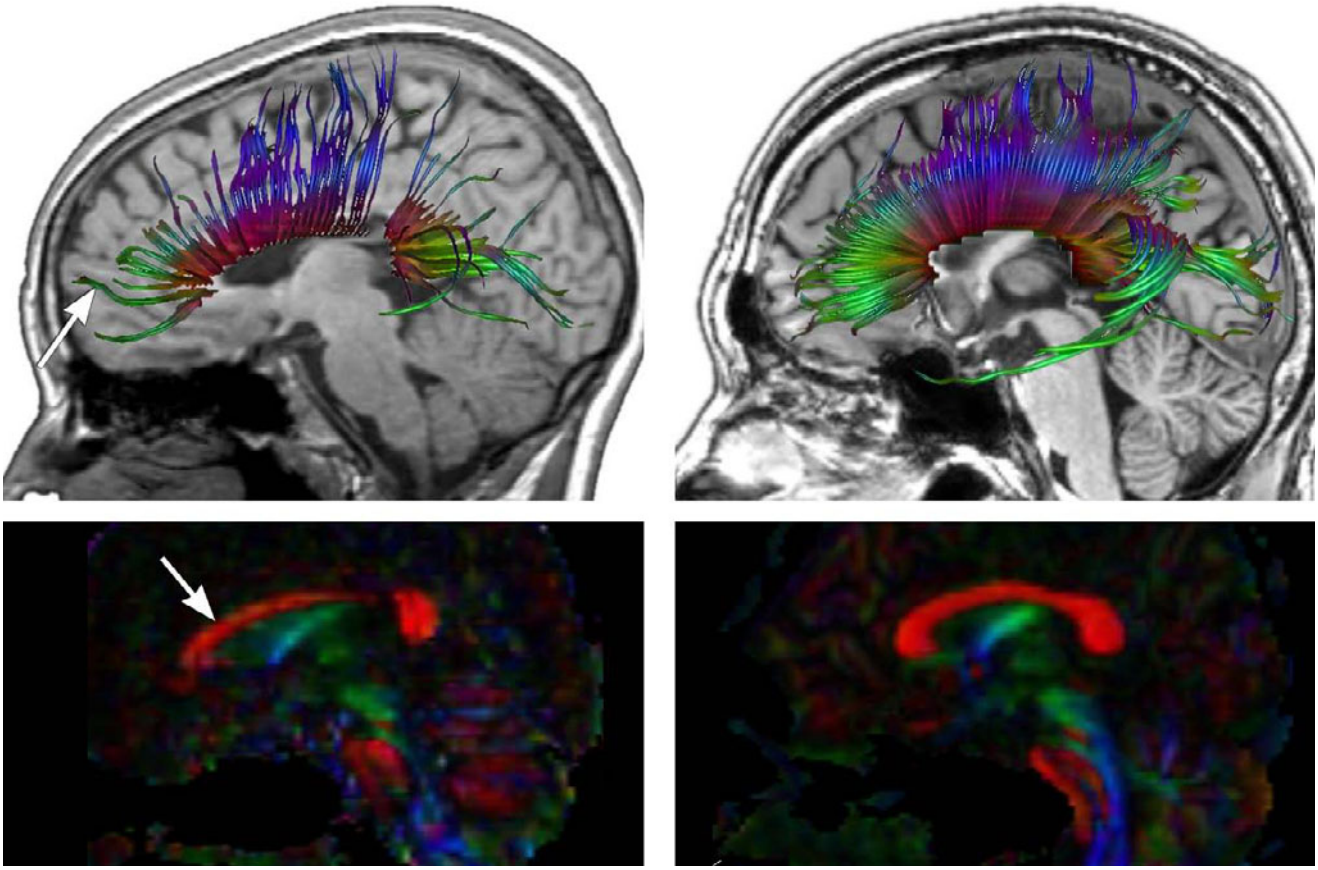


FIGURE 5–10. Diffusion tensor imaging (DTI) of the corpus callosum.

The left images show DTI tractography (upper left) of the corpus callosum superimposed on the T1 image of a traumatic brain injury patient who suffered a severe injury. Note, in comparison with the age-matched individual on the right without a history of brain injury, that the tractography demonstrates a significant reduction in the number of aggregate white matter tracts that can be identified coursing across the corpus callosum and projecting into the left hemisphere. The lower images show the midsagittal plane of the DTI color maps. The arrow in the lower left panel points to the corpus callosum highlighted in red, because DTI is sensitive to the directionality of the fiber tracts; red denotes lateral back-and-forth direction, whereas green reflects anterior-posterior and blue indicates vertical. The arrow in the upper left points to a corpus callosum tract coming out of the forceps minor projection system and is shown here to give the reader orientation for interpreting Figure 5–11.

5–9), was the mainstay in blood by-product detection. SWI is more sensitive (Tong et al. 2008) (Figure 5–8). Combined with focal WM signal changes detected on FLAIR or DTI, the presence of hemosiderin deposits also helps identify the full extent of shear lesions.

Diffusion Tensor Imaging (DTI)

DTI has already been introduced, but a more detailed description is presented here because of its emerging importance in understanding TBI (Tollard et al. 2009). All of MRI is based on the properties of water molecules exposed to brief pulses of strong magnetic fields and detectable changes in emitted radiofrequency waves (Levin et al. 2008; Mukherjee et al. 2008a, 2008b; Wang et al. 2008). DTI capitalizes on a vector analysis and a biological truism that water diffusion will occur in predictable ways based on the health of the tissue and membranes that constrain it. For TBI, DTI has a particular benefit in examining WM integrity because DTI assesses WM microstructure based on the characteristics of myelin sheaths and cell membranes of aggregate WM tracts that affect the movement of water molecules. Consequently, water molecules tend to move faster in parallel to nerve fibers rather than perpendicular to them. This characteristic, which is referred to as anisotropic diffusion and is measured by fractional anisotropy (FA), is determined by the thickness of the myelin sheath and of the axons. FA ranges from 0 to 1, where 0 represents maximal isotropic diffusion (e.g., free diffusion in perfect sphere) and 1 represents maximal anisotropic diffusion, that is, diffusion in one direction (e.g., long cylinder of minimal diameter).

Diffusion anisotropy varies across WM regions, putatively reflecting differences in fiber myelination, fiber diameter, and directionality. This also permits specified voxels to actually match voxels with similar characteristics, meaning that by connecting these voxels with similar characteristics aggregate WM tracts can be identified. The largest commissural WM tract of the brain is the corpus callosum, a structure particularly susceptible to shear-strain injury that oc-

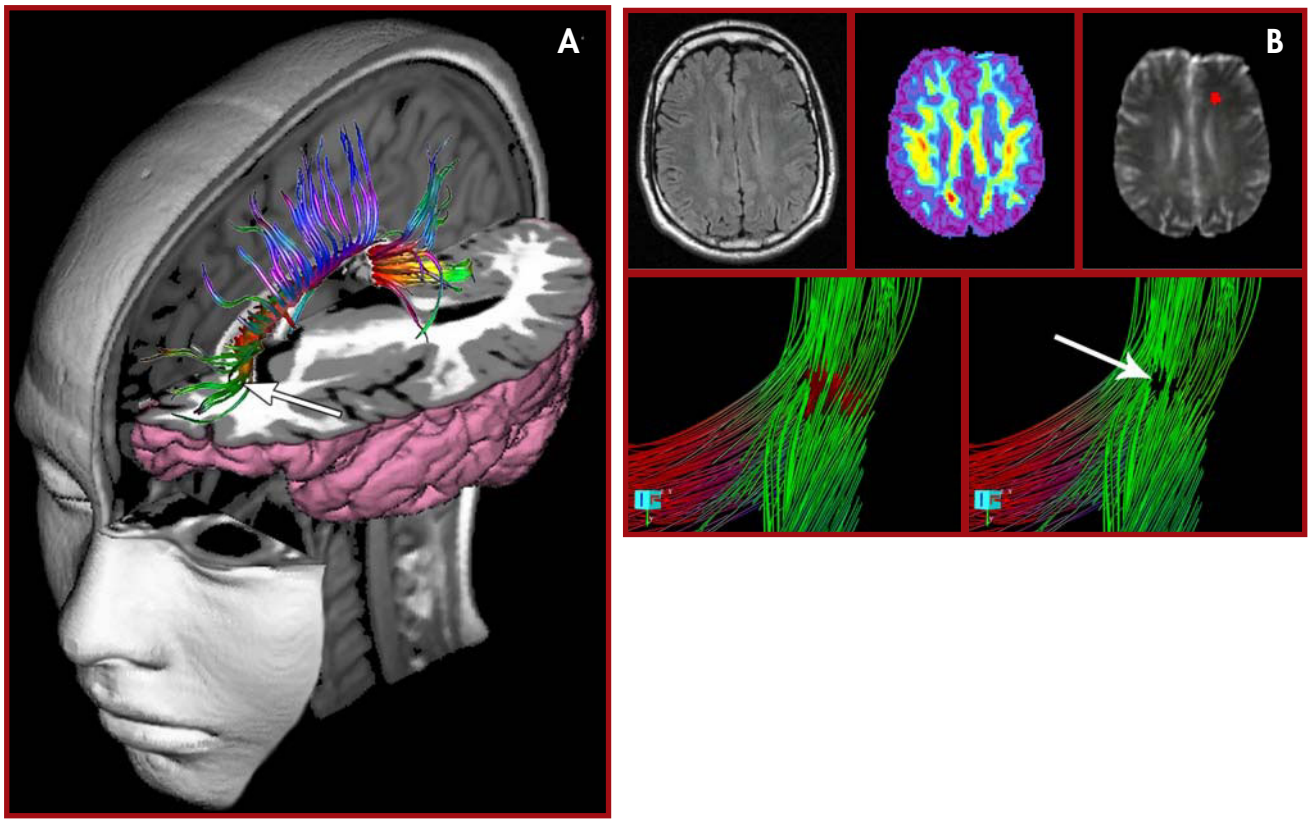


FIGURE 5–11. White matter damage in traumatic brain injury (TBI).

(A) The top 3-D image shows a cutaway with the left hemisphere diffusion tensor imaging (DTI) tractography findings from a child who sustained a severe TBI. Note the thinning out of tracts, similar to that observed in the case depicted in Figure 5–10. The arrow points to the location of the forceps minor region of white matter projection in the frontal lobe where the mild TBI case presented below shows discontinuity of the tracts in this region. Whereas the disruption of white matter tracts may be substantial in moderate to severe TBI, DTI findings when present in mild TBI are quite subtle and typically much less dramatic. (B) Fluid-attenuated inversion recovery (FLAIR) scan, fractional anisotropy (FA) map, and fiber tracking in a 49-year-old patient with TBI who was imaged 16 months after the initial trauma. The FLAIR image shows no abnormalities (top left). After analysis of the color-coded FA map (top middle), a region with reduced FA was identified in the WM of the left frontal lobe. This region of interest (ROI), illustrated in the top right T2-weighted image, included forceps minor and fronto-temporo-occipital fibers (bottom left), superior oblique view; the ROI is red and located centrally; the fibers are superimposed on an axial T2-weighted scan. At the level of the ROI, the respective fibers are discontinuous (arrow, bottom right; the ROI is left out in this image).

Source. Panel (B) images reprinted from Rutgers DR, Toulgoat F, Cazejust J, et al: "White Matter Abnormalities in Mild Traumatic Brain Injury: A Diffusion Tensor Imaging Study." *American Journal of Neuroradiology* 29:514–519, 2008. Used with permission of the American Society of Neuroradiology.

curs in TBI (see above discussion) as well as secondary Wallerian degeneration from cortical damage and disconnection (Guleria et al. 2008). Thus DTI can be used to show tract disruption from injury as well as metrics that actually measure tissue integrity as shown in Figure 5–10. Because WM is essential for neural conduction, the various DTI measures (i.e., FA) relate to speed of processing (Bazarian et al. 2007; Wilde et al. 2006b). Tractography methods are particularly useful in demonstrating pathological changes associated with brain injury (Bosnell et al. 2008; Wang et al. 2008).

DTI findings have been particularly important in advancing the understanding of how milder forms of TBI affect the brain (Belanger et al. 2007). For example, anisotropic metrics and tractography methods can be combined to depict subtle areas of pathological changes in WM pathways disrupted by even mild TBI. As with more severe injury, these abnormalities tend to be in the frontotemporal regions of the brain. There are now multiple DTI studies showing subtle pathological changes indicating microscopic WM abnormalities associated with mild TBI (Bazarian et al. 2007; Kraus et al. 2007; Lipton et al. 2009; A. Miles 1892; L. Miles et al. 2008; Niogi et al. 2008a, 2008b; Rutgers et al. 2008a, 2008b; Singh et al. 2010; Wilde et al. 2008). As shown in Figure 5–11, maps of DTI abnormality can be identified and used to localize the greatest likelihood for abnormality. Tractography is then applied to actually examine the integrity of aggregate WM pathways; DTI has shown how vulnerable commissural fibers are in TBI (Wilde et al. 2006a).

Magnetic Resonance Spectroscopy (MRS)

Like the anisotropy measures of DTI, other measures of tissue integrity can be achieved with MRI, including chemical composition based on spectroscopic analysis (Ashwal

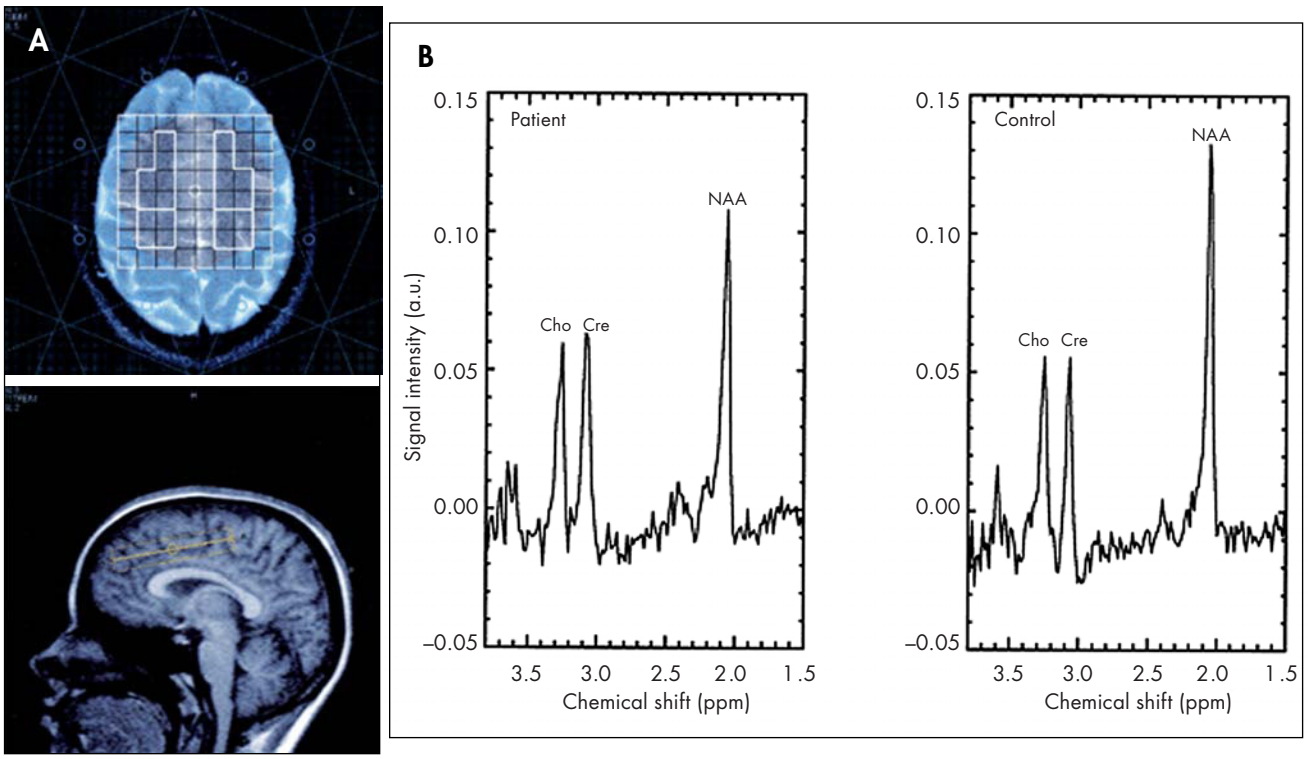


FIGURE 5–12. Magnetic resonance spectroscopy of traumatic brain injury.

(A) Position of the spectroscopic imaging voxel of interest (VOI), as viewed in the axial and sagittal planes. On the axial image, the outlined sections inside the VOI depict voxels typically selected for the four regions of interest, and the pattern surrounding the VOI is the area covered by the eight multiple regional saturation technique pulses for saturating lipid signals from the scalp. (B) Average spectra obtained from the left frontal lobe of a patient versus that of a control subject demonstrate a decrease in *N*-acetyl aspartate (NAA) after traumatic brain injury. Cho=choline; Cre=creatine; ppm=parts per million.

Source. Reprinted from Hunter JV, Thornton RJ, Wang ZJ, et al: "Late Proton MR Spectroscopy in Children After Traumatic Brain Injury: Correlation With Cognitive Outcomes." *American Journal of Neuroradiology* 26:482–488, 2005. Used with permission of the American Society of Neuroradiology.

et al. 2006; Hillary et al. 2007; Kraus et al. 2007; Marino et al. 2007; Pascual et al. 2007; Signoretti et al. 2008). Proton MR spectroscopy (^{1}H MR spectroscopy; MRS) provides biochemical information about detectable neurometabolites and mobile lipids (Rigotti et al. 2007). Most important to TBI (because of the vulnerability of axons and its specificity to neurons), MRS can detect levels of *N*-acetyl aspartate (NAA). NAA is considered a marker of neuronal health—reductions reflect abnormal neural tissue. Figure 5–12 (from Hunter et al. 2005) shows MRS comparisons, including NAA, choline (assessment of membrane integrity by membrane turnover rate), and creatine (which measures cellular energy status), between an individual with TBI and an age-matched control subject. The particular importance of MRS is that it permits assessment both of normal-appearing tissue that may be injured/dysfunctional and of how the presence of abnormalities may relate to neurobehavioral and cognitive outcome (Babikian et al. 2006; Gasparovic et al. 2009; Yeo et al. 2006).

Obvious lesions with conventional imaging can be easily visualized, clearly outlining regions of pathology, but normal-appearing tissue is more challenging to assess. As already mentioned, quantitative volumetric measures can be helpful, but MRS measures offer direct assessment of tissue integrity regardless of its clinical appearance on standardized imaging (Le and Gean 2009). As with DTI, MRS methods may also assist in detecting subtle abnormalities associated with mild TBI (Cohen et al. 2007). In addition, MRS can be integrated with volumetry and DTI methods (Cohen et al. 2007; Kraus et al. 2007), where such integration may improve the detection of clinically meaningful abnormalities.

Cortical Contusions and Their Most Likely Region of Occurrence

The most likely locations of cortical contusions are in the frontal and temporal lobe regions (see Bigler 2007). This is demonstrated by Levine et al. (2008) using a template approach to represent the common overlap of comparison as shown in Figure 5–13.

Figure 5–14 shows how a focal frontal lesion disrupts pathways distal from the area of focal damage. This reinforces the principle that the obvious focal areas of damage readily observed on conventional imaging show only a small part of the actual extent of neuropathology.

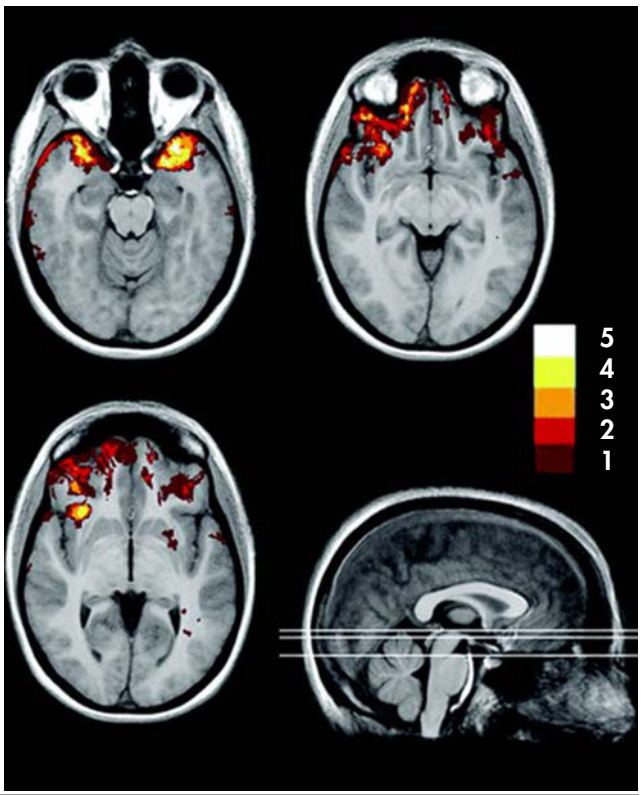


FIGURE 5–13. Lesion tracings are projected on selected axial slices of a template brain derived from 12 healthy control subjects.

The color scale indicates degree of lesion overlap across patients (max = 5). Lower right sagittal image indicates slice location of the three axial images, with the most ventral axial image appearing in the upper left, the middle axial image in the upper right, and the most dorsal axial image in the lower left.

Source. Reprinted from Levine B, Kovacevic N, Nica EI, et al: "The Toronto Traumatic Brain Injury Study: Injury Severity and Quantified MRI." *Neurology* 70:771–778, 2008. Used with permission.

Neuroimaging Evidence of Diffuse Brain Damage

Using the newer methods that provide voxel-by-voxel comparisons across the entire brain as well as comparative analyses using traditional volumetry methods, studies have clearly demonstrated the generalized nature of TBI (Maas et al. 2008; Maruichi et al. 2009). The generalized parenchymal damage is driven in part by the severity of injury, but even in more mild injuries the neuroimaging evidence is for nonspecific pathological changes (Chu et al. 2010). Focal damage is often easy to visualize with state-of-the-art contemporary neuroimaging, but the focal lesions represent just one aspect of the injury. Typically, the damage is far more widespread and disruptive, as demonstrated in Figure 5–14.

The child shown in Figure 5–14 sustained a focal injury to the frontal lobe. The degree of focal frontal atrophy is impressive, but more impressive is the change in the number of tracts that emanate from the frontal region as a consequence of the focal damage. In comparison with the age-matched control, substantial differences are widespread in terms of the number of aggregate fiber tracts and their projections. In this context, it is very important to view TBI at all levels. From a holistic perspective of integrative brain function dependent on complex neural networks that underlie human behavior and cognition (Hagmann et al. 2008; Honey and Sporns 2008), any brain injury is a disruption in the network of interconnected pathways. As shown in Figure 5–15, recent studies have also demonstrated that TBI-related whole-brain atrophy is associated with thinning of the cortical mantel (see Merkley et al. 2008) and that essentially every major brain region is affected in TBI.

Neurobehavioral Correlates

As shown by Schooler et al. (2008), who examined Vietnam war veterans with penetrating wounds (mostly low-velocity shrapnel fragments), the site of the lesion did not relate to the short-term memory impairment exhibited, but the mere presence of a lesion related to short-term memory impairment regardless of the lobe or hemisphere affected. Given the interconnectiveness of the brain, it is not surprising to find that a focal lesion in a particular brain region can be disruptive to distal areas (Honey and Sporns 2008). Likewise, the total number of lesions and lesion sites appears to be the best predictor of neurobehavioral outcome in TBI (Niogi et al. 2008a, 2008b). The rapid improvement in neuroimaging research and scan analysis techniques has resulted in more precise lesion detection. Given how this has allowed for neuroimaging findings to be integrated with neurobehavioral measures (Wang et al. 2008), it is likely that further algorithms will be developed for even better prediction of outcomes from TBI. For example, Figure 5–16 shows the relationship of impaired prospective memory to areas of focal atrophy that measure cortical thickness in pediatric TBI patients. Also, integrating functional MRI with quantitative MRI procedures has tremendous potential for illuminating how brain injury can disrupt neural function (see Mayer et al. 2009; McCauley et al. 2010).

Contemporary Clinical Neuroimaging of TBI

Each MRI sequence yields different information about potential parenchymal injury, details of which were provided in the first edition of this chapter (see Bigler 2005). In brief, the T1 sequence is best for overall gross brain anatomy, whereas the T2 sequence is best for showing CSF and CSF-related abnormalities as well as providing some nice contrast between WM and GM structures. The older proton density-weighted and gradient-recalled sequences, which could identify hemosiderin deposits, have been supplanted by the susceptibility-weighted sequence as shown in Figure 5–5, which has greater sensitivity to detect blood by-products secondary to parenchymal and vascular shearing and other types of hemorrhagic lesions from trauma. The FLAIR sequence provides excellent

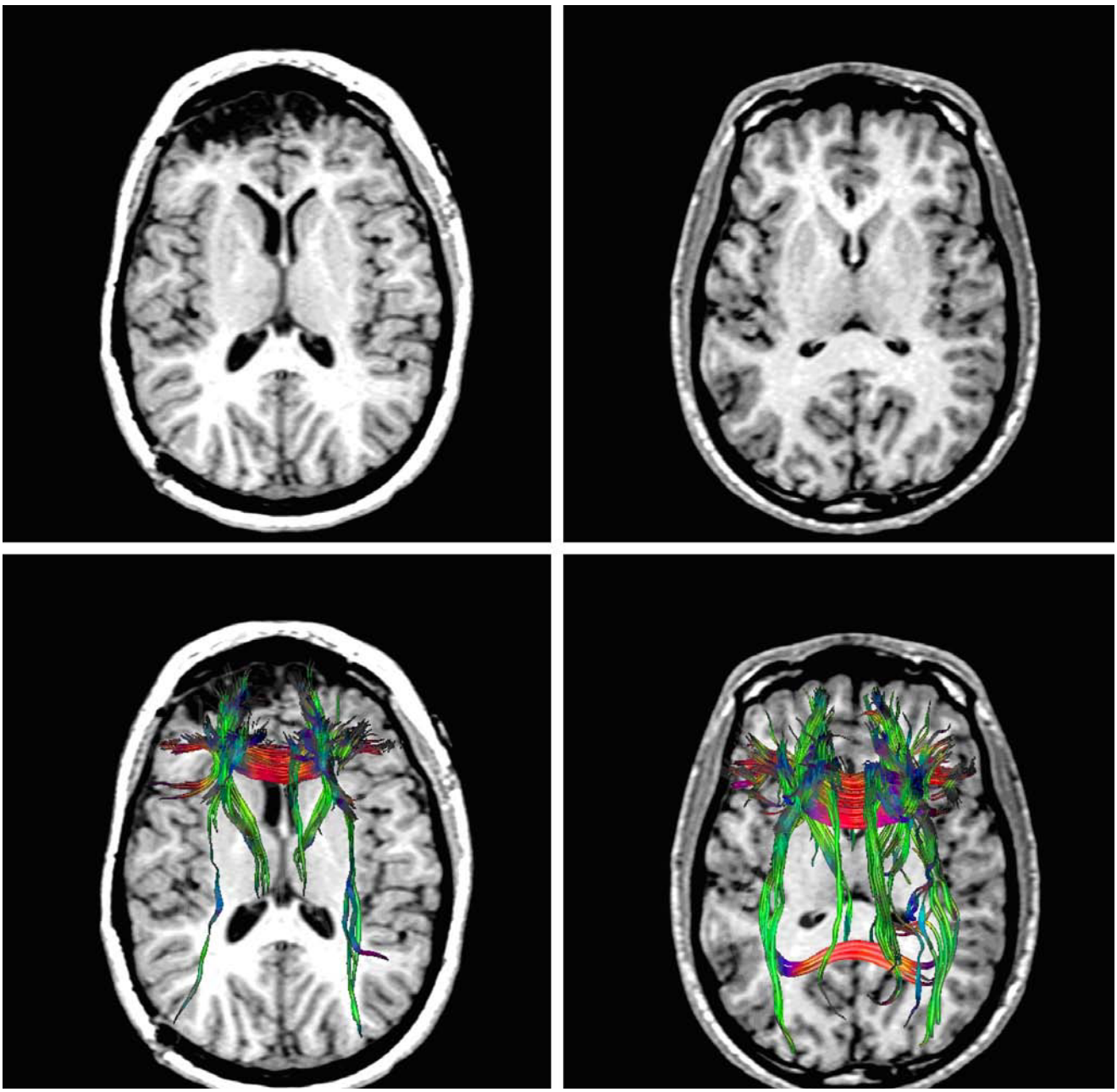


FIGURE 5–14. Loss of white matter tracts in traumatic brain injury (TBI).
(Top left) Severe TBI in a child with extensive frontal encephalomalacia. (Top right) Similarly aged and demographically matched child with normal scan. These anatomical scans do not permit a visualization of the extent of the loss of connectivity that occurs from damage. Note the dramatic differences in the complexity of the connectivity emanating from similar frontal regions when comparing a damaged frontal lobe with that of a typically developing child. Diffusion tensor imaging tractography projections are superimposed on an axial T1 anatomical magnetic resonance image in a 12-year-old female who had sustained a severe TBI (Glasgow Coma Score=5) as a result of falling backward off the back of a pickup truck, striking the back of her head on the pavement but sustaining significant contracoup frontal contusions. The same color schema applies as discussed previously. These images show that the frontal injury results in marked thinning and loss of frontal projecting tracts emanating from the frontal polar region of the brain. This illustration dramatically shows the loss of brain interconnectiveness as a consequence of focal damage distal to the endpoint of where fiber tracts project (see Oni et al. 2010 for additional information).

visualization of gross WM abnormalities, but DTI informs the clinician about WM microstructure.

Although the DTI images presented in this chapter provide impressive visualization of WM integrity, including aggregate fiber tracts, there are several metrics that can be applied to DTI to actually measure WM integrity. For example, MRI is based on the movement of water, and DTI is essentially measuring the diffusion of water molecules along the continuum of isotropic (where water is free to diffuse in any direction) to anisotropic diffusion (restric-

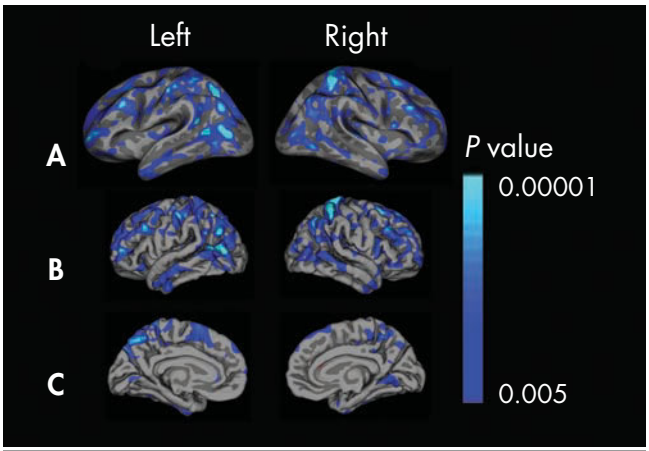


FIGURE 5–15. Regions of significant cortical loss in pediatric traumatic brain injury compared with brains of typically developing children, reflecting adjustments made for age and gender.

The *P*-value color scale indicates group differences ranging from dark blue ($P<0.005$) to light blue ($P<0.00001$). Results are displayed on a customized averaged pediatric subject. (A) Lateral view (with surfaces inflated to reveal the extent of significant regions) showing group differences bilaterally for temporal and frontal lobe ($P<0.005$). (B) Lateral view (now shown as pial surfaces) indicating the same significant regions as displayed in A. (C) Midsagittal pial surfaces showing significant cortical regional differences.

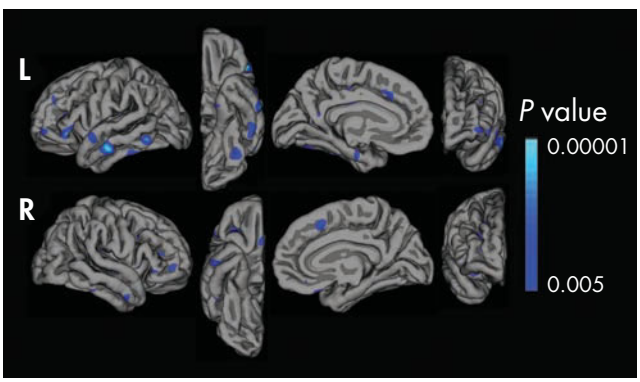


FIGURE 5–16. Cortical thinning related to impaired prospective memory in traumatic brain injury.

Areas of cortical thinning that were associated with event-based prospective memory (EB-PM) performance in pediatric traumatic brain injury are shown in sagittal, inferior, medial, and coronal views. As in Figure 5–15, the *P*-value color scale indicates group differences ranging from dark blue ($P<0.005$) to light blue ($P<0.00001$). Bilateral middle and inferior frontal, middle and inferior temporal, and parahippocampal and cingulate gyri thicknesses were found to be significantly related to EB-PM performance. Regions of significant brain-behavior relation appear to be spatially larger in the left hemisphere. Involvement of the temporal lobes and parahippocampal gyri highlights the inherent role of retrieval processes in supporting PM functioning.

tion of water movement). One of the most common DTI metrics is fractional anisotropy (FA), where FA ranges from 0.0 to 1.0, with 0.0 representing maximal isotropic diffusion (free diffusion in a perfect sphere) and 1.0 representing maximal isotropic diffusion in a single direction. FA varies across WM regions and is thought to reflect differences in fiber myelination, fiber diameter, and directionality of aggregate fiber tracts. There are several other common DTI metrics that can be applied to TBI as discussed by Mukherjee et al. (2008b), Sullivan and Pfefferbaum (2007), and Sundgren et al. (2004).

Quantitative Neuroimaging for the Clinician

Although computer-based methods for image quantification go back to the early 1980s (see Turkheimer et al. 1984), until recently all of these methods were time intensive and required laborious hand tracings of a region of interest. Now automated methods, as shown earlier in Figure 5–9 comparing the pixel-by-pixel density of WM, GM, or CSF concentration within a designated voxel, can be used to compare the individual with a group (also as shown in Figure 5–9), or the group effects of a TBI can be compared with a matched control sample. But most impressively, now individually automated image analysis can be performed on any volume acquisition MRI scan using methods such as FreeSurfer (Khan et al. 2008). Commercially available and medically approved by the U.S. Food and Drug Administration, image quantification for MRI is now available (Brewer et al. 2009). This fully automated program provides basic volumetric information, such as hippocampal and temporal horn volume.

Hippocampal damage is commonplace in TBI (Wilde et al. 2007), in which volume reduction of the hippocampus and concomitant temporal horn expansion indicate reduced structural integrity of the medial temporal lobe (see Bigler et al. 1997). For the clinician, knowing something about the integrity of the medial temporal lobe may be very important in relating neurobehavioral changes like emotional lability or presence of depression in the TBI patient as well as deficits in memory function. For example, although the medial temporal lobe is not shown in Figure 5–9, this patient's quantitative image analysis demonstrated that hippocampal volume was approximately one standard deviation below the normative data for this adolescent patient's age group, which clinically was assumed to be a likely factor in the demonstrated memory impairments noted on neuropsychological assessment.

Conclusion

In the TBI postmortem study by Jones et al. (1998), the DOI CT was examined in conjunction with follow-up MRI and gross as well as microscopic pathology of the brain at the time of death. Both CT and MRI were sensitive to gross lesions, but neither technique captured the full extent of underlying pathology, particularly nonhemorrhagic axonal injury. Thus, visually detected macroscopic lesions ob-

served in contemporary neuroimaging as reviewed in this chapter never fully detect the extent of actual trauma-induced neuropathological changes. DTI methods appear to be much better at detecting more subtle pathology but still only approximate the histological effects of the injury. The point of the Jones et al. study and the current review on structural imaging in TBI is that any detectable lesion likely has a much more widespread underlying pathology than what is shown on a scan image or metric (i.e., DTI or MRS measures). As elegantly shown by several authors (see review by Guye et al. 2008), brain organization and function should be viewed from the perspective of brain networks and connectivity. TBI disrupts that connectivity, and the presence and location of identifiable lesions associated with injury aid clinicians in understanding the neurobehavioral effects of a brain injury.

KEY CLINICAL POINTS

- Traumatic brain injury (TBI) is a heterogeneous disorder resulting from a variety of causes, extending from trivial and transient injuries to catastrophic damage and ranging from focal to diffuse injuries and outcomes.
- Contemporary neuroimaging methods provide unprecedented opportunity to image the injured brain.
- A particular aspect of TBI is damage to white matter (WM). This can be exquisitely examined using a variety of magnetic resonance imaging techniques, but the most promising technique for defining regions of WM pathology comes from diffusion tensor imaging (DTI).
- DTI provides a variety of metrics to assess WM integrity, including the visualization of aggregate tracts in the brain. In fact, technology now exists that permits DTI to define all major WM tracts in the brain.
- Brain connectivity is often affected in TBI, and DTI combined with functional neuroimaging techniques provides a method for direct examination of the patency of WM connections.
- Various neuroimaging methods permit a detailed neuroanatomical and functional assessment of the brain that relates to cognitive and neurobehavioral outcomes following TBI.

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CHAPTER 6

Functional Imaging

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TECHNOLOGICAL ADVANCES IN THE LAST CENTURY have allowed us unprecedented access to brain structure and function. Structural imaging techniques such as skull X rays, computed tomography (CT), and magnetic resonance imaging (MRI) have proved immensely helpful in assessment of extent of brain injury and in following the medical sequelae of traumatic brain injury (TBI), such as edema, intracranial bleeding, and degeneration. These tools provide increasing detail about bone and tissue injury sustained in TBI and many other medical conditions. However, these methods cannot assess the "function" or underlying cerebral metabolic rate (CMR) and cerebral blood flow (CBF) in the brain. Subtle brain changes after traumatic brain injury (TBI), although sufficient to affect a patient's ability to function at a normal level, may not be visible on structural imaging. The majority of mild TBI patients have normal CT and MRI scans (for review, see Belanger et al. 2007). Functional imaging techniques promise to help elucidate brain injury in these particularly challenging cases.

Functional brain imaging utilizes several methods to capture brain activity as reflected by regional CMR (rCMR) or regional CBF (rCBF) (Table 6–1). Clinical functional brain imaging in TBI is currently performed with single-photon emission computed tomography (SPECT) or positron emission tomography (PET). In both techniques a radioactive isotope is injected into the patient and its uptake is measured to give an indication of rCMR or rCBF. Another technique, functional magnetic resonance imaging (fMRI), makes use of the magnetic qualities of deoxygenated blood to create rapid images of brain blood flow. Magnetic resonance spectroscopy (MRS), which uses the same principles as MRI but gives information on cellular function, is also increasingly used in TBI research. It is described in Chapter 5, Structural Imaging. An advantage of both fMRI and MRS is that neither of them requires injection of ionizing radiation. These modalities represent the main functional imaging techniques available at this time. Other methods that are just coming into use will be reviewed briefly.

TABLE 6–1. Brain imaging techniques

Method	What is usually measured	Advantages	Approximate cost per study ($ per Medicare)	Time to complete study (minutes)	Limitations/issues
SPECT	Blood flow	Widely available; relatively inexpensive	300	≤30, depending on tracer	Requires ionizing radiation; resolution limited
PET	Metabolism or blood flow	Superior to SPECT for anatomical resolution; can measure metabolism	1,000	30–40 for FDG; 5 for ^{15}O	Requires ionizing radiation; not widely available
fMRI	Blood flow	No ionizing radiation; good anatomical resolution; repeat studies can be done quickly	Not applicable for TBI	Generally 45–60	Currently research-only for TBI; cognitive activation task usually used
MRS	Change in brain metabolites	No ionizing radiation; noninvasive neurochemical measurements	Not applicable for TBI	Generally 45–60	Currently research-only for TBI

Note. FDG=fluorodeoxyglucose; fMRI=functional magnetic resonance imaging; MRS=magnetic resonance spectroscopy; PET=positron emission tomography; SPECT=single-photon emission computed tomography; TBI=traumatic brain injury.

The ultimate hope is that functional imaging will allow clinicians to more accurately assess brain impairment, better predict potential for rehabilitation, and objectively measure recovery of function. Researchers also hope to use these tools to study brain function after TBI in humans, with the goal of improving our understanding of how tissue injuries can be treated and perhaps ameliorated. Use of functional imaging in the assessment of TBI has increased in the last three decades. The actual contribution of these modalities to improvement in clinical care and outcome, however, is still more promise than reality.

We begin with a discussion of how to evaluate the various types of studies available. We then review the literature for each modality, with emphasis on controlled studies with clear outcome measures that address the utility of functional imaging for clinical assessment of TBI. We also review studies that use functional imaging to examine possible neuropathological contributions to behavioral changes after TBI. SPECT and PET, which are the clinically relevant modalities, receive the most attention. Finally, we review recent work with fMRI and other modalities that may have promise for future clinical applications.

Understanding the Literature

As new techniques emerge, clinicians need to be able to evaluate current research and critically review published studies. This section gives an overview of the most critical factors in evaluation of research in functional brain imaging in TBI and in many other conditions. There are relatively few controlled studies of the utility of functional brain imaging for assessment and treatment of TBI patients. Many studies use data from functional scans originally obtained for clinical purposes, so that imaging data were not collected in a systematic, uniform manner. Standardized ratings of scans are the exception, although recent studies are more likely to use quantitative approaches such as statistical parametric mapping. Also, because the patients who are being studied must all be treated with the optimal therapies available at the time of the study, there are few opportunities for objective evaluations of treatment with functional imaging (due to the obvious ethical concerns). When patient data are compared with data from normal control subjects, care must be taken to ensure that control subjects are matched to the patient groups with regard to important variables such as age, handedness, sex, and general health, all of which can affect brain blood flow and metabolism. Matching for an equivalent level of physical trauma (orthopedic control) can also be valuable. Presence of active psychiatric symptomatology is common after TBI and can also affect these measures of brain activity. Finally, many injury-related factors such as bony injury, edema, changes in white matter integrity, and diffuse axonal injury may all complicate interpretation of functional imaging acquired using any of the various modalities (for review, see McAllister et al. 2001).

When reviewing the literature on functional imaging in TBI, important distinctions must be made between the type of information acquired in resting and activation scans. In resting scans the patient lies motionless with eyes closed, sometimes in a darkened room. Activation scans are acquired during performance of a cognitive task, such as memorization of words presented on a computer screen, which allows for assessment of function in a (relatively) isolated domain when compared with a baseline scan. All functional imaging studies are limited in that other factors such as physiological changes unrelated to what is being assessed are also present. Use of an activation paradigm may help to increase activity in a certain network of structures that are the focus of study. Activation studies are often limited to a single assessment some period after TBI, during which recovery is felt to have occurred (sometimes measured by improvement on performance of neuropsychological tests). Few studies use pre- and postrecovery scans, which offer the benefit of allowing for comparison in the same patients. For activation studies, control for level of education, fluency in the language in which stimuli are presented, and other demographic variables may also be important because these factors may influence the subject's ability to perform the task and, ultimately, the functional imaging results.

Single-Photon Emission Computed Tomography (SPECT)

In SPECT, brain blood flow is determined on the basis of the distribution of a radiopharmaceutical agent in the brain. A radiotracer is injected into a patient's vein. As the tracer decays, it emits a photon, which is detected and recorded by the SPECT gamma camera (Figure 6–1). The computer reconstructs these detections to produce a tomographic image of activity throughout the brain, similar to the "slices" produced by a CT or MRI examination. Like MRI, coronal, sagittal, and axial views as well as 3-D reconstructions are all available. This image can be visually interpreted by a nuclear medicine specialist and/or analyzed statistically using various software programs.

Older SPECT cameras, which were used for many of the studies discussed below, had limited detectors and produced poor quality images (Figure 6–2). More credence should be given to studies performed with the newer triple-head cameras. These provide a resolution of about 1 centimeter, allowing assessment of much smaller structures (Figures 6–3 and 6–4). Use of companion structural imaging studies (CT or MRI) in the same patient can provide greater precision of anatomical location. This method is called *co-registration* of the structural and functional images.

Tracers

The most commonly used radiotracer for clinical SPECT is technetium-99m hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO), which accumulates in endothelial cell membranes a few minutes after injection. Concentrations of this tracer are thus highest in regions receiving the most plentiful blood flow shortly following the injection and remain so for up to 24 hours. Because of this long half-life, multiple scans can be acquired on a patient following one injection, which can be helpful if the patient moves. How-

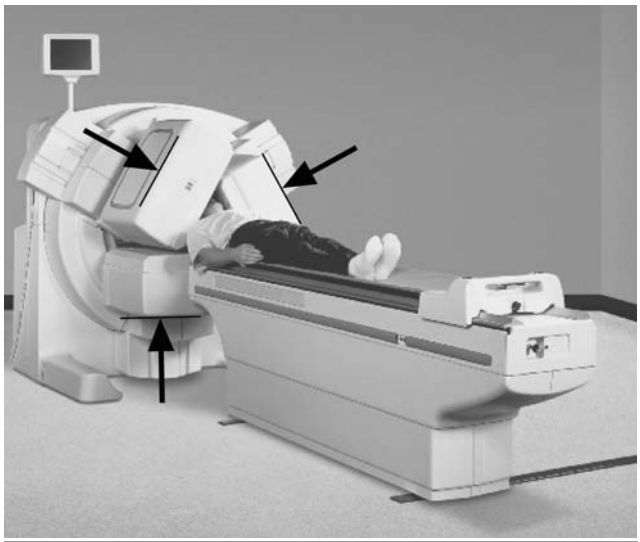


FIGURE 6–1. Procedure for obtaining a single-photon emission computed tomography (SPECT) scan.

The same scanner is used for imaging many body systems, including brain, heart, bone, and lung. Details of the procedure differ. Before brain imaging, the patient receives an intravenous injection of the radioactive tracer while lying in a darkened room. After a short period in the darkened room to allow the tracer to distribute through the brain, the patient is ready to be scanned. The tracer distribution is stable for several hours, thus allowing a considerable time window for scanning to occur. After the patient is positioned on the scanner table, the gamma camera heads are moved in as close to the patient's head as possible. Illustrated is a multidetector system (IREX, Philips Medical Systems, Andover, MA), with three cameras (arrows). The cameras rotate around the patient's head during the imaging examination, and data are collected from multiple positions. The data are transmitted to a computer that produces tomographic images in the desired plane(s) of section.

Source. Picture courtesy of Philips Medical Systems, Andover, MA.

ever, because the tracer was taken up at a certain time, the location of tracer concentration in the brain does not change; for example, for research purposes, one could not perform a visual activation study and then an auditory study on one patient using the same tracer injection.

Ligand studies, in which a radioactive ligand (marker) binds with a particular receptor, transporter, or protein, are becoming an important tool in both SPECT and PET and could contribute to future understanding of neurotransmitter change during cognitive processes. For example, if a ligand that binds specifically to one neurotransmitter type is administered, followed by a scan, and then an activation task is performed, a follow-up scan could potentially give information on how much ligand was displaced by the endogenous neurotransmitter, suggesting involvement of that system in the task. Receptor studies, for example, examining benzodiazepine receptor function in TBI, have also been conducted with SPECT but are not discussed (see Table 6–2 for a review of commonly used, U.S. Food and Drug Administration [FDA]–approved SPECT tracers). We limit our discussion here to blood flow studies because they are the most clinically relevant at this time.

Practical Considerations

SPECT scans can be obtained in most large medical centers and are substantially more affordable than PET. For clinical use, a resting SPECT scan of the whole brain is generally ordered. Intravenous radioactive tracer is injected into the patient a few minutes prior to scanning, preferably in a quiet, controlled environment to minimize blood flow changes due to anxiety and presence of loud noise. The patient should be able to lie still in a supine position in the scanner for the duration of the scan, up to half an hour. If the patient is too agitated to remain still, sedation may be given *after* tracer injection, to minimize effects on the uptake and distribution of tracer. With the most commonly used SPECT tracer (^{99m}Tc-HMPAO), the concentrations of tracer remain stable in the brain for up to a day, so that the patient can be imaged several hours after the injection is given. Because the patient is exposed to ionizing radiation with this technique, consideration must be given to the number and recency of prior scans using radioactive tracers.

Indications

At this time no clear guidelines exist for use of SPECT in evaluation and treatment of TBI. Clinicians generally order SPECT scans when brain injury is suspected but not seen on structural studies, or when structural studies do not indicate damage extensive enough to explain a patient's deficits.

Limitations

SPECT studies typically provide information only about relative CBF, not absolute CBF, as can be done with PET. The xenon gas inhalation technique produces quantitative CBF values, but the images are of relatively poor quality and low resolution, compared with PET. There are no SPECT tracers for study of cerebral metabolism. Interpretation is often performed by visual rating of scans for abnormalities rather than with use of quantitative or statistical methods, introducing problems inherent in use of subjective, nonstandardized ratings. Comparisons of results from different studies are challenging, because some groups may report only the presence of overall abnormality whereas other groups may report number of individual lesions seen in each scan. A particular issue is the common approach of comparing regions of interest (ROIs) with a brain region presumed to be free of injury (often the cerebellum). This is problematic in TBI, in which injuries can be diffuse and subtle. Also, blood flow is not the same as metabolism. The two are often highly correlated, especially in normal brain tissue, but an uncoupling of this relationship may occur after brain injury (Belanger et al. 2007).

Overview of Abnormal SPECT Findings in TBI

Although promising as an accessible, low-cost method for the study of brain activity after TBI and during recovery

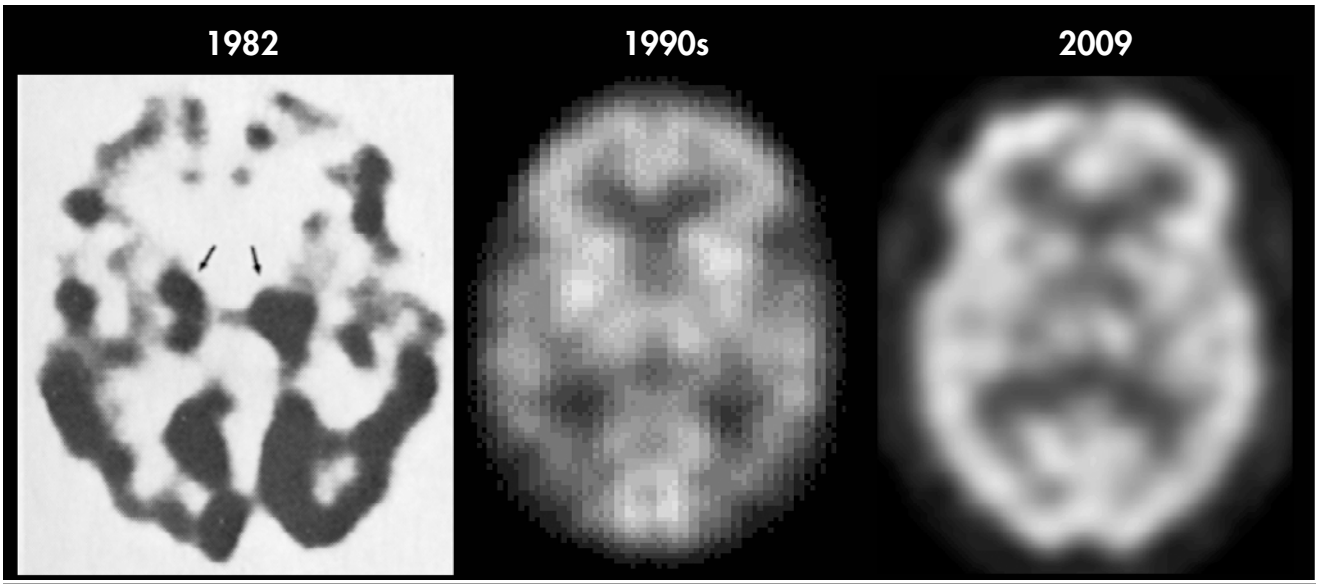


FIGURE 6–2. SPECT imaging then and now.

Axial single-photon emission computed tomography (SPECT) images of normal brain acquired in 1982, early 1990s, and 2009. Note the significant improvement in resolution since the 1980s.

Source. SPECT image (1982) reprinted from Hill TC, Holman, BL, Lovett RD, et al.: "Initial Experience With SPECT (Single Photon Computerized Tomography) of the Brain Using *N*-isopropyl I-123*p*-iodoamphetamine: Concise Communication." *Journal of Nuclear Medicine* 23:193, 1982. Used with permission of the Society of Nuclear Medicine.

from injury, there are relatively few methodologically sound SPECT studies in the literature. There are even fewer studies incorporating other methods of assessment, such as neuropsychological testing and standardized ratings for recovery, in conjunction with SPECT for evaluation of TBI.

Studies Using SPECT and Structural Imaging

SPECT has been used in combination with structural imaging in numerous studies. It should be noted that in most studies, the SPECT scan was not co-registered with a structural image. Instead, the scans were interpreted separately, and functional results were compared with those from structural modalities. In general, more abnormalities are seen on SPECT scans (Figures 6–5, 6–6, and 6–7) than on structural imaging such as CT and MRI in studies of both pediatric and adult TBI patients (acute and remote; mild, moderate, and severe), although these differences are not of large magnitude in all studies (for reviews, see Belanger et al. 2007; Dubroff and Newberg 2008; Munson et al. 2006; Van Boven et al. 2009). Especially in cases of mild TBI, SPECT may show abnormalities where no lesions were seen on structural imaging, which may be helpful in explaining the cause of persistent behavioral changes. In some cases, lesions on structural scans are not detected with SPECT. For example, a prospective study of patients with mild TBI compared CT and SPECT obtained within 72 hours of injury (Gowda et al. 2006). SPECT was positive (perfusion reduced at least 50% compared with cerebellum) in 63% (58/92) of patients. Of these, one-half also had CT findings. CT was positive in only two patients with negative SPECT. A weakness of this study is the use of cerebellum as a standard. In contrast to the commonly reported areas of decreased perfusion, one study of pediatric severe TBI found areas of increased perfusion at 3 years after injury (Chiu Wong et al. 2006).

Structural scans and SPECT are both generally interpreted by subjective visual analyses, so rater experience is an important variable. Often comparisons are made to an area assumed to have normal CBF, such as the cerebellum. As noted earlier, the highly individual nature of TBI makes the assumption that CBF of any particular region is unchanged in all TBI subjects problematic. Many SPECT studies do not include normal control comparison groups, which raises many issues about interpretation of results, as unsuspected neuroimaging abnormalities are sometimes present in healthy control subjects (Ichise et al. 1994). In the past decade, several studies using both quantitative methodology and comparison to healthy controls have confirmed that SPECT abnormalities are common even in cases of diffuse axonal injury (DAI), when structural imaging is much more likely to be normal (Okamoto et al. 2007; Shin et al. 2006; Stamatakis et al. 2002). In two studies, SPECT scans obtained early (13±4.6 and 2–18 days) after injury from patients with all levels of severity (Glasgow Coma Scale [GCS] 3–15) were analyzed using statistical parametric mapping (Shin et al. 2006; Stamatakis et al. 2002). The study of patients with DAI found areas of significantly reduced rCBF in all 13 patients (compared with age- and sex-matched control subjects), including 6 patients with no abnormal areas on MRI. The study of patients with either focal or diffuse injury found similar SPECT and MRI lesion volume for focal injuries but greater lesion volume on SPECT than MRI for diffuse injuries (Stamatakis et al. 2002). More lesions had resolved on MRI

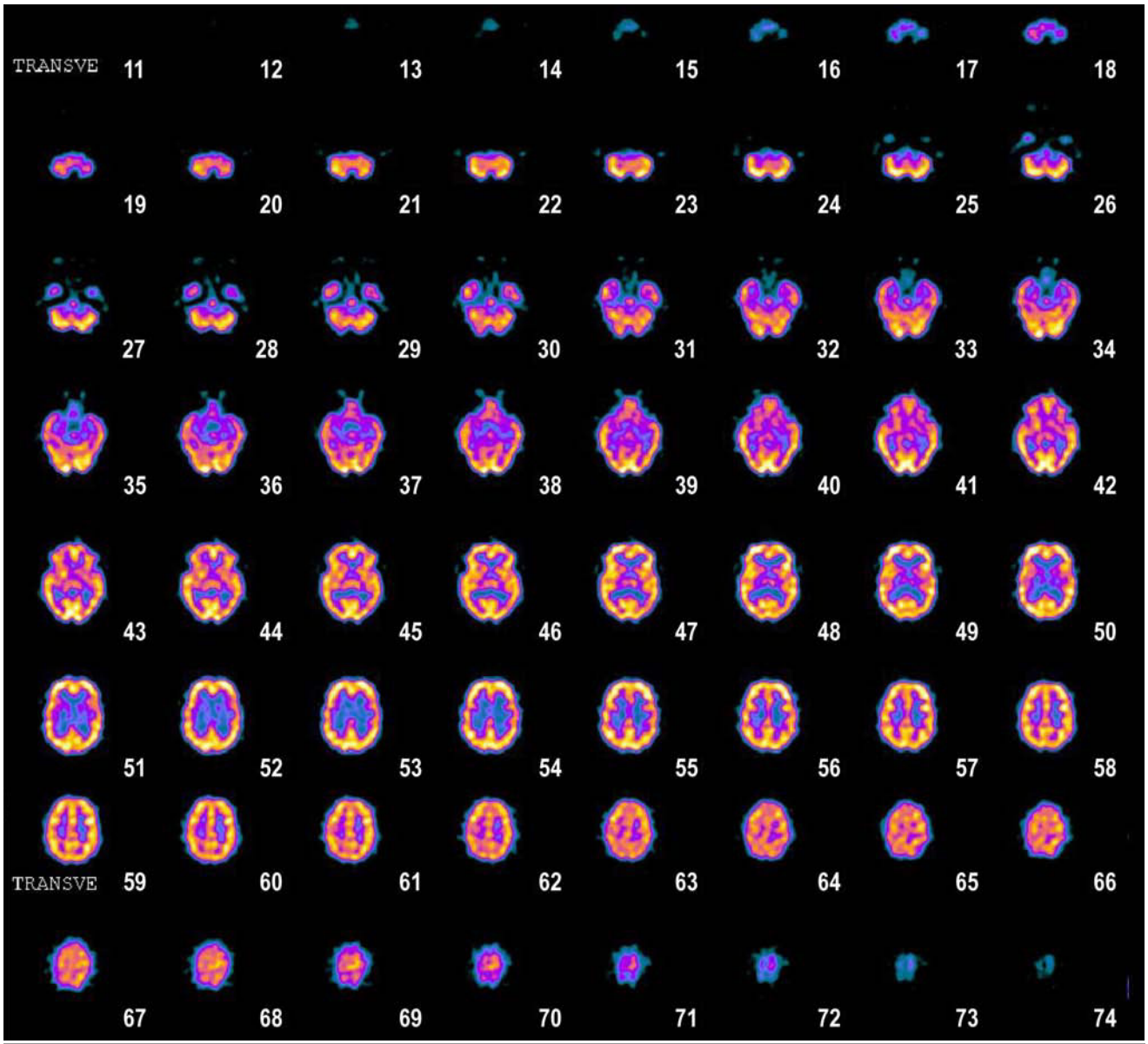


FIGURE 6–3. Serial axial SPECT images of a normal adult brain.
Reference numbers for brain slice order are shown next to each slice. SPECT= single-photon emission computed tomography.

than SPECT in both groups at follow-up (130–366 days). In the third study, SPECT scans obtained in the chronic stage (>3 months) from patients with all levels of severity (GCS 3–15) but no areas of hematoma or contusion on MRI were analyzed using the easy Z-score imaging system (Okamoto et al. 2007). There were areas of significantly reduced rCBF (compared with a normative database) in 89% (24/27) of patients, including 3 with no abnormality even on gradient echo MRI, which is more sensitive to DAI than T2-weighted or fluid-attenuated inversion recovery (FLAIR).

The limited work that has been done suggests that a normal SPECT scan after TBI is predictive of a good outcome (Jacobs et al. 1994, 1996). The predictive power of SPECT was assessed by following 136 mild TBI patients with normal CT scans for 1 year postinjury. Outcomes measured were neurological examination findings, postconcussive symptom checklist, and neuropsychological tests. Initial predictive power of SPECT was 44% at 3 months; thus, the likelihood of poor outcome at 3 months was 44% if initial SPECT was abnormal. This predictive power increased to 83% at 12 months. Negative predictive power (likelihood of a normal outcome if initial SPECT was normal) was 92% at 3 months and 100% at 12 months. Noting the high number of false-positive results in months 3 and 6 postinjury, the authors cautioned that an initial abnormal SPECT does not predict that recovery will be impaired. Thus, although an initial negative SPECT after TBI may be predictive of good clinical outcome, the utility of an abnormal scan for prognosis is less clear. However, it should be noted that little work has been done to elucidate the true relationship between an abnormal scan and objective outcome measures, especially for cases of subtle hypoperfusion.

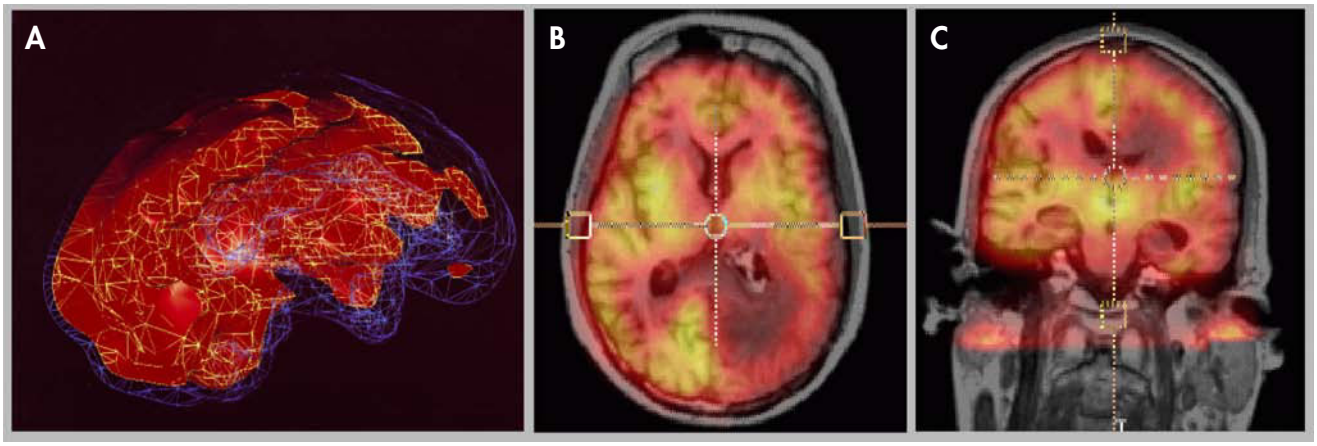


FIGURE 6–4. Current SPECT imaging capabilities.

Three-dimensional reconstruction of single-photon emission computed tomography (SPECT) results obtained 2 months post traumatic brain injury (A). Areas of normal blood flow are red. Note the absence of flow in the right anterior temporal and frontal lobes (foreground), resulting in visualization of the left temporal and frontal lobes from the medial side. Seeing blood flow deficits in three dimensions improves appreciation of the extent of lesions. Merging blood flow data with anatomical imaging also improves identification of areas of abnormality. Sectional SPECT images overlaid on T1-weighted magnetic resonance axial (B) and coronal (C) images.

Source. Pictures courtesy of Philips Medical Systems, Andover, MA.

TABLE 6–2. Commonly used U.S. Food and Drug Administration–approved tracers for SPECT

Tracer	Parameter measured	Comments
^{99m}Tc-HMPAO	Blood flow	Most commonly used clinical tracer for SPECT. Slow washout, so scan can be done long after injection of tracer.
^{123}I-IMP	Blood flow	Distributes quickly in brain, so scan must be done within 1 hour of injection.
^{201}Tl	Blood flow	Used for cardiac studies and assessment of malignancies throughout the body.

Note. ^{123}I-IMP=iodine-123–labeled *N*-isopropyl-*p*-iodoamphetamine; SPECT=single-photon emission computed tomography; ^{99m}Tc-HMPAO=technetium-99m hexamethylpropyleneamine oxime; ^{201}Tl=thallium-201.

Studies Using Behavioral Measures

Only a few studies have tried to correlate abnormal rCBF patterns with specific behavioral changes after TBI. Accurate assessments of behavioral problems prior to TBI, an important potential confound, are often missing. Utility of SPECT for prediction of which patients may be at risk to develop behavioral problems following TBI has not been explored to date.

A study of severe TBI found a significant correlation between frontal hypoperfusion and disinhibition; left hemisphere hyperperfusion and social isolation; and right hemisphere hypoperfusion and aggression (Oder et al. 1992). A study of mild TBI examined employment difficulties in patients who had been consistently employed prior to TBI and had normal postinjury structural scans (Varney et al. 1995). Both patient and control SPECT scans were rated by visual inspection, with the rater blind to whether the scan was from a patient or a control. All five control SPECT scans were rated as normal. Two of the mild TBI SPECT scans were also rated as normal. The remaining 12 patient SPECT scans demonstrated reduced rCBF, mainly in the anterior mesial temporal lobes and also, in some patients, in orbitofrontal regions. A study of pediatric mild TBI also reported a very high association between reduced rCBF in the medial temporal area and persistent postconcussive symptoms at 3 months (Agrawal et al. 2005). These studies suggest that even mild TBI can have an impact on a patient's functional abilities. In contrast, a retrospective study of mild TBI patients with persistent (>1 year) postconcussive symptoms found that although 40% (12/30) of patients had areas of reduced rCBF on SPECT (rated by visual inspection), these did not correlate significantly with psychiatric or cognitive symptoms (Lewine et al. 2007). A significant association was found between basal ganglia hypoperfusion and postconcussive headaches. These preliminary studies indicate that SPECT may prove helpful in assessment of behavioral sequelae of TBI.

Anosmia following TBI is a well-described clinical phenomena often associated with orbital frontal injury. Several recent studies have reported areas with normal structural imaging but reduced rCBF in patients with anosmia following TBI (Atighechi et al. 2009; Eftekhari et al. 2006; Mann and Vento 2006). When TBI patients with anosmia were compared with normosmic TBI patients, perfusion differences (determined both visually and semiquantitatively) were greatest in the frontal/orbital frontal region (Atighechi et al. 2009; Eftekhari et al. 2006). Hypoperfusion was also found in the left parietal and left temporal lobes (Atighechi et al. 2009). Mann and Vento (2006)

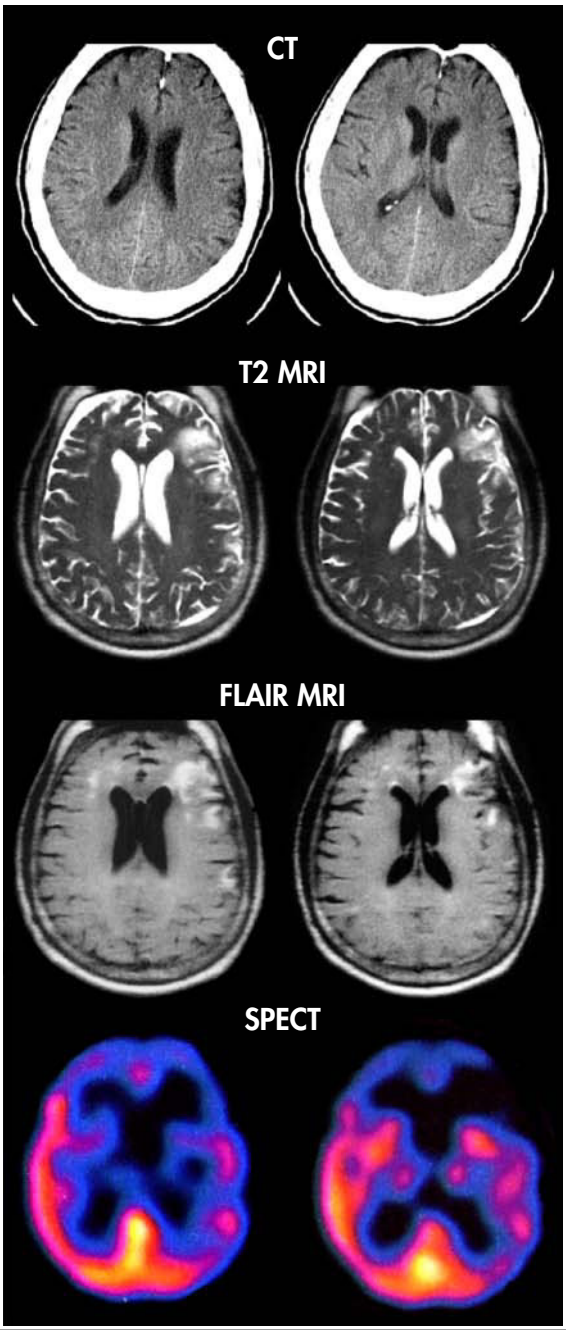


FIGURE 6–5. Early subacute presentation of traumatic brain injury on SPECT.

A 61-year-old man had a motor vehicle collision with a tree. This resulted in severe trauma with loss of consciousness requiring neurosurgical interventions. After several weeks of hospitalization, the patient was released. Within a few days, the patient's family brought him to a psychiatric emergency service with agitation, incoherence, cognitive impairment, and psychosis. Two different sectional levels in the brain are illustrated with companion axial CT, T2-weighted MR, FLAIR MR, and SPECT. Note that the injury is more apparent on the FLAIR images than on the T2-weighted MR and CT images. The true extent of the injury, however, can be appreciated only on the SPECT images.

CT=computed tomography; FLAIR=fluid-attenuated inversion recovery; MR=magnetic resonance; SPECT=single-photon emission computed tomography.

found SPECT to be more sensitive than MRI for detection of lesions in the frontal, temporal, and temporoparietal cortices in patients with anosmia following TBI.

Studies Using Neuropsychological Assessments

There have been limited comparisons of blood flow changes and performance deficits on neuropsychological testing in TBI patients. SPECT results have not been consistently correlated with neuropsychological test results in older studies. In one, a relationship was found between perfusion deficits and neuropsychological test performance in only 14 of 120 comparisons (Weidmann et al. 1989). In another, neuropsychological tests predicted SPECT findings, but the converse was not true (Umile et al. 1998). Results have been mixed in more recent studies. One found correlations between SPECT hypoperfusion in frontal, left posterior, and subcortical regions and neuropsychological test results in mild TBI patients who were studied an average of 5 years postinjury (Bonne et al. 2003). Another found some concordance between focal frontal and temporal abnormalities on SPECT (rCBF and cobalt uptake) and neuropsychological test performance in acute, mild TBI (Audenaert et al. 2003). A study in patients with DAI found SPECT hypoperfusion to be more consistent with neuropsychological test performance deficits than MRI (Okamoto et al. 2007). Another study in acute, mild TBI did not find any consistent relationship between SPECT abnormalities and neuropsychological test performance (Hofman et al. 2001). Thus, results have been less than encouraging. At the present time, SPECT cannot be used to predict neuropsychological/cognitive testing deficits.

Activation Studies

SPECT studies in which patients with TBI perform a cognitive or motor task during acquisition of brain images are few. In one, SPECT scans were obtained of patients with chronic diffuse severe TBI during resting conditions and performance (same session, split-dose paradigm, analyzed by statistical parametric mapping) of the Stroop interference test, which assesses a subject's ability to disregard distracting information (Goethals et al. 2004). The TBI patients' data showed impaired Stroop performance (longer response times) compared with normative data. This finding was associated with increased rCBF in posterior (mainly parietal) brain areas in addition to the normally activated anterior areas. As noted by the authors, this is consistent with recruitment of additional areas to support the attention management demands of the task. Another study compared odor-induced changes in rCBF in chronic mild-moderate TBI patients with posttraumatic smell impairment and healthy control subjects (Eftekhari et al. 2005). Resting and activation SPECT scans were separated by 2 days, and standardized ROIs were used to quantify differences. Smaller increases (4%–9% vs. 19%–25%) were found in all areas in TBI patients compared with healthy control subjects, suggesting that this method has potential for objective assessment of this condition. A weakness of this study is that it lacks a control group with

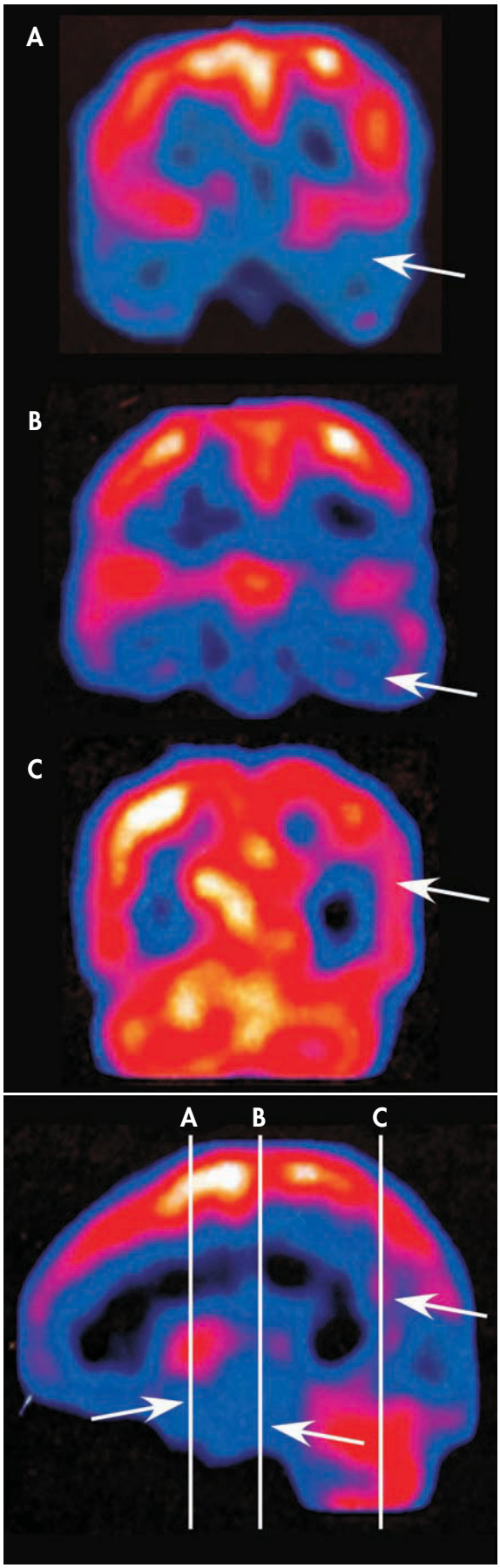


FIGURE 6–6. Late subacute presentation of traumatic brain injury.

A 24-year-old man had a motor vehicle accident with no loss of consciousness 10 years after a mild head injury. Shortly thereafter, the patient presented with severe cognitive deficits, depression, agitation, aggression, and psychosis. Symptoms were sufficiently severe to require prolonged psychiatric hospitalization. MR examination during this time was normal. Numerous perfusion abnormalities were evident on SPECT scans acquired 2 years later (a single sagittal and three coronal sections are illustrated). The most pronounced abnormality was moderately reduced perfusion in the left parietal lobe near the posterior Sylvian fissure and in both temporal lobes. Mildly reduced perfusion was noted in the occipital lobes (left greater than right) and basal ganglia (particularly near the caudate heads). Some of these abnormalities are visible on both the sagittal and coronal images (arrows). MR=magnetic resonance; SPECT=single-photon emission computed tomography.

TBI but without posttraumatic anosmia. A third study used the Paced Auditory Serial Addition Test (PASAT), which requires attention and working memory, in chronic mild TBI patients with cognitive fatigue as a major complaint (Hattori et al. 2009). Resting and activation SPECT scans were separated by 1 week, and individual scan sets were compared on a voxel-by-voxel basis. Compared with healthy control subjects, mild TBI patients were somewhat impaired on performance and had a larger area of cortical increased rCBF but a smaller area of cerebellar increased rCBF. The authors suggested that frontocerebellar dissociation may explain cognitive fatigue in mild TBI.

Studies Evaluating Potential Treatments

Only a few studies have examined the potential of SPECT to improve assessment of interventions. One group reported increased rCBF in injured regions following cognitive rehabilitation in two small studies of patients with varying levels of brain injury severity (Laatsch et al. 1997, 1999). However, in the first study no prerehabilitation SPECT scan was performed; rather the location of regions with suspected pathology was inferred from neuropsychological test results (Laatsch et al. 1997). A preliminary study of rehabilitation in patients with chronic TBI (2 mild, 1 moderate, 2 severe) obtained SPECT (both at rest and during a task) prior to, during, and after a 6-month program (Lewis et al. 2006). Group analysis indicated that resting rCBF was increased in the cerebellar hemispheres, vermis, and dorsomedial prefrontal cortex following completion of the program. Prior to treatment, motor task–associated increases were present in the cerebellar hemispheres and vermis. Following completion of the program, task-associated increases were present in the vermis and anterior cingulate cortex but not the cerebellar hemispheres. Two studies used SPECT to monitor medication effects (Barkai et al. 2004; Clauss and Nel 2004). One study found improved cerebral perfusion and resolution of cerebellar diaschisis on SPECT following treatment with zolpidem (Clauss and Nel 2004). The authors suggested that some pathology attributable to TBI involves the GABA (γ-aminobutyric acid) system and may be amenable to treatment with agents such as zolpidem. The other

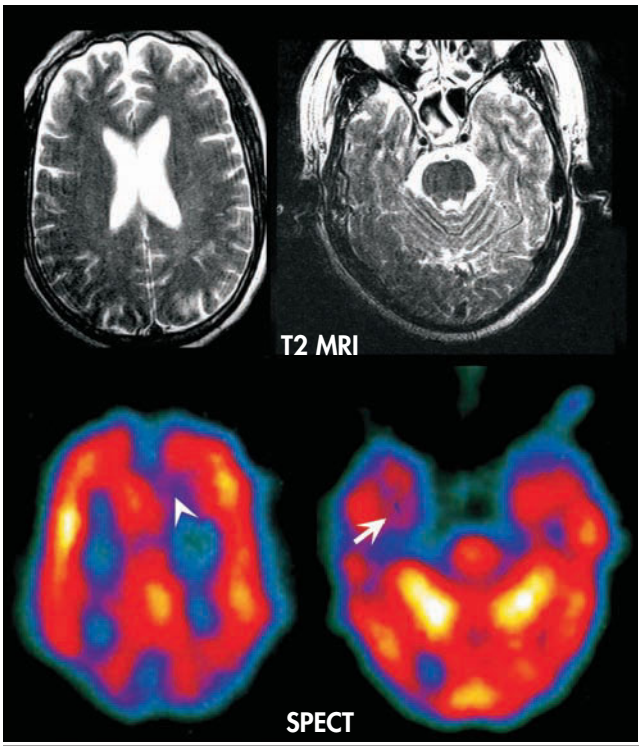


FIGURE 6–7. Chronic presentation of traumatic brain injury.

A 52-year-old man had a high-impact closed-head injury 30 years before scanning. He presented with a 30-year history of emotional incontinence and depression. The patient also reported a loss of singing ability after the accident. Two different sectional levels in the brain are illustrated with companion axial T2-weighted MR and SPECT. There are minimal white matter changes in the parietal region apparent on the MR image. Mildly decreased perfusion is evident in the medial frontal lobes (left greater than right, arrowhead). Moderately decreased perfusion is evident in the right anterior temporal lobe adjacent to the Sylvian fissure (arrow). MR=magnetic resonance; SPECT=single-photon emission computed tomography.

study found that both prefrontal perfusion and clinical symptoms improved following treatment with valproate (Barkai et al. 2004). An interesting aspect of this case report is that perfusion deficits were present prior to treatment only during acetazolamide challenge. Collectively, these studies suggest that SPECT may be helpful in assessing treatment approaches.

Chiu Wong et al. (2006) used SPECT to measure perfusion changes in eight children 3 years after severe TBI. They investigated brain plasticity, looking at differences in perfusion between children with severe TBI who showed good versus poor recovery in complex discourse skills such as abstraction of meaning from stories. The children showed increased perfusion as compared with normally developing control children, in contrast to the adult studies described earlier in which decreased perfusion is generally seen after TBI. The authors found a strong positive association between high perfusion in right frontal regions and better discourse abstraction abilities. Increased perfusion in left frontal regions was associated with lower abstraction. This type of pediatric work may further our understanding of brain plasticity in response to injury.

Several studies have used SPECT to assess the potential of hyperbaric oxygen therapy (HBOT) for treatment of chronic TBI (Barrett et al. 2004; Harch et al. 2009; Shi et al. 2006). In one study (Barrett et al. 2004), subjects at least 3 years post-TBI (severity not indicated) received 120 HBOT sessions (60 minute, 5 per week). Neurological, neuropsychometric, and exercise testing and SPECT (both visual and statistical parametric mapping analysis) were performed prior to, during, and following treatment. No consistent treatment-related changes were seen in any measures. In contrast, a study of patients with neuropsychiatric symptoms post-TBI in the early chronic stage (most <1 year) reported that all benefited from HBOT (Shi et al. 2006). Patients were selected from a larger group (252/310) based on presence of perfusion abnormalities on SPECT (47 also had CT findings). SPECT was repeated following administration of two courses of HBOT (90 minutes daily for 20 days). Semiquantitative ROI analysis indicated that 64% of patients (162/252) had full and 36% of patients (92/252) had partial resolution of perfusion abnormalities. Normalization of SPECT was accompanied by clinical improvement. Similarly, a case report of HBOT (2 sessions of 60 minutes daily, 39 total) in a veteran with both posttraumatic stress disorder (PTSD) and chronic symptoms after blast-related TBI documented posttreatment improvements in orbitofrontal and temporal rCBF and marked reduction in both PTSD and postconcussive symptoms (Harch et al. 2009).

Recommendations

Clinically, SPECT scans may be helpful in assessment of brain function in TBI cases in which behavioral problems or cognitive changes affect patient function but no lesion is found on structural imaging. However, a "normal" SPECT scan does not imply lack of pathology. When interpreting SPECT scan results for a particular patient, psychiatric comorbidity must be taken into account, because presence of symptoms such as depressed mood can affect SPECT results, as can substance abuse. SPECT abnormalities following TBI have not been shown to clearly correlate with behavioral change or neuropsychological test performance deficits; at this time, SPECT is not useful for evaluation of these problems, except possibly in cases of subtle TBI with behavioral and cognitive sequelae. SPECT research is limited, to date, by lack of consistent use of standardized, objective measures. Finally, for both clinical purposes and research studies, SPECT has limited resolution, especially on older cameras. Co-registration with a companion structural image may partially correct this problem, but this technique requires sophisticated technology and is not widely used in clinical settings at this time.

Positron Emission Tomography (PET)

PET imaging uses a method similar to that used for SPECT but with different radioactive tracers and more sophisti-

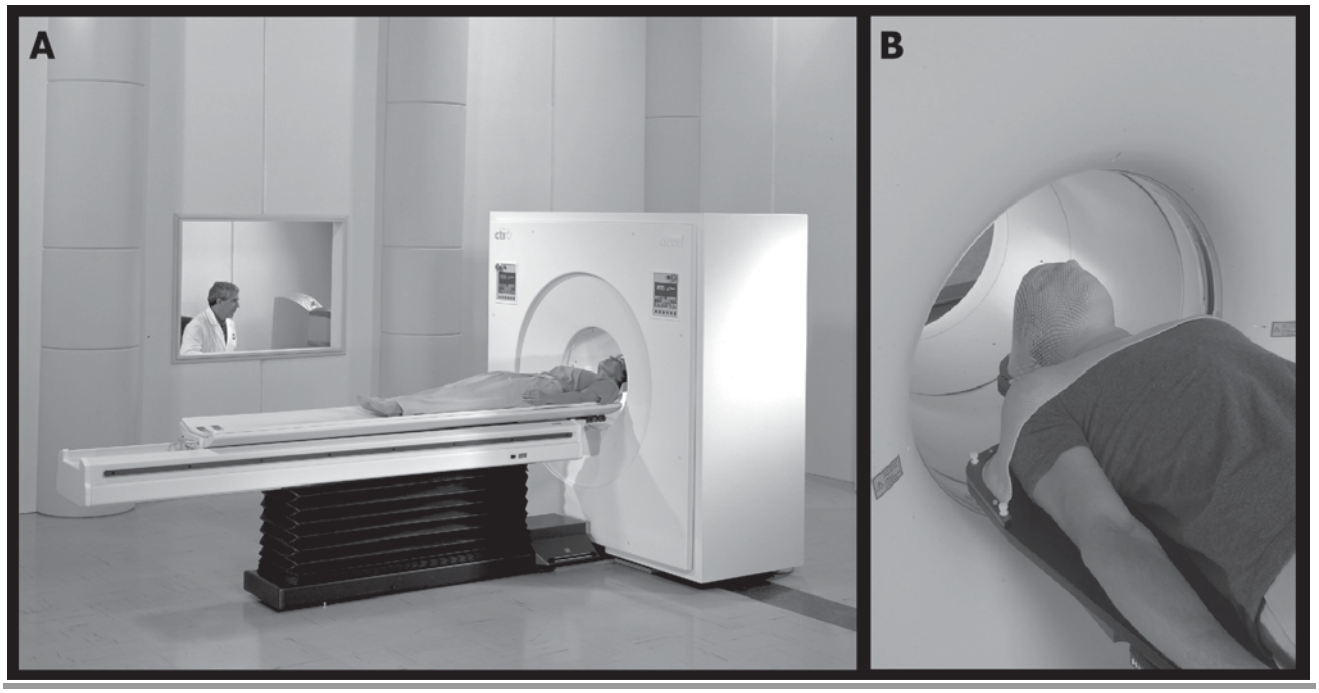


FIGURE 6–8. Procedure for obtaining a PET scan.

The patient receives an intravenous injection of the radioactive tracer while lying in a darkened room. After 20–30 minutes are spent in the darkened room to allow the tracer to distribute through the brain, the patient is ready to be scanned (A). Scanning usually begins within 1 hour of tracer injection and requires 30–45 minutes to complete. A headholder is often used to prevent head motion (B). PET=positron emission tomography.

Source. Pictures courtesy of CTI Molecular Imaging, Inc., Knoxville, TN.

cated detection equipment, which has improved with new technologies (Figures 6–8 and 6–9). As with SPECT, the physics behind PET limits its resolution, which is approximately 4 mm on high-quality scanners. Thus, PET images are much clearer and show greater anatomical detail than does SPECT. Like SPECT, a radiotracer is injected into the patient intravenously. As it decays, a positron is released. After collision with an electron, two photons are produced, traveling away from each other in a straight line at the speed of light. The photons are detected on opposite sides of the PET scanner simultaneously, and a computerized calculation is performed to pinpoint where in the brain the original positron was located. A record of these detections is made, which can be transformed by a computer into a tomographic image (Figure 6–10). Because two photons must be detected at the same instant to be "counted," the technique reduces errors in detection. Like MRI and SPECT, coronal, sagittal, and axial views are all available. Fusion with CT and 3-D reconstruction are also useful (Figure 6–11). Images can be visually interpreted but more commonly are analyzed statistically using various software programs.

Tracers

Like SPECT, PET uses injection of a radioactive tracer but, due to differences in the tracers used, can image either cerebral blood flow or metabolism. Table 6–3 provides an overview of FDA-approved PET radiotracers. ^{18}F-fluorodeoxyglucose (FDG) is the most commonly used tracer for clinical PET scans. It is taken into cells via the glucose transport mechanism, following which it is phosphorylated into FDG-6-phosphate. Because this is not a substrate for the glycolytic process, the FDG-6-phosphate remains trapped in the cell. Thus, FDG PET scans produce a measure of cerebral glucose metabolism (CMRglc) rather than CBF. The ^{15}O tracers provide measures of CBF, cerebral oxygen metabolism ($CMRO_2$), and oxygen extraction fraction (OEF) and are more commonly used in research because of the short half-life. The resolution with ^{15}O tracer is inferior to that obtained with FDG. However, the use of short-acting isotopes permits repeat studies in the same subject in a short period of time. This is useful if an activation paradigm, such as performance of a verbal memory task, is to be compared with scans done in other states, such as finger tapping.

Practical Considerations

PET uses a similar method to SPECT, but the patient is injected shortly before the image is obtained, and, due to the differing properties of the isotopes used in PET, the scan must take place within a few minutes or seconds. As with SPECT, a resting whole-brain PET scan is ordered for most clinical purposes. Depending on the tracer used, the scan lasts from 2 to 40 minutes, during which the patient must remain still in the scanner. FDG, the most commonly used PET tracer in clinical studies, requires a scan of 30–40

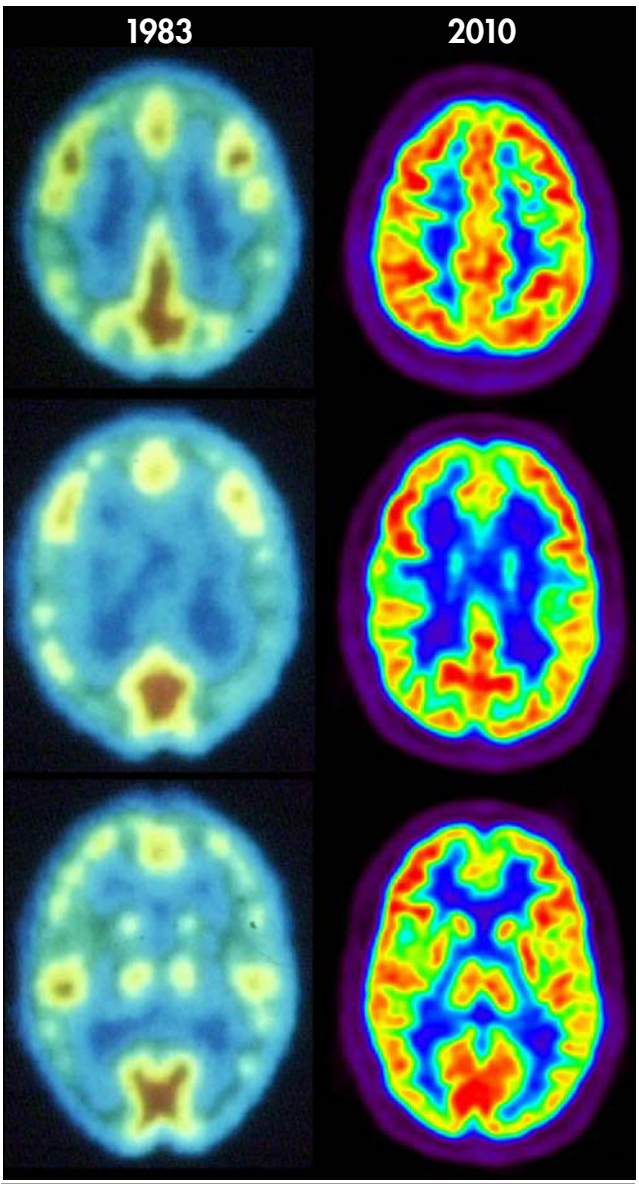


FIGURE 6–9. PET imaging then and now.

Axial positron emission tomography (PET) images acquired in 1983 and 2010 of normal brain. Note the significant improvement in resolution since the 1980s.

Source. 1983 pictures courtesy of CTI Molecular Imaging, Inc., Knoxville, TN.

minutes. As with SPECT, sedation may be given after isotope injection if the patient is extremely anxious or unable to remain still lying supine during the scan. In many centers, headholders are used during PET scanning to keep the patient's head in a stable position (see Figure 6–8). Headholders can be constructed of thermoplastic and individually fitted to the patient's head. Alternatively, they may be made of foam rubber or other soft material placed around the head to prevent motion. The degree of stabilization gained must be weighed against the amount of discomfort caused to the patient, especially those who are claustrophobic or are uncomfortable being somewhat restrained.

Indications

There are no clinical guidelines for use of PET in TBI at this time. As with SPECT, PET scans are often obtained when brain injury is suspected but not seen on structural studies, or when structural studies do not indicate injury extensive enough to explain a patient's deficits.

Limitations

Medicare costs for PET scans are around $1,000. In comparison, SPECT scans are $300. The higher price of PET is due to several factors, including the advanced technology used in PET scanners compared with SPECT. For certain short half-life isotopes, such as ^{15}O, the isotope must be made on site, limiting use to centers that have a cyclotron (another expense). Thus, PET is not available at many institutions.

Overview of Abnormal PET Findings in TBI

PET has been used in several studies of TBI patients to assess many measures, including evidence of functional abnormalities in patients who have normal structural scans, prognosis, correlations between post-TBI behavioral disorders and brain injury, and correlations between neuroanatomical damage and neuropsychological test performance deficits. Many PET studies involve small numbers of patients, making conclusions based on the data problematic. Use of PET in cognitive activation studies to assess neuroplasticity after TBI and for examination of neuropathological changes in these patients are two promising applications. In general, the scope of the clinical studies with PET is smaller than those with SPECT, but research applications of PET may ultimately prove to be more fruitful.

Studies Using PET and Structural Imaging

Like SPECT, PET commonly shows abnormalities in regions that appear normal on structural imaging in addition to abnormalities associated with focal lesions (Dubroff and Newberg 2008; Duckworth and Stevens 2010; Metting et al. 2007). Because PET can provide other data in addition to blood flow, one might expect differing utility of PET in prediction of outcome.

In recent years, studies in the acute stage have focused on moderate-severe TBI. Multiple studies have documented widespread metabolic abnormalities (e.g., altered CBF, CMRglc, OEF, and/or $CMRO_2$) in the acute stage after moderate-severe TBI, with areas within or near to focal lesions more profoundly affected than remote cortex (Abate et al. 2008; Coles et al. 2009; Hattori et al. 2004; Kawai et al. 2008; Wu et al. 2004; Xu et al. 2010). A study examining gray matter and white matter areas remote from focal lesions reported that reductions in CMRglc were localized to gray matter, whereas reductions in $CMRO_2$ were present in both gray matter and white matter, suggesting a shift to nonoxidative utilization of glucose in white matter (Wu et al. 2004). Studies combining PET with microdialysis

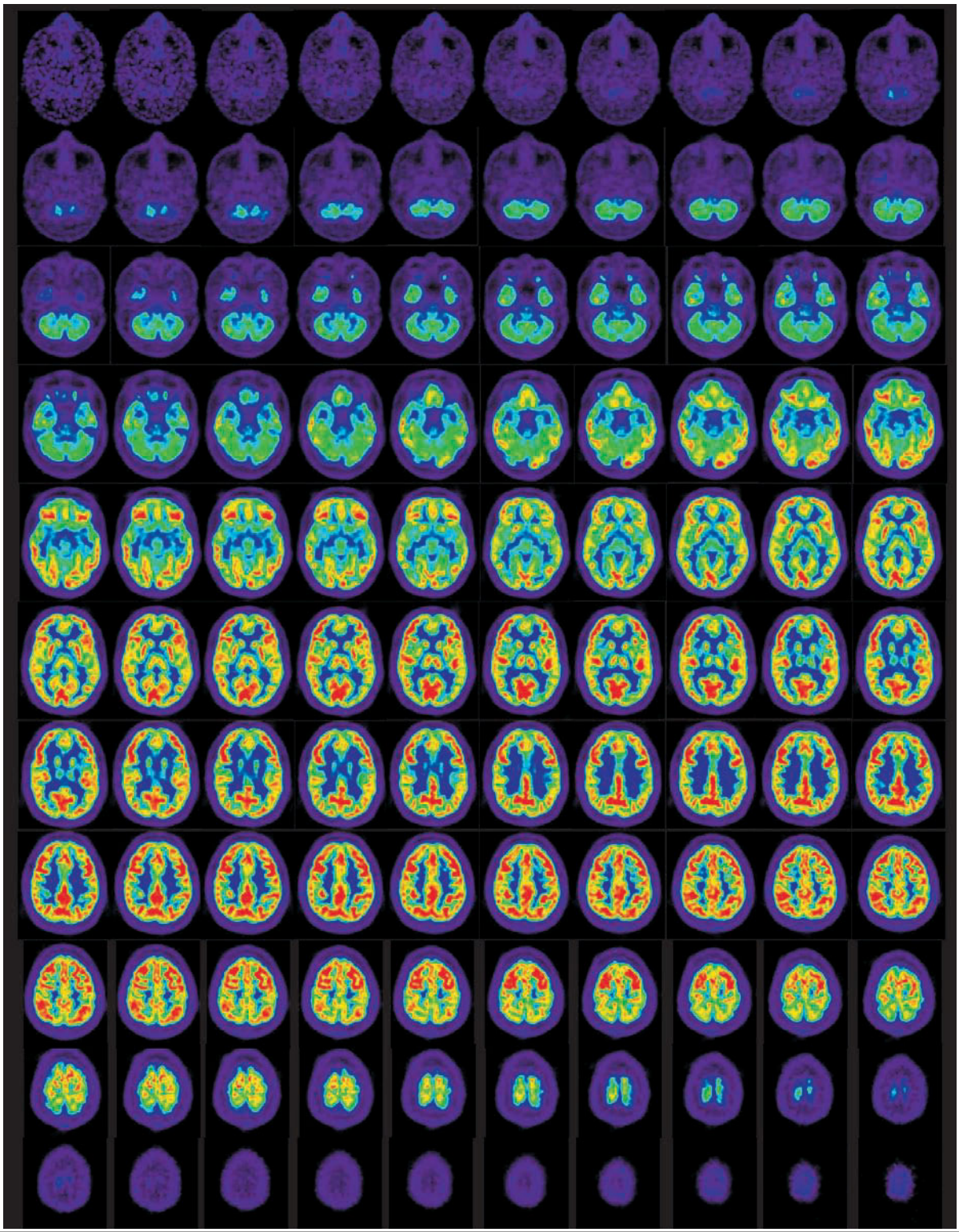


FIGURE 6–10. Serial axial fluoride-18 fluorodeoxyglucose PET images of a normal adult brain.
PET=positron emission tomography.
Source. Case contributed by Dr. Donald P. Eknoyan, W.G. (Bill) Hefner VA Medical Center, Salisbury, NC.

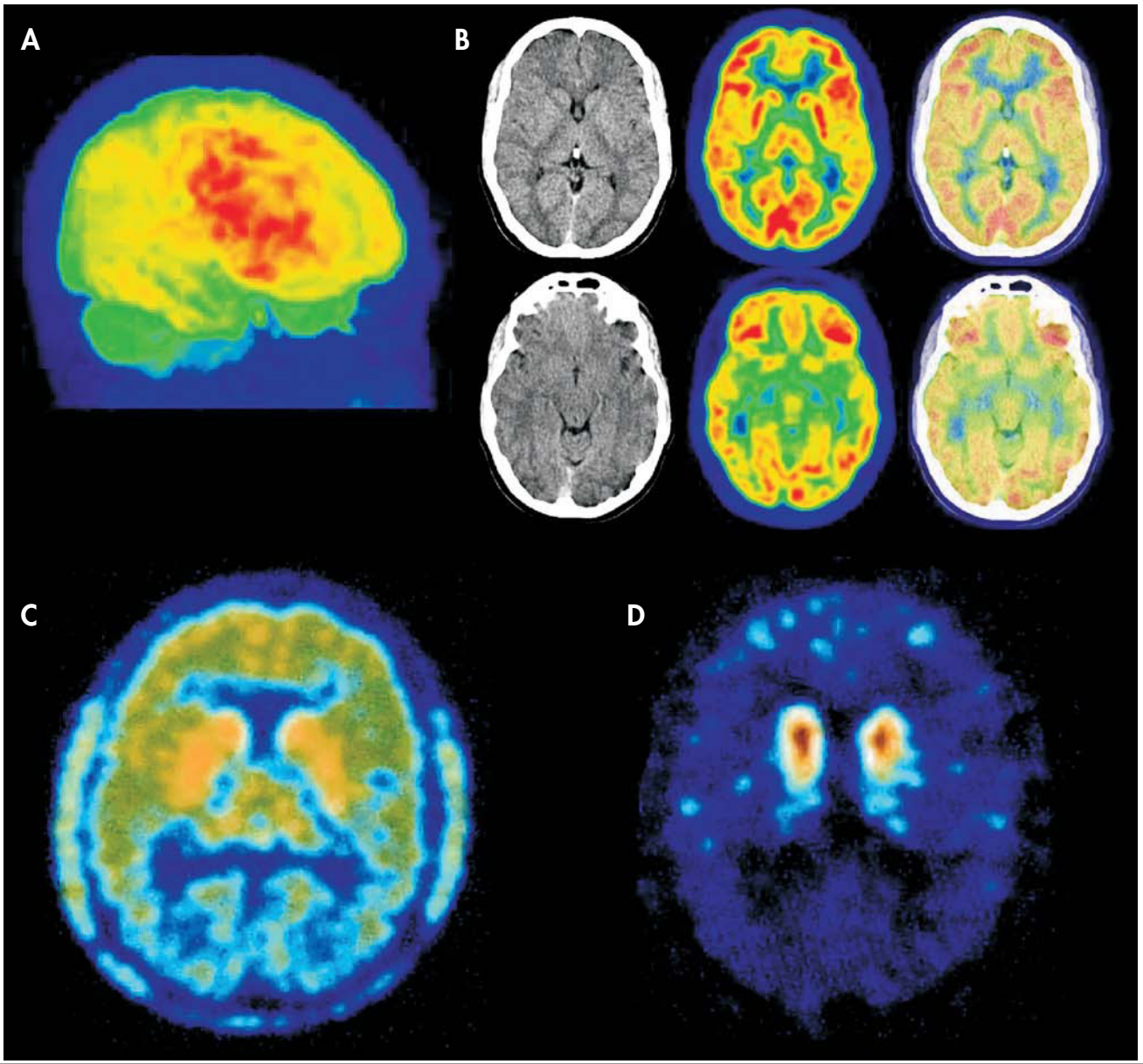


FIGURE 6–11. Current PET imaging capabilities.

Three-dimensional reconstruction of positron emission tomography (PET) results (A) and fusion of computed tomography and PET (B) improve appreciation of the extent of functional abnormalities. Neurotransmitter systems may also be imaged with PET. Presynaptic dopamine terminals can be labeled with ^{18}F-fluorodopa (C). Dopamine D_2 receptors can be labeled with ^{11}C-*N*-methylspiperone (D).

Source. Pictures courtesy of CTI Molecular Imaging, Inc.

reported that incidence of ischemia was surprisingly low (Vespa et al. 2005) and a shift toward anaerobic metabolism was not present (Hutchinson et al. 2009). The presence of considerable metabolic heterogeneity has raised the possibility that other types of energy failure in addition to ischemia are likely to be important.

Several studies of patients with moderate-severe TBI have examined the potential of PET measures in the acute phase for prediction of tissue survival. One study defined ROIs that were destined to be irreversibly injured based on MRI in the chronic phase and compared these areas with regions that appeared normal and with similar ROIs in healthy control subjects (Coles et al. 2009). Although lesion ROIs exhibited clear metabolic impairments (e.g., decreases in CBF, $CMRO_2$, and OEF), the considerable heterogeneity both within and between lesion and nonlesion ROIs resulted in substantial overlap in all measures. As noted by the authors, these findings suggest that either tissue survival is not determined by the measured physiological parameters or the normal-appearing tissue had actually sustained injury. Another study reported a significant correlation between hemorrhage volume and metabolic dysfunction in the acute phase, and between hemorrhagic lesion burden and both $CMRO_2$ and CBF in the acute phase with atrophy in the chronic phase (Xu et al. 2010). As noted by the authors, regional atrophy correlated with

TABLE 6–3. U.S. Food and Drug Administration–approved, commonly used tracers/radioligands for PET

Tracer/ligand	Parameter measured	Comments
^{18}F	Glucose metabolism	Commonly used in clinical studies; longer half-life than ^{15}O means only one scan may be acquired in each scanning session.
^{15}O	Blood flow	Short half-life means that multiple scans may be collected in one session with a subject; commonly used for cognitive research studies with cognitive activation paradigms.
^{13}N	Blood flow	Used in cardiac assessment.
^{55}Co	Calcium	Provides indications of areas where cell death is occurring.
^{11}C	Dopaminergic system	Used in research to study receptors.

Note. PET = positron emission tomography.

regional reduction in oxidative brain metabolism with no evidence of irreversible ischemia. Overall, these studies are consistent with an older study that found that reductions in global (whole-brain) CMRglc and time course of recovery were surprisingly similar across a wide range of injury severities (Bergsneider et al. 2001). In that study, metabolic recovery began approximately 1 month after moderate or severe TBI, a finding that may have implications for the timing of pharmacological or rehabilitational interventions following TBI.

The limited work thus far suggests that PET may be helpful in assessment of patients with TBI who have normal structural imaging but chronic behavioral problems or cognitive deficits (Belanger et al. 2007; Duckworth and Stevens 2010; Metting et al. 2007; Van Boven et al. 2009). Several studies from one group have compared FDG PET (resting scan) in chronic moderate-severe TBI patients with diffuse (rather than focal) brain injury with healthy control subjects using statistical approaches (Kato et al. 2007; Nakashima et al. 2007; Nakayama et al. 2006). They have identified (statistical parametric mapping) a pattern of decreased CMRglc in bilateral midline regions (e.g., medial prefrontal cortex, medial orbital cortex, cingulate cortex, thalamus), with more widespread and profound changes associated with greater impairment in consciousness (cognitively impaired, minimally conscious, vegetative) (Nakayama et al. 2006). Group comparison (3-D stereotactic surface projection) of cognitively impaired TBI patients with healthy control subjects identified areas of decreased CMRglc in predominantly midline areas (cingulate gyrus, lingual gyrus, cuneus) and cerebellum bilaterally (Nakashima et al. 2007). Individual comparisons indicated considerable differences in size and distribution of abnormalities. Of the neuropsychological tests examined, only full-scale IQ correlated significantly (statistical parametric mapping) with rCMRglc (cingulate and medial prefrontal gyri) (Kato et al. 2007). The authors noted that hypometabolism was present in many areas that appeared normal on structural imaging, suggesting presence of decreased neuronal activity due to functional disconnection. A large FDG PET study comparing chronic TBI patients (all severity levels; all involved in litigation) with (n=35) and without (n=40) acute structural imaging abnormalities and healthy control subjects used performance of a verbal learning task during tracer uptake to provide a standardized brain state (Zhang et al. 2010). Similar widespread patterns of reduced rCMRglu were found (statistical parametric mapping, cluster counting) in both TBI groups compared with healthy controls, indicating that both focal and diffuse brain injury can result in chronic diffuse metabolic abnormalities. Compared with healthy control subjects, the TBI groups had more large clusters of significantly reduced rCMRglc, and clusters tended to be closer to the brain edge (cerebral cortex). Of note, clusters of significantly reduced rCMRglc were also present in healthy control subjects, emphasizing the importance of appropriately chosen comparison groups for determination of statistical threshold. A large cluster of increased rCMRglc was also identified (encompassing anterior cingulate cortex, hippocampus, and amygdala), which the authors suggested might be indicative of the TBI group requiring greater cognitive effort to perform the task. An older FDG PET study of mild TBI patients with chronic behavioral and cognitive deficits that used a continuous performance task to provide a standardized brain state came to a similar conclusion (Gross et al. 1996). A recent FDG PET study of chronic blast-related mild TBI in military veterans compared with civilian healthy control subjects identified (3-D stereotactic surface projection) areas of reduced CMRglc predominantly in the cerebellum, vermis, pons, and medial temporal cortex (Peskind et al. 2010). The authors noted that the pattern of subtle neuropsychological impairments and behavioral symptoms identified in the TBI group is generally consistent with dysfunction in the cortico-cerebellar-cortical circuits. A study utilizing both ^{15}O gas and ^{11}C flumazenil PET in patients with chronic diffuse TBI (severity not indicated) with normal MRI compared with healthy control subjects identified multiple areas of reduced $CMRO_2$ (Shiga et al. 2006). Most of the TBI group had focal changes (frontal cortex, 7/10 patients; temporal cortex, 8/10 patients), but diffuse changes were also seen (2/10 patients). Flumazenil binding (an indirect probe of neuronal integrity) was low in the temporal lobe of both TBI patients with diffusely reduced $CMRO_2$ and in one-third (8/22 patients) of focally reduced areas, indicating that this tracer may be useful in distinguishing hypometabolism caused by neuronal loss from functional disconnection.

In some of the studies described above, the authors suggest that these abnormalities correlated with behavioral and cognitive complaints. As with SPECT, a causal link between a specific lesion seen on functional imaging and behavioral changes seen in a patient is difficult to assess. PET consistently shows abnormalities not seen on structural imaging, especially in cases of mild TBI. However, the actual clinical utility of this information has not been proven. PET has not been found to be useful in assessment of recovery but has suggested new avenues for research into early interventions.

Studies Using Behavioral Measures

Few studies have focused on use of functional imaging to assess patients with behavioral symptoms following TBI. Given the changes seen on PET scans of patients with primary psychiatric illness, one might expect some correlation between PET data and post-TBI behavior problems. One study used FDG PET to evaluate patients with mania after TBI (Starkstein et al. 1990). Three patients who had only subcortical injury on structural imaging were scanned during mania and showed right lateral basotemporal hypometabolism, implicating right-sided injury in the development of mania. Another study also reported a relationship between behavioral disorders in severe TBI and mesial prefrontal and cingulate metabolic abnormalities (Fontaine et al. 1999). Further work with detailed behavioral information and psychiatric diagnosis is needed in this area before utility can be assessed, although these preliminary studies suggest that PET studies in TBI may enhance research into neuroanatomical underpinnings of psychiatric symptoms.

Studies Using Neuropsychological Assessments

Older studies comparing PET results in TBI patients with neuropsychological test performance have reported varying results (Belanger et al. 2007; Metting et al. 2007; Van Boven et al. 2009). One study found that of the neuropsychological tests included in their battery, only full-scale IQ correlated with reduced rCMRglc (right cingulate gyrus and the bilateral medial frontal gyrus) in chronic moderate-severe TBI patients with DAI compared with healthy control subjects (Kato et al. 2007). A single case report has compared PET and SPECT directly for assessment of neuropsychological deficits in TBI (Abu-Judeh et al. 1998). Reduced frontal and parietal rCBF (SPECT) concurred with neuropsychological test results, whereas FDG PET indicated normal glucose metabolism. The authors suggested that, at least in mild TBI, vascular compromise due to injury may cause SPECT findings of flow loss, whereas the normal glucose metabolism indicates that underlying tissue is still viable. Although this example illustrates the possibility that different information from the two modalities could be complementary, little has been done to apply this finding clinically to date.

Activation Studies

Comparison of functional imaging in a resting state with scans acquired during performance of a behavioral task may be helpful in studying function of particular cognitive domains. Two studies have used $^{15}O\ H_2O$ PET in combination with a memory task (verbal recall and recognition of word lists, cued recall of semantically related word pairs) in chronic moderate-severe TBI patients compared with healthy control subjects (Levine et al. 2002; Ricker et al. 2001). These studies found that the overall patterns of activations were relatively similar but that the TBI groups exhibited areas of both increased and decreased rCBF compared with the control groups, indicating alterations in the network of areas utilized to perform the task. A study of mild TBI patients with chronic symptoms used both FDG PET to assess resting rCMRglc and $^{15}O\ H_2O$ PET to assess rCBF changes associated with performing a simple spatial working memory task (Chen et al. 2003). There were no differences between TBI and control groups in resting CBF in the prespecified ROIs (frontal, temporal). Analysis of task-related changes was based on regions significantly activated in the control group. Although task performance was similar, the TBI group had a smaller task-related increase in rCBF in the inferior frontal gyrus (BA 45) ROI compared with the control group. The authors suggested that it may be necessary to provide a cognitive challenge to bring out changes associated with mild TBI. Although limited by small subject numbers, these studies suggest that a cognitive challenge task may be particularly useful in elucidating pathological changes following TBI.

Studies Evaluating Potential Treatments

A few studies have used PET to assess the effectiveness of specific interventions in the acute phase, including hyperventilation (Hutchinson et al. 2002), increased perfusion pressure (Steiner et al. 2003), and normobaric hyperoxygenation (Diringer et al. 2007; Nortje et al. 2008). One study used FDG PET in a subset (6/22) of chronic TBI (all levels of severity) patients undergoing treatment with amantadine (Kraus et al. 2005). Compared with pretreatment measurements, improved executive task performance was significantly correlated with increased rCMRglc in left prefrontal cortex (ROI, statistical parametric mapping). Although preliminary, these studies may encourage new interventions and treatments for TBI, such as diminution of persistent excitotoxicity or medication interventions guided by observed changes in brain function.

Studies Using Other PET Tracers

As with SPECT, PET ligand studies are becoming an important tool for research (Figure 6–11). Although these techniques have not yet been used to study TBI, they may well provide the most important future contributions from PET. Potentially, radioactive ligands could provide information on disruption of receptor types, intracellular messengers, and proteins after TBI. For example, raclopride is used to study dopamine type 2 receptor density and may be useful in assessment of TBI. Ligands are also available, but less widely so, for research use in investigations of serotonergic, acetylcholinergic, and other neurotransmitter systems.

Recommendations

As of this writing, PET does not have a large role in evaluation of TBI. In very select cases for which more exacting localization of lesions is important, PET may be helpful, although correlation of specific lesion location with function is often problematic. Otherwise, the lower cost and greater availability of SPECT make it the best functional assessment in cases in which functional imaging may enhance evaluation of TBI. As with SPECT, PET may sometimes be useful in detection of lesions in cases in which behavioral symptoms or cognitive deficits are present in the patient with no apparent structural injury, although a "normal"

scan does not imply lack of pathology. PET is generally superior to SPECT for use in research studies of cognitive function and brain injury, due to its finer resolution. Use of ^{15}O-labeled tracers allows investigators to obtain several studies on a patient in one session, which is important when studying cognition. It is in such studies that PET may make the greatest contributions to our understanding of the effects of TBI on cognition and to our understanding of normal brain function. PET may also have a role in the investigation of pathophysiology of TBI. Most importantly, it might possibly be useful in determining whether pathophysiological events following TBI are dynamic in nature and, if so, when the optimum time for intervention occurs. PET scanning may also be a future technique for the study of putative mechanisms of cellular damage following TBI, including excitotoxicity and changes in neurotransmitter systems, which could direct novel interventions.

Functional Magnetic Resonance Imaging (fMRI)

Functional MRI allows measurement of activity-related changes in cerebral blood flow without the use of ionizing radiation. Functional MRI is based on the observation that the magnetic qualities of oxygenated and deoxygenated hemoglobin differ. As brain activity increases in a certain region, metabolic demand also rises. Blood flow increases to meet the demand, but increases slightly more than is required to sustain the activity. The resulting higher concentration of oxygenated hemoglobin in blood causes a slight increase in MR signal intensity. This signal change is what is measured by fMRI. The computerized data are then reconstructed into images with higher signal areas presumably reflecting regions of increased activation. These images are commonly co-registered with a companion structural MRI obtained in the same session, providing neuroanatomical detail. Most fMRI studies involve comparison of a baseline state to an activated state induced by performance of a task. Recently, a new approach has been developed in which a scan acquired in a resting state is used to generate a map of functional connectivity among brain regions (resting or default network).

Practical Considerations

Currently, fMRI is used only for research purposes. This technique holds great promise for future studies of normal brain function and for investigations of pathological change due to many conditions, including TBI. The advantages of fMRI include easy implementation on many existing scanners, lack of ionizing radiation exposure, ability to repeat multiple studies on one patient in a short time, and greatly improved anatomical resolution (1 mm) as compared with SPECT and PET.

Indications

Functional MRI is currently not used clinically in evaluation of TBI. The high resolution and the lack of ionizing radiation make it a promising technique for future investigations.

Limitations

Although fMRI can be performed on many standard MRI scanners after a few modifications, considerable technical expertise is needed to acquire reliable fMRI data. In addition, fMRI scans are generally not "read" as are PET and SPECT but rather are interpreted using statistical programs. Thus, knowledge of these programs as well as interpretation of the results generated by them is vital. Subjects generally must perform an activation task during scanning, limiting use to alert, cooperative subjects. Previous standardization of activation tasks would be needed before fMRI could be used widely for clinical purposes.

Overview of fMRI Findings in TBI

Multiple studies have now used fMRI in the TBI population, primarily in the subacute and chronic stages. TBI patients may have significantly different and sometimes more extensive activation patterns from those seen in healthy controls during performance of a cognitive activation task. Preliminary evidence for alterations in connectivity has also been reported.

Studies Using fMRI Very Early After TBI

Only a few studies have used fMRI in the acute stage. A study comparing functional imaging modalities in acute severe TBI (patients in coma) found good concordance between fMRI and brain functions suggested by evoked potential, and with metabolic activity demonstrated with FDG PET (Kremer et al. 2009). Two studies of acute (<1 week postinjury) sports-related concussion found increased amplitude and extent of task-related activations compared with either the individual's preseason baseline or healthy athletes (Jantzen et al. 2004; Lovell et al. 2007). In one study, the subjects with the highest working memory task-related activation in medial prefrontal cortex (BA 6) had the slowest recovery, suggesting the fMRI may have prognostic potential (Lovell et al. 2007). In the other study, differences in activation were present even when task performance (mathematical, memory, and sensorimotor coordination tasks) was not impaired, suggesting that fMRI may be more sensitive than neuropsychological testing (Jantzen et al. 2004). These results are similar to a study of sports-related concussion after symptoms resolved (at >10 and <30 days), which found no differences in task performance (spatial memory task in virtual reality environment) but increased amplitude and extent of activations compared with healthy control subjects (Slobounov et al. 2010). In contrast, a study spanning a longer postinjury interval (3–20 days) that compared mild TBI patients (some still symptomatic) with healthy control subjects found less than normal activation during an auditory orienting task (Mayer et al. 2009). As noted by the authors, the TBI group was impaired on several aspects of this task, so the lower level of activation might indicate failure to engage the required networks. Consistent with this view, preliminary results from a study of acute (<72 hours postinjury) sports-related concussion indicated virtual absence of expected activations to a working memory task, with normalization of task-related activation on follow-up only in patients with symptom resolution (Ptito et al. 2007).

Studies Using fMRI in the Subacute to Early Chronic Stage After TBI

Several groups have studied TBI patients within the first year after injury. A series of studies from one group have evaluated working memory (N-back task) in patients with uncomplicated mild TBI (~1 month after injury) and healthy controls (for review, see McAllister et al. 2006). In the 0- to 1-back condition (low effort) comparison, the TBI group had lower levels of activation than the healthy control group. In the 1- to 2-back condition (moderate effort) comparison, the TBI group had higher levels of activation than healthy controls and activated more areas. In the 2- to 3-back condition (high effort) comparison, the TBI group again had lower levels of activation than healthy controls. As noted by the authors, these results are consistent with impaired ability to activate and allocate processing resources supporting working memory. Consistent with this view, another group reported a positive association between symptom severity in mild TBI patients (~1 month after injury) and level of working memory (1- to 2-back condition) task-related activation (Smits et al. 2009). A positive association was also reported between symptom severity in moderate-severe TBI patients (~3 months after injury) and level of task-related (stimulus-response compatibility task) activation (Scheibel et al. 2009). In addition, there was a positive association between task performance and level of activation. As noted by the authors, this suggests that the overactivation might be compensatory. In contrast, a study using a different memory task (listening to familiar vs. novel words) found less activation in both mild and moderate TBI groups (~1 month after injury) compared with a healthy control group, with level of activation inversely correlated with injury severity (McAllister et al. 2006). The authors noted that this task is passive, requiring no overt responding. Thus the lesser activation may be a product of a decrease in the neural signals associated with recognition of familiar stimuli and detection of novel stimuli. Consistent with this interpretation, a series of studies of patients with persistent (months after injury) symptoms following sports-related concussion utilizing a different set of working memory (verbal and visual) tasks also have reported an inverse relationship between symptom severity and both task performance and level of task-related activity in areas activated in healthy controls, as well as altered activations in other areas (Ptito et al. 2007). An intriguing finding was that severity of depressive symptoms was one key factor. Both groups have reported follow-up studies in which recovery (diminution or resolution of symptoms) is associated with improved task performance and normalization of task-related activations (Chen et al. 2008; McAllister et al. 2006; Ptito et al. 2007).

Studies Using fMRI in the Chronic Stage After TBI

Most studies in the chronic (>1 year) stage are of moderate-severe TBI, with results generally similar to the studies described above. Greater amplitude and extent of activations in TBI groups (both adults and children) compared with healthy control subjects have been reported when task performance (alpha span task, paced visual serial attention task, continuous performance task, simple motor coordination task, perspective-taking task) was equivalent (Caeyenberghs et al. 2009; Kramer et al. 2008; Maruishi et al. 2007; Newsome et al. 2010; Turner and Levine 2008). Lower amplitude of activation in TBI groups compared with healthy control groups has been reported when task performance (N-back task, strategy-based verbal learning) was impaired (Sanchez-Carrion et al. 2008a, 2008b; Strangman et al. 2009). Lower amplitude of activation has also been reported to very simple tasks (fist-clenching task, covert verb generation) in both adults and children with TBI (Karunanayaka et al. 2007; Lotze et al. 2006). A study using the N-back task in children with TBI (moderate-severe) reported that those able to perform the 3-back task acceptably had higher levels of activation than typically developing individuals, whereas those only able to perform the 1- or 2-back task acceptably had lower levels of activation than typically developing individuals (Newsome et al. 2007). A study comparing task performance (visual search task, simple motor task) and task-related activations under single- and dual-task conditions between TBI (chronic severe) and healthy control groups reported reduced activation in the single-task condition and greater and more extensive activations in the dual-task condition (Rasmussen et al. 2008). Overall, these results are generally consistent with impaired ability to activate and allocate processing resources, and they underscore the importance of both injury severity and task load on activation level. A study that examined task-related (simultaneous matching to sample task) activation changes within trial (first half vs. second half) and across three trials between TBI (chronic moderate-severe) and healthy control groups found similar performance accuracy but increased activations in the TBI group in both comparisons (Kohl et al. 2009). The authors of this study noted that these results are consistent with the TBI group increasing effort over time to meet the task demands and may be the neural correlate of cognitive fatigue.

Studies Using fMRI for Prognosis or Assessment of Treatment

One study used resting-state fMRI to perform connectivity analysis in noncommunicative TBI patients at different levels of consciousness (locked-in syndrome, minimally conscious, vegetative, coma) compared with healthy control subjects (Vanhaudenhuyse et al. 2010). Connectivity in the default network was inversely correlated with degree of impairment in consciousness, suggesting that this technique may have prognostic potential.

Very few studies have used fMRI in prospective longitudinal studies of rehabilitation or recovery. A study of motor deficits following TBI (moderate-severe) found that pretreatment task-related (fist-clenching task) activations were reduced compared with those of healthy control subjects (Lotze et al. 2006). Longitudinal data in a subset indicated that patients who would not have a good motor recovery by several months later activated motor areas less than patients who would have a good motor recovery, suggesting that the magnitude of fMRI activation might have prognostic value. A study of memory rehabilitation following TBI (all levels of severity) found that pretreatment task-

related (strategically directed word memorization task) activations had a modest predictive value (Strangman et al. 2008). Moderate levels of activation were associated with improvements following 12 sessions of a group treatment program, whereas both low and high levels of activation were associated with less treatment response. A study comparing two learning approaches (errorless, errorful) found that the patients with DAI had lower accuracy and activated more areas during the errorful condition than healthy control subjects, supporting the value of errorless learning during rehabilitation (Ueno et al. 2009). Improved task performance and normalization of task-related activations following rehabilitation have also been reported (Kim et al. 2009; Sanchez-Carrion et al. 2008a). A recent study used resting-state fMRI to assess changes in functional connectivity during recovery from severe TBI by comparing network properties at 3 and 6 months after resolution of posttraumatic amnesia (Nakamura et al. 2009). During that interval, the overall strength of connectivity decreased without a change in the number of network connections, bringing the network closer to what is seen in healthy control subjects. The authors noted that these results are consistent with temporary recruitment of existing networks to support performance rather than creation of new connections.

Recommendations

Functional MRI is potentially a powerful tool for investigation of brain function, particularly cognition. As methods are standardized and comparisons with PET and SPECT results are conducted, application of this technique to studies of patient groups may be very helpful clinically, especially in prediction of outcome or response to treatments. The lack of ionizing radiation exposure makes it ideal for extensive investigation of behavior and cognitive processes and their disruption in TBI. The recent development of resting-state fMRI is particularly promising.

Other Promising Modalities

Two additional functional imaging techniques deserve brief mention.

Magnetoencephalography (MEG)

Magnetoencephalography (MEG) is a noninvasive method that uses superconducting sensors to measure the neuromagnetic fields generated by neuronal activation. These fields pass through the skull and scalp without distortion. Thus this method provides data similar to those seen with standard electroencephalogram (EEG) technology, but with fewer artifacts. Using computerized models to generate activation maps, MEG can be used to localize patterns of brain activity. The spatial resolution that can be achieved from MEG data is greater than can be obtained from EEG data. Like EEG, MEG directly measures neuronal activity in milliseconds. This is unlike the other functional imaging techniques, all of which provide indirect measures of neuronal activity. The ability of MEG to monitor rapid changes in neuronal activity makes it possible to separate components of a cognitive task, such as word reading.

Initial studies with MEG showed evidence of brain injury in both severe and mild TBI (Iwasaki et al. 2001; Lewine et al. 1999; Schiff et al. 2002). A more recent study of mild TBI suggests that MEG is more sensitive than other functional modalities (SPECT) or structural imaging (MRI) for evaluation of patients with somatic and cognitive symptoms that persist long after injury (Lewine et al. 2007). For patients with cognitive complaints, abnormalities were more likely to be seen on MEG (86%) than either SPECT (40%) or MRI (18%). MEG also showed associations between temporal lobe changes and declarative memory deficits, parietal pathology and attention problems, and frontal changes and executive function impairment. None of the results from any imaging modalities, including MEG, were associated with presence of psychiatric symptoms. Another study used both MEG and diffusion tensor imaging (DTI; see Chapter 5, Structural Imaging) to evaluate 10 patients with mild TBI without visible lesions on standard structural (MRI or CT) imaging (Huang et al. 2009). The combination of MEG and DTI was more sensitive than conventional imaging in detecting subtle abnormalities in mild TBI. Anatomical findings from MEG combined with DTI were consistent with postconcussive symptoms. In some patients, abnormal MEG signal was observed in the absence of DTI abnormalities, suggesting that MEG may be more sensitive than DTI in mild TBI. Thus, MEG may become a useful modality for evaluation of TBI patients, especially if combined with other imaging technologies. At present, due to the high cost of the technology, MEG is available as a research tool in a few large centers.

Xenon-Enhanced CT (Xe/CT)

Xenon-enhanced CT combines anatomic and CBF imaging (Figure 6–12). Stable xenon gas is both radiodense and lipid soluble. It dissolves in the blood and enters the brain parenchyma. Patients inhale a mixture of xenon gas and oxygen via a face mask. CT scans are acquired before, during, and sometimes after inhalation. CBF is calculated on the basis of the arrival of xenon at each standardized unit of brain measured (pixel) and the amount of xenon exhaled. In February 2001, the historic FDA status of xenon as a "grandfathered" X-ray contrast agent was withdrawn, thus halting its clinical use in the United States. As of this writing, the FDA-required studies are in progress. It is hoped xenon will be available again soon.

Xe/CT has several advantages over other functional imaging methods. Due to the rapid elimination of xenon from the body, Xe/CT can be repeated in as little as 15 minutes. It can provide functional imaging data for patients undergoing a standard structural CT scan at a relatively low cost (approximately $100 in addition to the cost of the standard CT). Xenon is nonradioactive, so the acquisition of the structural CT is the only radiation exposure required for the scan. The main drawback of Xe/CT is that patients may experience positive or negative changes in mood, either of which could be problematic, especially in neuro-

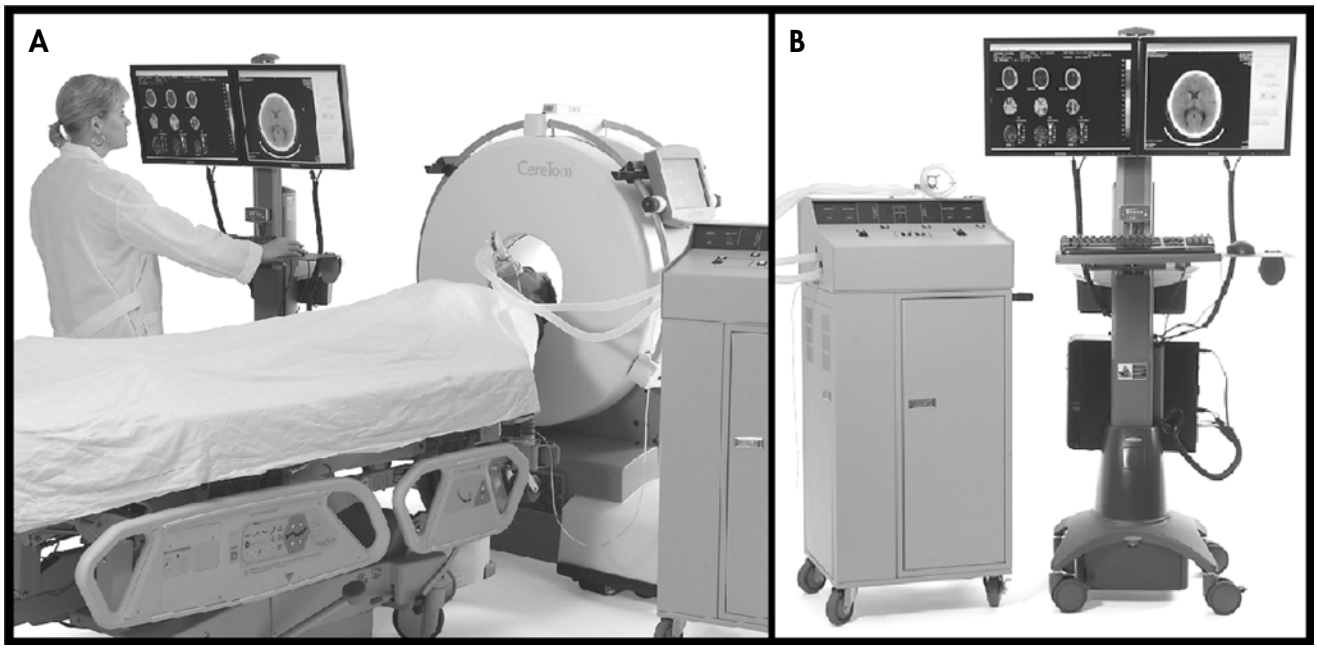


FIGURE 6–12. Procedure for obtaining a xenon-enhanced computed tomography (Xe/CT) scan.
Normal clinical CT scans are acquired as the first stage in an Xe/CT study. The patient then inhales a mixture of xenon gas and oxygen via a face mask (A) for several minutes. Xe/CT images are acquired during inhalation. A solid headholder may be used to minimize motion of the head.

Source. Picture courtesy of NeuroLogica Corporation, Danvers, MA. Used with permission.

psychiatric populations. Nausea also occurs in some patients. Apnea is a rare and reversible side effect. Sedation may also be needed for neuropsychiatric patients.

Xe/CT has been used primarily for evaluation of cerebrovascular accidents, bleeds, and aneurysms (Coles 2006). Some work has been done with TBI patients, including assessment of ischemic regions following TBI and prediction of prognosis based on metabolic and blood flow changes in severe TBI (Inoue et al. 2005; von Oettingen et al. 2002). Thus, Xe/CT may provide important research contributions to understanding of the pathophysiology of TBI in the future.

Conclusion

Despite the promise of functional brain imaging as a noninvasive means for evaluation of TBI, clinical utility has not been fully demonstrated at this time. Although both SPECT and PET allow visualization of lesions not seen on structural scans, especially in mild TBI, the clinical significance of this finding for an individual patient with TBI has not been convincingly shown. These techniques may have a role in prediction of outcome, and this is presently their most common clinical use. Their utility for assessment of brain changes correlating with findings on neuropsychological testing, behavioral symptoms, and progress in rehabilitation is unclear. Despite the superior resolution of PET, its higher cost makes it difficult to justify over SPECT in evaluation of most TBI cases. Functional MRI is a promising method for study of TBI. Activation paradigms are required for most fMRI studies, so standardization of cognitive tasks must occur for development of clinical examinations. Resting-state fMRI approaches may be particularly valuable because they do not place any demands on the patient. However, as with PET and SPECT, the clinical applicability of this information has yet to be established in TBI.

With all functional imaging modalities, caution must be used in interpretation of scans in TBI patients with concomitant (possibly preexisting) neurological or psychiatric conditions. Blood flow and metabolic changes are also seen on functional imaging studies of these populations. In all functional imaging modalities used to study TBI, there is a need for more controlled studies using standardized methods to evaluate imaging data. Comparison of modalities in a single study is also important, because it will help to establish how the modalities can be complementary to one another. Receptor studies may be important in future TBI work. As new ligands are developed, enabling studies of different neurotransmitter systems, it may be possible to image disruption of particular systems after TBI (e.g., dopamine transmission deficits) and to individualize treatment based on these data.

It is probable that the most significant contribution of functional imaging to the study of TBI will be in understanding its pathophysiology. All of the modalities described in this chapter, and many new ones still in development, will contribute to knowledge of how cell injury and death occur in TBI. It is possible that this information could lead to new treatments, such as neuroprotective therapies that can be used immediately following TBI to minimize neuronal damage.

KEY CLINICAL POINTS

- All of the imaging techniques discussed in this chapter provide the clinician with additional information on the status of brain functioning and cannot or should not replace a thorough clinical interview.
- Always discuss the noise of the scanner and tightly enclosing space with the patient prior to imaging.
- When possible, inject any radiotracers for study *before* giving medications for study sedation/claustrophobia.
- SPECT measures blood flow; PET can measure either metabolism or blood flow. Both are clinical techniques at this time.
- fMRI is an indirect measure of task-related brain activation and is a research technique at this time.

Recommended Readings

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CHAPTER 7

Electrophysiological Assessment

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CLINICAL ELECTROPHYSIOLOGY OFFERS A VARIETY of powerful and informative methods by which to study cerebral function and dysfunction after traumatic brain injury (TBI). Electroencephalography (EEG) was the first clinical diagnostic tool to provide evidence of abnormal brain function caused by TBI (Glaser and Sjaardema 1940; Jasper et al. 1940; Williams 1941). Such early observations led to the development of increasingly sophisticated clinical and research electrophysiological techniques, including quantitative EEG (QEEG), topographic EEG (also known as *brain electrical activity mapping,* or BEAM), evoked potentials (EPs), and event-related potentials (ERPs), magnetoencephalography (MEG), and magnetic source imaging (MSI). These techniques permit noninvasive measurement of brain activity with temporal resolution superior to that of other functional neuroimaging methods, including positron emission tomography, single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging. However, and as discussed later in this chapter, the gains in temporal resolution offered by these techniques are accompanied by relative losses in spatial resolution (at least when compared with that afforded by functional neuroimaging).

Clinical and research application of electrophysiological techniques requires substantial knowledge of human electrophysiology, knowledge and training related to electrophysiological recording, and the ability to analyze and interpret electrophysiological data. These issues limit broad clinical application of electrophysiological assessment of mild TBI. Nonetheless, it is advisable for clinicians working with patients with mild TBI to be familiar with electrophysiological techniques, their strengths and limitations, and their roles in the study, evaluation, and treatment of these patients.

Because the majority of TBIs are mild (Thurman and Guerrero 1999; Thurman et al. 1999), and because persons with these injuries of this type comprise the majority of those treated by neuropsychiatrists, neurologists, physiatrists, and primary care physicians, the remainder of this chapter focuses on the application of electrophysiological techniques to the evaluation of persons with mild TBI. A general review of the principles of clinical electrophysiology is provided first, followed by a review of the major types of electrophysiological assessment techniques used to evaluate persons with TBI. In this context, the limitations of electrophysiological assessment are discussed and future directions are suggested.

Basic Principles of Clinical Electrophysiology

Neurotransmitter-receptor interactions occurring at the apical dendrites on cortical neurons, which can be either of an excitatory or an inhibitory nature, create electrical activity within the cortical columns. Such activity establishes electrical dipoles whose orientations are parallel to that of the cortical columns. The electrical activity generated by a single excitatory or inhibitory postsynaptic potential at a single dendrite is both too small and too brief to be recorded by a scalp surface electrode. However, summed excitatory and inhibitory postsynaptic potential across groups of many (e.g., several tens of thousands or more) apical dendrites of cortical pyramidal neurons generate electromagnetic signals that are amenable to recording at the scalp surface.

The electrophysiological signals generated in this manner and recorded at the scalp surface spontaneously are organized into four major categories of rhythmic activity: beta (12.5–25 Hz), alpha (7.5–12.5 Hz), theta (4–7.5 Hz), and delta (<4 Hz), examples of which are shown in Figure 7–1. These dominant, spontaneous rhythms reflect different states of engagement of cortical neurons within the local corticocortical networks, corticothalamic circuits (loops), and reticulocortical networks in which they participate.

In adults, *beta* activity reflects active engagement of the system in information processing. This activity in awake, eyes-open, resting recordings generally is asynchronous and of relatively low amplitude, reflecting the many areas of concurrently active, parallel, and independently engaged cortex contributing to this scalp-recorded rhythm.

Alpha activity reflects (simplistically) "idling" cortex in an alert individual—for example, the activity of primary visual cortex with eyes closed (referred to as the *posterior dominant rhythm*). Alpha reflects entrainment of corticothalamic loops at the intrinsic pacemaking frequency of their thalamic elements. Once engaged in these thalamocortical loops, firing is relatively synchronous and produces a rhythm of modest amplitude.

Theta activity reflects a slower type of cortical activity that increases in early sleep stages, states of quiet focus (e.g., meditation), and possibly memory development. In the case of sleep and quiet focus, the slowing of the cortical rhythm appears to reflect the inhibitory influence of reticular thalamic neurons on the thalamocortical loops. Because larger groups of neurons are engaged in this inhibited state, the EEG appears more synchronous and the amplitude of activity recorded increases. It also has been suggested that theta is the frequency at which hippocampally mediated long-term potentiation (memory formation) occurs. However, in clinical electroencephalographic recordings the appearance of a prominent theta rhythm occurs during early sleep stages or as a marker of pathology (e.g., encephalopathy, lesion) in the record of awake individuals.

Delta activity reflects a marked decrease in cortical activity such as is seen in stage 3 or 4 sleep, severe encephalopathy, or coma. In the setting of relative reductions of reticulocortical or thalamocortical influences on their activity, cortical neurons (usually in large locally connected groups) fire at their intrinsic pacemaking rhythm (delta). Such relative reductions occur in deeper sleep stages or in pathological (including lesional) states that disrupt reticulothalamic, reticulocortical, and thalamocortical connections.

Another rhythm of potential interest in this context is the *mu* (also known as the *central, Rolandic, sensorimotor, wicket,* or *arceau*) rhythm. This relatively brief duration (0.5–2 seconds) rhythm is observed with the alpha (and, possibly, beta) band and maximally over the sensorimotor cortices in the absence of movement. Although the functional significance of the mu rhythm is a subject of debate and investigation, it has been suggested that it may reflect downstream modulation of motor cortex by prefrontal mirror neurons and that this rhythm represents an information processing function linking perception and action—in other words, transforming seeing, hearing, and feeling into behavior (Pineda 2005). This transformation appears to reflect an entrainment or gating mechanism that couples visual-, auditory-, and somatosensory-centered alpha rhythms. The mu rhythm is of potential clinical significance because it appears to be subject to volitional control, with training, and therefore is a potential target for neurofeedback interventions attempting to improve cognitive or motor function.

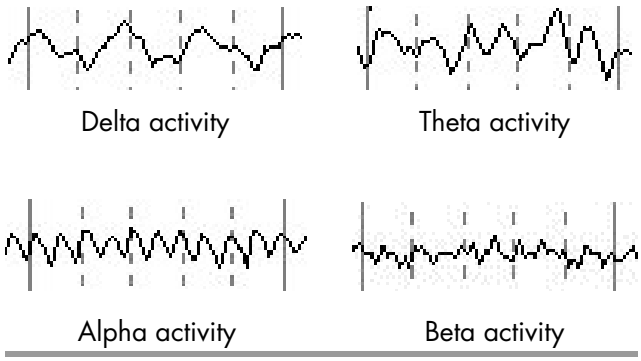


FIGURE 7–1. Examples of electroencephalography tracings illustrating activity in each of the four major frequency domains.
1 sec per block; sensitivity=7 μV/mm.

Both slow and fast cortical activity occur during wakefulness, and their relative predominance affects the background rhythm (usually alpha in the awake record). Slower background rhythms in the awake record are generally abnormal. When fast activity (alpha or beta) is superimposed on an abnormally slow background rhythm (low alpha through delta), this admixture of rhythms is referred to as *intermixed slowing.* Such slowing may be diffuse (generally indicating an encephalopathy) or focal (generally indicating a structural lesion underlying the area of slow activity on the scalp recording). The capacity for making transitions between slower synchronous rhythms and faster asynchronous rhythms in response to stimulation, referred to as *reactivity,* requires that the reticular activating system, thalamus, and relevant sensory cortices are capable of being engaged in different information processing states.

Abnormal events and patterns of cortical electrical activity generally fall into two major categories: paroxysmal spikes (or sharp waves) and slow waves. Spikes (duration ≤70 milliseconds) and sharp waves (70–200 milliseconds) are relatively high-voltage paroxysms of neuronal activity of the sort associated with seizure foci, although these events may occur among persons without clinical evidence of seizures or epilepsy. The term *slow waves* refers to activity with a frequency <8 Hz in a waking record; in such records, slow waves are usually regarded as abnormal. In some cases, spikes and slow waves occur together, forming spike-and-wave complexes; these complexes are frequently (but not always) pathological and are observed most commonly in the EEG of persons with epilepsies.

Clinical Neurophysiological Recording Methods

Cortical activity may be recorded using surface electrodes, magnetometers, or gradiometers (the latter two are types of

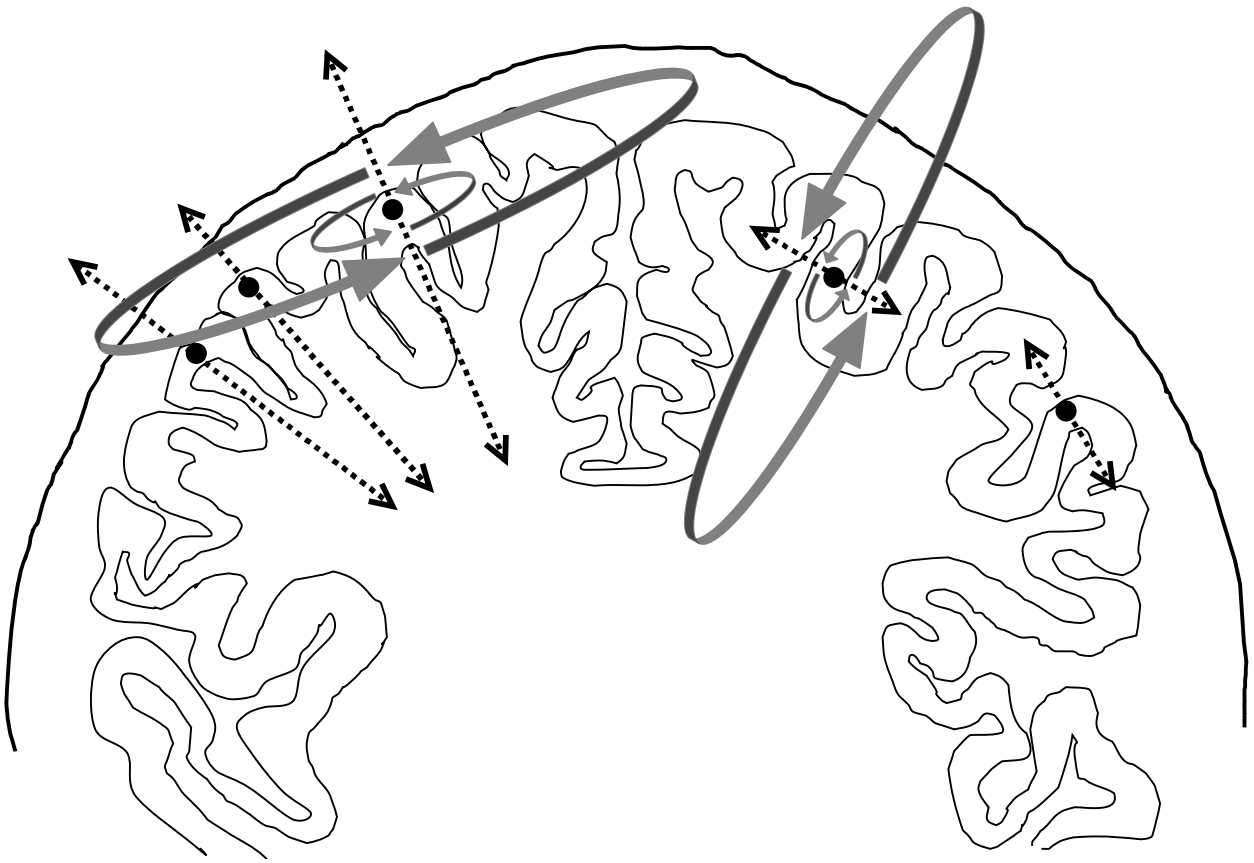


FIGURE 7–2. Illustration of the cortical mantle in the coronal plane.

Electrical dipoles (dashed arrows) and the magnetic fields (circular arrows around two such dipoles) generated by cortical columns are illustrated. Radially oriented (gyral) electric dipoles project to the scalp surface, but their magnetic fields remain tangentially oriented with respect to the scalp surface and appear at some distance from the dipole generating them. Tangentially oriented (sulcal) electric dipoles do not project to the scalp surface directly overlying them, but their magnetic fields do. Electrical dipoles are attenuated and diffused by the tissues through which they must pass before appearing at the scalp surface; magnetic fields do not suffer this attenuation and diffusion, but their strength falls off at $1/r^2$, where r=radius from the dipole source.

magnetic recording devices). The selection of one method of recording over another depends, at least in part, on the cortical areas to be recorded. Cortical columns are oriented from the cortical surface toward the gray-white junction regardless of whether those columns occur in gyral or sulcal surfaces. However, this cortical columnar organization results in both radial (gyral) and tangential (sulcal) electrical dipoles with respect to their appearance at the scalp surface (Figure 7–2). Both radially and tangentially oriented dipoles contribute to the electrical fields on the scalp, but radially oriented currents are the predominant contributor to scalp surface electrical fields. By contrast, tangentially oriented electrical dipoles produce a magnetic field that is radially oriented with respect to the scalp and is detectable through magnetoencephalographic recordings using an appropriately positioned magnetometer or gradiometer.

EEG, QEEG, EPs, and ERPs record electrical activity produced predominantly by radially oriented cortical columnar dipoles. Standardized recording methods are used to improve the reliability of electroencephalographic recording and interpretation within and across laboratories. The use of a standardized recording method, the 10–20 International System of Electrode Placement (Figure 7–3), is particularly important with respect to the detection, localization, interpretation, and reporting of abnormal electrical activity. Higher density or other nonstandard electrode arrays are sometimes used, particularly in neuropsychiatric research. Once placed, electrodes are linked physically or via software (in digital recordings) to create recording channels. Variously arranging recording channels creates several views, or *montages,* of cortical electrical activity. Analysis of findings within and between these montages is used to identify and localize abnormal activity.

Digital recording combined with software-assisted analytic methods permits quantitative electroencephalographic analyses. The most commonly used quantitative electroencephalographic measures include frequency composition of the EEG over a given period (spectral analysis), absolute and relative amplitude (μV/cycle/second) and power (μV^2/cycle/second) within a frequency range or at each channel, coherence (analogous to cross-correlation in the frequency domain between activity in two channels), phase (relationships in the timing of activity between two channels), or symmetry between homologous pairs of electrodes. Quantitative electroencephalographic

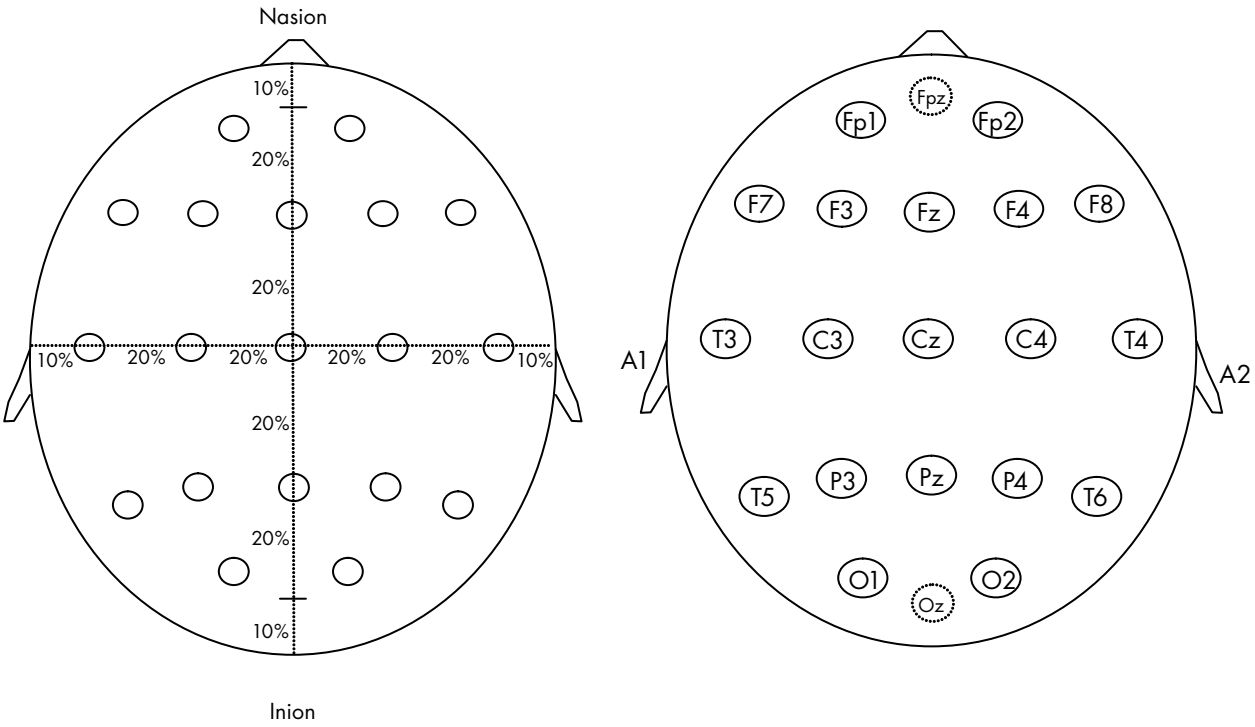


FIGURE 7–3. The 10–20 International System of Electrode Placement.

Electrodes are labeled according to their approximate locations over the hemispheres (F=frontal, T=temporal, C=central, P=parietal, and O=occipital; z designates midline); left is indicated by odd numbers and right by even numbers. A parasagittal line running between the nasion and inion and a coronal line between the preauricular points is measured. Electrode placements occur along these lines at distances of 10% and 20% of their lengths, as illustrated. In most clinical laboratories, the Fpz and Oz electrodes are not placed, but are instead used only as reference points. Fp1 is placed posterior to Fpz at a distance equal to 10% of the length of the line between Fpz-T3-Oz; F7 is placed behind Fp1 by 20% of the length of that line. O1 is placed anterior to Oz at a distance equal to 10% of the length of the line between Oz-T3-Fpz; T5 is placed anterior to O1 by 20% of the length of that line. F3 is placed halfway between Fp1 and C3 along the line created between Fp1-C3-O1; P3 is placed halfway between O1 and C3 along that same line. Right hemisphere electrodes are placed in similar fashion. Reference electrodes, in this case placed on the ears, are labeled A1 and A2.

data can be mapped over the scalp surface, a procedure known as *brain electrical activity mapping* (BEAM). Statistical probability mapping of BEAM data can be used to construct topographical maps for visual inspection (Figure 7–4).

EPs reflect automatic sensory information processing along the pathways from sensation to primary sensory cortex, whereas ERPs are regarded as reflecting later and more complex cognitive, sensory, or motor information processing. EPs and ERPs are generally named according to their polarity (positive or negative [P or N]) and latency (in milliseconds) poststimulus and to the sensory or motor modality in which they are evoked (Figure 7–5). Although the distinction between EPs and ERPs is somewhat arbitrary, there is general agreement that EPs develop 1–150 milliseconds after stimulus presentation and that ERPs develop 70–500 milliseconds after the event that evokes them. Another distinction is that EPs are generated in response to stimuli, whereas ERPs can be generated internally or even by omission of stimulation. The amplitudes of EPs and ERPs are small (0.1–10 μV) compared with that of the background EEG (10–100 μV). Consequently, digital signal averaging of many stimulus-evoked response trials is used to improve detection of these small signals. The speed with which these neurophysiological processes occur makes them relatively inaccessible to comparable study using self-report, neuropsychological assessment, behavioral assessments, or functional neuroimaging methods. It is this property, excellent temporal resolution, that makes EPs and ERPs potentially attractive methods by which to investigate the neurophysiological bases of neurological and neurobehavioral dysfunction after TBI.

Magnetoencephalographic systems use superconducting quantum interference devices to record cortically generated magnetic fields through current induction. Various magnetoencephalographic detection coils are available, each differing in their signal sensitivity and capacity for noise reduction. Modern magnetoencephalographic systems may have as many as 300 or more individual magnetic detectors (analogous to electroencephalographic electrodes). Unlike with EEG, magnetoencephalographic sensors do not need to be paired for differential recording, such that magnetoencephalographic measurements are free of the EEG reference electrode problem. Magnetic field strength is not attenuated by tissue interposed between the source of the signal and the magnetometer positioned to detect it. As such, MEG is able to detect both very high-frequency (up to 400–700 Hz) and ultra-low frequency (<1 Hz) signals that are not amenable to electroencephalographic recording. This can be important in disor-

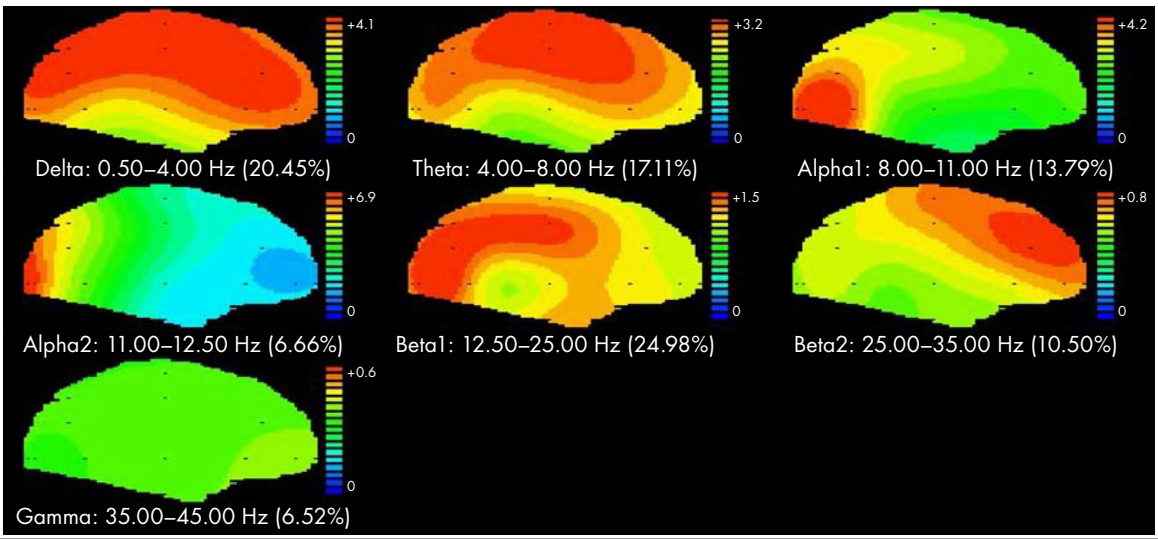


FIGURE 7–4. An example of spectral mapping.

This map describes relative power (percentage of total power) in the right hemisphere across several frequency ranges in a 25-year-old male with diffuse intermixed slowing on visual inspection of the electroencephalography record.

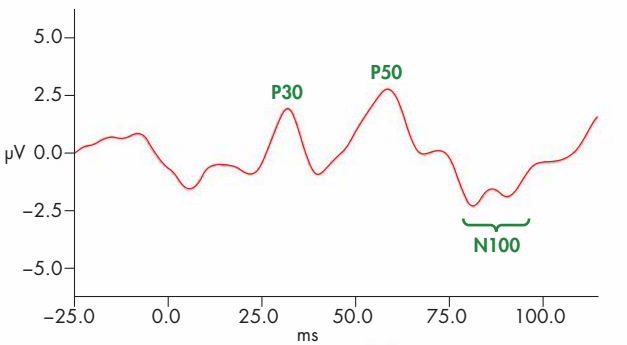


FIGURE 7–5. P30, P50, and N100 evoked potentials to a short-duration, moderate-intensity, broad-frequency binaural stimulus in a 34-year-old male control subject.

The actual latencies of these evoked potentials vary from their stated latency by about 10 ms; this degree of variability is normal and is expected in most recordings. The low-amplitude N100 in this tracing is "split," meaning that two definable but partially overlapping waveforms contribute to the evoked potential observed in this tracing.

ders such as epilepsy, for which new research implicates very high frequency (i.e., 200 Hz) oscillatory bursts that precede paroxysmal onset. Additionally, magnetic field characteristics can be used to estimate their cortical generators, a technique referred to as *magnetic source imaging,* defined as the integration/visualization of magnetoencephalographic-derived cortical current estimates on high-quality anatomical images such as those acquired by using magnetic resonance imaging (MRI). MEG is an attractive technology with which to evaluate cerebral dysfunction after TBI. However, the equipment, including a magnetically shielded environment in which MEG must be recorded, the operational costs of magnetoencephalographic recording systems, and the expertise needed to interpret magnetoencephalographic data limit the availability and application of MEG to TBI research and clinical practice.

Electrophysiological Studies of Mild Traumatic Brain Injury

Electroencephalography

Generalized or focal slowing and attenuated posterior alpha may occur in the first several hours after mild TBI among adults (Geets and de Zegher 1985; Nuwer et al. 2005). Among adult patients with loss of consciousness (LOC) of <2 minutes, 17% of 100 subjects recorded within 48 hours demonstrated electroencephalographic abnormalities, and electroencephalograms were abnormal in 56% of 25 subjects with mild TBI (LOC >2 minutes) (Geets and Louette 1985). Similar frequencies (15%–51%) of electroencephalographic abnormalities in the early period after mild TBI are reported elsewhere (Denker and Perry 1954; Geets and de Zegher 1985; Koufen and Dichgans 1978; Torres and Shapiro 1961; von Bierbrauer and Weissenborn 1998). In these cases, slowing, generalized bursts and focal abnormalities were the most common findings. However, such findings are not universal (Levin and Grossman 1978; Voller et al. 1999). Nonetheless, mild slowing is a common finding when EEG is performed within hours to days of a mild TBI. These changes are often subtle, not infrequently still within the range of normal findings in the general population, and may be apparent only when compared with follow-up electroencephalograms in the late postinjury period.

Among patients with mild TBI, electroencephalographic abnormalities often resolve completely within

3 months postinjury (Koufen and Dichgans 1978; von Bierbrauer et al. 1992) and remain in as few as 10% of individuals with mild TBI at 1 year postinjury. As reviewed by Nuwer et al. (2005), a low-voltage posterior alpha electroencephalographic pattern observed in the late period after mild TBI is as likely, and perhaps more likely, to be a sign of anxiety as it is a sequela of mild TBI.

It is important to note that epileptiform electroencephalographic abnormalities are relatively uncommon findings in the immediate postinjury period, and even when present they do not robustly predict the development of posttraumatic epilepsy. Nonetheless, persistence of epileptiform abnormalities in a patient with paroxysmal clinical events consistent with seizures after TBI strongly suggests posttraumatic epilepsy.

In short, conventional EEG may demonstrate abnormalities in the early postinjury period. However, the information yielded by EEG even in the setting of very recent mild TBI generally offers no information that is not otherwise available through careful history taking. As with the course of clinical recovery following mild TBI, return of EEG to normal is expected in the weeks to months in the majority of patients. The correspondence between clinical and electroencephalographic findings throughout the postinjury period is relatively poor (Nuwer et al. 2005), as is the correspondence of EEG with computed tomography, MRI, or SPECT abnormalities (Kant et al. 1997; Nuwer et al. 2005). The presence or absence of electroencephalographic abnormalities after mild TBI therefore is of uncertain clinical significance in many cases. Routine use of EEG as an assessment of mild TBI is not recommended and instead is best reserved for the evaluation of suspected posttraumatic epilepsy.

Quantitative Electroencephalography

QEEG has been used to investigate posttraumatic cerebral dysfunction, as a diagnostic assessment for mild TBI, and as a metric for the evaluation and prediction of outcome following mild TBI. Given the scope and complexity of the literature on this subject (see Coburn et al. 2006; Gaetz and Bernstein 2001; Nuwer et al. 2005), the review of QEEG and mild TBI presented here focuses on a limited set of findings and controversies.

QEEG has been used to define types and/or patterns of electroencephalographic abnormalities that might inform on the neurobiology of TBI (Fenton 1996; Korn et al. 2005; McClelland et al. 1994; Montgomery et al. 1991; Tebano et al. 1988; von Bierbrauer et al. 1992; Watson et al. 1995). Among the most consistent findings on QEEG in mild TBI are increased coherence and decreased phase between frontal and temporal areas, reduced differences in alpha and beta power between anterior and posterior cortical regions, and reduced alpha power posteriorly (Thatcher et al. 1989, 1991, 2001b). Also reported have been increased amplitudes in beta, theta, and delta ranges; reduced coherence between homologous electrode sites; increased amplitude variance (Randolph and Miller 1988); transient acute postinjury excesses in bitemporoparietal theta power (Montgomery et al. 1991); and reductions in alpha/theta ratios (Watson et al. 1995).

Thatcher et al. (1998b) reported that white matter T2 relaxation times negatively correlated with decreased coherence in short (7 cm) interelectrode distances and positively correlated with longer interelectrode distances. Also, gray matter T2 relaxation times were found to be more strongly related than white matter T2 relaxation times to decreased anteroposterior alpha coherence. In a related study (Thatcher et al. 1998a), white matter T2 relaxation times correlated positively with increased delta amplitude, whereas gray matter T2 relaxation times were inversely correlated with alpha and beta amplitude. Thatcher et al. (2001a) also observed relationships between T2 relaxation times and both alpha and delta-theta (0.5–5 Hz) power. Performance on cognitive assessments was related to some of these findings, with abnormalities in QEEG-MRI associated with relatively poorer neuropsychological test performance. These findings were interpreted as reflecting reduced integrity of the protein/lipid neural membranes and diminished efficiency of neural systems following mild TBI.

Kane et al. (1998), investigating the relationship between quantitative electroencephalographic indices and autopsy confirmed diffuse axonal injury (DAI) in 10 subjects with severe TBI, observed only a single significant correlation between DAI and interhemispheric coherence in the alpha band at the temporo-occipital site. No other clear or consistent relationships between interhemispheric coherence and the severity of DAI were observed. Although drawn from a small sample size, the failure to find an electrophysiological-pathological relationship between quantitative electroencephalographic indices (including coherence) and DAI after severe TBI raises concerns about the validity of suggesting such a relationship in mild TBI.

Nonetheless, the observation of relationships between findings in QEEG and MRI suggests the possibility that additional study may yield clinically useful insights into structural-functional changes produced by mild TBI, particularly if such insights obtain diagnostically at the single-subject (rather than solely at the group) level and also if they inform on prognosis and/or treatment selection. On the basis of these observations, considerable effort has been expended in the service of developing QEEG as a diagnostic assessment for mild TBI and particularly QEEG-based diagnostic discriminant functions. These are statistically derived analyses that facilitate pattern recognition in the complex data sets produced by QEEG and, in theory, facilitate accurate identification of electrophysiological changes that discriminate robustly those individuals with TBI from those without TBI (Johnstone and Thatcher 1991; Thatcher et al. 1989, 1991, 2001b). Such discriminant functions might also be of benefit in the medicolegal evaluation of patients with mild TBI whose clinical symptoms and neuropsychological impairments are not corroborated by abnormalities on conventional EEG or structural neuroimaging.

Although the quantitative electroencephalographic diagnostic discriminant function described by Thatcher et al. (1989, 2001b) appears to distinguish robustly between patients with TBI at various levels of initial injury severity and also between TBI and noninjured comparison subjects, its diagnostic utility is ultimately no better than, and in fact not quite as good as, that achieved by taking a good clinical history (the gold standard in these studies). Moreover, these quantitative electroencephalographic discrim-

inant functions do not address the more important clinical question of differential diagnosis: that is, whether the presenting symptoms of the patient are best attributed to TBI, depression, anxiety, attention-deficit/hyperactivity disorder, substance abuse, headaches, and so forth, including combinations of these conditions. It is very likely that the set of quantitative electroencephalographic variables that discriminate between mild TBI and normal control subjects (especially decreased posterior alpha amplitude and power and increased theta) overlap substantially with those produced by other neuropsychiatric conditions (e.g., anxiety, depression, substance abuse, headache) (Coutin-Churchman et al. 2003; Nuwer et al. 2005). With this in mind, use of a dichotomous quantitative electroencephalographic diagnostic discriminant function (TBI vs. no TBI) oversimplifies and fails to address the most pressing diagnostic challenge faced by clinicians—not whether a TBI occurred (which is a matter established by medical history taking) but whether the neuropsychiatric symptoms experienced by a patient are best attributed to TBI alone, to another neuropsychiatric condition, or some combination of both.

Until studies designed to ascertain the accuracy with which the TBI discriminant function addresses this challenge adequately are completed, the routine clinical or forensic use of discriminant function databases for the diagnosis of mild TBI is not advisable (Nuwer 1996, 1997; Nuwer et al. 2005). Having said this, it is important for clinicians to be aware that this is a matter of substantial, and at times acrimonious, debate (American Academy of Neurology 1989; Gaetz and Bernstein 2001; Hoffman et al. 1999; Luccas et al. 1999; Nuwer 1997; Nuwer et al. 2005). Clinicians involved in the care and medicolegal evaluation of individuals with mild TBI should review thoroughly these articles and the arguments regarding this technology before deciding whether to accept the recommendation made here regarding the inadvisability of the quantitative electroencephalographic diagnostic discriminant functions for clinical or forensic matters pertaining to mild TBI.

The neuropsychiatric consequences of mild TBI have not been the subject of extensive study using QEEG, although posttraumatic sleep disturbances (Parsons and Ver 1982; Williams et al. 2008), hostility (Demaree and Harrison 1996), treatment-resistant depression (Mas et al. 1993), and the "postconcussive syndrome" (Duff 2004; Fenton 1996; Korn et al. 2005; Watson et al. 1995) have been studied using this technology.

Watson et al. (1995) reported a significantly decreased alpha-theta ratio between postinjury days 0 and 10, after which a baseline level was established. Quantitative electroencephalographic recovery correlated with symptom counts 6 weeks postinjury, with slower electrophysiological recovery associated with more severe postconcussive symptoms. Relative delay in left temporal recovery was associated with residual psychiatric morbidity (as identified by the Index of Definition score on the Present State Examination) at 12 months postinjury.

Chen et al. (2006) observed significant increases in the average power of low alpha (8–9.8 Hz) and an increased low-alpha to high-alpha ratio, suggesting a shift to lower alpha frequency after mild TBI. Concordant with this observation, they also observed reduced theta/low-alpha ratio and increased theta/high-alpha ratio in their sample. After 3 months, 5% of subjects continued to demonstrate this pattern of quantitative electroencephalographic abnormality, which Chen et al. suggested might constitute a neurophysiological basis for persistent postconcussive symptoms. Unfortunately, their suggestion was not coupled with presentation of symptom versus quantitative electroencephalographic findings at their 3-month follow-up.

Korn et al. (2005) reported increased delta (1.5–5 Hz) and decreased alpha (8.5–12 Hz) power among subjects with persistent postconcussive symptoms. Quantitative electroencephalographic abnormalities were focal and widely distributed throughout neocortical areas and corresponded to SPECT-derived evidence of blood-brain barrier breakdown. By contrast, Montgomery et al. (1991) reported a relative excess of bitemporoparietal theta power immediately after mild TBI that significantly improved at reassessment 6 weeks later. No relationship between relative normalization of theta power and resolution of postconcussive symptoms was reported.

Unlike studies that focus on diagnostic discriminant functions, quantitative electroencephalographic investigations of the neurophysiological correlates of posttraumatic neuropsychiatric and/or functional problems (Leon-Carrion et al. 2008) may yield information that informs on the neurobiology of such problems and therefore also their treatment. To the extent that QEEG can be employed as a predictor of treatment response, whether to pharmacological or other rehabilitative interventions, it may become a particularly important component of the evaluation and treatment of persons with mild TBI. Additional studies addressing these issues are needed.

Evoked Potentials and Event-Related Potentials

Short-Latency Evoked Potentials

Short-latency EPs (brainstem auditory evoked potentials, pattern visual evoked potentials, brainstem trigeminal nerve stimulation, motor evoked potentials, and somatosensory evoked potentials) have been used to investigate mild TBI as well as the postconcussive syndrome and individual postconcussive symptoms (e.g., dizziness, cognitive impairment). Many of these studies identify short-latency EP abnormalities similar to those observed in more severely injured individuals. Such abnormalities are identified in approximately 10%–30% of persons with mild TBI.

The most common type of short-latency EP abnormality after mild TBI is delayed latency (Benna et al. 1982; Gentilini and Schoenhuber 1986; McClelland et al. 1994; Rizzo et al. 1983; Rowe and Carlson 1980; Schoenhuber and Gentilini 1986, 1987; Schoenhuber et al. 1983, 1987, 1988), although reduced amplitude is also described (Haglund and Persson 1990). These findings suggest that mild TBI sometimes produces electrophysiological abnormalities similar in type to those observed after severe TBI. These abnormalities, however, are of modest severity and are observed less often among persons with mild TBI.

The relationship between abnormal short-latency EPs and persistent postconcussive symptoms is variable (Gaetz

and Bernstein 2001; Gaetz and Weinberg 2000; Schoenhuber and Gentilini 1987; Schoenhuber et al. 1988; Werner and Vanderzandt 1991) and does not appear to be a particularly promising method of diagnosing or predicting recovery from mild TBI. With regard to short-latency EP abnormalities as a method of investigating specific postconcussive symptoms, the data are mixed (Benna et al. 1982; Freed and Hellerstein 1997; Rowe and Carlson 1980; Schoenhuber and Gentilini 1986; Schoenhuber et al. 1988) but not without some promise.

For example, Freed and Hellerstein (1997) observed visual EP abnormalities in 39 of 50 (78%) patients with mild TBI presenting for optometric rehabilitation in the postacute and late period after injury. Eighteen of these patients underwent optometric rehabilitation, and the remainder received no specific visual therapy. Visual EP testing was repeated 12–18 months later; visual EP abnormalities were present in 38% of treated patients and 78% of untreated patients. The nature of the interaction between optometric rehabilitation and improvement in visual EPs is not clear. However, this study suggests the possibility that closely pairing visual EPs with posttraumatic visual disturbances may offer information that substantiates the presence of symptom-related neurobiological dysfunction and a method by which to select patients for visual treatment and to monitor the neurobiological effects of such treatment. Whether or not identification and treatment of this and/or other postconcussive symptoms can be guided fruitfully by short-latency EPs requires further study.

Middle-Latency Evoked Potentials and Event-Related Potentials

We examined the middle-latency P50 response to paired auditory stimuli (a test of hippocampally dependent stimulus inhibition) among 20 adult subjects (11 mild TBI, 9 moderate to severe TBI) with persistent posttraumatic complaints of auditory gating, attention, and memory impairments in the late postinjury period (>1 year since injury) and 20 age- and gender-matched comparison subjects (Arciniegas et al. 2000). P50 ratios ([test P50 amplitude]/[conditioning P50 amplitude]) were abnormal (increased) in all of the TBI subjects and none of the control subjects. Importantly, P50 ratios among the TBI subjects, who were matched for outcome, did not differ as a function of initial injury severity.

In a subsequent study, the frequency of P50 nonsuppression among subjects with persistent posttraumatic attention and memory complaints was assessed (Arciniegas and Topkoff 2004). Forty-eight adult subjects (30 mild TBI, 18 moderate-to-severe TBI) of more than 1 year postinjury were evaluated. P50 recordings were unable to be obtained in 15% of the subjects (3 mild TBI, 4>mild TBI) because of slow-wave and/or eye-movement artifacts. Of the remaining 41 subjects, P50 ratios were normal in 7%, mildly abnormal in 12%, and markedly abnormal in 81%. As in our first study, P50 ratios and the frequency of P50 nonsuppression did not differ as a function of initial injury severity given that subjects were matched for outcome and clinical symptoms.

In a subgroup of 10 subjects (4 mild TBI, 6 severe TBI) and 10 healthy matched control subjects, hippocampal volumes were assessed for the purpose of investigating a structural-functional relationship relevant to the P50 finding. Reduced hippocampal volumes (controlled for the effects of total brain volume reductions) were observed in all P50 nonsuppressing TBI subjects when compared with the control subjects.

Using a 30-week randomized, double-blind, placebo-controlled crossover design, we used donepezil HCl as a probe of the cholinergic system among 10 subjects (9 women) with TBI (8 mild, 2 >mild) who had P50 nonsuppression and persistent posttraumatic gating, attention, and memory complaints in the late postinjury period. There was a significant effect of treatment condition on P50 ratio: P50 ratios normalized in 60% on low-dose donepezil HCl, 30% on high-dose donepezil HCl, 0 on placebo 1, and 10% on placebo 2.

Collectively, these findings suggest that the P50 evoked response to paired auditory stimuli is a relatively robust marker of persistent posttraumatic attention and memory complaints and reflects dysfunction in the hippocampally mediated, cholinergically dependent network involved in sensory gating, attention, and memory. Additionally, these findings serve as an example of the potential utility of applying ERPs (and, by extension, other electrophysiological assessment techniques) to the study of specific posttraumatic neuropsychiatric symptoms.

Long-Latency Evoked Potentials and Event-Related Potentials

Long-latency EPs/ERPs are widely regarded as markers of cortically mediated stimulus detection, categorization, attention, and allocation of cerebral resources for cognitive tasks. Because patients with persistent cognitive impairments after TBI frequently report difficulty performing cognitive tasks that are related to these functions, long-latency EPs and ERPs have been used extensively in the study of TBI-related cognitive impairments and the postconcussive syndrome.

The most frequently studied long-latency EPs and ERPs in the TBI population include the auditory mismatch negativity, auditory N200 (N2), P300 (P3a, P3b), and contingent negative variation (CNV). There are many reports of such long-latency EP and ERP abnormalities after mild TBI, particularly as they relate to cognitive dysfunction in the acute postinjury period (Pratap-Chand et al. 1988) and prognosis (Lew et al. 1999). More commonly, long-latency EPs and ERPs are used to investigate cognitive (Dupuis et al. 2000; Gaetz and Weinberg 2000; Gaetz et al. 2000; Lavoie et al. 2004; Naito et al. 2005; Reinvang et al. 2000; Reza et al. 2006; Sangal and Sangal 1996; Segalowitz et al. 2001; Solbakk et al. 1999, 2000, 2005) and other neuropsychiatric impairments (Lew et al. 2005; Reza et al. 2007) in the late period after mild TBI.

A few consistent themes arise from this literature. Significantly reduced amplitudes or delayed latencies of the N2, P300, and CNV suggest reduced and inefficient allocation of attentional processing resources after mild TBI, including repetitive concussions in athletes (De Beaumont et al. 2007; Gaetz et al. 2000). Delayed development of the P300a suggests slowed detection of stimulus novelty, and reduced P300a amplitude suggests inadequate allocation of novelty detection systems to incoming stimuli (e.g., in-

attention). Although less common, exaggerated P300a amplitude, which may be seen with frontal lobe lesions (Solbakk et al. 2005), suggests excessive direction of resources to novelty (e.g., distractibility). Persistently cognitively impaired TBI patients are less efficient in terminating processing of irrelevant stimuli and tend to misallocate attentional resources (as reflected by reduced ERP amplitudes).

Recovery of function after concussion is associated with the normalization of P300 latency and amplitude (Pratap-Chand et al. 1988; von Bierbrauer and Weissenborn 1998), although P300 amplitudes may remain chronically attenuated despite functional recovery (De Beaumont et al. 2007; Segalowitz et al. 2001). The persistence of such EP/ERP abnormalities into the late postinjury period in a substantial number of affected individuals suggests that their cognitive complaints may indeed reflect persistent posttraumatic neurophysiological dysfunction, but that dysfunction is of severity mild enough to be compensated for behaviorally during the relatively brief duration of routine neuropsychological testing.

Finally, it is worth noting that P300 amplitude is reduced and P300 latency is prolonged under conditions of relative cholinergic depletion (Frodl-Bauch et al. 1999) and that these abnormalities may be normalized during administration of cholinesterase inhibitors (Hammond et al. 1987; Meador et al. 1987). Pratap-Chand et al. (1988) also noted the links between cholinergic dysfunction after TBI, cholinergic dysfunction and P300 abnormalities, and P300 abnormalities and postconcussive cognitive dysfunction. They suggested that recognition of these links afford an opportunity for investigation of cholinergic pharmacotherapies for cognitive dysfunction after TBI using the P300 as a metric of cholinergic function. This avenue of P300 research has not, at the time of this writing, been pursued in this population. Nonetheless, their hypothesis and that which we described when using the P50 response to paired auditory stimuli reflect common formulations with respect to the usefulness of EPs and ERPs: as neurophysiological markers of cholinergic dysfunction and attentional impairments after TBI. Additional investigations clarifying these electrophysiological-neurochemical relationships are needed, and their results may suggest a role for EPs and ERPs in the identification of neurochemical dysfunction and the selection of treatments for cognitive impairment caused by TBI.

In summary, EPs and ERPs may offer information about the neurophysiological consequences of mild TBI. Based on our review of the literature, we are of the opinion that the use of EEG or QEEG for the purpose of diagnosing mild TBI in the late period after injury is inadvisable. However, pairing these recording and data-analytic techniques, as well as specific EPs and ERPs, with posttraumatic problems, particularly when coupled with history and other assessment methods, may facilitate identification of the neurobiological underpinnings of those problems. By understanding such problems more clearly, the development of neurobiologically informed treatment approaches may be developed more easily and with better likelihood of efficacy and effectiveness.

Magnetoencephalography and Magnetic Source Imaging

Reports of the application of MEG to the investigation or clinical evaluation of mild TBI are few. One study (Lewine et al. 1999) suggested that MSI indicated brain dysfunction in more patients with postconcussive symptoms than did either EEG or MRI, and that the presence of excessive, localized abnormal low-frequency magnetic activity correlates well with the degree of symptomatic recovery after TBI. A second study by the same authors (Lewine et al. 2007) suggested a role for MEG in the multimodal imaging assessment of persons with posttraumatic cognitive impairments. At present, no conclusions can be drawn regarding the usefulness of MEG or MSI in the assessment of persons with mild TBI, although this remains a potentially promising technology for this purpose.

KEY CLINICAL POINTS

- Clinical electrophysiology offers many noninvasive methods with which to study cerebral dysfunction after mild TBI.
- The temporal resolution of electrophysiological assessment methods exceeds that of other advanced neuroimaging techniques, but at the cost of spatial resolution.
- Electrophysiological assessments may yield data that support a clinical diagnosis of mild TBI.
- Electrophysiological assessment is not appropriately used as a stand-alone diagnostic test for mild TBI.
- The findings from electrophysiological assessment have not been demonstrated to be specific to TBI. Instead, neuropsychiatric conditions that disturb brain structure and function in ways similar to TBI tend to produce electrophysiological findings similar to those observed among persons with TBI.

- Electrophysiological assessment shows promise for potential research and clinical usefulness when employed as a method of investigating the neurobiological bases of specific posttraumatic neuropsychiatric problems.

- Middle-latency and long-latency ERPs, QEEG, and MEG appear to offer the greatest promise of advancing our understanding of the neurophysiological mechanisms underlying the posttraumatic cognitive, emotional, behavioral, and neurological sequelae of mild TBI. These electrophysiological investigations may be particularly fruitful if they do not attempt to diagnose mild TBI but instead focus on using these technologies to better define the neurobiology of posttraumatic symptoms and guide pharmacological and rehabilitative interventions.

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CHAPTER 8

Neuropsychological Assessment

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NEUROPSYCHOLOGICAL ASSESSMENT HAS BECOME a popular and useful tool within the field of neuropsychiatry. The neuropsychological evaluation is focused on the formal assessment of brain-behavior relationships using psychometric methods. This evaluation provides important information regarding type and severity of brain injury, course, and process of recovery, and it is particularly useful in structuring rehabilitation. In this chapter we review the use of neuropsychological assessment within the context of traumatic brain injury (TBI) with particular reference to the neuropsychiatric evaluation and treatment of the TBI patient.

Role of the Neuropsychologist

In the TBI population, the neuropsychologist most often works as part of a multidisciplinary team and contributes to treatment by determining the extent of cognitive, behavioral, and emotional deficits produced by damage to the central nervous system. In addition to identifying deficits, one of the primary purposes of the neuropsychological assessment is the quantification of an individual's relative strengths and weaknesses. The information gathered from psychometric testing is integrated with additional data acquired during the neuropsychiatric evaluation. This collaboration greatly enhances the diagnostic accuracy of the evaluation and leads to the development of more effective treatment recommendations for the rehabilitation team, the patient, and his or her family. Neuropsychology's emphasis on the measurement of the behavioral expression of brain injury within the context of the patient's interpersonal, social, and familial environment enables the treatment team to better address both pharmacological and psychosocial needs. Although modern anatomical and functional neuroimaging procedures have become increasingly helpful in localizing the site of brain injury following TBI, contemporary neuropsychological assessment focuses on understanding the relationship between the patient's neurocognitive deficits and the behavioral expression of these deficits within the environment. Additionally, neuroimaging is not always sensitive to subtle brain dysfunction, and patients who have suffered a TBI may not display any positive findings on standard neuroimaging procedures, especially when the injury is mild (e.g., mild TBI or concussion).

Approaches to Neuropsychological Assessment of Patients With TBI

Traditionally, three approaches to neuropsychological assessment have been popular: a fixed battery of neuropsychological tests, a flexible battery approach, and a combination of fixed and flexible approaches.

Fixed Battery Approach

The fixed battery is a preset selection of tests that are given to every patient in a standard manner regardless of the referral question or the patient's symptoms. The advantages of the fixed battery are its comprehensive assessment of multiple cognitive domains and the usefulness of its standardized format for research purposes. However, the battery's length of administration and lack of flexibility in different clinical situations pose disadvantages. The Halstead-Reitan Neuropsychological Test Battery (HRNB; Reitan and Wolfson 1993) is no doubt the most frequently used fixed test battery within neuropsychology (Lovell and Nussbaum 1994).

The HRNB is a comprehensive battery that measures cognitive functioning across multiple domains. The battery is frequently supplemented with measures of general intelligence from the Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III; Wechsler 1997a), and its most recent fourth edition (WAIS-IV; Wechsler 2008), memory from the Wechsler Memory Scale, 3rd Edition (WMS-III; Wechsler 1997b), and its most recent fourth edition (WMS-IV; Wechsler 2009), and tests of other specific functions such as an aphasia and sensory-perceptual battery or a measure of grip strength (Franzen 2000). The subtest results are used to calculate the Impairment Index, which represents the proportion of scores that fall within the impaired range. Although the Impairment Index was intended for making gross diagnostic discriminations, research indicates that conclusions regarding the simple presence or absence of brain damage based on this index have been found to be less accurate than those obtained by clinical judgment based on tests, interviews, and medical history (Tsushima and Wedding 1979). Other criticisms of the HRNB point to its lengthy time of administration (6–8 hours); its inappropriateness for elderly patients, patients with dementia, and patients with sensory or motor handicaps; and the cumbersome testing materials. Nonetheless, it is a widely researched battery that is effective in discriminating a variety of neurological conditions (Franzen 2000). The well-established reliability and validity of the HRNB as well as normative data for comparisons of psychiatric populations likely contributes to its extensive use in forensic settings. Additionally, some of the subtests demonstrate ecological validity in their correlation with occupational, social, and independent living criteria (Heaton and Pendleton 1981).

Flexible Battery Approach

The flexible battery is a battery of tests that are selected by the neuropsychologist on the basis of the patient's presenting illness or referral question. Thus, the battery is tailored to each individual based on the specific diagnostic question. The advantages of using a flexible approach include a possible shorter administration time, lower economic costs, a wider range of normative data, and the ability to adapt to varying patient situations and needs. For example, a neuropsychologist may conduct a shorter screening evaluation as a basis to explore particular areas in greater detail in a patient who becomes quickly fatigued. Disadvantages include the potential for examiner bias or omission of deficits from a lack of comprehensiveness, a lack of standardized administration rules for some of the tests, and a limited ability to develop a research database (Lovell and Nussbaum 1994).

Fixed/Flexible Battery Approach

A third approach for neuropsychological assessment is a combination of the fixed and flexible approaches. In this way, the examiner uses a core set of tests to assess the major cognitive domains described earlier and to supplement the battery with additional tests as needed. The core battery is administered to all patients, and additional tests are added to further explore areas of cognitive deficits (Bauer 2000). This approach has become more common and continues to increase in popularity as health maintenance organizations continue to restrict reimbursement for lengthy neuropsychological evaluations. Additionally, this fixed/flexible battery approach has been found to be equally as sensitive to brain dysfunction as the fixed HRNB (Loring and Larrabee 2006; Rohling et al. 2003).

The Neuropsychological Assessment Process

There are several major cognitive domains that should be assessed in a comprehensive neuropsychological exam for TBI. These include attention; memory; executive functioning; speech and language; visuospatial and visuoconstructional skills; intelligence; and psychomotor speed, strength, and coordination (Vanderploeg 1994). Measures of psychological functioning are also frequently administered. Numerous neuropsychological tests purport to measure specific aspects of neurocognitive functioning, and some of the more popular test instruments are listed in Table 8–1. This table provides a list of the major cognitive domains and examples of neuropsychological tests that are used to assess those domains.

Intelligence

Historically, intelligence was considered a unitary construct, though today is typically understood as a variety of mental skills and abilities including those measured by subtests described in the sections below. Likely the most commonly used neuropsychological test battery for "intelligence" is the Wechsler Adult Intelligence Scale, now in its fourth edition (Wechsler 2008). Individual subtests are separated into either verbal or nonverbal (performance) tasks and can be used alone to assess specific cognitive abilities such as vocabulary, working memory, and abstract reasoning.

Alertness and Orientation

Impairment in alertness and orientation is common in patients who sustain TBI, particularly in the immediate hours and days following their injury. A neuropsychological evaluation during this period would be difficult and most likely invalid. TBI patients have a high probability of developing a disorder of alertness in the presence of certain etiological factors that further compromise brain function (brainstem reticular activating system damage, supratentorial and subtentorial lesions, reduction in brain metabolism, organ failure, increased or decreased body temperature, seizure) as well as from sedating medications and lack of sleep (Stringer 1996). Patients with psychiatric disorders such as depression, schizophrenia, factitious disorder, and conversion disorder can appear sleepy, apathetic, or unresponsive, and this should be ruled out when determining whether the patient has impaired alertness. However, misattributing a patient's impaired alertness to psychiatric causes can have life-threatening consequences for the patient if the cause is actually physiological.

TABLE 8–1. Cognitive domains and representative neuropsychological tests

Attention and concentration
Digit Span subtest from the WAIS-III, WMS-III, WAIS-IV (Wechsler 1997a, 1997b, 2008)
Spatial Span subtest from the WMS-III (Wechsler 1997b)
Spatial Addition subtest from the WMS-IV (Wechsler 2009)
Digit Symbol subtest from WAIS-III (Wechsler 1997a)
Coding subtest from the WAIS-IV (Wechsler 2008)
Continuous Performance Test (Rosvold et al. 1956)
Paced Auditory Serial Addition Task (Gronwall 1977)
Stroop Color and Word Test (Golden 1978)
Digit Vigilance Test (Lewis and Rennick 1979)
Consonant Trigrams (Brown 1958; Peterson and Peterson 1959)
Memory and learning
California Verbal Learning Test, 2nd Edition (Delis et al. 2000)
Rey-Osterrieth Complex Figure test (Osterrieth 1944)
Hopkins Verbal Learning Test–Revised (Brandt and Benedict 2001)
Rey Auditory-Verbal Learning Test (Rey 1964)
WMS-III (Wechsler 1997b)
WMS-IV (Wechsler 2009)
Benton Visual Retention Test (Benton 1955)
Brief Visuospatial Memory Test–Revised (Benedict 1997)
Executive functioning, concept formation, and planning
Booklet Category Test (DeFilippis and McCampbell 1997)
Wisconsin Card Sorting Test (Heaton 1981)
Controlled Oral Word Association Test (Benton and Hamsher 1989)
Trail Making Test–Part B (Spreen and Strauss 1998)
Delis-Kaplan Executive Function System (multiple subtests, including Design Fluency) (Delis et al. 2001)
Language
Aphasia Examination (Russel et al. 1970)
Boston Diagnostic Aphasia Examination, 3rd Edition (Goodglass et al. 2000)
Multilingual Aphasia Examination (Benton and Hamsher 1989)
Western Aphasia Battery (Kertesz 1979, 1982)
Boston Naming Test (Kaplan et al. 1983)
Visuospatial and visuoconstructional skills
Visual Form Discrimination Test (Campo and Morales 2003)
Judgment of Line Orientation Test (Benton et al. 1975)
Hooper Visual Organization Test (Hooper 1983)
Rey-Osterrieth Complex Figure (Copy) (Osterrieth 1944)
Block Design subtest from the WAIS-III, WAIS-IV (Wechsler 1997a, 2008)
Intelligence
WAIS-III (Wechsler 1997a)
WAIS-IV (Wechsler 2008)
Motor processes
Finger Tapping Test (Halstead 1947)
Grooved Pegboard Test (Klove 1963)

Note. WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale.

The Galveston Orientation and Amnesia Test (GOAT; Levin et al. 1979) is a brief test that is often administered at bedside to assess the patient's current level of orientation and recall of events that occurred before and after the accident (Figure 8–1). The GOAT is particularly useful for determining posttraumatic amnesia within the acute hospital setting. During posttraumatic amnesia the patient is disoriented and confused, and his or her ability to learn and remember new information is disrupted. Another assessment of posttraumatic amnesia is the Orientation Log, a 30-point scale developed for consistent scoring procedures that easily distinguishes new learning and/or retrieval problems without examiner interpretation (Jackson et al. 1998; Novack et al. 2000). It has been shown to be both reliable and valid (Jackson et al. 1998). Whereas the GOAT incorporates both retrograde and anterograde amnesia into its assessment, the Orientation Log only uses posttraumatic amnesia to assess severity and duration of memory impairments. Posttraumatic amnesia is acute and time-limited, and its duration can be an important prognostic indicator of recovery from brain injury, with a longer period of posttraumatic amnesia (>1 or 2 weeks) predictive of poor recovery (Lovell and Franzen 1994). In mild TBI, research has shown that the presence of amnesia may be more predictive of symptom and neurocognitive deficits compared with loss of consciousness (Collins et al. 2003).

Attentional Processes

Disorders of attention are a common consequence of TBI. Attentional impairments can interfere with rehabilitation, especially if the deficit is severe. Patients with severe attentional impairments may be too distractible and unable to focus their attention long enough to learn compensatory strategies or to benefit from retraining (Lezak 1995).

Assessment of attention is necessary because it is a prerequisite for successful performance in other cognitive domains. Additionally, deficits in attention can mimic other cognitive deficits. For example, a patient who is unable to fully attend to the stimuli on a memory test will not adequately encode the information. This patient's test scores may indicate memory impairment when in fact it was a deficit in attention rather than in memory. Patients with attention deficits can also appear to have problem-solving deficits even though these cognitive processes are intact (Fisher and Beckley 1999). For example, a patient may respond impulsively or have difficulty maintaining attention to the task long enough to solve it correctly. He or she might appear to have poor problem-solving skills when in fact the deficit is in attention. Behaviorally, a patient with attention impairment may start many new tasks or projects but is unable to complete them. Socially, his or her conversation may shift from topic to topic without any issue being dealt with thoroughly (Stern and Prohaska 1996).

There are multiple components of attention, and specific tests are used to evaluate its different aspects. An individual's attention to the task at hand requires him or her to focus on some aspect of the environment (focused and/or selective attention), to sustain that focus for as long as necessary (sustained attention and/or vigilance), and to

shift the focus when required (cognitive flexibility and/or divided attention) (Anderson 1994; Campbell 1996).

When assessing attention, one should first assess the general level of arousal. Next, the attention span, or density, of information the person can hold in attention at one time is assessed. Tests such as Digit Span (WAIS-IV; Wechsler 2008), Spatial Span (WMS-III; Wechsler 1997a), and Spatial Addition (WMS-IV; Wechsler 2009) are often used to assess auditory and visual attention span. Divided attention (e.g., being able to maintain a conversation while ignoring environmental distractions) is often assessed with the Stroop Color and Word Test (Golden 1978), the color-word interference subtest from the Delis-Kaplan Executive Functioning System (D-KEFS; Delis et al. 2001), or the Paced Auditory Serial Addition Test (PASAT; Gronwall 1977). The Stroop test is commonly used because it addresses multiple aspects of attention such as focused and divided attention as well as other cognitive domain abilities (e.g., executive functioning). The interference score on the Stroop test has been particularly useful in looking at the ability to inhibit an overlearned response and cognitive flexibility (Groth-Marnat 2000). The D-KEFS uses two baseline conditions (color naming and word reading) prior to the administration of an alternation attention and higher level interference task similar to the Stroop test. It also adds a fourth condition switching procedure, requiring both verbal inhibition and cognitive switching (Delis et al. 2001), that has shown increased sensitivity especially in mild TBI (Bohnen et al. 1992). The PASAT, a challenging test of sustained and divided attention, is particularly useful as a measure of recovery from mild brain injury, and it is sensitive to the subtle but meaningful deficits that may occur following multiple head injuries (Gronwall 1977). The PASAT is also useful for assessing information-processing deficits in patients with brain injury (Gronwall 1977).

The third area of attention that should be assessed (in addition to attention span and divided attention) is sustained attention, or vigilance. This area, often referred to as distractibility, is the ability to sustain concentration on a set of stimuli that falls within the person's span of concentration while ignoring extraneous stimuli (Stringer 1996). Thus, it is the ability to maintain attention over time. Tests commonly used to measure vigilance include the Continuous Performance Test (Rosvold et al. 1956), the Digit Symbol subtest from the WAIS-III (Wechsler 1997a) and Coding subtest from the WAIS-IV (Wechsler 2008), and the letter and number cancellation tests such as the Digit Vigilance Test (Lewis and Rennick 1979).

Memory

Memory impairment is one of the most common complaints following TBI. Memory is a multifaceted process that can generally be described as the ability, process, or act of remembering or recalling, and the ability to reproduce what has been learned or experienced (Campbell 1996). Memory deficits can be temporary, as occurs with posttraumatic amnesia, or more permanent. In general, memory impairment can be classified as either retrograde amnesia or anterograde amnesia. Retrograde amnesia involves memory loss for a time period before the injury. Anterograde amnesia involves memory loss for events following the injury. Similar to attentional processes, memory is also a multidimensional cognitive process that involves multiple underlying brain structures. For example, the hippocampus is associated with transferring information from short-term to long-term memory (Carlson 2005).

The memory process begins with sensory information, which is either forgotten almost immediately or stored in short-term memory through rehearsal. The two main types of memory are short-term and long-term memory (Carlson 2005). Short-term memory is temporarily held (less than a minute) and consists of five to nine items of information for the average person. When information is temporarily stored, manipulated, and recalled in short-term memory (e.g., mental arithmetic problem), it is referred to as *working memory* and is commonly affected after brain injury. Memory for information after a delay of minutes to hours is referred to as *delayed recall* or *recent memory* (Anderson 1994). Once information is consolidated into long-term memory, it is more permanent and rarely affected by brain injury. In neuropsychological assessment, short-term and long-term memory for both verbal and visual information are formally measured. Additionally, the patient's acquisition, retention, and retrieval of newly learned information should be assessed.

Although patients with mild brain injury frequently complain of memory problems, their perceived problems may often be the result of impairment in the ability to attend to or acquire the material rather than to a memory disorder per se. Patients with more focal damage, as can occur in penetrating injuries, are likely to demonstrate material-specific deficits in learning and remembering as a result of selective damage to the language-dominant hemisphere (usually left) or language-nondominant hemisphere (usually right). Specifically, patients with dominant hemisphere damage are more likely to have impaired recall of verbal material but preserved recall of nonverbal material, although this is not always the case. The California Verbal Learning Test, 2nd Edition (CVLT-II; Delis et al. 2000), Hopkins Verbal Learning Test—Revised (Brandt and Benedict 2001), and the Rey Auditory-Verbal Learning Tests (Rey 1964) are commonly used to assess verbal memory. In each of these tests, the subject is verbally presented with a list of words over multiple trials. After the learning phase, the subject is presented with a second distracter list, which is followed by a recall of the original list, and then a longer delay (about 20 minutes) recall of the original list. Following the delayed recall, the subject is presented with a forced-choice recognition task. Auditory Consonant Trigrams is a working memory task that does not require the examinee to manipulate the information, but it does provide a distracter task to prevent rehearsal of the information presented (Lezak et al. 2004).

Visual memory is typically assessed through tests that require the patient to learn and reproduce spatial designs. The Rey-Osterrieth Complex Figure (Osterrieth 1944) assesses visual memory by having the patient reproduce a drawing of a geometric design at different time intervals after the initial presentation, which involves copying the figure (Lovell and Franzen 1994). The WMS-III (Wechsler 1997b) and WMS-IV (Wechsler 2009) are a battery of tests specifically designed to measure various aspects of both

Name: _____ Date of test: _____
Age: _____ Sex: M F Day of the week: S M T W Th F S
Date of birth: _____/_____/_____ Time: _____ A.M. _____ P.M.
Diagnosis: _____ Date of injury: _____/_____/_____

Instructions: Error points (shown in parentheses after each question) are scored for *incorrect* answers and are entered in the two columns on the extreme right side of the test form. Enter the total error points accrued for the 10 items in the lower right-hand corner of the test form. The GOAT score equals 100 minus the total error points. Recovery of orientation is depicted by plotting serial GOAT scores on at least a daily basis.

	Error	Points
1. What is your name? (2) When were you born? (4) Where do you live? (4)		
2. Where are you now? (5) city (5) hospital (unnecessary to state name of hospital)		
3. On what date were you admitted to this hospital? (5) How did you get here? (5)		
4. What is the first event you can remember *after* the injury? (5) Can you describe in detail (e.g., date, time, companions) the first event you can recall *after* the injury? (5)		
5. What is the first event you can remember *before* the accident? (5) Can you describe in detail (e.g., date, time, companions) the first event you can recall *before* the injury? (5)		
6. What time is it now? (1) for each ½ hour *removed* from correct time to maximum of 5		
7. What day of the week is it? (1) for each day *removed* from correct one to a maximum of 5		
8. What day of the month is it? (1) for each day *removed* from correct date to a maximum of 5		
9. What is the month? (5) for each month *removed* from correct one to a maximum of 15		
10. What is the year? (10) for each year *removed* from correct one to a maximum of 30		
Total		

FIGURE 8–1. The Galveston Orientation and Amnesia Test (GOAT).

Source. Reprinted from Levin HS, O'Donnell VM, Grossman RG: "The Galveston Orientation and Amnesia Test: A Practical Scale to Assess Cognition After Head Injury." Journal of Nervous and Mental Disease 167:675–684, 1979. Copyright © Williams and Wilkins, 1979. Used with permission.

verbal and visual memory functioning. Clinicians often supplement their evaluations with one or more of the subtests (e.g., Logical Memory and Visual Reproduction) from the Wechsler memory test batteries. The Brief Visuospatial Memory Test—Revised (BVMT; Benedict 1997) has also become a popular, brief visual memory assessment tool, especially because the test has multiple versions to retest and evaluate over time while minimizing practice effects. When administered the BVMT, the patient is asked to draw six designs over three 10-second exposures to the test stimuli assessing learning and immediate visual memory. Delayed memory is evaluated by having the patient draw the designs again without any new exposure after a 25-minute delay. Like most verbal memory tasks, delayed visual memory is also followed by a recognition task. The Benton Visual Retention Test is another visual memory task that has multiple forms for retesting over time. There are multiple trials with three figures presented each time and this measure is sensitive to unilateral spatial neglect, visual inattention problems, and immediate visual memory recall (Lezak et al. 2004).

Executive Functioning

Executive functioning encompasses the abilities necessary for an individual to perform a problem-solving task from beginning to end. The major areas of executive functioning include judgment, reasoning, concept formation, and abstraction; initiation and fluency; planning and organizing; response set and perseveration; and disinhibition and impulse control. These skills enable a person to engage with others effectively, plan activities, solve problems, and interact with the environment to get his or her needs met (Sbordone 2000). A deficit of executive functioning can be the most crippling impairment that afflicts the TBI patient and can intensify deficits seen in other cognitive processes such as memory (Lezak 1995).

Research suggests that executive functioning can become impaired when the brain region's frontal-subcortical circuit or loop is damaged (Cummings and Trimble 1995). This damage can occur either from lesions in the frontal-subcortical circuits or alterations in metabolic activity of the neural structures that form the circuit. Cummings and Trimble (1995) described five frontal-subcortical circuits. Three of these circuits (dorsolateral prefrontal, lateral orbitofrontal, and medial frontal/anterior cingulate) play an important role in executive function, and damage in these areas produces a neurobehavioral syndrome with executive functioning impairments. Thus, instead of one global "frontal lobe syndrome," there are now three distinct "frontal syndromes" that display executive impairments and can occur from damage to a prefrontal-subcortical circuit. Damage to the dorsolateral prefrontal area results in a syndrome characterized by an inability to maintain set, disassociation between verbal and motor behavior, deficits in motor programming, concrete thinking, poor mental control, and stimulus-bound behavior (Sbordone 2000). Orbitofrontal lesions produce a syndrome characterized by tactlessness, disinhibition, emotional lability, insensitivity to the needs and welfare of others, and antisocial acts (Sbordone 2000). Damage to the medial frontal cortex/anterior cingulated produces a syndrome characterized by apathy, diminished motivation and interest, psychomotor retardation, diminished social involvement, and reduced communication (Cummings and Trimble 1995). The cluster of executive deficits that accompany the previously mentioned neurobehavioral syndromes can be misinterpreted as emotional problems or personality aberrations (Lezak 1997). For example, the apathy, diminished initiative, reduced motor and verbal output, and impaired motivation that are typical of medial frontal injuries mimic depression. As a result, multiple sources should be used in a differential diagnosis, including brain imaging, a detailed clinical interview, and a thorough neuropsychological evaluation.

Executive functioning deficits can severely impact a patient's adaptive functioning. Problems with planning, impulsivity, and disinhibition can adversely affect everyday skills such as preparing a meal, handling finances, and social appropriateness (Sbordone 2000). The Category Test (Reitan and Wolfson 1993) and the Wisconsin Card Sorting Test (WCST; Heaton 1981) are two tests typically used to assess different aspects of executive functioning. The Category Test and its more portable and efficient format the Booklet Category Test (DeFilippis and McCampbell 1997) are considered tests of abstract concept formation, reasoning, and logical analysis abilities. Successful performance requires mental flexibility, attention and concentration, learning and memory, and visuospatial skills (Mitrushina et al. 1999). The Wisconsin Card Sorting Test (Heaton 1981) is an abstract problem-solving test that is particularly useful because it has received substantial research in its ability to measure perseveration common in frontal lobe injuries (Flashman et al. 1991). In general, the Wisconsin Card Sorting Test provides information across multiple behavioral domains, including ability to form concepts, problem-solving ability, ability to learn from experience, and capacity to shift conceptual sets (Lovell and Franzen 1994).

One widely used paper and pencil task that measures scanning, divided attention, and cognitive flexibility is Trail Making Test. First developed by U.S. Army psychologists, it utilizes two parts, A and B (Lezak et al. 2004). Part A measures motor speed and attention; Part B adds a switching and a cognitive flexibility component, both of which are sensitive to the effects of traumatic brain injury (Armitage 1946).

The Controlled Oral Word Association Test (COWAT; Benton and Hamsher 1989) and other verbal fluency tasks have also been found to be sensitive to brain dysfunction. COWAT asks the examinee to generate a list of words (excluding proper nouns) that begin with a particular letter of the alphabet, with a total score summed following three trials (Lezak et al. 2004).

More recently, Delis et al. (2001) introduced the Delis-Kaplan Executive Function System (D-KEFS), a more comprehensive assessment of frontally mediated abilities including cognitive flexibility, inhibition, planning, and abstract thinking. It can assess these higher level cognitive functions in children as young as age 8 and adults up to age 89. The full test takes approximately 90 minutes to administer, but one of its advantages is that particular subtests can be used to assess specific frontal lobe abilities (Delis et al. 2001). As a result, D-KEFS subtests are

often incorporated in flexible or fixed/flexible battery approaches.

Speech and Language

Language processes are often disrupted following TBI and vary greatly depending on the nature, localization, and severity of brain injury. TBI patients who have not suffered damage to the language centers tend to have minimal to no deficits on verbal tests of overlearned material and behaviors such as culturally common information and reading, writing, and speech. However, they may demonstrate difficulties with verbal retrieval of names of objects, places, and persons. These word-finding problems or dysnomias of TBI patients tend to show up as slow recall of the word, semantically related misnamings, and paraphasias or substituting the wrong word (Lezak 1995).

Injuries that are focal or penetrating and that involve the language-dominant hemisphere are more likely to demonstrate language impairments. Aphasia is a disorder of oral language and can include compromised verbal expression and/or comprehension. In addition, written communication (alexia and agraphia) is also frequently impaired in patients with aphasia. Specific lesion locations are likely to produce certain types of aphasia. For example, Broca's aphasia often results from lesions in the frontal operculum that extend to subjacent white matter, the anterior parietal lobe, the insula, and both banks of the Rolandic fissure. Conduction aphasia often results from lesions in the arcuate fasciculus (Stringer 1996). The major types of aphasia are differentiated by assessing three language domains: fluency, comprehension, and repetition. Although other aspects of language may be compromised, these three areas are typically considered the "cardinal" symptoms. For example, a patient with Broca's aphasia will have deficits in fluency and repetition but relatively adequate comprehension. Those with Wernicke's aphasia are fluent (although their verbalizations may be incomprehensible) but have poor repetition and comprehension.

Evaluation of speech and language usually involves assessing spontaneous speech, speech comprehension, naming, reading, writing, and repetition of words, phrases, and sentences (Lezak 1995). During the evaluation, it is important to attend to fluency, prosody, articulatory errors, grammar and syntax, and the presence of paraphasias (Goodglass 1986). The Aphasia Examination (Russel et al. 1970) is a useful screening instrument for uncovering language deficits that may need further assessment. The Boston Diagnostic Aphasia Examination (Goodglass and Kaplan 1972) and its most recent third edition (Goodglass et al. 2000) is a comprehensive and sensitive battery that is excellent for the description of aphasic disorders and for treatment planning (Lezak 1995). Rather than using the entire battery, many clinicians selectively use portions of the battery in combination with other neuropsychological tests. The Western Aphasia Battery (Kertesz 1979, 1982) developed out of the BDAE and examines spontaneous speech, auditory comprehension, repetition, and naming. Another aphasia battery is the Multilingual Aphasia Examination (Benton and Hamsher 1989), which measures receptive, expressive, and immediate memory related to functions of speech and language (Lezak et al. 2004). The Boston Naming Test helps identify naming impairments and is administered by presenting 60 ink drawings that the subject must identify (Kaplan et al. 1983).

Motor Processes

Problems with motor functioning can occur despite the capacity for normal movement and can be used in neuropsychology to identify specific motor dysfunction (Lezak et al. 2004). For example, several tests measure both motor speed and manual dexterity: The Grooved Pegboard Test (Klove 1963) consists of a board with slotted holes that are angled in different directions. The examinee must complete the task with both the right and left hand. The Finger Tapping Test (Halstead 1947) measures the rate at which one can use one's index finger to tap over multiple 10-second trials; this is not only compared to normative data, but also across person's right versus left hand. Although this test can be helpful in identifying a brain lesion, like other tests described in this chapter, it should not be used alone to make a diagnosis.

Assessment of Motivation and Malingering

In addition to assessing the major cognitive domains, neuropsychologists often have to include measures for motivation and malingering in their evaluation. This is particularly true in cases in which litigation may be pursued to assign blame and/or financial responsibility for the resulting disability. In these cases a patient may attempt to fake or exaggerate a brain injury. There are multiple neuropsychological tests (discussed below) that have been created to detect measures of effort level or malingering. "Pure malingering" as defined by Resnick (1997) is a complete fabrication of symptoms. It is solely for the purpose of an external reward, and the patient deliberately does not try his or her best. Other patients who have legitimate deficits following their TBI may not put forth their full effort and/or exaggerate their true symptoms in an attempt to receive needed treatments (rehabilitation), services (home care), and compensation (disability benefits) (Lovell and Franzen 1994). Additionally, TBI patients with legitimate deficits may unintentionally exhibit variable or poor effort because of a multitude of other factors, including chronic pain, psychiatric problems, or other conditions. For example, a patient with chronic pain may not be able to give his or her best effort as a result of ongoing pain symptoms, which should be taken into account. The discussion of malingering/effort can be complicated, and there is not one agreed-upon tool or way of measuring this construct. Thus, the end result is commonly a clinical decision based on multiple factors because no one test is sufficient to determine malingering/effort. Malingering/effort (regardless of the reason) can create difficulty in determining the patient's actual strengths and weaknesses and hinders the evaluation process. Addressing the issues of effort and motivation early on in the evaluation can help prevent unnecessary testing and an invalid evaluation. However, effort can be variable over time, and performing adequately on an effort measure at the onset of a 4-hour evaluation

does not guarantee consistent effort for the entire duration. Thus, effort should be assessed throughout the evaluation. Tests that are commonly used to assess for motivation and malingering include the following:

- 21-Item Test (Iverson et al. 1991)
- Rey 15-Item Memory Test with recognition (Rey 1964)
- Test of Memory Malingering (Tombaugh 1996)
- Word Memory Test (Green and Astner 1995)
- Portland Digit Recognition Test (Binder 1993)
- Victoria Symptom Validity Test (Slick et al. 1996)
- Rey Dot Counting Test (Lezak et al. 2004)

The 21-Item Test (Iverson et al. 1991) can be used as an initial screen for exaggerated deficits in verbal memory. The Rey 15-Item Memory Test (Rey 1964) was specifically designed to detect attempts at faking memory deficits. The patient is told the difficulty of remembering the 15 items prior to their presentation. However, the stimuli are overlearned sequences and redundant, which makes the items relatively simple to remember (Stringer 1996). Attempting to make the test more sensitive, Boone et al. (2002) introduced a recognition test following the initial recall. Using a combined score (recall and recognition-false positives), the sensitivity was increased from 47% to 71% while maintaining the test's already high specificity (>92%). Symptom validity testing is a method in which 100 trials of forced-choice stimuli that are relevant to the patient's presenting complaint are presented. Malingering is suggested if the patient performs below 50% correct (suggesting a performance that is worse than chance) (Crosson 1994). The Test of Memory Malingering is a visual memory recognition test that discriminates between true memory impairment and malingering with two learning trials and an optional retention trial following a delay (Tombaugh 1996). The Word Memory Test (Green and Astner 1995) is a verbal memory effort measure that consists of 20 orally presented word pairs that the subject must respond to both free recall and forced-choice formats.

Although some measures are specifically constructed for this area, other tests of cognitive functioning (e.g., memory) attempt to include subtests that are useful for assessing motivation and/or effort. The most common method is the use of a forced-choice format. Many instruments such as the WMS-III and WMS-IV (Wechsler 1997b, 2009) and CVLT-II (Delis et al. 2000) include these subtests in their measures. The premise of forced-choice tests is that the patient has a 50% chance of getting approximately half the items correct without even trying to answer correctly. Thus, a patient who incorrectly answers less than 50% of the items correct is likely highly motivated to perform poorly since their correct responses are less than pure chance.

In addition to administering tests designed to assess for malingering and biased responding, the clinician should compare the patient's performance on neuropsychological measures with his or her ability to function in everyday activities. For example, a patient who performs in the severely impaired range on neuropsychological testing yet continues to perform well in graduate-level coursework is demonstrating an inconsistency between test performance and academic functioning. Lastly, when assessing for malingering, the clinician should keep in mind that some patients may appear to be malingering but are not. A variety of factors can influence neuropsychological test performance—for example, psychiatric disorders such as depression, poor rapport with the evaluator, uncooperativeness, and the context in which the evaluation is conducted (Franzen and Iverson 1997). Franzen and Iverson (1997) noted that in assessments for malingering, "It is important to remember that these test instruments evaluate the likelihood of nonoptimal performance, not malingering itself. As such, the specific assessment instruments provide information about biased responding, that is, information about the probability that variables other than skill level have adversely affected the level of effort" (p. 396).

Neuropsychological Screening Instruments

At times, various factors may necessitate administration of a briefer, less detailed neuropsychological screening evaluation. These factors include but are not limited to patient fatigue or noncompliance, time restraints, and lack of health insurance or financial restrictions. Although the screening battery is cost effective and significantly faster to administer, this approach has limited value in making differential diagnosis. For example, the Mini-Mental State Examination (MMSE) is useful in determining the presence or absence of dementia but is not useful in differentiating types of dementia (e.g., Alzheimer's disease and vascular dementia). In addition, screening instruments have limited ability in discriminating mild head injury and are unable to provide specific information regarding rehabilitation (e.g., memory retraining) and individual strengths and weaknesses (e.g., impaired auditory memory but intact verbal memory). Examples of neuropsychological screening instruments include the following:

- Mini-Mental State Examination (MMSE)
- Repeatable Battery for the Assessment of Neuropsychological Status (Randolph 1998)
- Neurobehavioral Cognitive Status Examination (Kiernan et al. 1995)
- Shipley Institute of Living Scale (Shipley 1946)
- Barrow Neurological Institute (BNI) Screen for Higher Cerebral Functions (Prigatano 1991; Prigatano et al. 1991)

The MMSE is a widely known screening instrument that is brief and easy to administer. As mentioned, it is useful for identifying dementia especially when the impairment is moderate to severe. However, its sensitivity and specificity decline with other patient populations, particularly patients with mild cognitive impairment, focal neurological deficits, and psychiatric disorders (Spreen and Strauss 1998).

The Repeatable Battery for the Assessment of Neuropsychological Status (Randolph 1998) is a useful cognitive screening instrument that provides a total scale score and five specific cognitive ability index scores. It can be administered in less than 30 minutes and has more than one form for additional testing over time while minimizing

practice effects. It was designed for both identifying and characterizing abnormal cognitive decline in the older adult population and as a neuropsychological screening battery for younger patients (Randolph 1998).

The use of computer-based neurocognitive screening has become increasingly common over the past 5 years and has become particularly popular in organized sports and the military. In both of these environments, preinjury baseline assessment has been emphasized given that the individual is at an elevated risk for future injury. All major professional sports in the United States currently conduct baseline testing (Lovell 2009). Along similar lines, computer-based screening is becoming increasingly common in the military (Lovell et al. 2005). Computerized baseline testing has been adopted because it is economical, is efficient, and allows for the screening of large numbers of people within a short time frame. Computer-based testing also allows for the more accurate measurement of reaction time, and a highly trained test administrator is not necessary. Following a TBI, postinjury data can then be directly compared with the individual's preinjury status.

Although computer-based neuropsychological assessment has its place, it must be emphasized that this approach should be used as an adjunct to more traditional testing and not as a substitute. Current available computer-based tests (see Echemendia 2006) sample from limited neuropsychological domains and therefore do not represent a comprehensive approach to assessment.

Differential Diagnosis of TBI From Other Neuropsychiatric Conditions

Determining Premorbid Level of Functioning

TBI occurs within many different contexts, and one of the primary challenges to the neuropsychologist working with these patients is the separation of TBI-related sequelae from preexisting conditions. In addition, the neurocognitive effects of psychiatric disorders and TBI may be synergistic.

The initial task of the neuropsychologist is to assess the patient's probable level of preinjury functioning. This provides the basis for assumptions about post-TBI level of functioning and is an important aspect of the evaluation process. This is necessary because only rarely has the TBI patient undergone preinjury neuropsychological testing that would allow a direct comparison with his or her postinjury level of functioning. Although preinjury neuropsychological test results are not often available, intellectual and achievement testing is becoming increasingly popular in the school system, and the data can be very useful in estimating premorbid functioning. Collateral information provided by spouses, coworkers, and employers; school performance; educational level; and work history all contribute to the determination of premorbid functioning.

An additional method of estimating the patient's level of premorbid functioning involves the analysis of the pattern of neuropsychological test scores. This method is based on the assumption that cognitive processes such as basic reading skills and vocabulary tend to be less affected by TBI than other skill areas. A few tests that are considered to be relatively resistant to neurological impairment are the Vocabulary, Information, and Picture Completion subtests from the WAIS-III and WAIS-IV (Wechsler 1997a, 2008). These have traditionally been known as "hold" tests and have been considered to be relatively unaffected by TBI. However, caution is advised when implementing this method because the traditional hold tests can indeed be influenced by different types of brain injury, particularly if it is of a focal nature. For example, patients with aphasia would obviously perform poorly on the Vocabulary and Information subtests. Reading skill, as mentioned previously, is also considered to be resistant to TBI, and as a result, basic word reading tests, such as the North American Adult Reading Test, are frequently used for premorbid estimates. Another common method for estimating premorbid functioning is the use of demographic variables. This is based on the premise that certain demographic variables such as social class and education are correlated with scores on intelligence tests (Franzen 2000). In general, most clinicians use a combination of methods and measures to predict premorbid functioning.

Depression

Depression can interfere with the normal expression of cognitive abilities and can also cloud the diagnostic picture in an individual who has suffered a TBI. Patients with depression who have not suffered a TBI may demonstrate cognitive difficulties such as slowed mental processing, psychomotor retardation, mild attentional deficits, decreased drive and initiation, and impairments in short-term recall and learning for verbal and visuospatial material. Cognitive impairment is most frequently encountered in the areas of attention, specific aspects of memory, and psychomotor speed. Impairments in language, perception, and spatial abilities tend to be secondary to poor attention, motivation, or organizational abilities (Mayberg et al. 1997). A large body of research on patients with depression has focused on memory processes.

Certain key factors should be considered in attempting to differentiate the neurocognitive effects of depression from TBI. Neuropsychological testing of a patient diagnosed with depression reveals that the "memory deficit" is often expressed in free-recall retrieval errors rather than as a deficit in actually learning the information. As a result, the patient requires a cue or recognition stimulus for the memory to become available for recall (Lezak 1995). This can be evaluated by tests such as the California Verbal Learning Test (CVLT; Delis et al. 2001), which assesses the patient's ability to learn across trials as well as the patient's ability to benefit from semantic cues and recognition.

Differential diagnosis of the cognitive consequences of depression versus TBI is often clouded by the comorbidity of depressed mood with TBI. Depression has been the most common mood disorder found in the literature following all severity levels of TBI. A review by Busch and Alpern (1998) suggests that prevalence rates of depression after mild TBI is at least 35%, and other studies estimate depression onset following TBI from 10% to 77% (O'Donnell et al. 2004;

Varney et al. 1987). Onset of depressive symptoms is typically within the first year following injury; however, there is an increased risk for depression for many years (Dikmen et al. 2004) or even decades later (Silver et al. 2009). A careful and thorough history addressing the patient's premorbid cognitive and emotional functioning is essential in attempting to understand the contribution of both disorders. In addition, neuropsychological testing can provide beneficial information in a differential diagnosis. For example, Rapoport et al. (2005) found that over half of mild to moderate TBI patients without depression were unimpaired on multiple well-known neuropsychological measures assessing different cognitive domains (e.g., executive functioning). In addition, the authors also found depressed TBI patients' performances to be significantly worse across multiple cognitive domains, including attention, processing speed, and memory (Rapoport et al. 2005). More specifically, examining the pattern of the patient's performance on neuropsychological testing (e.g., learning vs. retrieval) and qualitatively looking at individual subtest scores and performance are helpful. For example, many patients with depression will perform adequately if given extra time and encouragement. Memory disturbances in depressed patients will likely be the result of attention and concentration difficulties typically associated with depression, whereas patients with TBI may have a more consistent pattern across the tests designed to assess memory. Assessing the rate of forgetting of information from immediate recall to a delayed recall is one method that can contribute to the differential diagnosis. Refer to Chapter 10, Mood Disorders, for more specific information regarding depression and related disorders.

Anxiety

Anxiety can interfere with the patient's ability to attend, learn, and remember new information and therefore can be similar to the pattern of deficits seen following mild TBI. The experience of anxiety is also common during the neuropsychological evaluation process and may relate to performance anxiety or general frustration on the part of the patient. It is therefore important for the clinician to create an atmosphere that reduces the normal anxiety that a patient might feel when undergoing the evaluation process. Patients with a history of anxiety disorders can have particular difficulty in participating in formal neuropsychological assessment and may manifest mental efficiency problems, such as slowing, scrambled or blocked thoughts and words, memory failure, and increased distractibility (Lezak 1995). Additionally, patients who are anxious about appearing "stupid" may respond with "I don't know" rather than providing their best response to a particular question. Encouraging patients to make their best guess and trying to optimize their effort is essential to obtaining a valid neuropsychological profile. In addition to performance-related anxieties that can occur during the evaluation, there are specific anxiety disorders that are likely to be more prevalent among the TBI population.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is common following TBI, and many patients with mild TBI vividly recall and are distressed by the details of their injury. TBI and PTSD have become the "signature injuries" of the wars in Iraq and Afghanistan, and there has been a dramatic increase in research in this area over the past 8 years (Lovell et al. 2005). The injuries that have been increasingly prevalent have been related to the detonation of improvised explosive devices. This type of blast injury is now recognized as a distinct type of injury compared with the acceleration/deceleration injuries that are most common in motor vehicle accidents and sports injuries (Belanger et al. 2009).

There is often symptom overlap between postconcussion syndrome and PTSD, and the two conditions can easily be confused. However, in general, TBI symptoms tend to decrease or remit within 3–6 months, whereas the course and duration of PTSD may be much longer (Evans 2000; Silver et al. 1997). Similar symptoms include, but are not limited to, amnesia for certain aspects of the traumatic event, difficulty concentrating, somatic complaints (headache, dizziness, fatigue, insomnia), perceptual symptoms (sensitivity to noise and light), and irritability (American Psychiatric Association 2000; Silver et al. 1997). Although much of the research on TBI and PTSD focuses on mild head injury, there is evidence to suggest that PTSD can develop after severe TBI even with impaired consciousness during the trauma and a relative absence of traumatic memories of the event (Bryant et al. 2000). Turnbull et al. (2001) found that amnesia did not protect against PTSD but did protect against the severity and presence of specific intrusive symptoms.

The DSM-IV-TR (American Psychiatric Association 2000) criteria for PTSD include a history of exposure to a traumatic event and symptoms from each of three symptom clusters: intrusive recollections, avoidant/numbing symptoms, and hyperarousal symptoms. According to DSM-IV-TR, a concussion or mild traumatic brain injury with specified symptoms persisting for 3 months or longer is a postconcussion syndrome. Symptoms of concussion or mild traumatic brain injury include but are not limited to headache, nausea, dizziness, sleep problems, mood changes (irritability), and perceived neurocognitive deficits (e.g. attention/memory problems, bradyphrenia). It can be difficult to differentiate psychological (PTSD) and neurological (TBI) etiology of neurocognitive deficits, and this becomes more complicated in those who are dually diagnosed. King (2008) reported several important "facts" regarding PTSD/TBI dual diagnosis. King stated that contrary to some previous beliefs, PTSD and TBI can and do co-occur, that mild TBI provides little to no protection against PTSD and may even increase its likelihood, that severe TBI offers significant (but not complete) protection against PTSD, and that there are at least six key considerations with a dual diagnosis. These considerations should be evaluated to help discriminate between TBI and PTSD and include overlap of symptoms, amnesia for the event, interaction or vicious cycle of symptoms, different treatment approaches, psychoeducation, and real versus pseudo-memories (King 2008).

Campbell et al. (2009) administered neuropsychological tests of processing speed and executive functioning to subjects with PTSD, TBI, and PTSD with comorbid TBI. All eligible subjects were administered effort testing and excluded if they did not meet pass criteria of 82.5% on the

Word Memory Test (described earlier, in the section Assessment of Motivation and Malingering). Interestingly, over 40% of the comorbid PTSD/TBI group did not pass, and were excluded as a result, whereas only 1 of 35 TBI-only subjects did not pass and all 16 PTSD-only subjects passed. Evaluation of effort was not the purpose of this study, though it is always important to evaluate and address effort, and patients with test results indicating low effort may have legitimate problems that require treatment. Among those subjects remaining in the study, results indicated that comorbid TBI/PTSD may further reduce speed of verbal processing over either diagnosis alone. In addition, despite more serious injuries, those with TBI alone did not perform worse that those with PTSD alone on any of the neuropsychological tests administered. This suggests the significant impact that PTSD may have on cognitive abilities compared to TBI months or years after the traumatic event (Campbell et al. 2009). Especially given the increasing numbers of military diagnoses of PTSD, TBI, and PTSD/TBI, it is to be hoped that continued research will provide increased understanding and treatment for those individuals.

Obsessive-Compulsive Disorder

Obsessive-compulsive-like behaviors can occur following TBI. These behaviors frequently evolve when mental inefficiency, such as the attentional deficits that are typically associated with slowed processing and diffuse damage, is the prominent feature (Lezak et al. 1990). Rigidity in thinking and perseverative tendencies can be evidenced on some of the tests typically used to assess executive functioning, such as the Wisconsin Card Sorting Test. Perseveration can also be detected across different subtests (e.g., carrying aspects of one subtest into the next subtest). Socially, these patients may act inappropriately and be disruptive from failing to respond to social cues (Stringer 1996). Patients who are perseverative may repeat a task in a stereotyped manner or may have difficulty switching topics during a conversation and appear to repeat themselves. They can also appear hypervigilant (Stern and Prohaska 1996).

Schizophrenia

It is difficult to use neuropsychological testing to differentiate the cognitive sequelae of schizophrenia from TBI, given that schizophrenic patients often demonstrate impairment on formal neuropsychological testing (Crosson 1994). It has been suggested that in some cases of schizophrenia the disorder may be the result of earlier cerebral insult rather than being merely an expression of the disease entity. This hypothesis is based on the high incidence of premorbid neurological disorders such as head injury, perinatal complications, and childhood illnesses (Lezak 1995; McAllister 1998).

Neuropsychological studies indicate that persons with schizophrenia demonstrate difficulties in attention, motor behavior, speed of processing, abstraction, learning, and memory (Sackeim and Stern 1997). However, reviews of the research suggest that the deficits seen in schizophrenia can be very broad, and no cognitive domain is entirely spared. It has also been suggested that cognitive deficits are not present in every individual at all times and that the pattern of deficits can change over time within an individual (Tamminga 1997). Malloy and Duffy (1994) reviewed literature on the frontal lobes in neuropsychiatric disorders and found that frontal dysfunction has been linked to the negative subtype of schizophrenia on the basis of neuropsychological, structural and functional imaging, and electrophysiological studies. However, they stated that there is controversy as to whether the results indicate distinct subtypes of patients with schizophrenia or predominant symptoms that occur at different stages of the schizophrenic process in the same patient.

A study by Sachdev et al. (2001) compared TBI patients who developed schizophrenia-like psychosis (SLP) after their injury with TBI patients who did not develop SLP. Their results indicated that the TBI patients who developed SLP had a mean age of onset of 26.3 years, a mean latency of 54.7 months after the head injury, and usually a gradual onset and a subacute or chronic course. The authors also found that prodromal symptoms were common, as well as the presence of depression at the onset of SLP. The predominant features were paranoid delusions and auditory hallucinations. However, formal thought disorder, catatonic features, and negative symptoms were uncommon. Additionally, the SLP group had more widespread brain damage on neuroimaging, particularly in the left temporal and right parietal regions, and was more cognitively impaired than the TBI group without SLP. Lastly, the authors found that a positive family history of psychosis and duration of loss of consciousness were the best predictors of SLP. The results from the Sachdev et al. (2001) study are inconsistent with past studies (Bond 1984; Kwentus et al. 1985), which indicate that schizophrenia-like symptoms after TBI are more likely to be of the negative subtype, with flat affect, suspiciousness, and social withdrawal as opposed to positive symptoms of delusions and hallucinations. The variability in research findings points to the need for further research into possible subtypes of schizophrenia and course of cognitive deficits.

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) is a disorder involving disturbances in attention span (e.g., poor attention to task), self-regulation (e.g., inability to consider consequences of behavior), activity level (e.g., motoric overactivity), and impulse control (e.g., impulsive behaviors) (Teeter and Semrud-Clikeman 1997). As has been mentioned throughout this chapter, deficits in attention are common following TBI. The diagnosis "attention-deficit/hyperactivity disorder not otherwise specified" can technically be used to diagnose adults with concentration problems resulting from brain damage. However, this diagnosis is misleading given that ADHD is considered a developmental disorder and some of the symptoms must be present before age 7 (Stringer 1996). During the clinical interview, it is important to assess for premorbid diagnosed and undiagnosed ADHD symptoms. It is useful to ask developmentally oriented questions and to seek information collaterally. This is particularly important because

there are commonalities in behavioral and cognitive sequelae of TBI and ADHD, especially in response inhibition (Konrad et al. 2000). Konrad et al. (2000) compared children with TBI and children with developmental ADHD on two inhibition tasks. They divided the TBI children, according to actigraph data, into hypo-, hyper-, and normokinetic subgroups. They concluded that slowing of information-processing speed is a general consequence of TBI in childhood and that inhibitory deficits are associated with postinjury hypo- and hyperactivity. Specifically, hyperactive TBI children had the same inhibitory deficit patterns as children with developmental ADHD.

Neuropsychological testing can contribute to the diagnosis of persons with ADHD without TBI and TBI patients who may have had ADHD premorbidly by highlighting the cognitive strengths and weaknesses and helping to distinguish attentional disturbances from an underlying memory disorder. Because there is a high comorbidity of ADHD with learning disorders, neuropsychological testing can also diagnose the presence of learning disabilities or other deficits that may be contributing to the clinical presentation of the patient (Cohen and Salloway 1997).

Learning Disorders

A learning disorder involves a deficit in the acquisition and performance of certain academic skills (Popper and Steingard 1996). DSM-IV-TR (American Psychiatric Association 2000) addresses four classifications of learning disorders: reading disorder, mathematics disorder, disorder of written expression, and learning disorders not otherwise specified. Although learning disorders are usually first evident in childhood, they can have major consequences for lifetime functioning. People with a learning disorder diagnosis are more susceptible to head injury. Additionally, the cognitive effects of learning disorders can be mistaken for those of head injury (Crosson 1994). In the head-injured population, determining whether current deficits are a result of a learning disability or TBI and evaluating recovery from the brain insult may be a referral question. As mentioned earlier, the clinical history and gathering of information to help form an estimate of premorbid functioning are essential, especially in patients with a known premorbid deficit.

Conclusion

This chapter has provided a summary of the role of neuropsychological assessment strategies in the evaluation of TBI individuals. Neuropsychological testing can be a useful adjunctive tool within the neuropsychiatric context and can help to separate TBI from other disorders, thus guiding the treatment planning and rehabilitation process. Neuropsychological assessment is helpful in identifying psychosocial and neurological components of TBI and is particularly helpful with regard to differential diagnosis.

KEY CLINICAL POINTS

- The neuropsychological evaluation provides important information about traumatic brain injury (TBI) through formal assessment of brain-behavior relationships using psychometric methods.
- The three main approaches to neuropsychological assessment (fixed, flexible, and fixed/flexible) all have shown sensitivity to TBI.
- In a comprehensive TBI evaluation, neuropsychologists assess major cognitive domains, including attention; memory; executive functioning; speech and language; visuospatial and visuoconstructional skills; intelligence; and psychomotor speed, strength, and coordination.
- Motivation and malingering should be assessed because patients may fake an injury or exaggerate legitimate deficits to receive treatments.
- Psychiatric symptoms (e.g., depression, anxiety) often mimic cognitive impairments commonly seen in TBI and should be differentiated by using a combination of subjective reports, objective neuropsychological testing, and clinical judgment.
- Neuropsychological testing can be very useful as an adjunctive tool within the neuropsychiatric context, especially for differential diagnosis following TBI.

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Part II

NEUROPSYCHIATRIC DISORDERS

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CHAPTER 9

Delirium and Posttraumatic Confusion

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Delirium and Posttraumatic Confusion: More Than Posttraumatic Amnesia

Posttraumatic Amnesia: History and Hazards

Posttraumatic amnesia (PTA) is a term coined by British neurologists William Ritchie Russell and Charles Symonds in the early 20th century to describe the period of impaired consciousness following traumatic brain injury (TBI). Symonds (1937) and Russell (1932) described a broad range of cognitive and neurobehavioral symptoms in TBI survivors during early recovery and acknowledged that the outstanding feature of this period was impairment of consciousness, but they argued that consciousness could not be practically defined and measured and that the return of consciousness following TBI coincided with return of memory. Therefore, PTA was proposed as a proxy measure for the duration of impaired consciousness and operationalized by them as the time when the patient "was fully oriented and able to answer questions intelligently" (Russell 1932, p. 553). Although Symonds and Russell suggested PTA as a proxy measure for a broader syndrome, the influence of their work has led medical and allied health professionals working in the TBI care continuum to focus solely on the duration of orientation and memory impairments and ignore the range and depth of the syndrome, and in so doing lose the essence of PTA as a proxy measure for a broader construct. PTA is a relatively robust predictor of injury severity and outcome (Brown 2005; Ellenberg et al. 1996; Katz and Alexander 1994; Nakase-Richardson et al. 2009), and the mistaken elevation of PTA from proxy measure to construct in the brain injury literature is perhaps attributable to lack of progress in developing better measures of injury severity and indicators of prognosis. Recent investigation in neurorehabilitation demonstrates that valuing only the duration of acute orientation and memory impairments represents a significant oversight. Stuss et al. (1999) found an ordered pattern of recovery of cognitive functions following TBI such that inattention, disorientation, or both cleared before memory deficits, suggesting that the representative symptoms extended beyond orientation and amnesia and that amnesia can be a persistent symptom beyond the confusional period. Similarly, Nakase-Thompson et al. (2004) studied patients after TBI during acute rehabilitation, using a broad set of measures, including the Delirium Rating Scale (DRS), the Galveston Orientation and Amnesia Test (GOAT), the Agitated Behavior Scale (ABS), and the Cognitive Test for Delirium (CTD), and found a broad range of impairments. These authors noted that "traditional measures of PTA do not fully capture the wide array of symptoms defining this early stage of recovery" (p. 140) and that "acute confusion is common and has a complex neurobehavioral presentation that is not adequately captured with traditional PTA measures alone" (p. 140). Kalmar et al. (2008) used a brief formal neuropsychological battery to assess patients in PTA and documented abnormalities in a wide range of cognitive domains, including attention, processing speed, cognitive flexibility, verbal fluency, executive functioning, naming, perceptual-motor ability, reading, verbal recall, and orientation. Sherer et al. (2009) found that psychotic-type symptoms, decreased daytime arousal, and nighttime sleep disturbance were the earliest resolving symptoms, whereas fluctuation and cognitive impairment

TABLE 9–1. Comparison of DSM-IV-TR criteria for delirium with Lipowski's and Stuss's descriptions

DSM-IV-TR (2000) diagnostic criteria for delirium	Lipowski's (1990) definition of delirium	Stuss et al.'s (1999) definition of posttraumatic confusional state
Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with a reduced ability to focus, sustain, or shift attention. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established or evolving dementia. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.	"Delirium is a transient organic mental syndrome of acute onset, characterized by global impairment of cognitive functions, a reduced level of consciousness, attentional abnormalities, increased or decreased psychomotor activity, and a disordered sleep-wake cycle."	"A confusional state can be defined as a transient organic mental syndrome with acute onset characterized by a global impairment of cognitive functions with a concurrent disturbance of consciousness, attentional abnormalities, reduced or increased psychomotor activity, and a disrupted sleep-wake cycle."

were the most persistent. Together, these studies show the construct to be broader than orientation and amnesia, consistent with the clinical descriptions and definitions throughout the study of TBI and suggest a temporal pattern of recovery.

Measuring the breadth of this syndrome appears to have prognostic significance. Using a multivariable logistic regression model, Nakase-Richardson et al. (2007) found that age, education, and symptom severity at 1 month post-TBI as measured using the Delirium Rating Scale–Revised-98 (DRS-R98), which measures severity of a variety of cognitive and noncognitive symptoms, were significant predictors of employment at 1 year postinjury, whereas duration of PTA using the GOAT and emergency room Glasgow Coma Scale score were not. In a study by Sherer et al. (2008) disorientation, cognitive impairment, fluctuation, agitation, nighttime sleep disturbance, decreased daytime arousal, and psychotic-type symptoms were considered as predictors of employability and productivity at 1 year post-TBI. Binary logistic regression analyses revealed all seven symptoms were significant predictors of employability, and all but nighttime sleep disturbance and daytime arousal were significant predictors of productivity. Collectively, these results suggest that symptoms of confusion do matter and not just duration of memory and orientation impairment. These rehabilitation studies suggest that the post-TBI acute confusional period has temporal phases in which the severity of a broad range of symptoms together contributes to outcome prediction and that acute confusion is a better predictor of longer-term functional outcomes than the duration of PTA.

Stuss et al. (1999) proposed an alternative, more accurate term to *posttraumatic amnesia—posttraumatic confusional state*. This is supported by the detailed prospective, longitudinal work by Sherer and his research teams (Nakase-Richardson et al. 2007; Nakase-Thompson et al. 2004; Sherer et al. 2005). In psychiatric nosology, *acute confusional state* is synonymous with *delirium* (Lipowski 1990). Stuss et al. (1999) referenced Lipowski's 1990 seminal textbook on delirium, and their definition of *posttraumatic confusional state* (PTCS) was essentially identical to Lipowski's definition of *delirium* (see Table 9–1). DSM-IV-TR criteria (American Psychiatric Association 2000) for diagnosing delirium require a disturbance of consciousness and/or attentional deficits; a change in memory, language, or orientation or perceptual disturbances with a fairly abrupt onset and a fluctuating course; and physical factors that are implicated as causative.

Current thought regarding this period of recovery from TBI has circled back to the decision by Russell and Symonds to coin the term *posttraumatic amnesia* and disregard the term *delirium,* even though delirium was being used by their contemporaries in psychiatry (Schilder 1934; Wolff and Curran 1935) to describe this period of recovery post-TBI. Delirium was a condition described by the ancient Greeks, and in its Latin translation *lira* means "to wander from one's furrow." Symonds posited that the term *delirium* "has the merit of describing clinical symptoms without the implication of pathology." We may speculate that Symonds did not want to use the term *delirium* because it was used by psychiatrists as a diagnosis for patients with or without identifiable structural brain lesions and because at that time a great rift existed between psychiatry and neurology (Martin 2002), or possibly that Symonds intended for his nomenclature to guide the field toward investigation of neural structures associated with memory because he believed them to be crucial to understanding the pathophysiology of acute confusion or recovery. In any case, the label *posttraumatic amnesia* stuck within the rehabilitation field and the term remains the conventional choice to describe the ubiquitous period of confusion following TBI.

Despite the widespread use of the PTA construct, it has been variably defined by clinicians and researchers. Head-to-head comparison of instruments designed to measure PTA demonstrated a lack of concordance between mea-

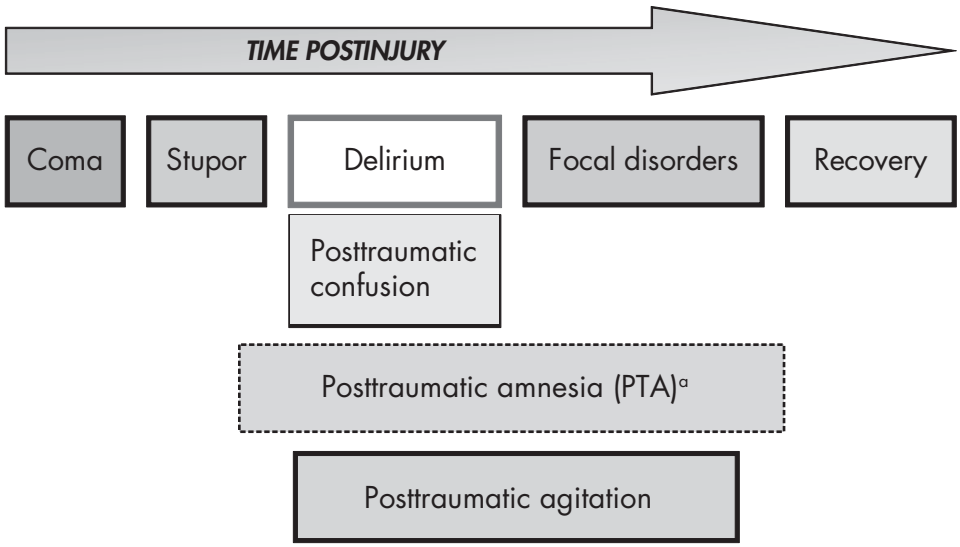


FIGURE 9–1. Comparing rehabilitation and neuropsychiatric terminology for post–traumatic brain injury (TBI) changes in consciousness and cognition.

Posttraumatic amnesia (PTA) is a commonly used term that may overlap with delirium depending on the use by researchers and clinicians, whereas *posttraumatic confusion* is comparable to delirium. *Posttraumatic agitation* is not synonymous with delirium and can occur at different stages of TBI recovery; many patients have motor retardation, and not agitation, that can be inadequately recognized.

[a]Some older studies included coma and stupor in PTA. *Posttraumatic amnesia* is defined as duration of return of new memory and not by broad symptom severity.

sures regarding the number of days to emergence from PTA, which brings into question both the validity of the construct and the measurement scales applied (Tate et al. 2000). Moreover, PTA measures lack empirical rationale for item content, which likely results from inadequate definition of the phenomenology of this period of recovery and contributes to the lack of agreement among scales (Tate et al. 2000). In addition, orientation and memory tasks that commonly comprise PTA assessments fail not only to assess the range of impairments noted during acute confusion but also do not distinguish patients in PTA from those with pure amnestic syndrome (Wilson et al. 1992) or those in the chronic phase of post-TBI recovery and judged not to be in PTA (Wilson et al. 1999).

In psychiatric nosology, delirium and amnesia are not interchangeable, the former being a neuropsychiatric disorder composed of diffuse cognitive deficits, language and thought abnormalities, psychomotor and affective changes, and sleep-wake cycle disturbances, whereas the latter involves only declarative memory impairment. Descriptions of PTA found in much of the TBI literature overlap significantly with what psychiatrists would call delirium followed by an amnestic disorder. PTA may encompass coma at one extreme or only focal memory deficits at the other and overlaps with a number of neuropsychiatric terms applied to those different clinical stages (Figure 9–1). Accordingly, the use of PTA and similar terms such as *impaired consciousness, posttraumatic agitation, posttraumatic disorientation,* and *altered consciousness* is problematic because these terms rarely have clear definitions of signs and symptoms or, when defined, are without a clear consensus regarding usage or practical assessment (Fortuny et al. 1980; Gronwall and Wrightson 1980; Sandel et al. 1995; Stuss et al. 1999; Tate et al. 2000). The varying definitions and criteria make interpretation of research on PTA confusing.

Although many have adhered to the term *posttraumatic amnesia,* there has been an evolution among TBI researchers to recognize increasingly the confusional state and even the delirium symptoms as a phase of acute recovery after TBI (see Figure 9–2). Ommaya and Gennarelli (1974) defined *delirium* ("confusion") as a separate state from either coma or amnesia in patients with TBI and specified the temporal relationship between them that is consistent with a neuropsychiatric conceptualization. Katz (1992) and Stuss (Stuss et al. 1999) both recognized the confusional state embedded in PTA and posited that *posttraumatic confusional state* would be a more accurate term than *posttraumatic amnesia*. Stuss et al. (1999) further noted the similarity to delirium and the prominence of attentional deficits during this period that is consistent with inattention as a cardinal symptom in delirium. Ptak et al. (1998) equated the severe acute confusional state following TBI to that associated with stroke, infections, and other brain diseases that reflect global disturbance of attention accompanied by disturbed sleep-wake cycles, lethargy, agitation, hallucinations, disorientation, and language and thought disorders. They noted that PTA was related but not identical to acute confusional state. There is a growing awareness (Katz 1992; Nakase-Richardson et al. 2007; Nakase-Thompson et al. 2004; Ptak et al. 1998; Sandel et al. 1995; Sherer et al. 2005; Stuss et al. 1999; Yuen and Benzing 1996) that *posttraumatic amnesia* may not be the most accurate term for this period of acute TBI recovery, which involves a breadth of cognitive and noncognitive neuropsychiatric symptoms. Careful evaluation of neurological and psychiatric symptoms following TBI is the recommended clinical approach (Riggio and Wong

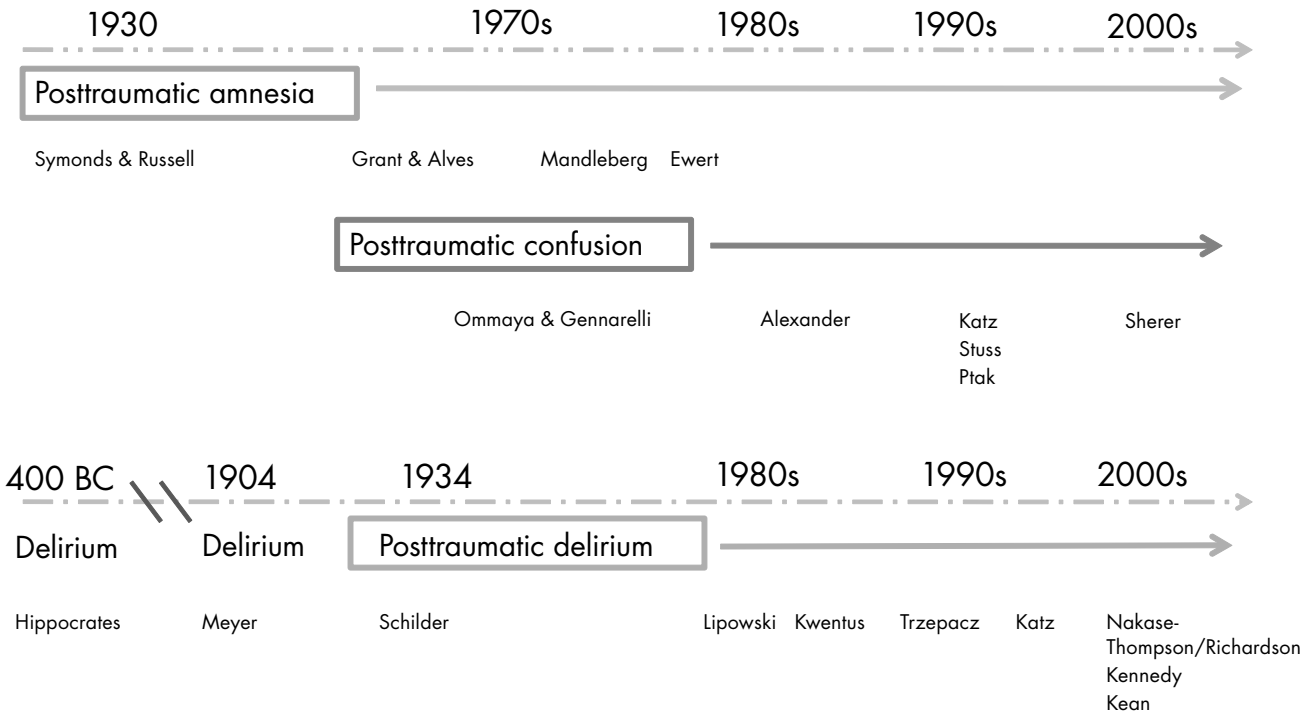


FIGURE 9–2. Terminology for post–traumatic brain injury (TBI) impaired consciousness over time.

The terms *posttraumatic amnesia, posttraumatic confusion,* and *delirium* have been applied to patients in acute recovery following TBI. All three terms continue to be used, but a growing number of rehabilitation specialists are recognizing the value of capturing the breadth of symptoms as defined in *delirium.*

2009). Clearly, additional study comparing the delirium following TBI with that from other primary etiologies is necessary to determine if there are unique variants of delirium and what the clinical implications of those variants might be. Furthermore, delirium after TBI is not monolithic, and other etiologies besides the trauma need to be considered in the differential diagnosis of the confusional state (see section below).

Delirium in Traumatic Brain Injury

Delirium is a neuropsychiatric disorder that represents an acute disturbance of consciousness that is distinct from stupor, coma, vegetative state, or minimally conscious state (Giacino et al. 2002; Schiff and Plum 2000). It is composed of inattention and other cognitive deficits, language and thought abnormalities, motor and affective changes, and sleep-wake cycle disturbances. Delirium is an abnormal state of consciousness that exists on a continuum between stupor or coma and normal consciousness. However, patients often progress directly from coma or brief loss of consciousness into delirium without a clearly defined stupor stage. *Subsyndromal delirium* describes a phase before or during the resolution of an episode of diagnosable delirium that is less severe. Although its characteristics are still under study, the core domains of delirium appear to be present. There has been little investigation of the resolution of delirium following TBI (Sherer et al. 2009; Stuss et al. 1999), and none that assesses the full range of symptoms across the continuum of recovery to determine if delirium following TBI resolves first into a syndrome best characterized as subsyndromal delirium or an amnestic disorder.

Delirium is caused by a wide variety of medical, pharmacological, traumatic, environmental, and postoperative conditions, often with more than one etiology during an episode. Approximately 18% of general hospital patients are delirious (Trzepacz et al. 2002), and delirium point prevalence ranges from 10% to 30% in general hospital patients (Fann 2000). Some populations have an even higher incidence of delirium—approximately 30% in postcardiotomy patients (Smith and Dimsdale 1989) and as much as 82% in medical intensive care unit patients (Ely et al. 2004). Those at extremes of age have higher incidences—pediatric and geriatric—because of either immaturity or vulnerability of the brain. Delirium incidence after structural damage to the brain such as from stroke, TBI, and tumor is thought to be particularly prevalent, especially with moderate to severe TBI and with loss of consciousness (LOC). For example, delirium can be caused even by small strokes in the anterior thalamus, nondominant posterior parietal, fusiform cortex, basal ganglia, and prefrontal areas, and commonly by TBI affecting frontotemporal regions with diffuse axonal injury—all of which are located to impair highly distributed information processing networks.

Stages of recovery following TBI have been described. Rao and Lyketsos (2000) describe four phases after TBI. The first period is brief LOC (sometimes with mild TBI) or coma (moderate to severe) soon after injury. The second

phase, which lasts from a few seconds or minutes in mild TBI to days or months in more severe TBI, is characterized by a mixture of cognitive and behavioral abnormalities, including agitation, confusion, disorientation, and alteration in psychomotor activity with inability to recall events, sequence time, and learn new information—a phase called *posttraumatic delirium.* The third phase is a rapid cognitive recovery period lasting from 6 to 12 months and leveling off 12–24 months after injury. Phase four is permanent cognitive sequelae or recovery. Katz et al. (2009) describes other states of impaired consciousness that can occur between coma and delirium (which he calls "confusion and amnesia") prior to postconfusional recovery of function—these are vegetative state and minimally conscious state (MCS) (Giacino et al. 2002). Not all patients pass through these states prior to becoming delirious.

Coma is a state of unconsciousness and unarousal without a sleep-wake cycle. It differs from *persistent vegetative state,* which involves arousal and a sleep-wake cycle but a complete unawareness of self or the environment. MCS differs from delirium in that MCS is a more severe impairment and lower level of consciousness (Giacino et al. 2002; Schiff and Plum 2000). MCS includes sustained visual fixation and ability to localize sounds but inconsistent unintelligible verbalizations and gesturing where intentionality cannot be attributed, and inconsistent following of commands. Both disorders have arousal and a sleep-wake cycle (unlike coma), although the latter can be disturbed. Unlike MCS, delirium is characterized by intentionality but with impaired awareness of self and the environment and impaired attentional and communicative abilities. Delirious patients are able to move their bodies unless otherwise affected by a specific condition such as paresis or fracture.

Delirium duration is often longer after TBI than with other etiologies of delirium (Ellenberg et al. 1996; Katz et al. 2009; Tate et al. 2001), which is probably related to the great extent of microstructural brain damage occurring with TBI that affects synaptic function and impacts highly distributed neural networks. Its duration increases with increased age in patients who are over 40 years old (Katz and Alexander 1994). This may be related to myelination and information processing speed that develop progressively during childhood and young adulthood until they peak at midlife around age 40 and then progressively decline with increased age.

Brief confusional periods occur after minor concussions (Lipowski 1990; Teasdale and Jennett 1974) and "disturbed consciousness is a feature found in most cases of head injury" (Russell and Smith 1961). The different systems for grading concussion severity each include "confusion" (Leclerc et al. 2001). High school athletes with three or more concussions are four times as likely to have confusion following a future concussion than those without a previous concussion (Collins et al. 2002).

The term *posttraumatic agitation* (PTAg) can overlap with delirium to some degree (see Figure 9–1), although agitation is not necessary in delirium. Agitation can be an isolated symptom or associated with a number of psychiatric and medical conditions besides delirium. For example, Nakase-Thompson et al. (2004) found that agitation occurred in both delirious and nondelirious patients. Lequerica et al. (2007) found that agitation only occurred in 6% of TBI acute recovery patients, which means that the majority are either normal or hypoactive.

TABLE 9–2. Delirium symptoms and characteristics

Disorientation (time, place, person)
Attentional deficits
Memory impairment (short and long term)
Deficits in higher-order thinking
Visuoconstructional dysfunction
Dysexecutive function
Change in mood/affective lability
Disorganized thinking
Delusions (distinguish from confabulation)
Perceptual disturbances (includes hallucinations)
Language impairments (especially semantic)
Motor behavior changes (retardation, agitation or mixed)
Sleep-wake cycle disturbances
Abrupt onset
Fluctuating course
Usually reversible

Fugate et al. (1997a, 1997b) surveyed by telephone 157 U.S. physiatrists for their understanding of symptoms of agitation and delirium during the acute recovery phase after TBI. Physiatrists did not appreciate use of the term *delirium,* although they did associate disorientation, amnesia, and memory impairment with *agitation* during acute recovery and associated symptoms of disorganized thinking, perceptual disturbance, disorientation, and disturbed sleep-wake cycle with the term *delirium.* Thus although they had some awareness of key delirium symptoms, they only recognized PTA and agitation symptoms as typifying the acute recovery period. A newer survey would be of interest to evaluate evolution of understanding.

Signs and Symptoms of Delirium (Phenomenology)

The phenomenology of delirium is related to the underlying brain regions and circuitry for information processing that are affected. Delirium is a disorder with characteristic symptoms and a cardinal feature of impaired attention. Characteristic symptoms of delirium are listed in Table 9–2 and include abnormalities of cognition, thought, language, affect, perception, sleep, and motor behavior. These generally have an abrupt onset and a temporal course in which severity fluctuates over a 24-hour period.

Delirium involves generalized cognitive deficits, differentiating it from most other psychiatric disorders except for dementias that also impair cognition broadly. Attentional deficits are required to diagnose delirium, in contrast to memory impairment as cardinal in diagnosing dementia. Delirium cognitive impairments include deficits in attention and concentration plus disorientation to time, place, and person (usually impaired in that order) and impairments of short-term memory with an inability to learn and retain new information, long-term memory, executive functions (e.g., abstraction, conceptualization,

temporal ordering, sequencing, mental flexibility), and visuoconstructional ability (including wandering and getting lost).

In addition to these cognitive deficits, delirium involves many other neuropsychiatric symptoms. These include an alteration in mood (anxious, depressed, irritable, hostile), affective lability (sometimes to the extent of pseudobulbar affect), and mood incongruency. Thinking is disorganized and may be rambling, tangential, circumstantial, or even loosely associated. Language abnormalities are variable but can include word-finding difficulty, paraphasias, dysnomia, dysgraphia, impaired repetition, impaired articulation, impaired comprehension, and perseveration of words or phrases. In the most severe cases, speech resembles a fluent or global aphasia. However, deficits in semantics of communication are the most characteristic language disturbance of delirium and serve to distinguish it from the language abnormalities associated with other psychiatric disorders. Motor behavior may evidence retardation or agitation, often mixed together. Related concepts are the motor subtypes of delirium, called *hypoactive* or *hyperactive* delirium, in which patients may appear apathetic and withdrawn, may be agitated and remove intravenous lines, or may wander or pace around. Hypoactive delirium is commonly misdiagnosed as depression (Nicholas and Lindsey 1995), and when severe it may be difficult to distinguish from stupor. Perceptual disturbances are common and may take the form of either illusions or hallucinations; visual (and occasionally tactile) hallucinations strongly suggest delirium, although auditory hallucinations or illusions also occur in delirium. Suspiciousness and persecutory delusions are common, but the latter usually are poorly formed and not well systematized, often incorporating many of the caregivers into the delusional ideation. Delusions need to be distinguished from confabulation in response to memory deficits. Patients may refuse tests because of suspiciousness, thus interfering with their own medical care. The sleep-wake cycle is disrupted and fragmented throughout the 24-hour period, with napping and nocturnal arousals that are often accompanied by nocturnal confusion and an inability to distinguish nightmares or dreams from reality. In the extreme, delirious patients may have severe sleeplessness.

These symptoms of delirium typically fluctuate in severity to some degree during a 24-hour period, with phases of increased lucidity alternating with more severe impairment. This waxing and waning makes it more difficult to assess the severity of delirium for short time frames and complicates determining exactly when the episode has ended.

Phenomenological work in delirium reveals the existence of three core domains of symptoms: "attention," "circadian," and "higher-level thinking." These core domains are based on studies of delirium in which inattention, sleep-wake cycle disturbance, motor activity alterations, and thought process/comprehension abnormalities are the most frequent, consistent, and differentiating symptoms of delirium and therefore may signify the most important symptoms of the syndrome that should be assessed (Franco et al. 2009; Meagher et al. 2007; Trzepacz et al. 2001). Further, measurement of these three domains using the Delirium Diagnostic Tool–Provisional was sufficient to predict full delirium in acutely recovering TBI patients with 97% accuracy when compared with independently diagnosed DSM-IV-TR delirium and DRS-R98 ratings (Kean et al., in press). Unfortunately, none of these domains is measured by PTA scales.

Study of the phenomenology of delirium occurring after TBI is likely to lead to greater understanding of its neuropathogenesis and to influence management and treatment decisions. There are two major considerations in examining the phenomenology of delirium after TBI: whether delirium after TBI differs in any particular aspects from delirium resulting from other causes and how symptoms in delirious TBI patients differ from nondelirious TBI patients. Thus far, phenomenological research supports delirium following TBI as being comparable with delirium from other causes (Meagher et al. 2007; Nakase-Thompson et al. 2004) (see Table 9–3). This likeness is further supported by electrophysiological and neuropathophysiological findings that parallel those found in delirium from other causes (see section below).

Phenomenology of Posttraumatic Amnesia and Posttraumatic Confusional State

Weir et al. (2006) studied problematic behaviors and new learning in a convenience sample of TBI inpatients with PTA. Using a rating scale created for the study, they noted inability to sustain attention in greater than 50% of patients, wandering in greater than 30%, incoherent verbalizations in greater than 20%, inappropriate behavior in approximately 15%, and mood swings in approximately 7%. These symptoms are consistent with descriptions of delirium. Agitation was observed in approximately 27% of patients and aggression in approximately 11%. They also noted that individuals in PTA demonstrated deficits in auditory and visual memory (as assessed by the Westmead or Oxford PTA scales), spatial memory (as assessed by locating object in the room or one's room on the ward), and self-care. Deficits in the latter two areas improved prior to the resolution of PTA, demonstrating that new procedural learning can still occur during delirium.

Studies of posttraumatic agitation also provide information regarding the phenomenology of TBI delirium. Motor agitation is common after acute brain injury and includes combativeness, truncal rocking, and arm thrashing (Levin and Grossman 1978). In a study by Levin and Grossman (1978), such agitation was found to be more common in younger patients, although the duration of coma was shorter (less than 24 hours) in those who were agitated than in those who were not. Also, agitation was not related to focal neurological signs, focal frontotemporal injury, or (inferred) mesencephalic injury but was associated with visual and auditory hallucinations and delusions. This parallels descriptions of hyperactive delirium from other causes when hyperactivity is more often associated with psychosis than hypoactivity (Meagher and Trzepacz 2000). Reyes et al. (1981) showed that patients with restlessness and agitation at the time of hospital discharge eventually had better recovery of premorbid physical and

TABLE 9–3. Frequency of positive symptoms on the Delirium Rating Scale–Revised-98 (DRS-R98) and percentage still with posttraumatic amnesia for the study sample (*N*=171)

	DDC+ (*n*=78)	DDC– (*n*=93)
DRS-R98 items		
Item 1. Sleep-wake cycle disturbance	45 (58%)	19 (20%)
Item 2. Perceptual disturbance	22 (28%)	01 (01%)
Item 3. Delusions	20 (26%)	01 (01%)
Item 4. Lability of affect	41 (53%)	16 (17%)
Item 5. Language	52 (67%)	29 (31%)
Item 6. Thought process abnormality	55 (70%)	15 (16%)
Item 7. Motor agitation	56 (72%)	23 (25%)
Item 8. Motor retardation	35 (45%)	27 (29%)
Item 9. Orientation	59 (76%)	23 (25%)
Item 10. Attention	71 (91%)	44 (47%)
Item 11. Short-term memory	73 (94%)	70 (75%)
Item 12. Long-term memory	71 (91%)	55 (59%)
Item 13. Visuospatial ability	60 (77%)	46 (49%)
Diagnostic items		
Item 14. Temporal onset	78 (100%)	92 (99%)
Item 15. Fluctuation of symptoms	71 (91%)	20 (22%)
Item 16. Physical disorder	78 (100%)	93 (100%)
No. in PTA by TBIMS GOAT criteria[a]	66 (85%)	28 (30%)

Note. DDC+=delirium diagnostic criteria positive; DDC–=delirium diagnostic criteria negative; DRS-R98=Delirium Rating Scale–Revised–98; GOAT=Galveston Orientation and Amnesia Test; PTA= posttraumatic amnesia; TBIMS=Traumatic Brain Injury Model System.

[a]TBIMS PTA was defined as the interval from injury until two consecutive GOAT scores of ≥76 were obtained within a period of 24–72 hours.

Source. Reproduced from Nakase-Richardson R, Yablon S, Sherer M, et al.: "Prospective Comparison of Acute Confusion Severity With Duration of Post-traumatic Amnesia in Predicting Employment Outcome After Traumatic Brain Injury." *Journal of Neurology, Neurosurgery and Psychiatry* 78:872–876, 2007, with permission from the publisher.

cognitive functions but with a greater need for psychological intervention. Corrigan et al. (1992) reported that agitation and cognition showed 50% shared variance, with most of this shared variance accounted for by attention, which is the cardinal feature of delirium. However, not all of the variance explained by cognition could be accounted for by agitation, or vice versa, suggesting that not all delirious patients are hyperactive and not all agitated TBI patients have delirium. This is consistent with Weir et al. (2006), who found a third or so of delirious TBI patients were agitated. Van der Naalt et al. (2000) found that agitation and restlessness resolved before PTA did and that approximately one-half of patients with TBI had agitation during PTA, which suggests that the delirium phase frequently includes motor disturbance. Using a cutoff score of ≥22 on the ABS, Lequerica et al. (2007) found about 6% of acutely confused subjects to be agitated, which was not significantly different from the nonconfused group. Unfortunately, TBI studies tend to focus only on agitation. For more accurate description of motor activity patterns in TBI, hypoactivity also needs to be assessed. The Delirium Motor Subtype Scale (Meagher et al. 2008) is a validated tool that can be used.

The most comprehensive examination of TBI delirium comes from a series of prospective studies conducted at the Traumatic Brain Injury Model Systems in Mississippi. Initial findings reported on 40 consecutive patients rated as Level IV or better on the Rancho Los Amigos Cognitive Scale (in which levels IV and V include delirium symptoms, Level III stupor, and Levels I and II coma) during inpatient rehabilitation hospitalization, who were prospectively evaluated using both neuropsychiatric and rehabilitation rating instruments (Nakase-Thompson et al. 2002). All subjects were rated on the DRS and independently using the ABS and GOAT. Twenty-four subjects met DSM-IV delirium diagnostic criteria (American Psychiatric Association 1994), whereas 26 did not. Using GOAT and ABS in a logistic regression model, the two groups were classified with 77.5% accuracy. Inspection of individual scores revealed that some subjects in the delirium group had scores meeting the cutoff for "normal" on the ABS (22.5%) and GOAT (7.5%), whereas some subjects in the nondelirious group had scores in the impaired range on the ABS (7.5%) and GOAT (27.5%). In a subsequent study (Sherer et al. 2005) of 93 TBI patients, 71% with DSM-IV-TR delirium met cutoffs for PTCS, whereas 86% of those diagnosed with PTCS also met DSM-IV-TR criteria for delirium. Individuals with PTCS had higher frequencies of disorientation, cognitive impairment, fluctuation of symptoms, motor restlessness, nighttime sleep disturbance, decreased daytime arousal, and psychotic symptoms than individuals without PTCS. Another report of 85 patients, with 59 meeting DSM-IV-TR delirium diagnostic criteria, had similar findings (Nakase-Thompson et al. 2004) in which those with delirium following TBI were more likely to show psychotic symptoms (perceptual disturbances, hallucinations, delusions), psychomotor disturbances, cognitive impairments, sleep-wake cycle disturbances, and affective lability than individuals with TBI but no delirium as measured using the DRS-R98. Nakase-Richardson et al. (2007) described post-TBI delirium, using the DRS-R98 in 78 patients with DSM-IV delirium and 93 nondelirious patients, where the incidence of symptoms was comparable to non-TBI delirium in the literature. There was an incomplete overlap with PTA (see Table 9–3). Thus delirium in TBI is associated with the same constellation of symptoms as delirium from other causes. The delirious group also had significantly worse scores on both the GOAT and the ABS than the nondelirious group, again highlighting the overlap between constructs, although certain symptoms were almost exclusively apparent during delirium such as psychotic symptoms.

Taken together, research in TBI phenomenology reveals incomplete overlap between delirium and PTA and posttraumatic agitation but high comparability between delirium and PTCS (see Figure 9–3). Apparent differences between delirium and PTCS are presumably more related to instruments than to symptom constellation.

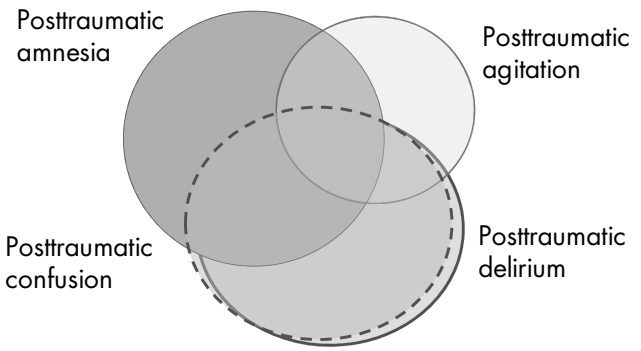


FIGURE 9–3. Schematic representation of the interrelationships among posttraumatic delirium, posttraumatic amnesia, posttraumatic confusion, and posttraumatic agitation.

The circles are representational of the overlap across disorders. Delirium is essentially synonymous with *posttraumatic confusional state* (PTCS), a recently applied term to replace *posttraumatic amnesia*. Minor differences between delirium and PTCS reflect small differences in incidence as detected by different instruments. *Delirium* is the recommended term because of its use across specialties of medicine and to enhance awareness that multiple etiologies besides trauma can contribute to delirium in patients with traumatic brain injury.

Temporal Patterns of Symptoms in Traumatic Brain Injury Delirium

There are few studies of the relationships between various signs and symptoms common to delirium and temporal course of individual symptoms in TBI recovery. As can be expected, most work has focused on memory and orientation indices. Sisler and Penner (1975) studied 28 patients with severe TBI in whom the temporal course of orientation and memory improvement was highly variable, with both resolving simultaneously in 50% of cases. Stuss et al. (1999) studied patterns of cognitive recovery in 108 patients with TBI and found that recognition memory improved before verbal recall memory (which was last), and attentional deficits were the first to recover. Ability to perform simpler tests preceded more effortful or strategic ones.

In a group of TBI patients with frontal lobe lesions, procedural memory improved over the course of PTA, whereas declarative memory deficits remained stable (Ewert et al. 1989). Episodic declarative memory deficits are more severe during disorientation than after it resolves (Levin et al. 1985). These findings suggest that the delirium component of PTA involves an alteration of both declarative and procedural memory and the portion of PTA after resolution of the delirium involves only declarative memory, consistent with being an amnestic syndrome. This is interesting because procedural memory remains relatively intact in amnestic patients, is implicit, and is not affected by the temporal lobe–diencephalon areas of the brain (Squire 1986). In contrast, declarative memory is impaired in amnestic syndrome; is "explicit" (conscious); is subserved by the medial temporal lobe, hippocampus, diencephalon, and ventromedial frontal lobe; and consolidates over time (Squire 1986). This suggests a possible difference in the neuroanatomical substrates of amnestic syndrome and delirium.

Using daily ratings of memory and orientation in patients with severe TBI diagnosed with PTA, Tate et al. (2000) found that disorientation recovered first—person, then place, and then time—replicating a prior study (High et al. 1990). This paralleled the pattern of cognitive recovery after electroconvulsive therapy–induced delirium (Daniel et al. 1987). In 94% of these patients, memory deficits resolved before disorientation; however, orientation to person preceded improvement in visual recognition memory, followed by orientation to place, then to time, and, finally, free recall (Tate et al. 2000). Thus their most sensitive memory measure was actually last to improve, and there was much individual variation. This also supports the idea that a confusional (delirium) phase precedes an amnestic phase. Both disorientation and amnesia occur in delirium, so as TBI delirium resolves, disorientation would be expected to improve, whereas some form of memory impairment could persist depending on the focal lesion locations (often frontotemporal).

Similar results can occur after mild injury; one study showed only 38% of patients to be well oriented during PTA (Gronwall and Wrightson 1980). Geffen et al. (1991) studied PTA and found that orientation returned first, followed by recognition and cued recall, and free recall was last. Schwartz et al. (1998) compared patients with TBI (mild to severe) with trauma center control subjects using serial GOAT ratings and ability to learn/retain new information (three words and three pictures). For the TBI group, the time sequence was later for recovering recall memory than for either recognition memory or obtaining a normal GOAT score, irrespective of TBI severity level, although recovery occurred sooner in subjects with milder injury. Picture memory recovered before verbal memory. De Monte et al. (2006) examined patients with mild TBI, finding that patients with disorientation had significantly poorer performance on measures of information processing speed and delayed verbal memory than patients without disorientation. Leach et al. (2006) performed an item-by-item analysis of the Westmead PTA scale administered daily to inpatient TBI admissions. Invariant, well-rehearsed long-term memory, represented by recall of date of birth, consistently recovered first. Long-term memory items that were not so well rehearsed (represented by recall of age, month, and year) and simple new learning reinforced by environmental cues (represented by recall of time and place) recovered next, but the order of recovery varied considerably. Complex new learning, represented by recall of the examiner's face and recall of three pictures, consistently recovered last.

A longitudinal study of DSM-IV-TR–diagnosed delirious TBI patients found a highly variable temporal recovery of impairments of orientation, memory, attention, executive function, comprehension, and sleep-wake cycle across individuals as the delirium cleared (Abell et al. 2009). Resolution of performance on a simple attention task occurred prior to or concurrently with memory or executive function recovery in only about half of the cases, and a simple motor Go-No Go or simple cued memory task recovered in over half prior to basic attention recovery. These findings are different than those of Stuss et al. (1999), although they are similar in that simpler tasks recovered prior to more complex tasks.

TABLE 9–4. Etiologies for delirium in any population that indirectly or directly affect the brain

Category	Causes
Drug intoxication	Anticholinergics, digoxin, histamine antagonists, antiarrhythmics, phenytoin, opioids, and others
Drug withdrawal	Alcohol, benzodiazepine, barbiturate
Metabolic/ electrolyte	Hepatic or renal insufficiency, change in pH, hyper- or hypoglycemia, hypothermia, hyponatremia, hypercalcemia, vitamin deficiency, dehydration
Infection	Any systemic; encephalitis, meningitis, abscess, tertiary syphilis, AIDS; bacterial, viral, protozoal, prion
Inflammation	Variety of peripheral or central nervous system inflammatory responses
Fever	Multiple possible causes
Hematological	Anemia, low white blood cell count
Endocrine	Hypothyroidism, hypo- or hypercortisolism, hyperparathyroidism
Seizures	Ictal and postictal states; partial complex status
Cancer	Metastases, brain tumor, carcinomatous meningitis, remote effects
Trauma	Blunt trauma, indirect mechanical impact injury, contusion, edema, fractures
Essential nutrient deficiencies/ excesses	Thiamine, B_{12}, metals, enzyme cofactors
Vascular	Stroke, transient ischemic attack, hypoperfusion, hypoxemia, subdural hematoma, shock, increased intracranial pressure, acute hypertension, pulmonary embolus, cardiac arrhythmia, myocardial infarction, vasculitis, thrombus, hemorrhage, hematoma
Environmental/ physical	Heatstroke, radiation, toxins, heavy metals (lead, mercury), industrial solvents, pesticides, electrocution, burns, carbon monoxide, hypothermia

Causes of Delirium

Etiologies

Delirium is caused by physiological, structural, traumatic, postsurgical, and/or pharmacological etiologies that affect the brain directly or indirectly. Often, more than one etiology exists in a given patient. Table 9–4 summarizes categories and examples of common etiologies that need to be considered for any patient with delirium with or without TBI. The most common causes include drug intoxication and withdrawal (polypharmacy is common) and metabolic, cardiovascular, infectious, inflammatory, and traumatic causes. The first step in the management of delirium is the diagnosis and treatment of these underlying etiological factors that tend to be multifactorial in a given individual. Although TBI may sufficiently disrupt brain function to result in delirium by itself, it is important to consider a broader range of potentially contributing etiologies in a given patient and not to presume the confusion is solely from the trauma-related brain damage. Table 9–5 lists etiologies of delirium that are more specific to the TBI population, although any of the problems listed in Table 9–4 also need to be considered in patients with TBI and managed actively in order to hasten resolution of the delirium. This is especially important because TBI delirium patients are often discharged from the general hospital into acute rehabilitation inpatient settings where the focus shifts away from a general medical approach and subspecialists in delirium may not be on staff.

TABLE 9–5. Common causes of delirium in patients with traumatic brain injury

Brain contusion
Central nervous system axonal shearing, swelling, deafferentation, and demyelination (including delayed effects)
Cerebral edema
Brain hemorrhage (punctuate or larger focal parenchymal; subarachnoid)
Infection
Systemic inflammation and proinflammatory cytokine release
Subdural or epidural hematoma
Seizure
Hypoxia (cardiopulmonary or local ischemia)
Increased intracranial pressure
Alcohol intoxication or withdrawal; Wernicke's encephalopathy
Illicit drug intoxication or withdrawal
Reduced hemoperfusion/microvascular changes
Fat embolism from fractures
Change in pH
Electrolyte imbalance
Medications (barbiturates, steroids, benzodiazepines, opioids, and anticholinergics)

TBI patients are at increased risk of morbidity and mortality from a variety of other nontrauma causes, with seizures, circulatory diseases, and respiratory diseases being particularly common (Kalisky et al. 1985; Shavelle et al. 2001). Recent work found that use of anticholinergic medications contributes to delirium severity in TBI patients (Abell et al. 2009). Delirium in TBI can be caused by both direct effects on the brain (e.g., acceleration, deceleration, concussion, subdural hematoma, intraparenchymal hemorrhage, edema, contusion) and by extracranial injuries such as multiple trauma, fat embolism, inflammatory response, hypoxemia from chest trauma or a compromised airway, and shock. TBI patients with systemic hypoxia or hypertension have an increased mortality (Gentleman and Jennett 1990) and may have both diffuse and focal brain lesions (Katz 1992). Hypoxic-ischemic injury (HII) patients also have worse longer-term prognosis, including vegetative states and a prolonged confusional phase. Increased intracranial pressure has been associated with a greatly

increased mortality in TBI, and strategies such as hyperventilation and barbiturate coma have been used to reduce acute brain swelling and metabolic rate (Lobato et al. 1988). These treatments, as well as these TBI complications, may contribute to delirium.

Risk Factors

Factors that increase the risk of delirium are listed in Table 9–6. Low serum albumin is an important risk factor that has been elucidated in a number of different patient samples (Levkoff et al. 1988; Trzepacz and Francis 1990). It can indicate poor nutrition or change in pharmacokinetics with increased free (unbound) serum levels of drugs and consequent increased potential for central nervous system (CNS) toxicity. Elderly patients are more vulnerable to delirium and are a sometimes forgotten population susceptible to head trauma (Galbraith 1987). Ellenberg et al. (1996) found older age, low initial Glasgow Coma Scale (GCS) score, nonreactive pupils, coma duration, and use of phenytoin to be associated with more prolonged PTA. Wilson et al. (1994) found a correlation between PTA duration and number of hemispheric lesions on magnetic resonance imaging (MRI) (r=0.37) and number of central brain areas with lesions (r=0.57), which parallels work in other causes of delirium in which subcortical lesions increase risk (Trzepacz 1999). However, patients who are traditionally considered to have a higher risk for delirium are nearly always excluded from PTA studies—especially alcoholic patients, elderly patients, those with prior psychiatric and neurological histories, and those with prior brain injury—which may have biased our understanding of more complicated delirium relevant to routine clinical care of TBI patients.

TABLE 9–6. Risk factors predisposing to delirium

Low serum albumin
Advanced age, with or without dementia
Brain damage or central nervous system disease
Preexisting cognitive deficits
Prior episode of delirium
Significant medical disease
Polypharmacy
Basal ganglia lesions on magnetic resonance imaging
Cerebral atrophy with right-hemisphere focal lesions
Apolipoprotein E4 allele status

Rating Scales

The majority of validated and widely used tools for PTA in the rehabilitation literature focus on only one or a few cognitive domains, usually orientation and memory, whereas delirium scales from the psychiatry literature include not only many cognitive domains but also other neuropsychiatric symptoms and can more fully evaluate TBI patients during phases of recovery. PTAg scales only assess agitation symptoms. PTCS scales have been developed to more broadly assess the confusional state. Table 9–7 lists scales and their content.

Each PTA scale has drawbacks, and none of them adequately assesses delirium, such as the GOAT or Westmead. There is a growing appreciation for the inadequacies of scales for the acute recovery period that measure only one or two aspects of cognition or agitation but do not include attention (cardinal symptom of delirium) and a fuller range of neuropsychiatric symptoms (Kalmar et al. 2008; Sandel et al. 1995; Tate et al. 2000; Wilson et al. 1999). Wilson et al. (1999) recommended tests of orientation, memory, attention, and visuospatial function for patients with PTA on the basis of their serial neuropsychological testing of patients with severe TBI in PTA (n=9), patients with severe TBI without PTA (n=10), and healthy control subjects (n=13). Specifically, they suggested measures of orientation, reaction time, visual recognition memory, and speed of information processing show a much wider range of deficits than people with chronic memory impairment or amnestic syndrome. Without measuring a wider range of symptoms, it can be difficult to determine when the confusional state ends and a more persistent focal syndrome begins. Therefore, the scales listed to evaluate PTA in Table 9–7 are not recommended to assess the delirium TBI recovery stage, but they may be more useful for the focal cognitive stages.

Motor activity in TBI is traditionally assessed using agitation scales. To study the full range of motor presentations, we recommend that objective motor activity monitoring and/or a recently validated motor activity rating scale (Meagher 2009; Meagher et al. 2008) be used to determine hyperactive, hypoactive, or mixed motor presentations in TBI patients. It is possible that TBI delirium management has been biased toward the agitated person, which commonly happens in delirium from other causes because hyperactive patients get more staff attention. This lends some skepticism to reports that hyperactive TBI patients have a better prognosis than hypoactive TBI patients (Reyes et al. 1981) if clinical management is different between the hyperactive (nuisance) versus calmer patients and therefore biased. The Delirium Motor Subtype Scale is currently being studied in TBI populations.

The Toronto Test of Acute Recovery after TBI (TOTART) (Stuss et al. 1999) was created as part of a study on PTCS. It is a clinician-administered scale that contains items from the GOAT and the Westmead PTA scale, as well as tests of attention and vigilance, but does not include noncognitive items. Validation was performed by examining patterns of recovery for 108 TBI rehabilitation inpatients. The TOTART showed those with mild TBI recovering to normal performance first, moderate TBI next, and severe TBI last, as would be expected. No reliability data have been reported.

The Orientation Log (O-Log; Jackson et al. 1998) and Cognitive Log (C-Log; Alderson and Novack 2003) are more recently developed tools for the assessment of PTA and general cognitive abilities, respectively. The O-Log is a 10-item questionnaire designed to measure orientation, including awareness of time, place, and circumstance, and was validated through comparison with the GOAT despite the fact that the GOAT measures both orientation and memory, whereas the O-Log measures orientation only. The C-Log was developed as a companion measure to the

TABLE 9–7. Instruments and scale content used to assess acute recovery period in patients with traumatic brain injury

Scales by category (references)	Items
Posttraumatic amnesia (PTA)	
Galveston Orientation and Amnesia Test (GOAT) (Levin et al. 1979b; see also Chapter 8)	Orientation and retrograde memory
Oxford PTA scale (Fortuny et al. 1980)	Anterograde memory and orientation
Westmead PTA scale (Shores et al. 1986)	Orientation and anterograde memory
Orientation Group Monitoring System (Corrigan and Mysiw 1984; Corrigan et al. 1985)	Orientation
Julia Farr Centre PTA scale (Geffen et al. 1991)	Orientation, recognition, and recall memory
Rivermead PTA Protocol (King et al. 1997)	Return of continuous memory
Rancho Los Amigos Cognitive Scale (Hagen et al. 1972; see also Chapter 4)	Cognition in broad categories, overlapping with levels of consciousness: 8-point scale along a continuum from coma to a state close to normal
Glasgow Coma Scale (Teasdale and Jennett 1974; see also Chapter 1)	Coma to normal consciousness; three axes each on a separately scored subscale: motor responsiveness, verbal performance, and eye opening
Orientation Log (O-Log) (Jackson et al. 1998)	Orientation, including awareness of time, place and circumstance
Posttraumatic agitation (PTAg)	
Agitated Behavior Scale (ABS) (Corrigan and Bogner 1994; Corrigan 1989; see also Chapter 14)	Broad assessment of agitation within three categories: aggression, disinhibition, lability
Overt Agitation Severity Scale (Yudofsky et al. 1997; see also Chapter 14)	Verbal and physical agitation and aggression in brain injury
Posttraumatic confusional state (PTCS)	
Cognitive Log (C-Log) (Alderson and Novack 2003)	Orientation (name of hospital, date, and time), as well as seven additional items designed to assess attention, memory, and executive skills
Toronto Test of Acute Recovery after TBI (TOTART) (Stuss et al. 1999)	Orientation, retrograde, and anterograde memory (using items from GOAT and Westmead scale), vigilance, verbal recall and recognition, attention, and working memory
Neurobehavioral Rating Scale (NBRS) (Levin et al. 1987)	Wide variety of psychiatric symptoms that are not specific to delirium (derived from the Brief Psychiatric Rating Scale): disorientation, inattention, anxiety, disinhibition, guilt, agitation, poor insight, depressed mood, fatigability, hallucinations, blunted affect, and speech articulation deficit
Confusion Assessment Protocol (CAP) (Sherer et al. 2005)	Orientation, cognitive impairment (using CTD and TOTART items), agitation (uses ABS), sleep disturbance, daytime arousal, psychotic-like symptoms, and fluctuation of symptoms (these derived from DRS-R98)
Delirium	
Delirium Rating Scale (DRS) (Trzepacz et al. 1988a)	Cognition, psychosis, psychomotor behavior, perception, delusions, affective lability, sleep-wake cycle, fluctuation, temporal course, physical disorder
Delirium Rating Scale–Revised-98 (DRS-R98) (Trzepacz et al. 2001)	Orientation, attention, short-term memory, long-term memory, visuospatial ability, sleep-wake cycle, language, thought process, delusions, affective lability, motor agitation, motor retardation, perception, fluctuation, temporal course, physical disorder
Delirium Diagnostic Tool–Provisional (DDT-Pro) (Kean et al., in press)	Vigilance and comprehension (derived from CTD) and sleep-wake cycle (from DRS-R98)
Cognitive Test for Delirium (CTD) (Hart et al. 1996)	Orientation, attention, comprehension, memory and vigilance (measures nonverbal modality)
Confusion Assessment Method (CAM) (Inouye et al. 1990)	Temporal course, inattention, disorganized thinking, and/or altered level of consciousness
Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (Ely et al. 2001)	Temporal course, inattention and disorganized thinking (anchored using CTD items), and/or altered level of consciousness
Delirium Motor Subtype Scale (Meagher et al. 2008)	Hyperactive and hypoactive motor symptoms; criteria derived from comparisons with control subjects and validated against motor actigraphy

O-Log and also includes 10 items: the three most difficult items from the O-Log (name of hospital, date, and time) and seven additional items designed to assess attention, memory, and executive skills. The C-Log was validated through correlation with a number of neuropsychological tests and found to contribute significantly to the prediction of outcome of attention, executive functioning, and visuomotor-visuospatial abilities.

Although the TOTART and C-Log assess a broader range of cognitive symptoms than most measures developed for use with TBI patients, the full range of symptoms documented in the phenomenological study of recovery following TBI are not covered (Nakase-Thompson et al. 2004; Sherer et al. 2005; Stuss et al. 1999).

The Confusion Assessment Protocol (CAP) (Sherer et al. 2005) is a seven-item scale administered by a clinician for rating PTCS. It is a composite of items drawn from other scales that measure delirium (DRS-R98, CTD; described below), PTA (GOAT, TOTART), and agitation (ABS). The CAP does not include motor retardation (only agitation), and the 24-hour circadian disturbance captured by the sleep-wake cycle disturbance item of the DRS-R98 was altered to become separate daytime arousal and nighttime sleep items. Initial development studies were performed using 62 admissions at a TBI rehabilitation inpatient unit, with items from the candidate scales and cutoff values selected so as to maximize discrimination between individuals with and without DSM-IV-TR–defined delirium. Validation was performed using 93 TBI inpatient rehabilitation admissions and comparing the diagnosis of PTCS using the CAP to DSM-IV-TR diagnosis of delirium. Although the DRS-R98 was administered in that study, those scores to allow a comparison with the newly created CAP were not reported.

The DRS-R98 is a widely used, well-validated scale for evaluating broad phenomenology and symptom severity of delirium from any cause. Validated against dementia and other psychiatric groups it has anchored ratings for its 16 items (Trzepacz et al. 2001). It is available in many translations and revalidated in at least six languages. The Confusion Assessment Method (CAM) and Confusion Assessment Method in the ICU (CAM-ICU) are popular screening tools for delirium in medical-surgical settings because of their brevity but have not been validated against other neuropsychiatric disorders and tend to underdiagnose delirium.

The Delirium Diagnostic Tool–Provisional (DDT-Pro), a three-item tool designed for use by nondoctoral clinicians to identify delirium, has been validated in TBI but is not yet widely used (Kean et al., in press). It assesses the three core domains of delirium and has a high predictive accuracy (97%) for delirium independently diagnosed by DSM-IV-TR criteria in post-TBI patients. It is based on items from the DRS-R98 and CTD.

The CTD (Hart et al. 1996) was designed for nonverbal delirious patients and assesses five domains of cognition. It correlates with the DRS-R98 and DRS. Using a cutoff of 22 points, the CTD has lower prediction of DSM-IV-TR–diagnosed delirium in TBI (71% sensitivity and 72% specificity) than do delirium tools that also measure noncognitive symptoms (Kennedy et al. 2003). Only the vigilance item made a unique contribution to prediction of delirium, which supports the cardinal delirium symptom being inattention. For each point of worsening on the vigilance item (item range 0–6), the odds of having delirium in TBI increased by 43%.

Given that PTCS is considered by many as synonymous with delirium, it is prudent to use delirium scales that are accepted across branches of medicine and that are revalidated and used worldwide. The range of items on the DRS-R98 subsumes those in the CAP and describes symptoms using nomenclature derived from the specialists in the fields relevant to those symptoms (e.g., sleep medicine, speech pathology, psychiatry, neuropsychology) using descriptive anchors for rating that enhances interrater reliability.

Therefore, we recommend the use of standardized, widely used, well-validated delirium instruments that have been used in both TBI and non-TBI populations. The DRS, DRS-R98, and CTD have been used in both populations (Kennedy et al. 2003; Nakase-Richardson et al. 2007; Sherer et al. 2005, 2008).

Duration and Outcomes of Traumatic Brain Injury Delirium

Severity and Location of Injury

It is believed that more severe brain injuries result in more prolonged coma and PTA (Williams et al. 1990). PTCS and PTA may persist for weeks or months, although the inadequacies of research definitions as noted in the above sections make it unclear how much can be attributed to delirium, subsyndromal delirium, dementia, amnestic syndrome, or other focal neuropsychiatric syndromes.

Katz (1992) reported that when HII contributes to the neuropathogenesis of TBI, confusion may be particularly prolonged. A variety of brain lesions, especially those in the brain stem, have been associated with protracted coma and PTA (Jellinger and Seitelberger 1970). Deeper brain lesions were associated with more severe brain injury (Ommaya and Gennarelli 1974) and resulted in longer duration and degree of coma and/or PTA (Katz et al. 1989; Levin et al. 1988; Ommaya and Gennarelli 1974). The degree of mechanical shearing caused by acceleration/deceleration forces may determine the depth of lesion along a continuum from the surface of the cortex to the brain stem (Ommaya and Gennarelli 1974). Basal ganglia (Katz et al. 1989) and basal forebrain lesions (Salazar et al. 1986) were more associated with unconsciousness than more superficial lesions. The severity of impaired consciousness did not differ among lesions located in frontal and temporal lobes, however (Levin et al. 1988). Hemispheric lateralization of lesions was not related to behavioral sequelae (Levin and Grossman 1978), but left-sided lesions were associated with longer duration of PTA than right-sided lesions (Levin et al. 1989). Patients with severe TBI had more symptoms consistent with delirium (conceptual disorganization, unusual thought content, excitement, and disorientation) even though patients were studied after the most severe confusional symptoms had resolved (Levin and

Grossman 1978). Brain regions involved in maintaining consciousness probably involve the cerebral cortex, tertiary association cortices, default brain network nodes and thalamus. When these are impaired delirium can occur, but when deeper regions including brainstem reticular activating system and thalamus are involved, there is a higher likelihood of unconsciousness (unarousal).

Ellenberg et al. (1996) found that the proportion of 16- or 25-year-olds still in PTA was lower than that of 40-year-olds (Cox proportional hazards survival curves) when determined by a GOAT score of 75 points or higher after emergence from coma, consistent with older age as a risk factor for delirium. Salazar et al. (1986) found that coma was more associated with left hemisphere penetrating head injury (in 26% of patients) versus right-sided wounds (in 9% of patients). Levin et al. (1989) found longer median duration of coma in patients with TBI with left-sided lesions (32.8 days) versus right-sided lesions (8.8 days) on the basis of the time from injury until they were able to obey commands.

Longer-Term Outcomes

Several features of PTA are related to outcome after TBI (Katz et al. 1989; Levin et al. 1979a). Residual medical, cognitive, behavioral, linguistic, and psychosocial problems all may impede recovery to premorbid levels (Levin 1995). The relationship between duration of coma or duration of PTA to outcome varies in different studies (Smith 1961). Although increased duration of coma correlates with poorer outcome and duration of PTA increases with longer coma, duration of PTA may or may not correlate with outcome. A study of 314 patients with severe TBI found that PTA duration was predicted by coma duration and initial GCS score, suggesting a relationship between coma and delirium (Ellenberg et al. 1996). Smith (1961) found that after excluding patients with focal injuries, duration of PTA correlated better with outcome; also, longer duration of PTA was associated with a higher incidence of seizures.

Ellenberg et al. (1996) found that duration of PTA, nonreactive pupils, time in coma, and use of phenytoin were predictive of the 6-month outcome after severe TBI in their retrospective study of 314 patients. Wilson et al. (1994) found that TBI coma survivors whose PTA was disproportionately long compared with coma duration (i.e., brief coma) had more numerous hemispheric lesions on MRI than patients whose LOC was more proportional to PTA duration. In a study of 65 TBI acute-care or rehabilitation inpatients, 45 of whom met DSM-IV criteria for delirium, Nakase-Thompson et al. (2002) found that those whose delirium was not resolved by discharge had higher levels of disability and lower cognitive function ratings than those whose delirium resolved before discharge, even after controlling for severity of injury and initial admission ratings for these variables.

Among 30 patients with severe TBI, those who overestimated their actual behavioral competencies several months after injury had significantly longer duration of PTA ($r=0.41$, $P<0.05$) and lower admission GCS scores ($r=-0.39$, $P<0.05$) (Prigatano et al. 1998). This finding suggests that more severe delirium may result in worse self-awareness, thereby affecting level of disability during recovery from TBI.

Duration of PTA was predictive of functional outcome in 276 TBI patients admitted to a Level I trauma center (Zafonte et al. 1997). Duration of PTA was even more predictive of Disability Rating Scale and Functional Independence Measures scores, with PTA accounting for 20%–45% of the variance.

Patients with severe TBI with reactive pupils whose PTA lasted 10 days had an 80% probability of a satisfactory outcome, whereas the worst prognosis was PTA longer than 40 days and nonreactive pupils (Ellenberg et al. 1996). However, studies using delirium-specific instruments are needed to be certain. Tate et al. (2001) used the modified Oxford PTA scale and the GOAT for daily ratings of early PTA duration from measurements during the first week after injury. However, they excluded patients with important and common delirium risk factors from their study, including prior neurological events, psychiatric problems, developmental disability, and drug/alcohol dependency.

Sherer et al. (2005) noted that individuals with PTCS had significantly poorer functional status during rehabilitation as measured by rehabilitation length of stay and after rehabilitation, as measured by the Disability Rating Scale. Nakase-Richardson et al. (2007) examined employment outcomes of 171 consecutive rehabilitation inpatients at approximately 1 year postinjury. Higher delirium severity as measured by the DRS-R98 at a median of 1 month postinjury significantly contributed to reduced employment ability after adjustment for other factors. Sherer et al. (2008) found that more severely confused TBI patients had three times worse employability and productivity at 1 year, and all symptoms individually contributed except sleep and daytime arousal. Psychotic-like symptoms at 21 days were particularly predictive of occupational dysfunction.

In summary, the severity and duration of delirium are predictive of longer-term outcomes and, although not inconsistent with previous findings regarding PTA prognostic predictions, offer a more specific snapshot of TBI acute recovery phases that can be compared with other disease states' delirium outcomes research.

Neuropathophysiology of Delirium in Traumatic Brain Injury

Delirium is considered to be a syndrome in which a characteristic constellation of signs and symptoms can result from a variety of different causes. It has been hypothesized that the pathophysiological mechanisms of different etiologies affect the brain in such a way that they converge into a final common neural pathway that produces the syndrome (Trzepacz et al. 2002). This proposed final common neural pathway involves a network of regions and circuits. The ultimate precipitating neuropathophysiologies probably involve oxidative metabolism, intracellular cytoarchitecture and protein changes, cytokine and other inflammatory-related activity, synaptic dysfunction, and neurotransmitter activity alterations that give rise to the characteristic symptoms. There is a large literature

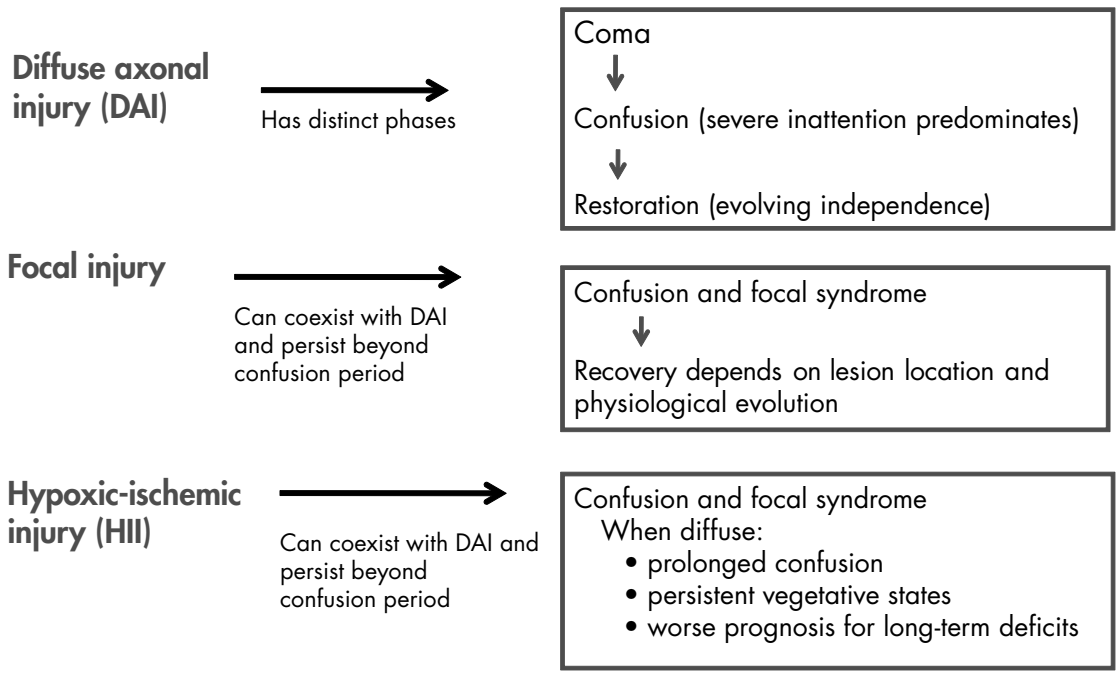


FIGURE 9–4. Traumatic brain injury pathology and confusion.

Three types of brain injury can each result in delirium (confusion), which commonly occurs following emergence from coma or minimal conscious state. Diffuse axonal injury alone or in combination with focal injuries can lead to delirium; when these are combined with hypoxic/ischemic damage, the resultant delirium can be especially prolonged.

Source. Adapted from Katz 1992; Katz and Alexander 1994; Povlishock and Katz 2005.

supporting perturbation of neurotransmission in delirium across numerous etiologies in which decreased cholinergic and increased dopaminergic activity result in delirium (Trzepacz 1996, 2000; Trzepacz et al. 2002).

Delirium/PTCS occurs more commonly after diffuse axonal injury (DAI) and HII than after focal cortical contusion (Katz and Alexander 1994). Focal injury presents with confusion depending on its location and whether it is accompanied by inflammation and edema. However, because focal injury is often comorbid with DAI, delirium can occur from that diffuse pathology (see Figure 9–4) (Katz 1992; Katz and Alexander 1994; Povlishock and Katz 2005). The prognosis following HII is often poor and may involve persistent vegetative state and particularly prolonged delirium, which may be attributed to the neurological damage because of the combination of DAI, focal injury, and ischemic injury.

On the basis of structural and functional neuroimaging studies, certain brain regions may be more implicated in delirium—in particular, prefrontal cortex, thalamus, right posterior parietal cortex, and fusiform cortex and basal ganglia (Trzepacz 1999), consistent with a recent single-photon emission computed tomography (SPECT) report (Fong et al. 2006). Most of these brain regions also play a role in various components of attention and higher-level information processing. The thalamus plays a key role in sensorimotor gating and attention and is reciprocally interconnected with all cortical regions. In animals, increased systemic aminergic activity and increased dopaminergic tone in the nucleus accumbens cause sensorimotor gating failure and administration of haloperidol, a dopamine-2 (D_2) blocker, attenuates this effect (Mansbach et al. 1988). Animal models of sensorimotor gating impairment using prepulse inhibition report improvement using either dopamine receptor D_2 blockers or muscarinic M1/M4 agonists (Jones et al. 2008). It is possible that such overactivity initially contributes to impaired attention and consciousness as seen in post-TBI delirium. The thalamus is poised at the intersection of the reticular activating system and circuitry to the cerebral cortex. It is reciprocally connected to the cerebral cortex and supports the desynchronized fast-wave electroencephalogram (EEG) recording of wakeful conscious states, which is cholinergically mediated. Its interlaminar nuclei, which are highly cholinergic, are involved in sensorimotor gating and support cerebral cortical activation, along with the medial reticular activating system, and are important in subserving consciousness (Perry et al. 1999).

Although a number of different neurotransmitters may be involved or affected from effects of the various etiologies of delirium, acetylcholine and dopamine neurotransmitters are well poised to participate in a final neural common pathway because of their pattern of EEG effects and brain functions they support, including sleep, motor behavior, mood, attention, memory, and executive function (Trzepacz 2000). Generalized EEG slowing can be associated with reduced cholinergic or increased dopaminergic activity. An animal model for delirium used atropine and resulted in cognitive, motor, and EEG abnormalities consistent with human delirium (Leavitt et al. 1994; Trzepacz et al. 1992). In an experimental rat model of TBI (Dixon et al. 1994), acetylcholine levels surge immediately after the injury (along with the excitatory neurotransmitter gluta-

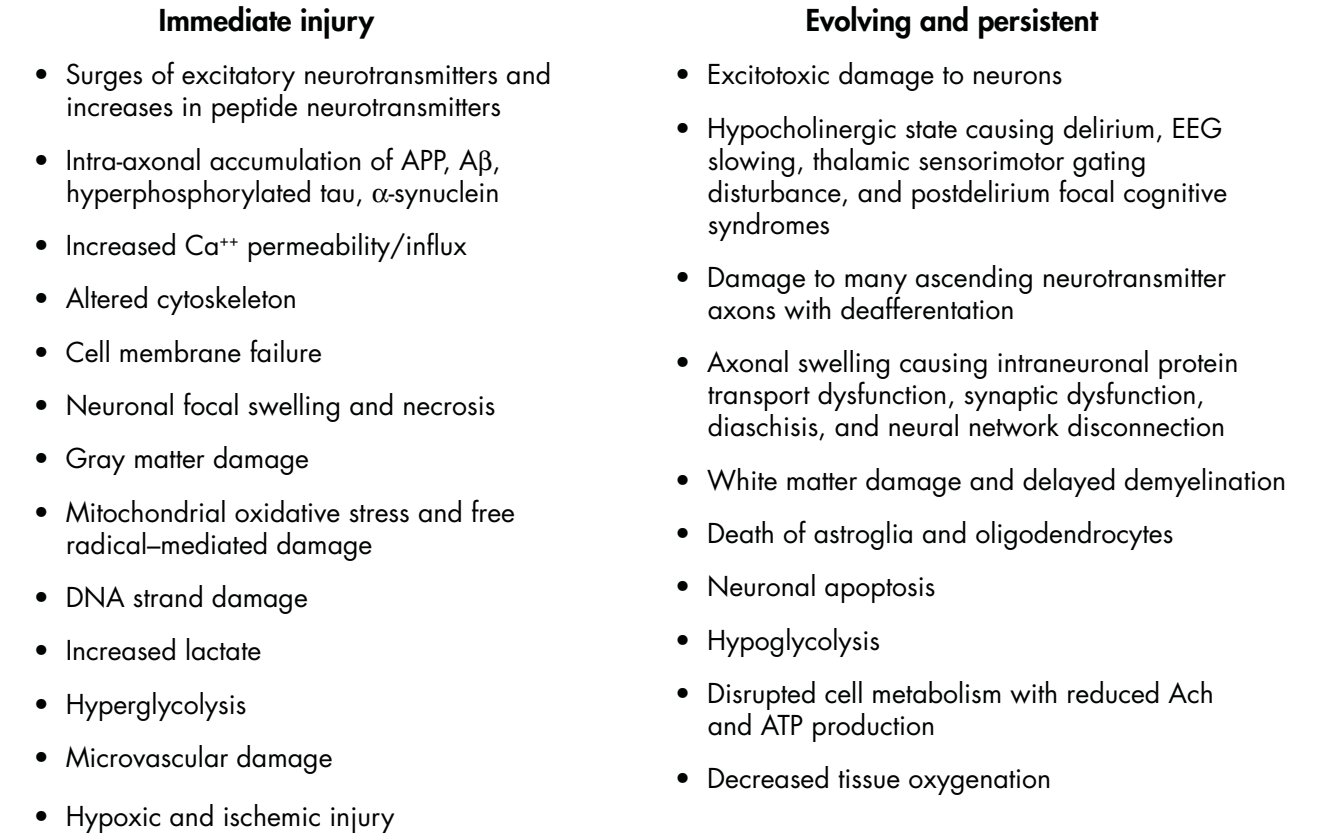


FIGURE 9–5. Neurobiological phases of acute recovery following traumatic brain injury.

Numerous alterations of brain function and structure, especially at the cellular level, occur immediately at the time of brain injury. The severity of these alterations depends on whether the injury is mild, moderate, or severe. Within hours to days these changes evolve and also induce consequences that impair the normal electrochemical and neural network functioning of the brain. Cortical and thalamic impaired function result in delirium. Ach=acetylcholine; APP=amyloid precursor protein; ATP=adenosine triphosphate; Aβ=amyloid beta; EEG=electroencephalogram.

mate) but then sharply decline followed by a prolonged period of continued cholinergic hypofunction that is associated with cognitive and behavioral abnormalities (Dixon et al. 1995). Cholinergic neurons are particularly vulnerable to acute trauma-mediated dysfunction (Arciniegas 2003). In humans with TBI, delirium occurs during the acute recovery phase in which severe decline in cholinergic neurotransmission is expected.

Amnestic or other more circumscribed cognitive disorders occur/persist after the delirium clears when cholinergic activity is still suppressed but less so than during the delirium phase. TBI patients are sensitive to cognitive impairment because of use of anticholinergic drugs during their recovery, consistent with the rat data. Medications to treat posttraumatic delirium may need to have different characteristics from those to treat postdelirium cognitive problems, on the basis of an evolving neurochemical and clinical picture that includes severe damage to neuronal microstructure. Physostigmine has been reported to improve protracted PTCS (Eames and Sutton 1995) and donepezil has been used for persistent postacute memory impairment (Taverni et al. 1998).

Figure 9–5 summarizes the immediate and then acute neurological changes that occur following TBI (Katz 1992; Katz and Alexander 1994; Povlishock and Katz 2005) and are processes that are capable of causing delirium, including altered cellular metabolism leading to reduced production of adenosine triphosphate (ATP) and acetyl coenzyme A (CoA) (necessary for acetylcholine production), mitochondrial oxidative stress, and synaptic dysfunction related to impaired intraneuronal protein transport.

These pathophysiological processes underlie coma, MCS, and delirium stages as the TBI patient evolves through these recovery phases. The immediate phase includes neurotransmitter surges, especially of excitatory amino acids such as glutamate that may overstimulate neurons to initially increase release of many peptide neurotransmitters, followed by a decrease in acetylcholine and amines. These surges can also initiate necrotic sequences for neurons. Initial hyperglycolysis and hypermetabolism on functional neuroimaging probably reflects the surges in neural activity, followed by hypoglycolysis and hypometabolism on neuroimaging. At the cellular level, many processes occur that damage cytoarchitecture and cellular metabolism at the mitochondrial level and result in reduced neuronal function and altered consciousness. These would be paralleled by slowing on EEG and abnormal somatosensory evoked potentials (see next section), consistent with delirium.

Additionally, intracellular protein abnormalities seen in chronic neurodegenerative diseases occur in acute TBI and these are associated with neurotransmitter abnormal-

ities and an increased risk for delirium. Rapid accumulations of amyloid precursor protein (APP), amyloid beta1–42 ($A\beta_{42}$), alpha-synuclein, presenilin-1, hyperphosphorylated tau, and beta-site amyloid precursor protein cleaving enzyme (BACE), related to production of $A\beta_{42}$ occur after TBI (Uryu et al. 2007). $A\beta_{42}$ further damages mitochondria, which increases free radical damage and a cascade toward neuronal injury and death. Also, $A\beta_{42}$ interferes with acetylcholine production acutely and preferentially damages cholinergic neurons chronically (Kar 2002). This oxidative and cholinergic dysfunction is compatible with other descriptions of the delirious state. Three-year survivors of TBI have fewer amyloid plaques even though they still have intra-axonal accumulations of $A\beta_{42}$, as compared with those who died sooner (Chen et al. 2009), and they also had more neprilysin, an enzyme that degrades plaques.

Hypoxia is a well-known cause of delirium and is itself associated with reduced cholinergic release and increased dopamine and glutamate release (Gibson et al. 1976; Seaman et al. 2006; Zaubler et al. 2009). Lactate formation is associated with anaerobic metabolism as a result of ischemia and hypoxia, although it serves as an alternate energy source for the brain that is dependent on peripherally delivered nutrients. During the immediate post-TBI period, ischemia, hypoxia, and edema overshadow glutamate-induced astrocytic glycolysis, although later during acute recovery the increased glutamate-induced lactate formation is associated with a better outcome (Alessandri et al. 1999).

Intra-axonal transport function becomes impaired, which reduces neurotransmitter delivery to synapses, resulting in reduced neuronal signaling. Axonal swelling as well as frank damage to oligodendrocytes is evidence of microstructural damage that impairs neural networks and is more subtle than shearing lesions seen on MRI, occurring prior to demyelination which can be delayed (Garnett et al. 2000). Increased choline/creatine (Cr) and decreased *N*-acetyl aspartate (NAA)/Cr ratios on magnetic resonance spectroscopy reflect neuronal integrity and occur even in mild TBI as a sign of increased neuronal turnover, whereas NAA is a mitochondrial by-product and may indicate impaired oxidative metabolism during the acute recovery period.

Therefore, there is ample evidence that impaired intracellular metabolic processes, neurotransmission abnormalities, white matter damage affecting highly distributed networks such as those for executive function and attention, and gray matter damage occur during DAI and are associated with informational processing abnormalities typical of the delirium period.

Electroencephalography

Since the seminal research in the 1950s by Engel and Romano, it has been recognized that a diagnosis of delirium is supported by an objective finding of generalized slowing on EEG (see Chapter 7, Electrophysiological Assessment), particularly of the dominant posterior rhythm (Engel and Romano 1959; Trzepacz et al. 1988b). Most cases of delirium are associated with electroencephalographic slowing, except for some cases of alcohol or sedative-hypnotic withdrawal (superimposed increased fast-wave activity), partial complex status epilepticus (epileptiform complexes), or superimposed focal brain lesions (focal abnormalities). Most EEG studies of PTA are consistent with the usual finding of diffuse slowing as reported in delirium from other causes (Koufen and Hagel 1987; Levin and Grossman 1978; Wallace et al. 2001) and may be especially indicative of DAI and HII. Focal EEG findings are appropriately indicative of a focal lesion, such as contusion, ischemic injury, hemorrhage, or hematoma.

Koponen et al. (1989) used quantitative EEG (QEEG) in elderly delirious patients (most of whom had comorbid dementia) and found reduced alpha percentage, increased theta and delta power, and slowing of the peak and mean frequencies. Reduced alpha percentage and mean frequency were correlated with declining cognitive function, whereas increases in delta percentage were correlated with longer duration of delirium and hospitalization. Patients with delirium and dementia had the most abnormal QEEG. Also, patients with hyperactive and hypoactive delirium showed no differences in mean electroencephalographic frequency. Jacobson et al. (1993) compared elderly delirious patients with dementia and control subjects using QEEG. They found an increase in slow-wave power and decrease in alpha power correlated with worsening delirium and Mini-Mental State Examination (MMSE) scores. Further, delirium is associated with generalized slowing of the dominant posterior rhythm on QEEG (Jacobson and Jerrier 2000). The alpha-delta ratio is significantly reduced in demented patients with delirium as compared with demented patients without delirium (Thomas et al. 2007).

EEG diffuse slowing occurs during "psychosis with amnesia" in TBI, which suggests that delirium may be being described, and may not resolve for weeks; focal abnormalities are also common and tend to normalize within several months, persisting longer in patients with traumatic epilepsy (Koufen and Hagel 1987). QEEG has been useful for predicting prognosis and in detecting nonconvulsive seizures (Wallace et al. 2001). It has revealed increased focal or diffuse theta activity, decreased alpha activity, decreased coherence, and increased asymmetry in PTA irrespective of TBI injury severity (Hughes and John 1999; Nuwer et al. 2005; Thatcher et al. 1989). Using QEEG, the delta-alpha ratio, which reflects slowing of the background rhythm, was the best predictor of functional outcome after acute neurorehabilitation (Leon-Carrion et al. 2009). This ratio is also important in delirium from other causes. Spatial analysis of EEG wavelet quality information was more sensitive than neuropsychological testing in postconcussive student athletes, especially to detect more abnormalities after a second concussion (Slobounov et al. 2009). Given that the cholinergic system is responsible for maintaining the waking EEG at the thalamus, damage to cholinergic white matter tracts is associated with slowing on EEG (Babiloni et al. 2009).

Thatcher et al. (2001) did not find a correlation between QEEG discriminant scores (coherence, phase, and amplitude) and PTA duration in 108 TBI patients, but did find a correlation between QEEG and GCS score (r=–0.85, P=0.001) and hours of LOC (r=0.56, P=0.001). However, Bagnato et al. (2010) found that EEG abnormalities corre-

lated with cognitive scores during impaired consciousness after TBI at admission ($P<0.01$) and also predicted cognitive variation after 3 months ($P<0.01$). Because DRS-R98 scores were found to predict longer-term outcomes, and EEG slowing is associated with delirium, EEG can be considered a useful marker for TBI delirium.

The relationship between EEG and neuroimaging in TBI has been explored. Computed tomography (CT) scans showed evidence of cerebral edema associated with electroencephalographic slowing (Koufen and Hagel 1987). QEEG combined with MRI imaging in the TBI postacute to chronic period found that gray matter lesions were related to decreased alpha and beta amplitudes and that white matter lesions were related to increased delta amplitudes (Thatcher et al. 1998). White matter lesions could disrupt neural circuits important in causing delirium. Cognitive deficits were correlated with increased delta amplitude and decreased alpha and beta amplitudes, as is found in delirium from other causes. Further, during a sustained attention task DAI patients showed mild cortical activation on QEEG in the prefrontal region, spread equally throughout both brain hemispheres, whereas control subjects showed strong predominant activation of the right prefrontal area, which supports impairment of distributed networks in TBI (Molteni et al. 2008).

Somatosensory evoked potentials (SSEP) show delayed conduction in traumatic coma and PTA; conduction times improve as the PTA clears (Houlden et al. 1990; Hume and Cant 1981). The degree of abnormality on SSEP is predictive of outcome (Carter et al. 2005; Hume and Cant 1981). Damage to subcortical areas, including the medial lemniscus, has been hypothesized in TBI in addition to cortical factors (Hume and Cant 1981; Lindsay et al. 1981). These findings are consistent with the slowed conduction of SSEP in delirious patients with hepatic insufficiency, wherein a subcortical as well as a cortical pathophysiology was considered (Trzepacz et al. 1989).

Structural Neuroimaging

CT scans are useful in evaluating TBI delirium to diagnose structural lesions such as hemorrhage, subdural hematoma, stroke, and contusions (Feuerman et al. 1988) (see Chapter 5, Structural Imaging). Cerebral atrophy (at times preexisting) usually suggests a brain that is more vulnerable to delirium. In addition, evidence of cerebral edema from compression of the third ventricle and basal cisterns correlates closely with increased intracranial pressure (Teasdale et al. 1984), which is a known cause of delirium and coma in TBI. Overall, reports suggest a relationship between more intracranial lesions and a higher incidence of longer duration of delirium.

One study focused on the relationship between early behavioral disturbances and admission CT scans in 43 patients with mild TBI and 24 patients with moderate TBI (van der Naalt et al. 2000). Initial CT scans were available from 55 patients. Behavioral disturbances—agitation, inappropriate behavior, and restlessness—were seen in 52% of patients and occurred more commonly in moderate injury. In all patients, restlessness and agitation disappeared before PTA resolved, and PTA was significantly increased among patients with agitation and restlessness. Early behavioral disturbances were correlated with the number of lesions on CT, with affected patients having more than twice as many lesions as patients who were unaffected. Patients with behavioral disturbances had significantly more lesions on CT (81% vs. 39%), which were mostly located in the frontotemporal region. Feinstein et al. (2002) divided 282 TBI outpatients into four groups according to their PTA duration (<1 hour, <24 hours, <1 week, and >1 week). The percentage in each group who had an abnormal CT scan was significantly different ($P=0.001$), with higher percentages for groups with more prolonged PTA (lowest=28% to highest=63.2%). Livingston et al. (2000) found that even grade 3 concussions (brief LOC or PTA) seen in an emergency department (GCS=14 or 15) had intracranial abnormalities on unenhanced CT scan in 217 of 1,788 prospectively studied TBI cases (13% positive rate).

Several studies have shown MRI to be more sensitive than CT in detecting intracranial abnormalities after TBI (Levin et al. 1992). However, initial neuropsychological deficits after TBI tend to be pervasive in nature and poorly associated with focal abnormalities (Levin et al. 1992; Wilson et al. 1988). Correlation with injury location and neuropsychological deficits were more consistent after several months of recovery, at which time many lesions had improved or resolved (Levin et al. 1992; Wilson et al. 1988). This suggests that diffuse lesions, edema, subtle damage not detected on structural neuroimaging, focal lesions with widespread downstream effects (e.g., diaschisis), or neurochemical abnormalities may underlie the acute confusional phase.

Using the MRI pulse sequence FLAIR (fluid-attenuated inversion recovery) in 45 patients with mild TBI during PTA, Wakamoto et al. (1998) detected changes not evident on MRI or CT. These changes were apparent only if PTA lasted >2 hours and consisted of periventricular lesions in the anterior horn of the lateral ventricle (60%), basal frontal lobe (16%), and/or deep cerebral white matter (24%). Etiology was presumed to be consistent with either brain edema or contusion with hemorrhage. Increased duration of PTA was associated with increased frequency of these lesions: 19% in PTA less than 30 minutes, 63% in PTA greater than 30 minutes and less than 2 hours, and 88% in PTA greater than 2 hours. Lesions had resolved by 1-month follow-up. This may be evidence of reversible microstructural damage causing delirium, affecting brain regions that could disrupt neural circuits connecting thalamus, prefrontal cortex, and basal ganglia.

Proton magnetic resonance spectroscopy studies in hepatic encephalopathy have shown decreased levels of myoinositol and choline and increased levels of glutamate. These abnormalities resolved after liver transplantation, suggesting that these were markers reflecting the reversible nature of the disorder (Lerner and Rosenstein 2000). In contrast, magnetic resonance spectroscopy studies in TBI have generally shown elevations in myoinositol and choline and reductions in NAA, which are thought to indicate neuronal loss or metabolic depression (Brooks et al. 2001). Such changes tend to normalize over a period of several months, indicating potential neuronal recovery. Patients with persistent abnormalities tend to have poorer outcomes (Brooks et al. 2001). Other studies have shown

substantial correlations between neurometabolite ratios with PTA (Garnett et al. 2001) and general cognitive function (Friedman et al. 1998).

Functional Neuroimaging

Cerebral blood flow (CBF) studies using xenon SPECT scans have been performed in TBI patients who are in coma or emerging from coma in an effort to better understand the underlying physiology of brain damage (Deutsch and Eisenberg 1987; Jaggi et al. 1990; Obrist et al. 1984) (see Chapter 6, Functional Imaging). Under most circumstances, CBF is coupled to metabolism in essentially a 1:1 relationship (Raichle et al. 1976), except for acute vascular events such as stroke when luxury perfusion of an ischemic area is much higher than the actual metabolic demand and CBF does not accurately reflect physiological needs (Lassen 1966). Acute brain trauma is another condition in which metabolism and CBF are not tightly coupled (Obrist et al. 1984). A reduction of frontal CBF as compared with the normal resting pattern (i.e., a reversal of the normal anteroposterior gradient) was noted in comatose patients after TBI (Deutsch and Eisenberg 1987); with increased global blood flow (hyperemia), this pattern was more exaggerated, but on regaining consciousness, this frontal defect normalized.

SPECT studies in hepatic encephalopathy have demonstrated decreased levels of CBF (Lerner and Rosenstein 2000). Specific deficits have been noted in the right anterior cingulate gyrus (O'Carroll et al. 1991) and frontal and anterior cortices (Trzepacz 1994). In TBI, SPECT studies detect lesions not apparent on CT and MRI, particularly in mild to moderate head injury (van Heertum et al. 2001). These functional lesions also correlate better with neurological clinical findings than with anatomical studies (Carmago 2001). The pattern of abnormalities differs depending on the severity and type of injury (i.e., motor vehicle, blunt trauma, or fall) (Abdel-Dayem et al. 1998). A rather specific pattern for TBI consists of focal, well circumscribed areas of decreased perfusion at one or more sites, although other, less specific patterns can also be seen. It remains to be seen if delirium resulting from TBI shows similar deficits on SPECT as do other disorders.

Positron emission tomography (PET) studies in TBI typically show a triphasic pattern of cerebral metabolic glucose utilization (Bergsneider et al. 2001). After a brief period of hyperglycolysis, the brain enters into a second period of metabolic depression, followed by a third phase of metabolic recovery. These phases correspond to three stages in recovery: unconsciousness, delirium (confusion), and postdelirium restoration (Povlishock and Katz 2005). In animal studies, persistent neurologic deficits remain during the period of metabolic depression, and the rate of recovery of behavioral function parallels that of recovery of metabolic function. Making an exact association between delirium and PET changes in TBI is difficult without research specifically using delirium evaluations—although one might speculate that a cortical metabolic depression phase would occur during delirium. Regional CBF decreases on PET in brainstem, thalamus, and cerebellum correlate with level of consciousness post-TBI, whereas global CBF does not, In contrast, global decreased CBF correlates with impaired conscious (PTCS) and is independent of TBI severity (Povlishock and Katz 2005).

There is a reduction of gray matter cerebral metabolic rate (CMR) for glucose on fluorodeoxyglucose (FDG)-PET acutely following TBI that correlates with worse level of consciousness, and overall cortical gray matter versus white matter CMR ratios found better 1-year recovery in those with higher gray to white matter ratios (Wu et al. 2004). Therefore, cortical damage is also important in addition to circuitry damage.

Treatment

Treatment of delirium after TBI is not standardized and differs among different specialists. Many psychiatrists treat TBI delirium in essentially the same way as delirium from other causes (Lipowski 1990). The principles of treatment involve a workup for etiologies, treatment of the underlying etiology when possible, manipulation of the environment, and medication.

Search for Underlying Causes and Status Monitoring

The search for underlying causes can be guided by considering the many possible etiologies as outlined above and as listed in Tables 9–4 and 9–5, individualized according to each patient's needs. Though TBI is obvious, specific lesion information and consideration of other etiologies is important. The clinician must reduce polypharmacy, discontinuing or replacing medications that produce delirium. Anticholinergic medications are particularly deliriogenic (Holder et al. 2008). Laboratory tests, cerebrospinal fluid examination, CT or MRI brain scans, arterial blood gases, intracranial pressure monitoring, electrocardiogram, blood cultures, and so on can all be performed as needed to investigate various potential causes.

If the diagnosis of delirium is uncertain, use of a specific delirium symptom rating scale (see earlier section on rating scales) can be used along with EEG and bedside cognitive tests. The EEG shows the usual pattern of diffuse background slowing (Engel and Romano 1959; Koufen and Hagel 1987), sometimes with the presence of sleep spindles (Koufen and Hagel 1987). Bedside cognitive tests such as the MMSE (Folstein et al. 1975); Trail Making Tests (Trzepacz et al. 1988b); CTD; and specific attentional, visuoconstructional, and executive function tasks (see Chapter 8, Neuropsychological Assessment) are useful in determining the degree of diffuse cognitive dysfunction and can be followed over time. In addition, physiatrists use other cognitive tests such as the GOAT, Rancho Los Amigos Cognitive Scale, O-Log and C-Log scales, although for delirium only the C-Log offers broader cognitive coverage. Psychiatric consultation can be useful.

Environmental Manipulations

Traditionally, efforts are made to help familiarize and structure the delirious patient's environment (Table 9–8). The delirious patient requires external structure to com-

TABLE 9–8. Environmental manipulations in the treatment of delirium

Familiarize the environment	Put family pictures nearby
	Play familiar music
Structure the environment	Have a clock in full view
	Put large calendar on wall, with days marked off
	Use night-light
	Reorient the patient frequently
	Have natural window light to assist day-night biorhythms
Adjust sensory stimulation level	Minimize loud noises
	Do not remove all stimulation
	Use soft-walled portable room for severe agitation
Ensure safety	Use a sitter
	Minimize use of restraints whenever possible

pensate for a disorganized and cognitively impaired internal mental state. When the patient is so confused or frightened that physical harm to self or others might inadvertently happen or uncooperativeness with medical treatment occurs, then physical restraints may be appropriate. Restraints must never be used to replace good nursing observation but rather should be used only to supplement other treatment efforts. However, some have expressed opinions about the negative aspects of using restraints in patients with TBI (Berrol 1988; DeChancie et al. 1987). The increased use of restraints in patients with TBI has been associated with a patient's alcohol use but not with a lower level of consciousness (Edlund et al. 1991); these restrained patients also had longer lengths of stay, more combativeness and aggression, and more alcohol withdrawal symptoms, but few were seen in consultation by a psychiatrist. The use of sitters can often reduce the need for restraints while assisting with observations and reassurance of the confused patient.

One view is that instead of medication ("too sedating") and restraints ("increases agitation") for agitated delirious TBI patients, a portable, Naugahyde padded room enclosure should be used to allow freer movement (DeChancie et al. 1987). This is essentially a seclusion room, a comfortable room with a mattress and devoid of objects, which is well known to psychiatrists and has been used for decades to reduce distracting sensory stimulation and provide safety. Although this may be a useful adjunct, it should not preclude appropriate use of medication, because changing the environment will not by itself alter the pathophysiology of delirium. In addition, a balance must be struck between minimizing excessive or confusing sounds and providing enough environmental structure (e.g., family photos) to reduce anxiety from disorientation and cognitive deficits that contribute to agitation. Deafness, blindness, and other causes of sensory deprivation actually increase the risk for delirium (Lipowski 1990).

In one study, playing music increased calmness and enhanced orientation to year and place in agitated PTA patients, significantly decreasing scores on the ABS ($P<0.001$) (Baker 2001). Both taped and live music, chosen on the basis of the patient's preference in style, were effective.

Medication

There are no FDA-approved medications with an indication for delirium (American Psychiatric Association 1999). However, appropriately chosen and monitored medication for reducing the cognitive, behavioral, and psychotic symptoms of delirium is the clinical standard of care and is supported by over 30 prospective trial reports in a variety of medical, surgical, and neurological patient types, in which a small number of them have been controlled, blinded, and randomized. Neuroleptic medication appears to be the treatment of choice for TBI delirium, where atypicals have supplanted conventional agents (Elovic et al. 2008). There have been concerns about use of conventional antipsychotic agents in treating TBI delirium, and there are FDA black box warnings for all antipsychotic agents for increased mortality when used in agitated demented elderly patients. There is a paucity of reliable safety data in TBI patients using antipsychotics.

When a comorbid psychotic disorder is present in TBI, antipsychotics are the treatment of choice to treat psychosis and agitation (Rowland and DePalma 1995). Neuroleptics should be tapered and discontinued after the TBI delirium clears and continued only if a psychotic disorder persists (or preexisted, such as mania or schizophrenia) into the rehabilitation phase. The risk-benefit ratio of prescribing antipsychotic drugs for the short-term treatment of agitated delirium remains unclear. Conventional antipsychotic medications may cause cognitive and motor impairment in healthy individuals (Killian et al. 1984). However, for patients who are severely agitated, the potential side effects of antipsychotic medications may be less harmful than the long-term disruptive effects of agitation on cognitive recovery. Some speculate that the dopamine-blocking effects of neuroleptics may delay or interfere with the TBI patient's cognitive rehabilitation (Feeney et al. 1982) because dopaminergic medications have been shown to enhance memory (Gualtieri 1991) and even to arouse chronically comatose TBI patients (Cope 1990). Whether the neurochemical mechanisms and medication strategy for treating one phase of TBI recovery (coma or amnestic syndrome) apply to delirium is unanswered. Animal studies in both rats and cats have shown that doses of haloperidol can reinstate motor deficits after frontal cortex injuries, although only certain behaviors are affected (Feeney and Sutton 1987). Haloperidol has also been shown to block the acceleration of motor recovery produced by amphetamine in animal models and to block the acceleration of depth perception recovery produced by amphetamine in cats (Feeney and Sutton 1987). Kline et al. (2008) found that both haloperidol and risperidone impaired cognitive and motor performance in a rat model of TBI, especially with chronic dosing. However, whether the findings from these animal studies have relevance to TBI delirium in humans remains to be seen.

Animal studies of the effects of atypical antipsychotics in TBI as compared with conventional antipsychotics are more encouraging. Wilson et al. (2003) compared effects of haloperidol and olanzapine on recovery from lateral fluid-

percussion–induced TBI in rats. Treatment for 15 days postinjury with haloperidol caused further impairment of cognition as compared with injured control subjects and a trend toward impairment in motor functions at higher doses, whereas treatment with olanzapine did not impair cognitive or motor recovery as compared with injured control subjects. Goldstein et al. (2002) had similar findings with clozapine when compared with haloperidol in a rat TBI model.

One retrospective review of patients with severe TBI showed no statistical difference in the rehabilitation outcomes of patients who were treated with haloperidol versus those not receiving haloperidol (Rao et al. 1995). There were trends toward poorer outcome in the haloperidol-treated group; however, individuals treated with haloperidol also had significantly longer PTA. Because PTA is widely used as a marker for injury severity, it would not be surprising that the more severely injured group would also have poorer outcome. Although no controlled trials have been conducted for supporting evidence, many physiatrists have reported individual cases in which haloperidol was effective when other drugs failed (Fugate et al. 1997b). Other typical antipsychotics have also been reported as effective in case studies and series. Three TBI patients in rehabilitation were administered serial neuropsychological tests over a 3-week period during taper and discontinuation of an antipsychotic drug each had been taking (Stanislav 1997). Thioridazine-discontinued patients showed more improvement on certain cognitive tests (e.g., Trail Making Test Part A) when not taking the drug than did patients who discontinued haloperidol. This was attributed to greater anticholinergic effects of thioridazine, which is also more sedating. However, these patients were tested years after their TBI and apparently were not still in delirium. Krieger et al. (2003) reported a single patient showing resolution of TBI delirium following administration of loxapine (20–60 mg/day as needed), after failure of olanzapine to control symptoms. Lescot et al. (2007) reported that 10 mg of intravenous loxapine was well tolerated in seven patients with TBI delirium treated in the neurointensive care unit, but they did not report on cognitive effects beyond nonspecific EEG changes; it was not accompanied by deleterious hemodynamic or systemic effects and was associated with concomitant reduction in intracranial pressure without any significant change in CBF velocity.

Atypical antipsychotics may offer new alternatives in the treatment of delirium after TBI. Their side-effect profiles tend to be more tolerable than typical neuroleptics, making their use more acceptable to patients. Furthermore, the atypical antipsychotic drugs act more specifically in the neuroanatomical areas thought to be responsible for the symptoms of delirium (Morton et al. 2000).

There have been few investigations of atypical antipsychotics for the TBI population. One series of case reports noted that clozapine was effective in treating patients with post-TBI psychosis, agitation, and aggression (Michals et al. 1993). However, the incidence of side effects (including seizures) was reportedly high for clozapine. Zimnitzky et al. (1996) described the successful use of risperidone to treat a 19-year-old man with ischemic brain damage–related psychosis after failed trials of typical antipsychotics and valproate. A few case reports have specifically addressed the effect of atypical antipsychotics in TBI delirium. Torres et al. (2001) described a case of TBI delirium responding to quetiapine 25 mg nightly. Krieger et al. (2003) initially treated a TBI delirium patient with olanzapine 20 mg per day; the patient did not respond but subsequently responded to loxapine. Temple (2003) successfully treated delirium occurring after TBI with 0.5 mg daily of risperidone. Noé et al. (2007) reported on six patients with agitation and PTA following TBI who were treated with ziprasidone 20–80 mg per day, resulting in notable improvements in agitation as measured by the ABS.

The uncertainty related to the risk-benefit ratio of antipsychotic drug treatment is reflected in the prescribing practices of many physiatrists. The physiatric field as a whole infrequently prescribes antipsychotic medication. In an older survey (Fugate et al. 1997b), haloperidol was the antipsychotic medication most likely to be prescribed. However, it was ranked only the fourth most frequently used drug to treat TBI-related agitation among physicians classified as "nonexperts" (less than 70% of practice devoted to TBI). Among "experts," haloperidol was ranked as only the eighth most frequently prescribed drug for TBI-related agitation. Target symptoms for haloperidol use were typically aggression or disinhibition. Frequently cited reasons for haloperidol use included sedating effects, rapid onset, availability of multiple modes of administration, and effectiveness when other treatments failed (Fugate et al. 1997b). Whether this still reflects current practice is unknown.

The selection of an antipsychotic drug to treat TBI-related agitation or delirium should be based on minimizing adverse side effects, because there have been no studies demonstrating a consistent advantage of one drug over another in this population. As noted, atypical antipsychotics have the most favorable side-effect profiles. The common practice is to start with low doses and slowly titrate upward, monitoring responsiveness to treatment with a standardized delirium scale. The brief duration of antidelirium treatment and the morbidity, mortality, and poor longer-term outcomes associated with delirium argue for careful use of neuroleptics in TBI delirium.

Benzodiazepines can worsen delirium and further impair cognition, and thus their prescription is usually avoided unless specifically indicated for seizures or alcohol withdrawal. Benzodiazepines are the safest of the sedative class of drugs and can be used if the sleep-wake cycle disturbance does not normalize after adjusting the dose of haloperidol, or if extreme agitation is not responsive to haloperidol, although this is usually not necessary. The choice depends on the need—lorazepam has a shorter half-life than diazepam. Unlike most benzodiazepines, lorazepam can be effectively administered intramuscularly because it is well absorbed by that route.

Other classes of medications have occasionally been used to treat delirium. Agents that enhance acetylcholine by blocking acetylcholinesterase, such as physostigmine and donepezil, theoretically should treat delirium by reversing the cholinergic deficiency (Trzepacz 1994, 1996, 2000; Trzepacz et al. 2001). This has been shown in a few uncontrolled reports (Fischer 2001; Wengel et al. 1999).

Cholinomimetic agents have been used for treatment of chronic delirium after TBI, including chronic intravenous injections of physostigmine (Eames and Sutton 1995), although with mixed results (Blount et al. 2002). Delirium prophylaxis following stroke has been demonstrated using chronic dosing of rivastigmine (Moretti et al. 2004). Newer agents directly targeting the muscarinic receptors hold promise for TBI delirium, such as muscarinic positive allosteric modulators (Conn et al. 2009; Jones et al. 2008) that also may alter amyloidogenic processing and muscarinic receptor subtype–specific agonists (Bodick et al. 1997) that improved cognition and behaviors in dementia.

Agitation in 21 patients with severe TBI improved more with propranolol LA, 60–240 mg, than placebo in a double-blind randomized trial (Brooke et al. 1992), as measured by the Overt Aggression Scale. Agitation intensity and need for restraints decreased for patients taking propranolol, whereas episode frequency did not differ; these patients may not have been delirious, however.

Electroconvulsive therapy has been reported to treat cases of prolonged "organic stupor" and agitated delirium after TBI (Kant et al. 1995; Silverman 1964). Carbamazepine, 400 mg/day plus buspirone, 30 mg/day, reduced delirium in four TBI patients within 36 hours (Pourcher et al. 1994).

Conclusion and Future Research

Recent years have brought increasing recognition that the acute recovery period following TBI causing impaired consciousness involves a much broader constellation of symptoms than measured by PTA. The term *posttraumatic confusion* is a major improvement over *posttraumatic amnesia,* although it should be replaced by the term *delirium*, similarly to terms like *confusion* or *encephalopathy* having been replaced in the remainder of medical practice. Use of a common term, *delirium,* not only will enable better clinical detection and management but also will enable more specific research on phenomenological features, risk factors, duration, treatment, neuropathophysiology, prognosis, and outcome after TBI. The broad adoption by rehabilitation clinicians and researchers of diagnostic criteria for delirium and the use of rating scales and cognitive tests that assess the whole range of neuropsychiatric symptoms of delirium are necessary to move the TBI field forward.

The exclusion of certain patients from most TBI PTA studies has excluded some of the patients at greatest risk for TBI related to comorbidity, namely those who abuse alcohol (Honkanen and Smith 1991) and other substances and those who have antisocial personality disorder, mania, schizophrenia, attention-deficit/hyperactivity disorder, suicidal depression, and so on. Whether these psychiatrically impaired persons have a higher risk for delirium is unknown but could be hypothesized for at least some of them (alcoholic and bipolar patients). Neurologically impaired persons are also excluded from TBI PTA studies, yet they are at higher risk for delirium. A person with impaired cognition or prior brain injury that alters personality (e.g., aggressive) or frontal lobe executive functions (e.g., judgment and abstraction) may be at increased risk for recurrent TBI from fighting or falling, for example, and would likely have an increased risk for delirium after TBI. Therefore, "real-life" TBI may not be reflected in research reports if preexisting conditions are excluded.

Elderly patients, with or without dementia, have diminished brain reserve and reduced ability to withstand the effects of TBI (Galbraith 1987). Neuropathological changes associated with aging and neurodegenerative disorders also occur in TBI patients. A methodological problem in many studies is not accounting for effects of medications in study outcomes, for example, in research on the duration of PTA. Naturalistic studies without treatment or carefully controlling medications in a randomized, blinded fashion are needed to more accurately determine relationships between outcomes and other variables.

The neuropathophysiology of TBI delirium probably involves initial surges of excitatory neurotransmitters (glutamate and aspartate) with damage occurring to cholinergic neurons. Oxidative stress and mitochondrial impairment, intra-axonal pathology that impairs synaptic function, white matter damage and degeneration, and dysfunctional circuitry probably underlie the delirium following TBI, paralleling that of other delirium etiologies. Deficiency of cholinergic neurotransmission that may include an imbalance with dopamine probably occurs in TBI delirium as in other causes of delirium. A relative excess of dopamine, which alters thalamic gating and EEG, may not persist in later phases of recovery when dopaminergic agents can be helpful for cognitive functioning.

Randomized, double-blind, placebo-controlled trials are needed in TBI delirium to determine whether any of the agents currently being used are truly effective; otherwise the natural course of episode duration and variability among individuals in case reports or open studies might explain so-called treatment responses.

KEY CLINICAL POINTS

- *Posttraumatic amnesia* is an inadequate term and concept for the broad range of symptoms that occur following acute TBI. These are better accounted for by the terms *confusion* or *delirium.*

- The full range of delirium symptoms needs to be evaluated in recovering TBI patients. The severity of all of these symptoms should be monitored over time instead of only during the time until resolution of orientation and memory.

- Both hypoactive and hyperactive presentations of TBI delirium need to be evaluated.
- The clinician should search for and clinically manage etiologies in addition to the brain trauma itself as other potential causes of delirium.

Recommended Readings

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CHAPTER 10

Mood Disorders

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ASSOCIATIONS BETWEEN TRAUMATIC BRAIN INJURY (TBI) and a variety of neuropsychiatric disorders have been reported in the medical literature for many years. Lishman (1973), in his classic study on the Oxford collection of head injury records, analyzed potential etiological factors involved in the development of psychiatric disturbances following TBI. These studies stressed the importance of biological variables such as the extent of brain damage, lesion location, and the presence of posttraumatic epilepsy in determining the type and duration of psychiatric disorder.

From a pathological standpoint, TBI is characterized by changes in diverse cortical areas, subcortical structures, and the white matter tracts that connect them. Recent evidence suggests that diffuse neuronal damage and cell loss may progress over weeks to months after the initial insult in selectively vulnerable regions of the prefrontal cortex, hippocampus, thalamus, striatum, amygdala, and forebrain nuclei. The resulting functional changes in neuronal circuitry may constitute the neurological substrate of cognitive and behavioral deficits that are frequently seen after TBI (Bigler et al. 2002; Buki and Povlishock 2006; Clark et al. 2000; Colicos et al. 1996; Conti et al. 1998; Grady et al. 2003; Graham et al. 2000; Levine et al. 2008; MacKenzie et al. 2002; McIntosh et al. 1998; Royo et al. 2006; Wilde et al. 2007).

Psychopathological disturbance and, in particular, mood disorders occur in the context of profound changes in cognitive and emotional processing that follow TBI. There is an extensive literature concerning the cognitive changes observed after TBI. TBI patients frequently show a dysexecutive syndrome (Alexander and Stuss 2000; Levin and Kraus 1994; Levin et al. 2002; McAllister et al. 2006) that includes deficits in stimuli saliency attribution, goal formation, selection of adequate responses, and monitoring of ongoing behavior.

Emotional processing following TBI has not been as extensively examined. However, several studies described the detrimental effect of prefrontal injury on patients' performance in social cognition (Adolphs 2003; Karafin et al. 2004) and theory-of-mind tasks (Bibby and McDonald 2005; Turkstra et al. 2004). These changes may have a clinical expression as altered self-representations and dysfunctional interpersonal relationships, increasing patients' vulnerability to develop affective episodes.

Overall, the cognitive and behavioral consequences of structural brain damage will have a decisive impact on the frequency, phenomenology, and clinical course of mood disorders occurring after TBI. In turn, affective disorders negatively influence the recovery process and constitute a major determinant of functional and psychosocial outcome.

Prevalence of Mood Disorders

Neuropsychiatric illness is a highly prevalent complication of TBI (Bryant et al. 2010). Fann et al. (2004) examined the risk of psychiatric illness after TBI in an adult health maintenance organization population. They compared the frequency of psychiatric disorders among 939 TBI patients and 2,817 control subjects. The prevalence of any psychiatric illness in the first year was 49% following moderate to severe TBI, 34% following mild TBI, and 18% in the control group. Among subjects without a history of psychiatric illness, the adjusted relative risk for any psychiatric illness in the 6 months following moderate to severe TBI was 4.0 (95% confidence interval [CI], 2.4–6.8) and following mild TBI was 2.8 (95% CI, 2.1–3.7), compared with those without TBI. Among subjects with previous psychiatric disorders, the adjusted relative risk for any psychiatric illness in the 6 months following moderate to severe TBI was 2.1 (95% CI, 1.3–3.3) and following mild TBI was 1.6 (95% CI, 1.2–2.0). Prior psychiatric illness was a significant predictor of psychiatric morbidity following TBI. Furthermore, patients with mild TBI and prior psychiatric illness had evidence of persisting psychiatric problems (Fann et al. 2004).

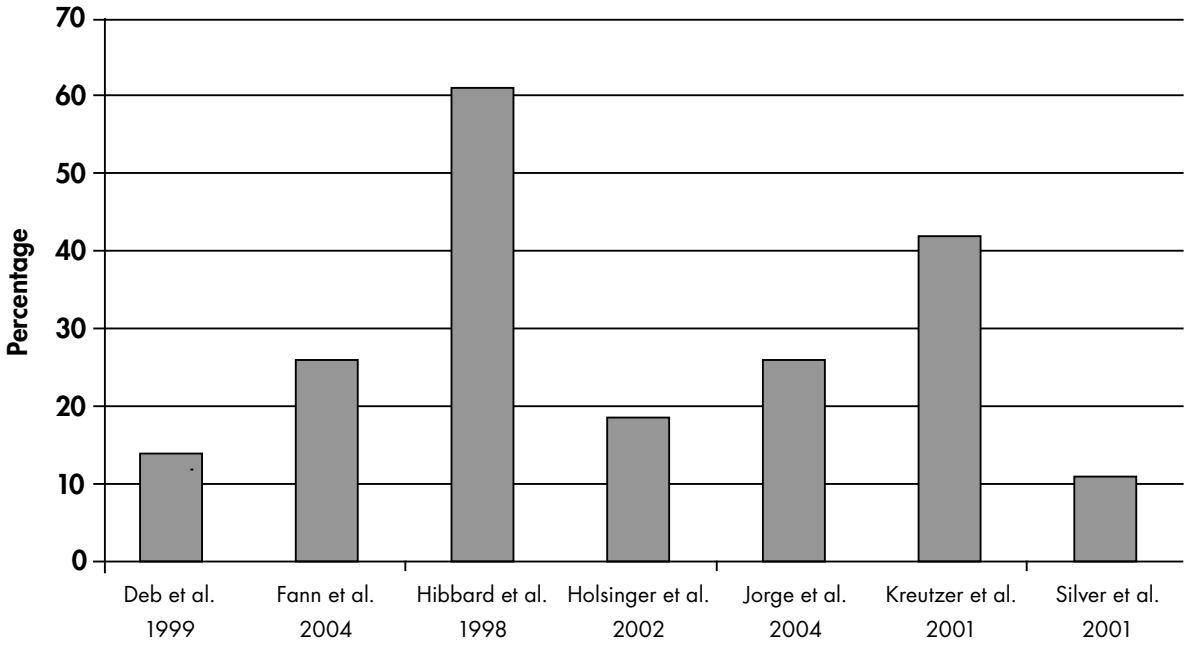


FIGURE 10–1. Frequency of major depression after traumatic brain injury in different samples.

Another study examined prospective rates of Axis I disorders among 188 patients within the first 6 years after TBI (Ashman et al. 2004). The authors found a decreased probability of having an Axis I diagnosis (particularly mood, anxiety, and substance use disorders) over time. The prevalence of psychiatric disorders, however, continues to be significantly higher in TBI patients than in control groups many years after the traumatic injury (Anstey et al. 2004; Holsinger et al. 2002; Koponen et al. 2002).

The reported frequency of depressive disorders following TBI has varied from 6% to 77% (Brooks et al. 1986; Deb et al. 1999; Fann et al. 1995; Gualtieri and Cox 1991; Hibbard et al. 1998; Holsinger et al. 2002; Jorge and Robinson 2002; Jorge et al. 2004; Kreutzer et al. 2001; McKinlay et al. 1981; Schoenhuber and Gentilini 1988; Silver et al. 2001; van Reekum et al. 1996) (Figure 10–1). The variability in the reported frequency of depressive disorders, particularly major depression, may be due to the lack of uniformity in the psychiatric diagnosis. Most of the studies relied on rating scales or relatives' reports rather than on structured interviews and established diagnostic criteria (e.g., DSM-IV-TR; American Psychiatric Association 2000).

However, Hibbard et al. (1998) used a structured interview and DSM-IV (American Psychiatric Association 1994) criteria to identify Axis I psychopathology in 100 adults with TBI who were evaluated, on average, 8 years after trauma. The prevalence of major depression in this series was 61%. Kreutzer et al. (2001) studied the prevalence of major depressive disorder among a sample of 722 outpatients with TBI, evaluated an average of 2.5 years following brain injury. Major depression, defined using DSM-IV criteria, was diagnosed in 303 patients (42%). In addition, Seel et al. (2003) studied the frequency of depressive symptoms in a sample of 666 outpatients with TBI who were evaluated from 10 to 126 months after injury. The authors found that 27% of patients met DSM-IV criteria for a diagnosis of major depressive disorder.

In a study of 559 adults with complicated mild to severe TBI, Bombardier et al. (2010) found that approximately half (53%) of patients met criteria for major depressive disorder at least once during the first year after TBI. Major depressive disorder was frequently associated with significant anxiety, history of affective illness, and history of substance misuse. In addition, depression was an independent predictor of poorer health-related quality of life.

Finally, Koponen et al. (2002) reported that major depression had a lifetime prevalence of 26.7% in a group of 60 TBI patients followed for an average of 30 years. These findings emphasize the need of careful psychiatric follow-up of patients who have suffered TBI.

Although less extensively studied, secondary manic syndromes also have been reported to occur after TBI (Bracken 1987; Clark and Davison 1987; Nizamie et al. 1988). Shukla et al. (1987) reported on 20 patients who developed manic syndromes after closed head trauma. These authors found a significant association between mania and the presence of posttraumatic seizures, predominantly of the partial complex type (temporal lobe epilepsy). There was no association, however, with family history of bipolar disorder among first-degree relatives.

Mood and Anxiety Disorders Following TBI in the Military

TBI has been described as the "signature wound" of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF). As of March 2006, 28% of all injured individuals in these conflicts had a TBI, with blast being the wounding etiology in the majority of cases (88%) (Warden 2006).

Previous studies suggest that mental health disorders are highly frequent among OIF/OEF military personnel (Hoge et al. 2004, 2006). An epidemiological study of 103,788 OIF/OEF veterans first seen within the Department of Veterans Affairs system following active duty in Iraq and Afghanistan reported that approximately 25% of all veterans received a mental health diagnoses and 11% had mood disorders (Seal et al. 2007). In another study, posttraumatic stress disorder (PTSD) was diagnosed in 16.6% of 2,863 soldiers 1 year after their return from duty in Iraq. Its occurrence was associated with greater medical burden and increased utilization of health services (Hoge et al. 2007).

Work From Our Laboratory

We have studied the prevalence, duration, and clinical correlates of mood and anxiety disorders in a group of 66 patients with TBI admitted to the Shock Trauma Center of the Maryland Institute of Emergency Medical Services System (Fedoroff et al. 1992). The patients in our sample were mostly white males of lower socioeconomic classes in their third decade. The principal cause of brain injury was motor vehicle accidents. The majority of patients (68%) had moderate brain injuries, 11 patients (17%) suffered severe brain injuries, and 10 patients (15%) were categorized as having mild brain injuries. Almost one-third of these patients (30%) had a history of alcohol/drug abuse, and 11 patients (17%) had a personal history of psychiatric disorder (excluding alcoholism and/or drug abuse).

In the acute stage of TBI (i.e., approximately 1 month after brain injury), 17 of 66 patients (26%) developed major depression and another 2 patients (3%) developed minor (dysthymic) depression (Fedoroff et al. 1992). The prevalence of major depression during the year following TBI remained stable at 25%, with some patients recovering from major depression and other patients developing delayed-onset depression (Jorge et al. 1993c). Minor depression was diagnosed in 8 patients during the course of the year. Of the 17 acutely depressed patients, 7 patients (41%) also met DSM-III-R (American Psychiatric Association 1987) criteria for the presence of generalized anxiety disorder (GAD), whereas none of the 47 nondepressed patients met criteria for GAD (Jorge et al. 1993d). There were 11 patients who developed delayed-onset major depression at some point during the follow-up period (i.e., 4 patients at 3 months, 4 patients at 6 months, and 3 patients at 12 months after brain injury). Thus, 28 of the 58 patients (47%) in whom we have follow-up data available met DSM-III-R criteria for major depression during the first year after the traumatic episode (Jorge et al. 1993b).

In this series, patients who developed major depression during the acute period had an estimated mean duration of depression of 4.7 months, with a minimum of 1.5 months and a maximum of 12 months. Anxious depression had a significantly longer duration than nonanxious depression, with a median duration of 7.5 months, whereas nonanxious depression had a median duration of 1.5 months (Jorge et al. 1993d). Delayed-onset major depression, in turn, had an estimated duration of 4.0 months (Jorge et al. 1993c).

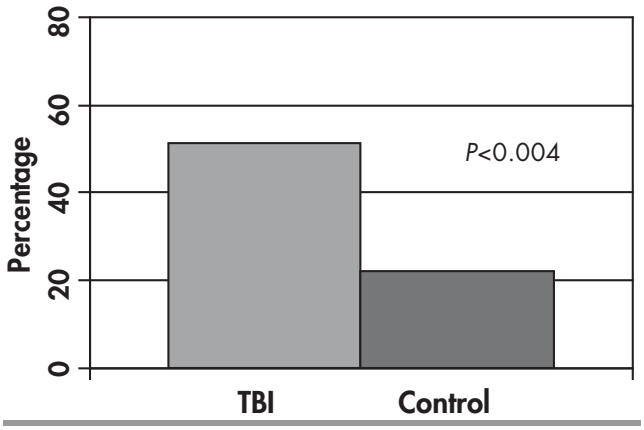


FIGURE 10–2. Frequency of mood disorders during the first year after traumatic brain injury (TBI).

Frequency of mood disorders was significantly greater in TBI patients than in a control group of patients with orthopedic injuries.

We have also prospectively studied a group of 92 patients with TBI of different severity along a 1-year follow-up period. Patients were recruited at the neurosurgery and rehabilitation departments of the University of Iowa Hospitals and Clinics in Iowa City and of the Iowa Methodist Hospital in Des Moines. The majority of patients were also white males from middle and lower socioeconomic status. However, as opposed to the patients enrolled in Maryland, a significant proportion of these patients lived in rural settings. The frequency of mood disorders was significantly greater in TBI patients than in a control group of patients with orthopedic trauma. Of the 92 patients with TBI, 47 (51.1%) developed a mood disorder at some time during the first year after injury, compared with 6 of 27 patients (22.2%) with multiple traumatic injuries but without central nervous system involvement (Figure 10–2). In addition, the frequency of major depressive disorder was also significantly greater in the group of patients with TBI (Jorge et al. 2004). Thus, mood disorders were significantly more frequent in patients who suffered TBIs than in patients with similar background characteristics who underwent similar levels of stress (e.g., motor vehicle accidents) but who did not sustain brain injury. This suggests that neuropathological processes associated with TBI constitute an important contributing factor to the development of these mood disorders.

Major depressive disorder following TBI was significantly associated with the presence of anxiety disorders. Of 30 patients with major depressive disorder, 23 patients (76.7%) met diagnostic criteria for a comorbid anxiety disorder, compared with 9 of 44 patients (20.4%) who did not develop a mood disorder but met criteria for an anxiety disorder during the first year following TBI (Figure 10–3). Major depression was also associated with the occurrence of aggressive behavior that was categorized using the Overt Aggression Scale (Silver and Yudofsky 1991). Of the 30 patients with major depression, 17 patients (56.7%) demonstrated significant aggressive behavior, compared with 10 of 44 patients (22.7%) who showed the same level of aggression without mood disorder during the first year after TBI (Tateno et al. 2003) (Figure 10–3).

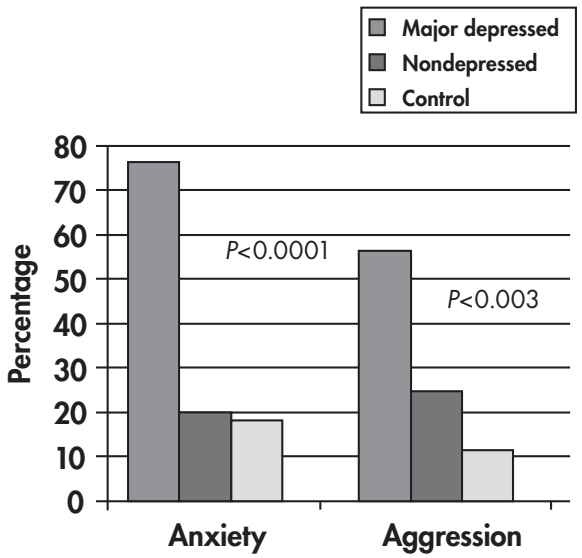


FIGURE 10–3. Coexistent anxiety and aggression among patients with major depressive disorder after traumatic brain injury.

TBI patients also showed abnormal emotional processing. For instance, pathological laughing and crying (PLC), a condition that has been consistently described among different groups of neurological patients for many years, has also been observed among brain-injured patients. Tateno et al. (2004) examined the prevalence and clinical correlates of PLC among the 92 patients recruited in Iowa. The prevalence of PLC was surprisingly high: 10.9%. Compared with patients without PLC, patients with PLC had significantly more depressive, anxious, and aggressive behaviors and had poorer social functioning. Additionally, PLC was associated with focal frontal lobe lesions, especially in the lateral aspect of the frontal lobes (Tateno et al. 2004).

With regard to the frequency of mood disorders with manic or mixed features, we have previously reported that 6 of 66 TBI patients (9%) developed secondary mania at some point during the first year following TBI (Jorge et al. 1993e). Although manic episodes were short (lasting approximately 2 months), the presence of an expansive mood or irritable mood had a mean duration of 5.7 months. Secondary mania was not related to the type or severity of brain injury, the presence of posttraumatic epilepsy, the degree of physical or intellectual impairment, the level of social functioning, or the presence of family or personal history of psychiatric disorder. Secondary mania was, however, associated with the presence of lesions in the ventral and anterior aspects of the temporal lobe and the orbitofrontal cortex (Jorge et al. 1993e).

Phenomenological Features

To characterize the affective disturbances occurring after TBI, we have adopted a disease perspective (McHugh 1992; McHugh and Slavney 1998) assuming that mood disorders, although diagnosed through a recognized constellation of symptoms, have an identifiable biological substrate, a distinct clinical prognosis, and a predictable treatment response. Other authors, however, argue that the use of categorical variables (e.g., depressed vs. nondepressed) might ignore important dimensional information that characterizes the complex affective response of a patient recovering from TBI. The combination of structured diagnostic interviews, self-report, and caregiver-based measures may represent a comprehensive approach to the assessment of mood disorders following TBI (Rosenthal et al. 1998; Seel et al. 2003).

Furthermore, we can ask ourselves if is it reasonable to pursue a categorical diagnosis of mood disorders according to a nomenclature that has not been validated among patients with neurological damage. For instance, symptoms of major depression such as sleep, appetite, or libido change may occur in patients with TBI as a consequence of brain injury or as a nonspecific consequence of an acute medical illness. Thus, they could be independent of the associated mood disturbance.

We longitudinally examined the specificity of symptoms of depression after TBI (Jorge et al. 1993a). Depressive symptoms were divided into autonomic and psychological subtypes using the distinctions proposed by Davidson and Turnbull (1986). We then analyzed their frequency among patients who presented with a depressed mood (no other depressive symptoms were required) compared with those without a depressed mood. We found that among patients who acknowledged a depressed mood, the frequency of autonomic and psychological symptoms was more than three times higher than the frequency of these symptoms observed in patients who denied having a depressed mood. Consistent with this, Rapoport et al. (2003) found that TBI patients with depression reported a significantly higher number of postconcussive symptoms than TBI patients without a depressed mood. We were also able to identify those symptoms that were significantly related (i.e., specific) to depressed mood. If we required the presence of at least three specific symptoms (including depressed mood) as a criteria for diagnosing major depression, standard DSM criteria would have a 100% sensitivity and 94% specificity at the initial evaluation, 88% sensitivity and 94% specificity at 3 months, 91% sensitivity and 96% specificity at 6 months, and 80% sensitivity and 100% specificity at 1-year follow-up. Thus, the standard diagnostic criteria (DSM-based) have a high sensitivity and specificity for identifying depressed patients when compared with alternative specific-symptom diagnostic criteria.

We have also analyzed the factor structure of psychiatric symptoms that are included in the Present State Examination, a structured psychiatric interview that examines the occurrence of depressive and anxiety symptoms necessary for a DSM-based diagnosis and provides a severity score for each of them (Wing et al. 1990). Principal component analysis (with varimax rotation) yielded three factors. The first factor accounted for 27% of the variance and comprised the core symptoms of depression, including depressed mood, anhedonia, suicidal ideation, and changes in self-attitude such as feelings of worthlessness, hopelessness, and guilt. The second factor accounted for 12%

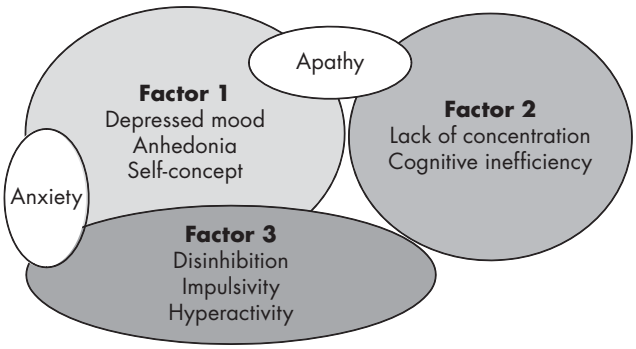


FIGURE 10–4. Factor structure of depression and anxiety symptoms after traumatic brain injury.

of the variance, and its greater loadings were related to subjective complaints of cognitive inefficiency (e.g., lack of concentration and memory disturbance). Finally, the third factor, which accounted for 11% of the variance, presented high loadings for psychomotor agitation, irritability, disinhibited behavior, and euphoria. Psychological and physical symptoms of anxiety had high loadings on both the first and the third factor, whereas apathetic symptoms had high loadings on both the first and second factors (Figure 10–4).

We analyzed individual scores of each of these three factors. As expected, TBI patients with major depressive features had significantly higher Factor 1 scores compared with TBI patients without mood disturbance and patients who experienced mood disorders with manic features ($P<0.001$). Manic and, to a lesser extent, major depressed TBI patients had significantly higher Factor 3 scores than patients without mood disorders ($P<0.002$). There were no significant differences between the groups in Factor 2 scores (i.e., subjective complaints of cognitive problems). Women and patients older than 50 years have significantly higher Factor 1 (depression core) scores in the aftermath of TBI. However, there were no significant differences in any of the three factors scores between patients with mild, moderate, or severe brain injury.

Diagnosis of Mood Disorders

Depression

According to the DSM-IV-TR diagnostic criteria, depressive disorders associated with TBI are categorized as mood disorder due to a general medical condition with the following subtypes: 1) with major depressive-like episode (if the full criteria for a major depressive episode are met) or 2) with depressive features (prominent depressed mood but full criteria for a major depressive episode are not met).

The differential diagnosis of post-TBI major depression includes adjustment disorder with depressed mood, apathy (Marin et al. 1995), emotional lability, and PTSD. Patients with adjustment disorders develop short-lived and relatively mild emotional disturbances within 3 months of a stressful life event. Although they may present with depressive symptoms, they do not meet DSM-IV-TR criteria for major depression. PTSD is another differential diagnosis. It occurs following an unusually severe distressing event and is characterized by symptoms of reexperiencing the trauma ranging from transient flashbacks or vivid nightmares to severe dissociative states in which the patient behaves as if he or she is actually living the traumatic event. In addition, patients typically avoid all the circumstances related to the trauma and become withdrawn and emotionally blunted.

PLC is another differential diagnosis of major depression. It is characterized by the presence of sudden and uncontrollable affective outbursts (e.g., crying or laughing), which may be congruent or incongruent with the patient's mood. These emotional displays are recognized by the patient as being excessive to the underlying mood and can occur spontaneously or may be triggered by minor stimuli. This condition lacks the pervasive alteration of mood as well as the specific vegetative symptoms associated with a major depressive episode.

Finally, TBI patients may present with apathetic syndromes that interfere with the rehabilitation process (see Chapter 18, Disorders of Diminished Motivation). A study by Kant et al. (1998) of 83 consecutive TBI patients referred to a neuropsychiatric clinic because of behavioral disturbance showed that 59 patients (71.1%) were apathetic; however, 50 of these 59 patients were also depressed. In our experience, apathy is frequently associated with psychomotor retardation and emotional blunting. Among patients with stroke, we reported that half of the patients with apathy also met diagnostic criteria for major or minor depression (Starkstein et al. 1993). Thus, apathy is frequently comorbid with depression but can be distinguished from it by the failure to meet appropriate diagnostic criteria. Although apathy is frequently associated with frontal lobe damage, the relationship between apathy and the type, extent, and location of TBI has not been systematically studied.

Secondary Mania

DSM-IV-TR defines secondary manic syndromes as an Axis I disorder: mood disorder due to a general medical condition, with manic or with mixed features. As with depressive disorders due to TBI, the presence of TBI should be noted on Axis III. This diagnosis should not be made if the mood disturbance occurs only during the course of a delirium characterized by sudden onset, fluctuating level of consciousness, disorientation, and prominent attentional deficits. Such confusional states are frequently observed during the acute recovery phase of TBI (Stuss et al. 1999).

The differential diagnosis of mania following TBI includes the following:

1. *Substance-induced mood disorder* may occur as a result of intoxication or withdrawal from different drugs. This is a particularly important consideration with regard to TBI patients, who show an increased frequency of substance abuse and also are often medicated with psychotropic drugs for their medical condition. Substance-induced mood disorder is usually

identified by a careful clinical interview and/or toxicological screening.
2. *Psychosis associated with epilepsy* is frequently observed among patients with epileptic foci located in limbic or paralimbic cortices. Psychotic episodes may be temporally linked to seizures or may have a more prolonged interictal course. In the latter case, the clinical picture is characterized by the presence of partial or complex-partial seizures and of a schizoaffective syndrome. Electroencephalographic and functional neuroimaging studies (e.g., single-photon emission computed tomography and positron emission tomography) will usually define ictal and interictal disturbances.
3. *Personality change due to TBI* may include mood instability, disinhibited behavior, and hypersexuality. However, these patients lack the pervasive alteration of mood that characterizes secondary manic syndromes.

Risk Factors for the Development of Post-TBI Mood Disorders

In his seminal study of the Oxford collection of head injury records, Lishman (1968, 1973) emphasized the importance of preinjury risk factors for the development of psychiatric complications after TBI. These include genetic, developmental, and psychosocial factors as well as their complex interactions.

Only a limited number of studies have assessed the effect of genetic factors for the development of behavioral problems after TBI. A study by Koponen et al. (2004) examined the association between apolipoprotein E epsilon 4 (*APOE*E4*) genotype and psychiatric disorders among 60 patients assessed an average of 30 years after severe TBI. Cognitive disorders were significantly more common with the presence of *APOE*E4*. The frequency of mood disorders, however, did not differ between patients with and without the *APOE*E4* allele. Polymorphisms in genes coding for proteins involved in the regulation of ascending aminergic systems and of the hypothalamic-pituitary-adrenal axis (e.g., 5-hydroxytryptamine transporter or 5HTT polymorphisms, tryptophan hydroxylase, monoamine oxidase, catechol O-methyltransferase, and FK506 binding protein 5 or FKBP5) and the interactions between genetic polymorphisms and environmental influences (Caspi et al. 2003) might play a role in the likelihood of developing mood disorders (Arango et al. 2003; Binder et al. 2004; Lasky-Su et al. 2005; Lotrich and Pollock 2004; Patkar et al. 2002; Sen et al. 2004; Smith et al. 2004; Sun et al. 2004; Tunbridge et al. 2004; Zubenko et al. 2003). Unfortunately, the effect of these factors on the psychiatric consequences of TBI has not been extensively studied. However, genetic polymorphisms modulating central dopaminergic pathways can affect prefrontal function following TBI (Lipsky et al. 2005; McAllister et al. 2008). In addition, a study by Chan et al. (2008) failed to demonstrate an association between 5HTT polymorphisms and depression following TBI.

Early psychosocial adversity (e.g., history of physical or sexual abuse), life stress, and limited social support are also well-recognized risk factors for the development of psychiatric illness (Heim et al. 2000, 2001). These psychosocial factors have not been adequately integrated in an explicative model among TBI populations. We found, however, that personal history of mood and anxiety disorders and previous poor social functioning are associated with the occurrence of major depression in the aftermath of TBI (Jorge et al. 1993c, 2004).

Epidemiological studies have shown that alcohol misuse is significantly associated with TBI, particularly when it occurs as a consequence of motor vehicle accidents or assault. We examined the relationship between alcohol misuse and the frequency of mood disorders among a group of 158 patients followed for a year after TBI (Jorge et al. 2005). Of the 55 TBI patients with a history of alcohol misuse, 33 (60%) developed a mood disorder during the first year of follow-up, compared with 38 (36.9%) of 103 patients without a history of alcohol misuse (χ^2=7.8, P= 0.005) (Figure 1 from Jorge et al. 2005).

We also found a significant association between alcohol misuse and mood disorders among patients who abused alcohol after their TBI. Of 20 patients with evidence of alcohol abuse in the year after TBI (18 patients who relapsed and 2 incident cases), 15 (75%) developed a mood disorder, compared with 37 (44%) of 84 patients who did not abuse alcohol but who developed a mood disorder during this period (χ^2=6.2, P=0.01). This is not surprising given the significant degree of overlap between the circuits involved in addiction and the circuits that regulate emotion and mood (Davidson 2002; Davidson et al. 2002, 2003; Drevets 2001; Drevets et al. 2002). It is also likely that alcohol toxicity and TBI interact to produce more severe structural brain damage and more profound changes in the ascending aminergic pathways that modulate reward, mood, and executive function (Donnemiller et al. 2000; Gilman et al. 1998; Goldstein and Volkow 2002; Hill et al. 2002; McIntosh 1994; Wilde et al. 2004; Yan et al. 2002).

OIF/OEF veterans are different from civilian populations at risk for TBI. For instance, the frequency of preinjury psychiatric illness, particularly substance use disorders, is lower in the armed forces compared with that observed in well-characterized TBI samples (e.g., TBI associated with motor vehicle accidents). In addition, poor social functioning and limited social support, major risk factors to develop emotional disturbance following TBI, are significantly less frequent in the military (Vasterling et al. 2006; Warden 2006). A careful analysis of risk factors for the development of mood disorders in this population awaits completion.

Behavioral Impact of Post-TBI Neurotransmitter and Neuroendocrine Changes

Although complex behavioral disorders cannot be reduced to quantitative changes in a group of neurotransmitters or neuromodulators, there is extensive evidence that certain behavioral abnormalities occurring after TBI are

related to changes in specific neurochemical systems. For instance, poor memory performance has been consistently associated with cholinergic deficits and aggressive behavior with serotonergic dysfunction (Arango et al. 2003; Arciniegas 2003).

During the past few years, there have also been numerous reports of posttraumatic changes in major neurotransmitter systems in the brain. Glutamate has been extensively studied because of its role in excitotoxic injury (Leker and Shohami 2002). There is also evidence of the role of glutaminergic pathways in maladaptive stress responses and subsequent atrophic changes in brain areas involved in mood regulation (e.g., hippocampus and prefrontal cortex) (Herman et al. 2004; Moghaddam and Jackson 2004).

TBI has been associated with significant changes in forebrain cholinergic systems. These changes may contribute to persisting dysfunction of memory and cognition in head-injured patients who survive (Murdoch et al. 2002; Salmond et al. 2005). Although cholinergic modulation of affective processes has not been systematically studied among TBI patients, cholinergic deficits observed in patients with Alzheimer's disease have been associated with behavioral changes including lack of motivation and anhedonia as well as agitation and disinhibited behavior (Cummings 2000; Cummings and Back 1998).

Dopamine neurotransmission may be also altered following TBI, contributing to executive dysfunction among these patients. Disruption of dopaminergic pathways may be associated with executive and memory functions as well as with the presence of apathetic syndromes that are observed in a significant proportion of patients recovering from TBI (McAllister et al. 2005). Functional neuroimaging studies (e.g., functional magnetic resonance imaging [fMRI]) offer the potential of assessing the behavioral correlates of dopaminergic dysfunction (McAllister et al. 2006, 2008). There is also evidence of changes in serotonergic neurotransmission following TBI (Wilson and Hamm 2002). Serotonergic depletion might be also associated with the occurrence of affective disturbance, disinhibition, and aggressive behavior, a constellation of symptoms that is frequently observed in TBI patients.

Functional Anatomy of Mood Disorders Following TBI

It is reasonable to expect that TBI, a pathological condition that selectively affects prefrontal and anterior temporal structures and produces widespread axonal injury, is associated with an increased prevalence of mood disorders. Lishman (1973) reported that depressive symptoms were more common among patients with right hemisphere lesions several years after penetrating brain injury. In addition, Grafman et al. (1996) also reported that several years following head injury, patients' depressive symptoms were more frequently associated with right orbitofrontal lesions than with any other lesion location.

In our first series of TBI patients, major depression was associated with the presence of left dorsolateral frontal and/or left basal ganglia lesions and, to a lesser extent, with right hemisphere and parieto-occipital lesions (Fedoroff et al. 1992). In our more recent series, we used MRI-based morphometric techniques to study the cerebral changes associated with major depression following TBI. Major depression was associated with reduced gray matter volume in the lateral aspects of the left prefrontal cortex (Jorge et al. 2004) (Figure 10–5). This finding is consistent with other studies of secondary depressive disorders that found decreased metabolic rates in inferior frontal regions in patients with Parkinson's disease (Mayberg et al. 1990), Huntington's disease (Mayberg et al. 1992), and caudate stroke (Mayberg 1994).

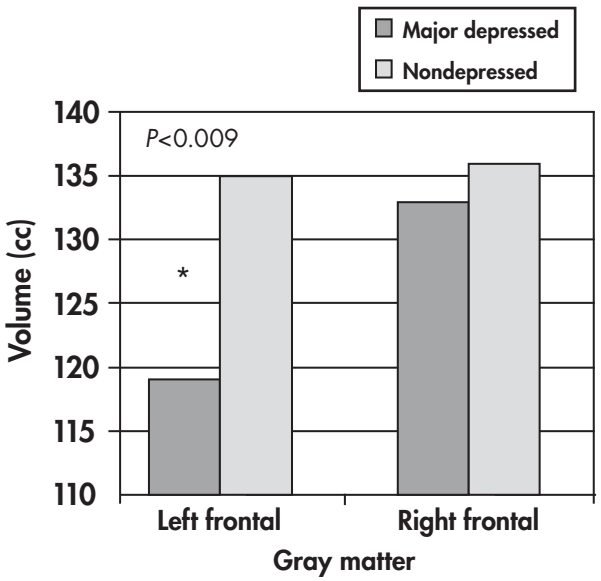


FIGURE 10–5. Gray matter volume in patients with major depressive disorder after traumatic brain injury (TBI).
TBI patients with major depression showed significantly lower frontal gray matter volumes than a group of nondepressed TBI patients matched for age, gender, and severity of TBI.
*Frontal gray matter volumes were significantly decreased in major depressed patients ($P<0.009$).

It is unclear whether the reduced prefrontal volumes observed in patients with major depressive disorder are the result of the pathophysiological mechanisms initiated by TBI or if they constitute a preexistent trait associated with an increased risk to develop mood disorders. For instance, patients with chronic mood or anxiety disorders, substance abuse, or antisocial personality disorder might show prefrontal volumetric changes unrelated to the traumatic insult (Ballmaier et al. 2004; Raine et al. 2000, 2002; Wilde et al. 2004). However, when controlling for these factors, we did not find evidence to support the idea that asymmetrical differences in frontal lobe volume preexisted the brain injury, suggesting that the decreased left frontal lobe volume is the result of resolving lesions approximately 3 months postinjury (Jorge et al. 2004).

Animal models of TBI suggest that diffuse neuronal damage and cell loss may progress over weeks to months after the initial insult in selectively vulnerable regions of the neocortex, hippocampus, thalamus, and striatum (Golarai et al. 2001; Raghupathi et al. 2000; Smith et al. 1997). On the other hand, neuroimaging studies of TBI patients

have demonstrated delayed cerebral atrophy on computed tomography and MRI scans (Bigler et al. 2002; Shiozaki et al. 2001; Yount et al. 2002), as well as altered metabolic patterns consistent with neuronal loss and inflammation as evidenced by proton magnetic resonance spectroscopy (Brooks et al. 2000; Garnett et al. 2000). Furthermore, behavioral outcome appears to be more strongly correlated with delayed rather than early imaging findings (Garnett et al. 2001; Kesler et al. 2000).

The prefrontal cortex is involved in the modulation of subcortical networks involved in the appraisal of aversive stimuli and their contextual circumstances. Hariri and colleagues used blood oxygen level–dependent (BOLD) fMRI paradigms to assess neocortical modulation of amygdala responses (Hariri et al. 2002, 2003). They found that the right prefrontal cortex is activated during the cognitive evaluation of aversive stimuli and that this activation is associated with the attenuation of limbic responses to the same stimuli. Furthermore, this pattern was reflected in changes in skin conductance. The authors emphasized the importance of neocortical regions, including the right prefrontal and anterior cingulate cortices, in regulating emotional responses. In this sense, major depression could result from deactivation of more lateral and dorsal frontal cortex and increased activation in ventral limbic and paralimbic structures, including the prelimbic cortex and the amygdala (Drevets 1999; Drevets et al. 1992; Mayberg et al. 1999).

Abnormal prefrontal modulation of limbic structures was also reported by Dougherty et al. (2004) among patients with major depressive disorder with anger attacks. This specific subgroup of major depressed patients showed a positive correlation of regional blood flow between the left ventromedial prefrontal cortex and left amygdala following anger induction with ad hoc scripts. On the other hand, euthymic control subjects showed the expected negative correlation between measures of regional blood flow in the aforementioned structures.

The cognitive abnormalities observed in TBI patients with major depression are consistent with left lateral prefrontal dysfunction. It is interesting that high levels of amygdala activation may be associated with an increased prevalence of anxiety symptoms and negative affect (Davidson et al. 2002), a pattern of symptoms that closely resembles what we observed in our group of TBI patients (Jorge et al. 2004). Moreover, faulty prefrontal modulation of medial limbic structures could explain the impulsive and aggressive behavior observed in these patients (Fava 1998; Parsey et al. 2002).

Consistent with these findings, athletes who have experienced a concussion and present with depression symptoms showed reduced activation in the dorsolateral prefrontal cortex and striatum and gray matter loss in these areas (Chen et al. 2008). We have also used structural MRI volumetric techniques to study the contribution of hippocampal damage to the development of mood disorders following TBI (Jorge et al. 2007). We found that patients who developed mood disorders had significantly lower hippocampal volumes than patients without mood disturbance (Figure 10–6). Furthermore, there was a significant interaction between mood disorder diagnosis and severity of TBI, by which patients with moderate to severe

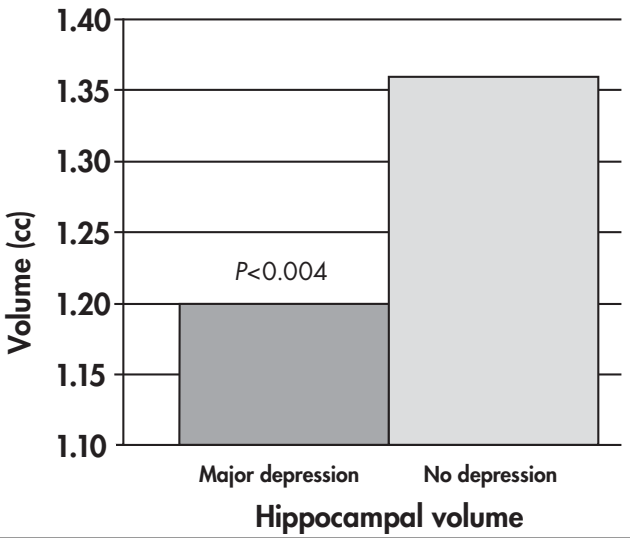


FIGURE 10–6. Mood disorders and hippocampal volumes of traumatic brain injury (TBI) patients.
When compared with TBI patients who did not develop depression, hippocampal volume was significantly reduced among depressed TBI patients with moderate to severe injuries.

TBI who developed mood disorders had significantly smaller hippocampal volumes than patients with equivalent severe TBI who did not develop mood disturbance. These findings are consistent with a double-hit mechanism by which neural and glial elements already affected by trauma are further compromised by the functional changes associated with mood disorders (e.g., the neurotoxic effects of increased levels of cortisol or excitotoxic damage resulting from overactivation of glutaminergic pathways). Early administration of antidepressants might prevent the occurrence of progressive structural and functional alterations in hippocampal networks and, consequently, the psychiatric and functional morbidities associated with their disruption.

Effect of Mood Disorders on the Outcome of TBI Patients

TBI has been associated with a host of physical, cognitive, and behavioral deficits that influence the community reintegration of these patients (Fann et al. 1995). Although there has been significant progress in determining the factors associated with poor outcome, we are still uncertain about what are the most successful restorative interventions. For instance, estimates of the number of TBI patients who will return to competitive employment are still alarmingly low, varying from 10% to 70% (Yasuda et al. 2001).

We examined the factors that contributed to deterioration in social functioning, activities of daily living (ADL), or intellectual function during the first year after TBI (Jorge et al. 1994). We assumed that an effect of depression on long-term outcome would only be identifiable in those depressive disorders with a longer course. Thus, patients

with prolonged major depression (i.e., 6 or more months) constitute the major depression group. There was a significant association between poor psychosocial outcome and the presence of major depression. Patients with short-term depression (i.e., less than 3 months) recovered like nondepressed patients. Half of the patients with major depression and initial ADL impairment had poor outcomes, whereas none of the nondepressed patients had a poor ADL outcome. Thus, major depression had a deleterious effect on both psychosocial and ADL outcome. This finding has been replicated in different samples of TBI patients. For instance, Satz et al. (1998) examined the relationship of depression with recovery among a group of 100 patients with moderate to severe TBI 6 months after trauma. The results showed a significant association between depression and recovery status as measured by the Glasgow Outcome Scale. Bowen et al. (1998) found a similar association between psychosocial handicap and the occurrence of mood disorders. Fann et al. (2002) reported that patients with depression or anxiety were more functionally disabled and perceived their injury and cognitive impairment as more severe. Another study analyzed the association of major depression with behavioral outcome among 170 patients with mild TBI. Individuals who developed major depression had objective evidence of poorer outcome (Rapoport et al. 2003). There is also evidence that the effect of depression on activities of daily living functioning is independent of the presence of neuropsychological deficits (Chaytor et al. 2007). Finally, Bryant et al. (2001) reported that patients who were diagnosed as having PTSD at 6 months following severe TBI had significantly lower Community Integration Questionnaire scores than TBI patients without TBI. Taken together, these studies emphasize the need of recognizing and treating mood and anxiety disorders during the rehabilitation process.

We have also examined the effect of a history of alcohol misuse on vocational outcome at the 1-year follow-up evaluation. This was assessed by determining the proportion of patients who were competitively employed or were able to return to their previous occupation at the 1-year follow-up versus those who were not able to achieve these goals. A logistic regression model included age, severity of brain injury as measured by Glasgow Coma Scale scores, premorbid social functioning as measured by baseline scores on the Social Functioning Exam (Starr et al. 1983), previous alcohol abuse or dependence, the occurrence of mood disorders during the follow-up period, and recruitment site (i.e., Iowa or Maryland) as independent variables. The whole-model test was significant (log likelihood, $\chi^2=19.2$, $P=0.004$). Analysis of the individual variables showed that the occurrence of mood disorders (Wald $\chi^2=4.9$, $P=0.03$) and a history of alcohol abuse or dependence (Wald $\chi^2=4.8$, $P=0.03$) were associated with poor vocational outcome. Moreover, 15 (50%) of 30 patients with a history of alcohol misuse returned to their previous occupation or were competitively employed at the 1-year follow-up compared with 58 (78%) of 74 patients without a history of alcohol misuse ($\chi^2=8.2$, $P=0.004$). Furthermore, patients with a history of alcohol misuse who also developed mood disorders following TBI had the worst vocational outcome ($\chi^2=15.7$, $P=0.001$) (Figure 2, from Jorge et al. 2005).

Finally, we have also observed that reduced hippocampal volumes were associated with poor vocational outcome at 1-year follow-up (Jorge et al. 2007). Although psychiatric disturbance will certainly have a negative impact on the clinical recovery and quality of life of injured veterans, the frequency, phenomenological characteristics, and clinical correlates of mood and anxiety disorders occurring after TBI have not been described among veterans returning from Iraq and Afghanistan.

Treatment of Mood Disorders

Treatment of mood disorders occurring after TBI involves different pharmacological and nonpharmacological strategies. Unfortunately, there is a lack of adequately controlled clinical studies that are needed to provide a solid scientific basis for neuropsychiatric treatment (Warden et al. 2006). Currently, data derived from small inconclusive trials and clinical expertise are the only things that support many of our daily treatment decisions.

Patients with brain injury are more sensitive to the side effects of medications, especially psychotropic agents. Silver and Arciniegas (Chapter 35, this volume) propose several general guidelines for their use in this population. Doses of psychotropic medication must be prudently increased to minimize side effects (i.e., start low, go slow). The patient must receive, however, an adequate therapeutic trial with regard to dosage and duration of treatment. Brain-injured patients must be frequently reassessed to determine changes in treatment schedules. Special care must be taken in monitoring drug interactions. Finally, if there is evidence of a partial response to a specific medication, augmentation therapy may be warranted, depending on the augmenting drug's mechanism of action and potential side effects.

There is some preliminary evidence that desipramine may be effective for treating depression in patients with severe TBI (Wroblewski et al. 1996). An 8-week nonrandomized, placebo run-in trial of sertraline in 15 patients with mild TBI showed statistically significant improvement in psychological distress, anger, and aggression as well as in the severity of postconcussive symptoms (Fann et al. 2000). Sertraline may also lead to a beneficial effect on cognitive functioning (Fann et al. 2001). Rapoport et al. (2008) examined rates of response and remission associated with citalopram treatment for major depression following TBI. Patients were treated with open-label citalopram with a flexible dosing schedule (20 mg/day to a maximum of 50 mg/day). At 6 weeks, response and remission rates were 27.7% and 24.1%, respectively. At 10 weeks, response and remission rates increased to 46.2% and 26.9%, respectively. These findings are consistent with effectiveness of citalopram to treat major depression occurring in the absence of TBI. Selection among competing antidepressants is usually guided by their side-effect profiles. Mild anticholinergic activity, minimal lowering of seizure threshold, and low sedative effects are the most important factors to be considered in the choice of an antidepressant drug in this population.

There have been no systematic studies of the treatment of secondary mania. Lithium (Joshi et al. 1985; Schneck 2002), carbamazepine (Stewart and Hemsath 1988), and

valproate (Monji et al. 1999; Stoll et al. 1994) therapies have also been reported to be efficacious in individual cases. It has been proposed that both lithium and valproate have neuroprotective effects (Gould and Manji 2002; Gould et al. 2004), which would certainly constitute an important therapeutic effect among brain-injured populations. However, data from the only controlled trial of valproate in TBI fail to identify a beneficial effect on cognitive and functional outcomes (Dikmen et al. 2000). The role of other anticonvulsants such as lamotrigine or topiramate as mood stabilizers has not been tested in TBI populations. A case report, however, reported adequate control of problematic behaviors with lamotrigine treatment (Pachet et al. 2003). In addition, there have been brief reports that suggest a beneficial effect of quetiapine on aggression and mania following TBI (Kim and Bijlani 2006; Oster et al. 2007).

Psychotherapy is an essential part of the treatment strategies implemented to improve the long-term outcome of patients with TBI (Prigatano et al. 1984); see also Chapter 36, Psychotherapy, this volume). Although there have not been controlled studies of the efficacy of psychotherapy for treatment of mood disorders following TBI, preliminary data suggest that peer support and family therapies are a promising approach to enhance coping for both TBI patients and their family members (Hibbard et al. 2002). Behavioral interventions, such as the Differential Reinforcement of Other Behavior, may successfully reduce the frequency of problematic behavior (Hegel and Ferguson 2000). In addition, psychotherapy groups implemented in postacute rehabilitation settings may focus on treatment of substance abuse and anger management through education, social support, and development of interpersonal skills (Delmonico et al. 1998).

Bell et al. (2004) demonstrated the feasibility of using the telephone as a means of providing education and psychotherapeutic support during the first year after moderate to severe TBI. Cox et al. (2003) examined the efficacy of systematic motivational counseling (SMC) to treat substance abuse comorbidity among TBI patients. The group that received the SMC intervention showed significant improvements in motivational structure and a significant reduction in negative affect and the use of addictive substances. Finally, Bryant et al. (2003) examined the efficacy of cognitive-behavioral strategy in 24 patients with acute stress disorder following mild head injuries. Patients who received cognitive-behavioral treatment had less reexperiencing and avoidance symptoms at 6-month evaluation than patients receiving supportive counseling.

Electroconvulsive therapy (ECT) is not contraindicated in TBI patients and may be considered if other methods of treatment prove to be unsuccessful. ECT should be administered with the lowest possible effective energy, using pulsatile nondominant unilateral currents, with an interval of 2–5 days between treatments and four to six treatments for a complete course (Silver et al. 1994).

As is obvious from this discussion of therapeutic interventions, treatment options are based on logic and current standards of practice rather than empirically based controlled treatment trials. There is a great need for randomized, double-blind, placebo-controlled trials to establish the most effective treatments for the variety of mood disorders that occur in TBI patients.

KEY CLINICAL POINTS

- Mood disorders are the most common psychiatric complications of traumatic brain injury (TBI).
- Mood disorders occur more frequently among patients with TBI than patients with other traumatic injuries, suggesting that structural and functional alterations of the neural circuits regulating mood and emotions play an important role in the genesis of these disorders.
- A significant proportion of these disorders will have a chronic and refractory course.
- Mood disorders have a significant impact on the levels of disability, quality of life, and community reintegration of TBI patients.
- There is an urgent need to develop efficacious strategies to treat and prevent these disorders.

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CHAPTER 11

Psychotic Disorders

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AN ASSOCIATION BETWEEN TRAUMATIC BRAIN INJURY (TBI) and the subsequent development of psychopathology, including psychosis, has been suggested since the nineteenth century. Early in the twentieth century, Emil Kraepelin (1919) hypothesized that brain injuries in childhood might either cause or release a predisposition to schizophrenia, implicating a causative role for TBI in psychotic illness.

Psychosis is a plausible outcome of severe brain injury. The period of greatest risk for TBI is from the mid-teens through the mid-20s, prior to the onset of most psychotic disorders, with males having a several-fold higher risk for TBI than females. Also, key brain regions that are abnormal in psychosis (and schizophrenia), such as the prefrontal cortex, temporal lobes, and hippocampus, are particularly vulnerable to TBI.

An understanding of the association between TBI and posttraumatic psychosis is important in several regards. This association is fundamental to the diagnostic approach to psychosis occurring with a history of prior TBI and has implications for prevention and prognosis. It is also of particular interest with regard to the pathophysiology of both psychosis and TBI. There is now extensive evidence of an association between TBI and psychosis, as psychotic symptoms are consistently found to occur more frequently in individuals who have had TBI, and patients with psychotic disorders are consistently more likely to have prior TBI than the general population. Although psychosis is not among the most common psychiatric sequelae of TBI, it is a disturbing and disabling outcome with great morbidity and cost. About 3 million people incur TBI in the United States each year. These individuals have a two- to fivefold greater risk of developing psychosis than does the general population (Ahmed and Fujii 1998). There has also been a marked increase in military-related TBI. Thanks to improved protective equipment, soldiers are better able to survive injuries that would previously have been fatal, but such injuries frequently entail brain injuries.

In this chapter, we review epidemiological evidence supporting a relationship between TBI and posttraumatic psychosis, diagnostic issues related to TBI and psychotic illness, the neuroanatomy of TBI and its implications for psychosis, and evaluation and treatment.

Relation of TBI to Subsequent Psychosis

Follow-Up Studies of Psychosis Occurring After TBI

Many studies of brain-injured persons have proceeded since Kraepelin (1919) first proposed that such injury may cause dementia praecox. Together, these studies offer substantial evidence of elevated psychosis incidence among those exposed to TBI, although the reported rates vary greatly and many of these studies have methodological problems, such as the absence of clear diagnostic criteria. In one of the first studies, Kornilov (1980) followed 340 patients with brain injury and found "psychotic symptoms" and a "personality transformation" consistent with negative symptoms in 26.5% of these patients. In Thomsen's (1984) 10- to 15-year follow-up study of 40 patients who incurred severe TBI, 20% of the patients were found to develop posttraumatic psychosis, although the criteria

for this determination were not defined. In an earlier study of Finnish veterans that also did not use standardized criteria, Hillbom (1960) found that 7.95% of 415 randomly ascertained Finnish soldiers with a brain injury went on to develop posttraumatic psychosis. About one-third of the posttraumatic psychosis group had a clinical picture resembling schizophrenia, with paranoia and hallucinations, and 40% had sustained temporal lobe injuries.

A much lower rate of posttraumatic psychosis was found when more contemporary diagnostic criteria were used. In a retrospective chart review study of 670 World War II British soldiers with penetrating head injuries (Lishman 1968), only 5 of the veterans (0.7%) developed psychosis during the 4 years of follow-up. This study was among the first to use contemporary diagnostic criteria, and, notably, mood disorders, dementias, and amnestic disorders were counted separately.

In an analysis of consolidated data from eight long-term follow-up studies published between 1917 and 1964, Davison and Bagley (1969) found an overall rate of psychosis of 0.7% to 9.8% following head trauma, with a median of 1.35%. The subjects of these reports ranged from civilians incurring concussions to soldiers suffering combat injury. Different diagnostic criteria were used, and follow-ups ranged from as little as 3 months to more than 20 years. Davison and Bagley noted that the incidence of psychosis increased over time and that many individuals did not become psychotic until years after the injury. In comparing this range of 0.7% to 9.8% (with a median of 1.35%) to the 0.8% lifetime incidence of psychosis in the general population over a period of 25 years, Davison and Bagley concluded that brain trauma increased the observed incidence of psychosis by two- to threefold over a period of 10–20 years. More recent studies report rates of posttraumatic psychosis in the range found by Davison and Bagley (Achte et al. 1991; Violon and De Mol 1987).

Although Kraepelin (1919) suggested that brain injury specifically during childhood may predispose an individual to psychosis, this has not been borne out by prospective studies of children incurring TBI. However, it must be noted that very few studies have been done and the time of follow-up in these studies were brief, on the order of 1–2 years.

Retrospective Studies of TBI in Patients With Schizophrenia

A connection between TBI and subsequent psychosis is also supported by retrospective studies of premorbid brain injury in patients with schizophrenia, which reveal elevated rates of prior TBI compared with other groups. In a review of five studies published between 1932 and 1961, Davison and Bagley (1969) found the frequency of premorbid TBI in hospitalized patients with schizophrenia ranged from 1% to 15%. A blinded chart review of 659 patients admitted to a large tertiary care center between 1934 and 1944 found premorbid TBI in 11% of patients with schizophrenia (Wilcox and Nasrallah 1987). Likewise, in a sample of Nigerian patients diagnosed with research diagnostic criteria, patients with schizophrenia were found to have significantly more premorbid TBI than did manic patients (Gureje et al. 1994). More recently, AbdelMalik et al. (2003) compared the childhood history and severity of head injuries between 67 subjects with schizophrenia or chronic schizoaffective disorder as defined by DSM-III-R (American Psychiatric Association 1987) and 102 of their unaffected siblings. Subjects in the schizophrenia group were more likely to have had childhood head injury. Furthermore, those subjects with both schizophrenia and a childhood head injury had a significantly younger age at onset of psychosis.

In contrast, in a combined pedigree sample (of families with bipolar disorder and schizophrenia, $N=1,832$), although Malaspina et al. (2001) found a threefold greater rate of reported premorbid TBI for subjects with schizophrenia compared with their never mentally ill family members, patients with schizophrenia were not significantly more likely to have incurred TBI than were patients with bipolar or depressive disorder.

Risk Factors and Predictors of Posttraumatic Psychosis Among Individuals With TBI

Location of Injury

Accumulated evidence suggests that injuries to the left hemisphere and to the temporal lobes may be most closely associated with risk of posttraumatic psychosis (Davison and Bagley 1969). Hillbom (1960) found that 40% of individuals with posttraumatic psychosis had temporal lobe injuries, which was a higher proportion than in those with nonpsychotic psychiatric disturbance. In a case-control study that compared brain-injured patients with and without subsequent schizophrenia-like psychoses (SLP), the SLP group had more evidence from neuroimaging of brain damage, especially in the left temporal and parietal regions (Sachdev et al. 2001). In an interesting study that evaluated electroencephalogram (EEG) abnormalities over 2 years in a cohort of 100 psychotic patients on a head injury hospital ward, posttraumatic psychosis was found in the majority of cases to be associated with EEG foci in the temporal lobes bilaterally (Koufen and Hagel 1987).

Severity of Injury

Many studies have found that severity of TBI is related to risk of posttraumatic psychosis. Davison and Bagley's (1969) review cited eight studies reporting that increased severity of injury with more diffuse brain damage and coma longer than 24 hours were risk factors for the development of posttraumatic psychosis. Hillbom (1960) found that the rate of psychosis increased with the severity of the injury: 2.8% of those with mild injuries, 7.2% of those with medium-severity injuries, and 14.8% of those with severe injuries had become psychotic. These findings are corroborated by the more rigorous case-control study of Sachdev et al. (2001), who found that duration of loss of consciousness predicted posttraumatic SLP and that compared with brain-injured control subjects, patients who developed SLP after TBI had greater evidence of brain damage as seen on computed tomography (CT) scan and as

suggested by neuropsychological testing. However, other studies have not found severity of injury to be a predictor of posttraumatic psychosis (Malaspina et al. 2001; Violon and De Mol 1987). In fact, there was a trend for the control group to have had more severe injuries (Fujii and Ahmed 2001).

Type of Injury

There is inconsistent evidence on whether type of head injury is related to psychosis risk. Studies have not found a link between psychosis risk and type of injury (closed vs. open) (Fujii and Ahmed 2001; Sachdev et al. 2001).

Age and Gender

Age at injury has not been found to determine psychosis risk (Fujii and Ahmed 2001). Although there are suggestions in the review literature that male gender may be a risk factor for posttraumatic psychosis (Arciniegas et al. 2003; Zhang and Sachdev 2003), no studies have rigorously evaluated the role of gender in risk of posttraumatic psychosis. In addition, many of the earlier studies focused on veterans, who were invariably men.

Inherent Vulnerability to Psychosis

Risk of posttraumatic psychosis has been linked to pretraumatic psychological characteristics and vulnerability to psychosis. Previous psychopathological disturbances have been reported for 83% of individuals who developed psychosis after TBI (Violon and De Mol 1987). Lishman (1987) found that psychosis was more likely to follow TBI in individuals who are predisposed to schizophrenia. Sachdev et al. (2001) found that genetic vulnerability to psychosis, identified by having a first-degree relative with any psychotic disorder, was among the strongest predictors of who would develop psychosis after a TBI. There was a history of psychosis in 24% of the first-degree relatives of patients with TBI as compared with a 3% rate among relatives of nonpsychotic brain-injured control subjects.

IQ and Cognition

Fujii and Ahmed (2001) found no differences in IQ between brain-injured persons who did and did not subsequently develop psychosis. In contrast, Sachdev et al. (2001) found that the group that developed SLP had more neurological deficits than the brain-injured control group, with lower IQ, significantly worse verbal and nonverbal memory, and greater impairments in language and frontal and parietal lobe functioning, consistent with a diffuse impairment in neuropsychological functioning.

Prior Neurological Disorder

Fujii and Ahmed (2001) found that patients who went on to develop psychosis after a TBI had significantly more premorbid neurological pathology than did the brain-injured control subjects (80% vs. 40%), including prior brain injury (14/25), seizures (3/25), learning disability (3/25), birth complications (2/25), attention-deficit/hyperactivity disorder (1/25), and congenital syphilis (1/25). This supports their hypothesis that psychosis may be more likely to follow TBI if the brain was already vulnerable before the injury. However, Sachdev et al. (2001) did not find differences in perinatal or developmental abnormalities in the group that developed psychosis after TBI as compared with the brain-injured control group.

Posttraumatic Epilepsy

Seizure disorders are associated with both TBI and psychosis. The association between seizures and TBI increases with severity of injury, with rates for seizure disorders from 0.8% for mild TBI up to 12% for severe brain injuries (Annegers et al. 1980). There is a similar a relationship between seizure disorders and psychosis. A rigorous study in Iceland that involved clinical interviews found that 7% of epileptics had psychotic symptoms (Gudmundsson 1966). Psychotic patients, in turn, are three to seven times more likely than the general population to have features of epilepsy, and interictal psychoses frequently resemble chronic schizophrenia. However, case-control studies did not find a difference in the frequency of epilepsy between patients with posttraumatic psychosis and brain-injured control subjects (Fujii and Ahmed 2001; Sachdev et al. 2001). In fact, Sachdev et al. found a trend toward less epilepsy in patients compared with control subjects. They speculated that seizures may be a mitigating factor for development of psychosis. However, this theory is controversial (Arciniegas et al 2003). It may be that a longer time of follow-up after TBI is needed to detect a relationship. Davison and Bagley (1969) found that posttraumatic epilepsy was associated with delayed onset of psychosis, as opposed to immediate onset of psychosis; the mean interval between onset of seizures and onset of psychosis was noted to be about 14 years.

Diagnosis

Posttraumatic psychosis is a generic term for psychotic illness in a person who has experienced brain trauma. It is an empirical description that denotes a temporal rather than a causal relationship. Posttraumatic psychosis is not itself a DSM-IV-TR diagnosis (American Psychiatric Association 2000), so in any given individual, this phenomenon will fall under either the DSM rubric of "psychotic disorder due to a medical condition" or a primary psychotic disorder.

One study (Feinstein and Ron 1998) aimed to determine the predictive and construct validity of the diagnosis "psychosis due to a general medical condition." The authors suggested that the disorder of psychosis due to a general medical condition was differentiated from schizophrenia by 1) later mean age of onset of psychosis (about age 35); 2) fewer premorbid schizoid and paranoid personality traits; 3) lower incidence of having a first-degree relative with schizophrenia (7%); 4) briefer duration of psychosis; 5) more rapid response to low-dose neuroleptics; 6) less need for maintenance neuroleptics; and 7) better outcome with greater return to premorbid work levels. There may be

group differences between this patient group and psychotic patients without a diagnosis of neurological disorder, but there is substantial overlap in characteristics of these two groups, so that discriminating between psychosis due to a general medical condition and primary psychotic disorder remains difficult in the diagnosis of individual patients.

Diagnostic Confounds and Differential Diagnosis

The term *psychosis* has historically meant different things. Different definitions have included loss of ego boundaries, gross impairment in reality testing, and even impairment that grossly interferes with the capacity to meet ordinary demands of life. Over time, the concept of psychosis has been operationalized and more strictly defined, as reflected in DSM-IV-TR. In its narrowest sense, psychosis is currently defined as the presence of delusions or hallucinations, without insight that the hallucinations are pathological in nature. This definition of psychosis is used for psychosis due to a general medical condition. A broader sense of psychosis is drawn from the positive symptoms of schizophrenia, which extend beyond delusions and hallucinations to encompass disorganized speech and grossly disorganized or catatonic behavior.

The conundrum in the diagnosis of posttraumatic psychosis is the ability to distinguish between a primary psychotic disorder and a psychotic disorder that is caused by a prior brain injury. This distinction is further complicated by emerging data suggesting complex interactions between brain injury and risk for development of schizophrenia. On the basis of a review of literature from 1978 to 2006, the American Neuropsychiatric Association concluded that "the issue of a temporal versus causal relationship [for posttraumatic psychosis] is not possible to resolve in the absence of a clearer understanding of the pathophysiological mechanism underlying posttraumatic psychosis and a reliable means of distinguishing this process from that underlying idiopathic psychosis" (Kim et al. 2007, p. 111). There are various reasons for this difficulty.

First, as already noted, the temporal association may not be entirely clear. DSM-IV-TR does not specify a time delay between the general medical condition and psychosis. Existing literature suggests that psychosis may follow a TBI by months to years later.

Second, symptom profiles are also of somewhat limited help. While there is evidence to suggest that atypical features of psychosis may follow a TBI, such as olfactory and tactile hallucinations, the absence of these features does not necessarily rule out TBI as a causative factor. Nonetheless, there is evidence that posttraumatic psychosis frequently resembles a primary mental disorder, such as schizophrenia, and in those instances may be better accounted for by a primary psychotic disorder.

Third, schizophrenia and other primary psychotic disorders are complex heterogeneous illnesses that arise from the interaction of multiple etiologies, including genes, obstetric complications, and other exposures. TBI may be an etiological factor with small or large effects depending on inherent genetic vulnerability and other exposures. It is interesting that having relatives with schizophrenia increases one's risk for both incurring TBI and developing schizophrenia, but then exposure to TBI further elevates the risk for schizophrenia in individuals with a family history.

In the process of evaluating posttraumatic psychosis, particularly in the more acute stages of injury, other posttraumatic syndromes may better account for psychosis and warrant close consideration. These include posttraumatic amnesia, posttraumatic mood disorders, and medication/drug intoxication or withdrawal (Arciniegas et al. 2003).

Clinical Features

Characteristic Presentation

On the basis of an amalgamation of several reports including a review by Davison and Bagley (1969), Zhang and Sachdev (2003) suggested the following profile for individuals with posttraumatic psychosis. Patients with posttraumatic psychosis are typically young male (but see caveats above in discussion of gender as a risk factor); there are typically prodromal symptoms (e.g., functional deterioration and incongruent, atypical mood and behavior); and delusions (usually paranoid) and hallucinations are the predominant psychotic phenomenology (Fujii and Ahmed 2002; Sachdev et al. 2001). Others have also reported that paranoia and delusions are reported to be common elements in post-TBI psychosis (Cutting 1987).

In contrast, thought disorder and negative symptoms that are prototypical of schizophrenia are typically described as less common, if not entirely absent (Fujii and Ahmed 2001; Sachdev et al. 2001). This is consistent with previous reports of relative absence of formal thought disorder and of blunting of affect in schizophrenia following TBI (McKenna 1994).

One criterion listed in DSM-IV-TR for distinguishing psychosis secondary to a general medical condition from a primary psychotic disorder is the presence of atypical features, such as visual and olfactory hallucinations and religious delusions. For example, there are case reports of Lilliputian hallucinations (in which objects, people, or animals seem smaller than they would be in real life) occurring in individuals with previous brain trauma (Cohen et al. 1994). DSM-IV-TR describes that right parietal brain lesions can lead to a contralateral neglect syndrome in which patients disown parts of their body to a delusional extent. Lesions in the right hemisphere have been linked to various misidentification delusions, such as Capgras syndrome (loved ones replaced by identical appearing impostors), Fregoli's syndrome (persecutor able to change appearances and appear as different people), and reduplicative paramnesia (familiar place exists in two different places at the same time).

Cognition

Elements of cognition are impaired in posttraumatic psychosis, but there is no clear consensus as to whether posttraumatic psychosis can be differentiated from primary psychotic disorders by the extent of impairment. In one sample of schizophrenia patients, those with a history of childhood brain trauma that required hospitalization had poorer scholastic performance as children (Gureje et al. 1994). However, there are also data (Corcoran et al. 2000) that among patients with schizophrenia, those with a history of TBI actually had

better cognition than those who did not. Up to half of individuals with moderate to severe TBI have reduced awareness of their deficits (Flashman et al. 1998). Poor insight complicates compliance with treatment recommendations for both psychotic and brain-injured patients.

A similar overlap between populations with psychosis and a history of brain injury is seen in the deficits on formal neuropsychological testing. One neuropsychological function, executive function, involves planning and problem solving needed for activities such as balancing bank accounts, writing letters, planning one's week, and driving or taking public transportation. These activities are difficult for brain-injured patients. Poor performance on tests of executive function is common in both brain-injured patients and patients with schizophrenia (reviewed in Johnson-Selfridge and Zalewski 2001). Both schizophrenia patients and brain-injured patients also show deficits in explicit memory as well as decrements in volume of the hippocampus, the part of the brain thought to be responsible for explicit memory. Notably, in both groups of patients, the extent of memory deficit is associated with the degree of volume reduction of the hippocampus (Gur et al. 2000; Tate and Bigler 2000).

Family History/Genetic Vulnerability

Early studies suggested that brain trauma could contribute to schizophrenia either directly or through an interaction with latent vulnerability and that these two pathways yielded different symptom patterns. For example, Shapiro (1939) evaluated 2,000 cases of dementia praecox (schizophrenia) in residents of a large public hospital and found that "a large number . . . showed some relationship to a severe head injury" (p. 253). Other studies have suggested that TBI can contribute to schizophrenia risk. Among patients with schizophrenia, those without premorbid TBI have more genetic vulnerability for psychotic disorders than do those with prior TBI, who in turn have no greater rates of family members with psychosis than do the general population (Davison and Bagley 1969). In a reexamination of a database of 722 probands with schizophrenia, the diagnosis of schizophrenia was confirmed in a subsample of 660, and the prevalence of schizophrenia in the parents and siblings of these 660 probands was examined. It was found that the risk for schizophrenia was particularly low in siblings of probands whose onset of illness occurred within a year of major brain trauma (Kendler and Zerbin-Rudin 1996). Malaspina et al. (2001) also found that TBI may interact with schizophrenia genetic vulnerability to increase the risk of schizophrenia.

Populations at Risk

Homeless Individuals

Homeless people have high rates of SLP and TBI history. Studies have shown that homeless persons have an elevated prevalence of schizophrenia that ranges between 13.7% (Koegel et al. 1988) and 25% (Susser et al. 1989). Over 40% of homeless individuals with SLP who were treated at a university hospital in New York had a history of premorbid TBI (Silver and McKinnon 1993).

Prisoners on Death Row

An interesting study of 15 death row inmates showed that all 15 had histories of severe brain injury, and 9 had recurrent psychoses (with hallucinations, delusions, thought disorder, and bizarre behavior) that antedated incarceration (Lewis et al. 1986). Remarkably, these subjects were not selected for clinical evaluation because of any evident psychopathology but were chosen for neuropsychological testing in the hope of appealing for clemency when their executions were imminent. These death row inmates had repetitive episodes of brain trauma beginning in childhood that were quite dramatic, including severe physical abuse, falling from heights, getting hit by and run over by cars, and getting hit with baseball bats.

Children and Teens

The NIH [National Institutes of Health] Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury (1999) reported that the highest incidence of brain trauma is among individuals ages 15–24 years (and the elderly), with another peak in children younger than age 5. Motor vehicle accidents are the major cause of TBIs in this group, and alcohol is frequently involved. Sports injuries and violence also are a major cause of brain injury in teens. Child abuse and assault is also a significant cause of TBI in children. Notably, reported rates of prior child abuse are 52% (20/38) of patients with first-episode psychosis (Greenfield et al. 1994) and 44% (27/61) of patients with chronic psychosis (Goff et al. 1991).

Military Personnel

TBI has been identified as a signature injury of the post-2001 military conflicts in Iraq and Afghanistan. In particular, the use of improvised explosive devices has led to an increase in blast exposure and the possibility of blast-induced TBI. Overall, the preponderance of brain injuries sustained in the Iraq/Afghanistan conflict are mild (Schwab et al. 2007). Because posttraumatic psychosis is more likely associated with severe TBI, the risk of psychosis among individuals subjected to blast exposure may not be significant. At the same time, it is not unusual for combat personnel to be subjected to multiple blast exposures, and the long-term effects of blast-induced TBI are not well characterized or understood (Warden 2006). Given the large number of troops who serve in these present-day conflicts, clinicians will need to be increasingly aware of this potential risk factor as servicemen and servicewomen return to the civilian population.

Neuroanatomical Effects of TBI and Implications for Psychosis Pathophysiology

The presence of similar clinical features in TBI and schizophrenia also suggests an overlapping neuroanatomy. Key clinical similarities between TBI and schizophrenia

include deficits in insight, executive function, and memory, which indicate pathology in orbitofrontal regions, the dorsolateral prefrontal cortex, and hippocampi. Common deficits in sensory gating may also implicate abnormal connectivity between various parts of the brain in both conditions.

Primary Sites of Lesion

Brain trauma frequently leads to injury of the frontal and temporal cortices. Psychosis resulting from other neurological conditions, such as metachromatic leukodystrophy and cerebrovascular disease, usually involves pathology in the frontal cortex and temporolimbic areas. In epilepsy, visual hallucinations have been found to result from seizure foci in the temporal lobes or orbitofrontal regions, and delusions of passivity ("Forces are acting upon me," "I am being controlled") have been linked to left temporal lobe seizure foci. Also, deficits in frontal lobe function are a widespread finding in schizophrenia; in particular, it has been hypothesized that attendant working memory deficits (holding on to information while attending to other tasks) may be a key pathophysiological feature of this disease.

Secondary Sites of Lesion (Hippocampus)

It is of considerable interest that brain trauma can lead to injury in regions far from the primary site of impact. Animal studies, in which brain trauma is enacted either by a weight drop or through fluid percussion, show that the hippocampus is a part of the brain that is vulnerable to TBI, even in injuries whose primary impact is far from the hippocampus (Chen et al. 1996). The cell loss in the hippocampus was found to be progressive over 1 year after TBI in rats, suggesting a model for what is observed in humans: ongoing changes in the brain months to years after the initial injury, that is, a chronically progressive degenerative process initiated by brain trauma (Smith et al. 1997).

The special vulnerability of the hippocampus to TBI is relevant for the hypothesis that TBI can contribute to schizophrenia pathophysiology, as the hippocampus is consistently found to be abnormal in schizophrenia. A meta-analysis of 18 studies showed a bilateral reduction of volume in the hippocampus in schizophrenia of 4% (Nelson et al. 1998). Magnetic resonance spectroscopy studies suggest that neuronal integrity may be compromised in the hippocampus in schizophrenia, as low *N*-acetyl aspartate has been found across several studies. Intriguingly, cognitive and magnetic resonance imaging (MRI) volumetric assessments of twins discordant for schizophrenia suggest that hippocampal abnormality is more prevalent in the affected twin, suggesting nongenetic influences operating on the hippocampus in schizophrenia (Cannon et al. 2000).

It has also been speculated that the various symptoms of schizophrenia could result from disturbances in connectivity among different regions of the brain. For example, studies of white matter using diffusion tensor imaging have implicated a relationship between white matter deficits and both positive (Skelly et al. 2008) and negative (Wolkin et al. 2003) symptoms. It is plausible that TBI could contribute to schizophrenia expression through injury to axons and consequent disruption of cross talk among various brain regions. Further, TBI can impair the ability to filter incoming sensory information; deficits in the gating/filtering of sensory information are also characteristic of schizophrenia. It has been hypothesized that these abnormalities result from disruptions in connections between different parts of the brain and that the inability to filter out stimuli can lead to sensory flooding by irrelevant information.

Clinical Evaluation

A thorough assessment of the patient with posttraumatic psychosis is an essential prerequisite to the prescription of any treatment (Arciniegas et al. 2000). A comprehensive evaluation must include detailed histories of birth, development, neurological features, psychiatric symptoms, medical status, education, substance use, social functioning, and any family illnesses, as well as physical and neurological exams, detailed mental status exam, neuropsychological testing using a standardized battery, structural imaging (CT or MRI), and EEG. Premorbid history and current medication treatment are important because they can influence neuropsychiatric symptoms (Arciniegas et al. 2000). Family members and other corroborating sources should be included because individuals may not recall details of brain injury if it occurred either when they were children or when they were intoxicated, and the neuropsychological correlates of both psychosis and TBI can interfere with the ability to recall one's history in detail.

As noted earlier, there are important states to rule out, specifically delirium, before one makes a diagnosis of posttraumatic psychosis. It should be determined whether there are autonomic nervous system abnormalities, a waxing and waning mental status, or an inability to orient on mental status exam. Delirium can begin days to months after the TBI. If patients are delirious, medications should be carefully evaluated and serum levels obtained. Anticonvulsants, sedatives, and anticholinergic medications can all contribute to a confusional state.

It is also important to detect whether the patient with posttraumatic psychosis has a seizure disorder, because this can be treated with anticonvulsants, and also because so many psychiatric medications can lower the seizure threshold. It is essential to determine if there are mood symptoms such as depression or mania, because these may be associated with suicidality or impulsivity that can be life-threatening to the patients and others. Also, any use of substances must be carefully assessed for, because substance use/abuse/dependence may aggravate the neuropsychiatric symptoms the patient has, interfere with compliance with and efficacy of treatment of symptoms, and require attention and treatment themselves.

Treatment

Any existing delirium, seizure disorder, mood disorder, or substance abuse or dependence must be diagnosed and attended to. If these disorders are not present, if psychotic symptoms are life-threatening, or if psychotic symptoms persist beyond the treatment of these disorders, then an antipsychotic medication may be warranted. However, despite anecdotal clinical experience in the psychopharmacological management of behavioral complications in neuropsychiatric settings, there remains a dearth of evidence-based data supporting the use of a particular antipsychotic medication or class (i.e., conventional vs. atypical antipsychotic) in the management of posttraumatic psychosis (Warden et al. 2006), with the exception of two case reports meeting Brain Trauma Foundation class III evidence in support of the use of olanzapine. Information largely comes from case reports and extrapolation from studies in other populations of patients with brain damage. Given these caveats, many experts advise that neuroleptics should be used specifically for psychotic symptoms and not for agitation only. In light of this paucity of evidence-based data, the following general guidelines are offered.

In general, care should be taken in administering neuroleptics, as animal studies suggest that dopamine antagonists (antipsychotic medications) can impede recovery after brain injury (Feeney et al. 1982). Problems with motor function, gait, arousal, and speed of information processing are common in brain-injured patients and may be exacerbated by the sedation, psychomotor slowing, parkinsonism, and anticholinergic side effects of neuroleptics.

Medication dosing should be "low and slow." Many experts suggest starting with one-third to one-half of the usual dose (McAllister 1998). The clinician must be wary of medications with significant sedative and anticholinergic properties. Therefore, among typical neuroleptics, high-potency antipsychotic medications such as haloperidol may produce fewer of these side effects than low-potency antipsychotics such as chlorpromazine. However, it should be noted that TBI may also make patients more vulnerable to developing tardive dyskinesia (Kane and Smith 1982).

Benzodiazepines should be used sparingly if at all. McAllister (1998) suggested that augmenting the effects of one medication by using a second low-dose agent with a different method of action is a way to address the problem of sensitivity to side effects in these patients.

Clozapine is a candidate for the treatment of posttraumatic psychosis in that it yields a low incidence of extrapyramidal symptoms and tardive dyskinesia. However, clozapine can lead to seizures and other adverse events, such as sedation and dizziness, for which brain-injured patients may have greater vulnerability. Additionally, there are risks of agranulocytosis (minimized with weekly blood draws), tachycardia, orthostatic hypotension, hypersalivation, and weight gain.

Conclusion

Although psychosis is not common after TBI, it is a disturbing and disabling outcome with great morbidity and cost. There is a complex interrelationship in terms of vulnerability, causality, and pathophysiology between brain injury and posttraumatic psychosis. Although this relationship is still poorly understood, there is strong evidence of an increased rate of psychosis among patients with a history of TBI. Diagnosis of posttraumatic psychosis—specifically the distinction between a primary psychotic disorder and one attributable to the preceding brain injury—is limited by methods for direct ascertainment of causality. The current diagnostic approach must include a careful and detailed history that takes into account premorbid history and risk factors along with clinical presentation and, to the extent possible, diagnostic studies. Subpopulations at particular risk for posttraumatic psychosis must be kept in mind. Current treatment of posttraumatic psychosis is largely based on anecdotal clinical observations and extrapolation from management of other neurological conditions, highlighting the need for randomized controlled studies in this area.

KEY CLINICAL POINTS

- Individuals who have had TBI have a two- to fivefold greater risk of developing psychosis, and patients with psychotic disorders are consistently more likely to have prior TBI than the general population.
- Data suggest that risk factors for the development of posttraumatic psychosis include injuries specifically to the left hemisphere and to the temporal lobes, severity of TBI, and presence of pretraumatic psychological abnormalities.
- The DSM-IV diagnosis for patients with posttraumatic psychosis is generally either psychotic disorder due to a medical condition or a DSM-IV primary psychotic disorder. However, clear distinction between these two diagnoses is often confounded by uncertainty in causality and temporal association.

- While there are no pathognomonic symptoms for posttraumatic psychosis presumed secondary to TBI, delusions (usually paranoid) and hallucinations are the predominant psychotic phenomenology; thought disorder and negative symptoms are less common.

- In the more acute stages of injury, other posttraumatic syndromes may better account for psychosis. These include posttraumatic amnesia, posttraumatic mood disorders, and medication/drug intoxication or withdrawal.

- Evaluation of individuals with posttraumatic psychosis requires a comprehensive assessment that should not overlook seizure disorder or substance abuse (both of which have treatment implications) and mood symptoms (which may be associated with life-threatening suicidality or impulsivity).

- At the present time, there is limited evidence to support the use of a particular antipsychotic medication or class in individuals with posttraumatic psychosis. In general, neuroleptics should be used specifically for psychotic symptoms and not for agitation only. Whatever medication is chosen, dosing should be "low and slow," typically starting with one-third to one-half of the usual dose.

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CHAPTER 12

Posttraumatic Stress Disorder

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MANY BRAIN INJURIES ARE CAUSED BY TRAUMATIC events, such as high-speed motor vehicle accidents, assaults, and military combat engagement. These events also commonly precipitate acute anxiety and stress reactions, including posttraumatic stress disorder (PTSD). The association between traumatic brain injury (TBI) and PTSD has received increased recent attention in the context of U.S. military injuries in Iraq and Afghanistan. Because of the high prevalence of exposure to explosive munitions, TBI has been labeled a "signature injury" of the war in Iraq (Keltner and Cooke 2007; Okie 2005). A large proportion of these TBIs are mild. A question that is receiving considerable attention is the nature of the interaction between PTSD and mild TBI (mTBI). It has become increasingly apparent that the combination of postdeployment PTSD and history of deployment-related mTBI is an extremely common and important, but poorly understood, phenomenon associated with current military conflict. Considerable attention and ongoing research investigations are focused in this area.

Approximately 80% of all brain injuries are mild. This statistic is fairly consistent across both civilian and military samples. It is commonly acknowledged in the civilian and noncombat military settings that an mTBI, or concussion, is common and self-limiting. The majority of individuals who experience a mild brain injury will experience transient symptoms such as mental confusion, headache, fatigue, and dizziness. Typically, these symptoms gradually remit over the course of a few seconds to minutes in the mildest cases and up to a few months in the most serious of mild injuries. However, other factors may cause a deviation from this typical uncomplicated course of recovery. The persistence of common postconcussive symptoms after TBI has been labeled postconcussion syndrome. Symptoms included in this syndrome occur in the areas of physical, cognitive, and emotional functioning. When symptoms continue beyond 6 months postinjury, the term persistent postconcussion syndrome (PPCS) has been applied. PPCS remains a controversial entity, owing to the nonspecific nature of the symptoms and their questionable etiology. Chronic symptoms are less directly attributable to mTBI with increasing time postinjury and with the occurrence of a variety of potentially symptom-inducing life events. One factor that influences symptom expression after mTBI is the psychological and emotional state of the individual. A specific example that is relevant to the topic of this chapter is the influence of the psychological stress inherent in the combat environment on recovery from mTBI related to military combat. Both the circumstances at the specific time of the injury and general environmental factors in the deployed setting are potentially influential in the recovery process (see Chapter 26, Traumatic Brain Injury in the Context of War).

In contrast to the temporary and expected acute emotional responses to combat and other types of traumatic stress, PTSD represents a continuation and magnification of anxiety-related symptoms. Three characteristic symptom clusters—reexperiencing, avoidance, and hyperarousal—must be present for at least 1 month and cause impairments in functioning to meet diagnostic criteria for PTSD (American Psychiatric Association 2000). In contrast to the generally nonspecific and commonly occurring symptoms of postconcussion syndrome, the reexperiencing symptoms of PTSD, such as nightmares, flashbacks, and intrusive memories, are unique to this disorder, distinguishing it from other anxiety disorders. PTSD-related avoidance symptoms and autonomic hyperarousal can be seen in other anxiety disorders and in a lesser form in the population at large. Aside from these diagnostically relevant symptoms, there are other symptoms common to both PTSD and postconcussion syndrome that make diagnostic specification difficult. These include cognitive symptoms

such as poor attention and memory, behavioral manifestations such as impulsivity and disinhibition, and emotional changes such as mood lability and depression. Secondary effects of both disorders can include social isolation, interpersonal difficulties, and functional impairments in work and home environments.

To provide a more complete understanding of the potential linkage between mTBI and PTSD, we summarize the basic diagnostic and epidemiological information on PTSD. We then describe the major paradigms proposed to explain the relationship between TBI and PTSD and review the literature on these disorders in a variety of clinical contexts. This is followed by a summary of the primary factors that provide confounds and challenges to fully understanding the relationship between mTBI and PTSD. Next, we review areas of biological overlap in these conditions. Finally, we provide a summary of some of the emerging technologies that are shedding new light on this relationship.

Posttraumatic Stress Disorder

Acute stress disorder and PTSD are common diagnoses following violence and other life-threatening events. Exposure to traumatic events and resultant psychological reactions including PTSD are worldwide phenomena crossing national, geographic, cultural, and ethnic boundaries.

Definition

Diagnostic criteria for PTSD according to the DSM-IV-TR (American Psychiatric Association 2000) include four major criteria listed in Table 12–1. The symptoms must cause marked impairment in social, occupational, or other important areas of function and persist for at least 1 month after the traumatic experience (American Psychiatric Association 2000). If the duration of symptoms is less than 3 months, the disorder is considered acute; if symptoms last 3 months or more, it is classified as chronic; and delayed onset of PTSD is at least 6 months posttrauma but can occur even years after traumatic exposure.

Epidemiology

Historically, PTSD was first noticed during World War I and was sometimes termed *battle fatigue* to describe unknown physical and psychological symptoms related to the war. PTSD was first defined as a mental disorder by the DSM-III in 1980 (American Psychiatric Association 1980) in response to the increased recognition of this condition among Vietnam War veterans. In general, the severity of the trauma relates in a direct fashion to the development of PTSD whether the traumatic experience is sexual assault, combat exposure, natural disaster, or terrorist attack. Prevalence of PTSD is elevated in populations at risk for repeated exposure to traumatic experiences, such as paramedics, firefighters, and first responders, with reported rates ranging from 17% to 22% (Corneil et al. 1999). In comparison, the estimated lifetime prevalence of PTSD is approximately 7% to 9% in community samples in the United States (Yehuda 2004).

TABLE 12–1. Summary of DSM-IV-TR diagnostic criteria for posttraumatic stress disorder

Criteria	Symptoms
Exposure to or witnessing of a threatening event	Intense fear
	Helplessness
	Horror
	Symptoms of reexperiencing
Recurrent or intrusive memories	Nightmares
	Sense of reliving the trauma
	Psychological or physiological distress when reminded of the trauma
Avoidance	Inability to recall parts of the trauma
	Withdrawal
	Emotional numbing
Increased autonomic arousal	Sleep disturbance
	Irritability
	Hypervigilance
	Difficulty concentrating
	Exaggerated startle response

Source. Adapted from the *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision. Washington, D.C., American Psychiatric Association, 2000. Used with permission. Copyright © 2000 American Psychiatric Association.

The increased risk of developing PTSD with combat service and combat injuries is a topic of current interest because of the military conflicts in Iraq and Afghanistan. The National Survey of Veterans, which includes data from over 20,000 veterans living in the United States and Puerto Rico, reported that across all war eras, 39% of veterans reported exposure to combat and 36% reported exposure to the dead, dying, or wounded. However, results from specific cohorts differed. For example, 54% of World War II veterans reported experiencing combat whereas only 19% of veterans of the Korean War did (Spiro et al. 1994). A common theme is that the specific nature of traumatic exposure and war-specific demands differ for American military veterans of different war eras. Correspondingly, different conflicts yield different rates of PTSD as a reflection of these combat-specific factors. PTSD symptoms have been approximated at 30% of veterans following service in Vietnam and as much as 10% of U.S. military personnel returning from the 1991 Gulf War (Dohrenwend et al. 2006). There is preliminary evidence that as many as 10%–17% of current combat-deployed personnel to Iraq and Afghanistan have PTSD symptoms following combat deployments with heavy enemy engagement (Hoge et al. 2004; Smith et al. 2008). These numbers may increase as personnel continue to be deployed and with the passage of time after their return.

Outcome

PTSD frequently runs a chronic course, with symptoms waxing and waning over many years. It is known that combat intensity, mortality risk, and acute stress reactions me-

diate the development of later PTSD. Comorbid conditions are frequently present, including depression, other anxiety disorders, and substance use disorders. PTSD is also often associated with physical health problems. The presence of traumatic and stressful experiences throughout life increases the incidence, severity, and chronicity of PTSD.

Compared with other types of trauma, combat trauma is particularly distressing. In a national sample of 1,703 men reporting a traumatic event in the National Comorbidity Survey, those reporting combat trauma as the worst trauma were more likely to have lifetime PTSD, delayed PTSD symptom onset, and unresolved PTSD symptoms. The negative influence of PTSD symptoms on life in general was revealed by higher rates of unemployment and divorce and increased likelihood of having been fired from a job and of imposing physical spouse abuse.

In a study of 1,709 combat soldiers and marines surveyed 3–4 months after returning from Operation Iraqi Freedom (OIF) deployment (Hoge et al. 2004), 12%–20% met screening criteria for PTSD on a standardized instrument. There was a trend toward a positive relationship between PTSD symptoms and deployment location and combat experiences. Hoge and colleagues emphasized that differences in measured rates of PTSD occur with the use of different screening instruments and with differences in the timing of surveys. An example was cited (Bliese et al. 2004) indicating that service members are more than twice as likely to report mental health concerns 3–4 months after deployment compared with immediate reports on return. This has led to a decision by the U.S. military to include a repeat PTSD screening measure at 90–180 days after deployment.

Current Paradigms

In recent years, investigators have attempted to understand the interface between mTBI and PTSD through the lens of combat-induced blast TBI, the most complicated of these relationships. This focus has led to different perceptions and paradigms. One paradigm posits that persistent residual symptoms following mTBI or concussion arise as secondary effects of primary psychological factors. This view is supported by research with a large population of military combat veterans in which PTSD and depression were found to be the primary mediators of the relationship between mTBI and physical health problems (Hoge et al. 2008).

Another theoretical model posits that postconcussive symptoms following mTBI or concussion are caused by neurological effects of the brain injury itself. As will be reviewed, there are a number of biological changes that occur in TBI with the potential to affect biological components associated with many of the symptoms of PTSD. This paradigm relies primarily on biological changes that are a direct consequence of injury to neural structures. Although these changes are often discussed in the context of more severe TBI, results of recent studies are consistent in suggesting that subtle forms of many of these neurological changes also occur with mTBI.

A third model attempts to conceptualize these syndromes as intersecting, as depicted by an overlapping Venn diagram (see Figure 12–1). This paradigm recognizes the possibility that these conditions may mutually affect one another rather than invoking diagnostic concepts that require all symptoms to be attributed either to TBI or to PTSD. An example of this perspective includes cognitive models proposing that PTSD is maintained when trauma survivors have inadequate cognitive resources to manage their traumatic memories and to use adaptive cognitive strategies. At a minimum, it is likely that symptoms from TBI compromise the ability to cope with the stress of PTSD (e.g., through disinhibition of executive control processes), and PTSD likewise compromises the ability to navigate the cognitive and other manifestations of TBI. Other examples of interaction include mutual effects on symptom severity and temporal effects in which causality of symptoms is a function of time after the injury. The time-dependent nature of the relationship between TBI and PTSD is characterized by initial postconcussive symptoms closely tied to acute neurochemical changes from the TBI and persistent symptoms that become increasingly related to other factors such as the presence of comorbid PTSD.

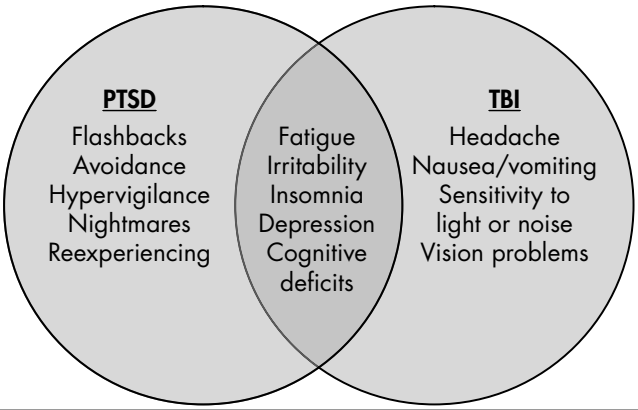


FIGURE 12–1. Overlap of posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI) symptoms

mTBI and PTSD in Different Populations and Contexts

Clinical contexts and potential confounding factors involved in the mTBI-PTSD relationship are reviewed to allow for an objective assessment of the above paradigms. To better understand the entanglement of PTSD and TBI among service members injured by explosive munitions in OIF and Operation Enduring Freedom (OEF; Afghanistan war), it may be of benefit to dissect some of the components. This dissection will provide information on potential differences in the mTBI-PTSD association in civilian versus military samples, the extent to which the mTBI-PTSD association is related to the mechanism of injury (blast vs. nonblast), and the influence of combat and deployment experience on the mTBI-PTSD relationship in military samples.

mTBI and PTSD in Civilian and Military Populations

Civilian

In a review of the literature on neuropsychiatric complications following TBI, research studies support that survivors of TBI can develop subsequent PTSD symptoms. Statistically, the incidence of PTSD after TBI in civilian samples ranges from 13% to 33% (Hiott and Labbate 2002) compared with the lifetime prevalence of PTSD in the general civilian population of 7% to 9%. These statistics suggest that PTSD is a relatively frequent consequence of events and accidents involving TBI in civilians. A related question is whether PTSD relates to the severity of TBI. In a sample of 100 community residents in New York state who incurred TBI at least 1 year prior to interview, anxiety disorders including PTSD were more common in women than in men, but rates did not differ on the basis of other demographic or injury characteristics including age, time since injury, and severity of TBI (Hibbard et al. 1998). In another similar study, 36% of 107 individuals were diagnosed with PTSD after motor vehicle accidents (Hickling et al. 1998). There was no significant difference in the occurrence of PTSD across four categories: 1) whiplash, 2) striking their head, 3) lost consciousness, and 4) none of these. In a study of children involved in traffic accidents, those with and without associated mTBI had equivalent rates of reported PTSD at 6 weeks and 13 weeks after the accident (Mather et al. 2003). Results of these studies confirm that PTSD is a common emotional disorder following TBI but fail to provide evidence for an interaction between rates of PTSD and severity of TBI.

Military

Compared with the civilian population, military personnel, even in peacetime, are at increased risk for sustaining a TBI (Centers for Disease Control and Prevention 2002; Scott et al. 2005). In a large sample of over 5,500 cases of TBI in the military medical system during fiscal year 1992, the age-adjusted head injury rates for individuals between the ages of 15 and 44 resulting from noncombat falls, motor vehicle crashes, fist fighting, and sports were higher in active-duty individuals compared with other beneficiaries (1.6 times greater for men and 2.5 times greater for women) (Ommaya et al. 1996). Literature is sparse in reporting the rates of PTSD after noncombat TBI in military samples. However, preliminary data from a sample of 193 active-duty military service members who sustained noncombat, primarily mild, TBIs in nondeployed settings found that 12% met symptom criteria for PTSD based on self-rated symptoms on the Posttraumatic Checklist (PCL). Of this sample, 8% had total PCL symptom severity scores greater than 50, an established cut point for discriminating PTSD diagnosis (J.E. Kennedy, M.S. Jaffee, L. Ryan, et al., unpublished data, 2008). The 8%–12% incidence of PTSD in this sample is similar to the estimated lifetime 7%–9% prevalence rate of PTSD in the general civilian population but lower than the 13%–33% estimated incidence of PTSD following TBI in civilian samples. It is also much lower than rates of PTSD following mTBI among combat veterans, as described below.

mTBI and PTSD After Blast Versus Other Mechanisms of Injury

Civilian

In the general civilian population, mTBI occurs from a variety of mechanisms. These commonly include falls, motor vehicle collisions, assaults, and sports-related accidents. Occasionally, civilians are also exposed to explosive blast from acts of terrorism, war, and occupational accidents. Studies evaluating survivors of human-made disasters from explosions provide information about the incidence of PTSD after blast exposure and associated blast-related TBI. The evidence shows high rates of PTSD among survivors of these events. According to a prospective study of posttraumatic stress in 70 victims of the bombings that occurred in a Paris subway in December 1996, 41% of participants met PTSD criteria at 6 months and 34.4% still had PTSD at 18 months (Jehel et al. 2001). In another prospective evaluation of the prevalence of PTSD, 39 victims of suicide bombings, missiles, and mortar attacks in Israel had higher rates of PTSD in comparison with 354 survivors of motor vehicle accidents (37.8% vs. 18.7%) (Shalev and Freedman 2005). According to the National Trauma Registry in Israel, 30% of blast victims suffer from head injuries due to primary blast effects and associated shrapnel injuries. Similarly, after the Oklahoma City bombing, over one-third of the survivors were diagnosed with PTSD, of whom 73% had an associated acceleration brain injury. Those survivors with an associated head injury were at a statistically greater risk for development of PTSD than those who were uninjured (North et al. 1999). These findings corroborate that blast explosion is often associated with brain injury and suggest that the incidence of PTSD is increased among blast survivors with TBI.

Military

Similar to the civilian population, mTBI among military personnel occurs from a variety of mechanisms. Although blast-related mTBI to military personnel can occur in other contexts, the vast majority are received during combat deployment. As discussed in the next section of this chapter, the stress of deployment to a combat theater of operations itself, as well as specific combat experiences, is associated with PTSD.

Many wars have occurred throughout history, and with each war new technological advancement and improved explosive devices have evolved. Of patients injured by explosive munitions and hospitalized in Belgrade between 1991 and 1994 from the armed conflict in the former Yugoslavia, 51% had symptoms and physical signs that were compatible with the clinical diagnosis of primary blast injury. Reported complaints among patients included symptoms such as excitability, irrationality, retrograde amnesia, apathy, lethargy, poor concentration, insomnia, psychomotor agitation, depression, anxiety, and physical complaints of fatigue, headache, back and diffuse pains, vertigo, transient paralysis, and "heavy" feeling extremities (Cernak et al. 1999). The acute presence of elevated levels of eicosanoids signaling physiolog-

ical stress and long-term signs and symptoms were interpreted as evidence for the existence of primary blast effects on the central nervous system. Based on the effects on the central nervous system, it was suggested that primary blast injury could be responsible for some aspects of PTSD.

In the current era of modern warfare, members of the U.S. military are sustaining new and complex patterns of injuries. The majority of injuries received during OIF and OEF are associated with explosive munitions. It is estimated that up to 30% of soldiers injured in combat requiring air evacuation return with some form of TBI: mild, moderate, severe, or penetrating (Hoge et al. 2004). Although the exact incidence of blast-related TBI among OIF/OEF veterans is not readily available, estimates from an array of tracking sources suggest that TBI accounts for approximately 60% of war injuries caused by high-order explosives and blasts (Keltner and Cooke 2007). Postdeployment surveys of service members returning to major deployment bases with their units indicate that 10%–20% of combat-exposed troops from Iraq and Afghanistan sustained at least one concussion during their deployment. Hence, blast from explosive munitions is a leading cause of TBI among active duty military service members deployed in war zones (Defense and Veterans Brain Injury Center 2010; Okie 2005).

Hoge et al. (2008) reported that the presence of mTBI in soldiers serving in OIF is highly associated with PTSD 3–4 months after return from deployment. Most of the injuries in this study were blast related, although other causes were also included. Of those reporting TBI with associated loss of consciousness, 43.9% met criteria for PTSD, as compared with 27.3% of those reporting TBI with only altered mental status, 16.2% with other injuries, and 9.1% with no injury. In terms of symptom report and outcome when assessed 3–4 months postinjury, soldiers with mTBI, especially those with loss of consciousness, reported poorer general health, more missed workdays, increased numbers of medical visits, and more somatic and postconcussive symptoms than did soldiers with other injuries. However, PTSD symptom severity accounted for the majority of the variance in these symptoms and outcomes. These results highlight the extent of overlap in TBI and PTSD among individuals with combat-related injuries. They are also consistent with the known recovery trajectory of mTBI in which symptomatic remission in the majority of cases occurs within 3 months postinjury. Continued symptoms and poor functional outcomes after this time apparently relate highly to the presence of comorbid PTSD symptoms. Confounding the relationship of mTBI and PTSD among combat-deployed service members are specific deployment-related and/or combat-related factors that are influential in the development of PTSD, as discussed below.

PTSD and Military Combat

There is a preponderance of evidence showing increased rates of PTSD after military deployment to a combat theater and combat experiences. Some of the more robust longitudinal data in this area come from studies of Vietnam veterans, revealing a 30% lifetime prevalence of PTSD in male veterans compared with a lifetime prevalence of 5% in age-matched control subjects. In contrast, 2%–10% prevalence rates of PTSD have been reported among veterans of the first Gulf War. It is clear that the circumstances involved in each conflict and the types and severity of combat experiences affect subsequent rates of PTSD.

Mental Health Advisory Team reports, directed by the U.S. Army Surgeon General annually from 2003 to 2006, found prevalence rates of acute stress ranging from 10% to 15% among deployed army soldiers, based on self-report of symptoms on the PCL. During the most recent survey in the 5th year of the war, statistics revealed a 17.9% incidence of anxiety, depression, and acute stress. It is unclear how these in-theater symptoms relate to subsequent development of PTSD after deployment (Ramchand et al. 2008), although earlier information from 214 Israeli veterans of the 1982 Lebanon War found that those with combat stress reaction during the war were 6.6 times more likely to develop PTSD than those without this acute emotional reaction (Solomon and Mikulincer 2006). Although these statistics are intriguing, cross-cultural comparisons need to be interpreted cautiously due to differences in life events, exposure to cultural violence, social unrest, and so forth.

A longitudinal study of relevance to this issue was conducted with military personnel enrolled in the Millennium Cohort Study from 2001 to 2003. Participants were later evaluated after many had been deployed in OIF/OEF. Results found that combat exposure, rather than deployment per se, was the primary determinant of PTSD rates. Specifically, rates of self-reported PTSD symptoms among those with combat experiences during deployment were three times greater than symptoms endorsed by those who were deployed but not exposed to combat experiences (Smith et al. 2008). In general, there is a strong relation between the prevalence of PTSD and combat experiences, such as being shot at, handling dead bodies, knowing someone who was killed, or killing enemy combatants. Among military soldiers deployed to Iraq, the prevalence of PTSD increases in a linear fashion with increasing numbers of firefights in which they were involved (none to more than five). Rates of PTSD to date have been significantly higher after combat duty in Iraq than after combat duty in Afghanistan. These differences are explained by the greater frequency, intensity, and type of combat exposure in Iraq compared with Afghanistan during that time.

When a physical wound or injury is received during combat, PTSD symptom development is more likely. Across a number of studies, receiving a combat-associated wound has been associated with positive screen for PTSD (Ramchand et al. 2008). Data from the beginning of OIF/OEF suggest that sustaining any kind of physical injury in theater increases a service member's risk for PTSD (Hoge et al. 2004). In addition, other factors in a deployed setting are also important in the development of PTSD. Several general mission-related stressors increase the probability of developing posttraumatic stress symptoms, including the experience of perceived threat, difficult living and working environment, and lack of preparedness for deployment. Although these and other findings provide strong documentation that combat exposure relates to the development of PTSD, a relationship between TBI and PTSD has been found, even when combat exposure is controlled (Chemtob et al. 1998).

Examination of the available literature in a variety of contexts suggests a complex relationship between PTSD and TBI among civilian and military populations. Literature investigating the development of PTSD after mTBI is limited. However, conclusions from the studies that are available suggest that there may be a unique interaction between mTBI and the development and/or maintenance of PTSD. Elevated PTSD rates occur following exposure to explosions, which are in turn associated with high rates of TBI. Limited information suggests that the occurrence of mTBI during an explosive event may increase the risk for subsequent PTSD. Aspects of deployment, combat exposure, and being injured or wounded are associated with elevated rates of PTSD among military service members. However, evidence suggests a relationship between mTBI and PTSD, even when combat experience is controlled. Overall, individuals with mTBI appear to be at increased risk for PTSD, although other factors can confound this relationship.

How do these findings relate to the paradigms proposed to explain the mTBI-PTSD association? Does the psychological trauma by itself form the basis for the symptoms exhibited by the individual? It appears that this explanation may be valid but incomplete, given that there is an increased rate of PTSD after TBI across a variety of populations and settings. Do neuropathological changes that occur following TBI predispose the individual to develop PTSD symptoms? This explanation also appears lacking, in that not all individuals develop PTSD after TBI. The most parsimonious explanation appears to be that the unique interface between a central nervous system insult and concurrent psychological distress leads to signs and symptoms that are characteristic of both postconcussion and PTSD. In addition, this relationship is dynamic, and the relative contributions of etiological factors contributing to the symptoms change over time.

Challenges in Understanding the Relationship Between PTSD and mTBI

The complete understanding of the intertwining of these conditions has been challenged by several factors, including the inability to meet diagnostic criteria for PTSD in the presence of posttraumatic amnesia, the overlap of clinical symptoms, and the interplay between various symptom clusters of both mTBI and PTSD.

PTSD in the Context of TBI With Amnesia (Moderate-Severe TBI vs. mTBI)

An important question debated in the literature is whether PTSD can develop after a person sustains a TBI with amnesia. In most cases of more severe TBI with amnesia, the full diagnostic criteria for PTSD cannot be met in the context of impaired memory. Proponents in the debate suggest that amnesia associated with TBI serves as a "protective" mechanism against the development of PTSD. However, the opposing literature has demonstrated the presence of PTSD after TBI with associated amnesia. Proposed explanations for this phenomenon include the existence of islands of memory within the period of posttraumatic amnesia, short or incomplete amnesia, memories from before and/or after the actual time of the event, implicit unconscious memories, and memories based on things the individual has later heard or seen about the event (for further information, see Recommended Readings section). Regardless of the injury mechanism involved, it is clear, according to this view, that PTSD can occur following TBI with an associated period of amnesia. This issue is, of course, less relevant to the development of PTSD after mTBI, in which there is a much less extensive period of posttraumatic amnesia.

Overlapping Clinical Symptoms

Another major challenge in sorting out the relationship between mTBI and PTSD is the presence of a common set of symptoms. As outlined earlier in this chapter, PTSD is characterized by the presence of three defining symptom clusters in areas of reexperiencing, avoidance, and increased arousal (American Psychiatric Association 2000). Associated symptoms of PTSD also include 1) cognitive effects such as impaired concentration, learning, and decision making, memory impairment, forgetfulness, confusion, and slower processing speed; 2) behavioral symptoms of irritability, increased relational conflict, social withdrawal, alienation, reduced relational intimacy, and impaired work and school performance; and 3) somatic complaints of exhaustion, insomnia, headaches, startle response, hyperarousal, and cardiovascular, gastrointestinal, and musculoskeletal disorders (National Center for Posttraumatic Stress Disorder, www.ncptsd.va.gov). The overlap between these PTSD-associated symptoms and postconcussive symptoms is striking.

Looking at postconcussive symptoms, Rao and Lyketsos (2002) stated the most common post-TBI anxiety symptoms include free-floating anxiety, fearfulness, intense worry, generalized uneasiness, social withdrawal, interpersonal sensitivity, and anxiety dreams. These symptoms are similar to characteristic PTSD symptoms and are therefore insensitive for purposes of differentiating posttraumatic stress from postconcussive etiology. Changes in personality as a result of mTBI such as impulsiveness, reduced insight, rigid thinking, and reduced motivation may be misattributed to PTSD. Furthermore, frontal, temporal, and subcortical brain areas typically affected in mTBI overlap with those involved in PTSD. Differential diagnosis between the two presenting neurological and psychological conditions is challenging and complicates treatment formulations.

Despite this pervasive overlap of symptoms, the presence of some particular characteristics can aid in the differential diagnosis of PTSD and mTBI. This includes the presence of diagnostically relevant reexperiencing symptoms of PTSD, such as disturbing images, thoughts or perceptions of the traumatic event, recurrent nightmares, flashbacks, and distress imposed by cues that are similar to some aspect of the traumatic event. Acute symptoms

such as headaches, vertigo, and nausea may be more suggestive of mTBI. However, these symptoms are not considered specific enough for diagnostic certainty. Hence, differential diagnosis of PTSD requires considering the etiology of those symptoms commonly observed following mTBI.

Interdependency of Symptom Clusters

The interrelationship among symptoms complicates the diagnostic picture. As mentioned previously, symptoms following mTBI are often categorized into three main clusters: physical symptoms (headaches, vertigo, insomnia, seizures, and nausea), emotional symptoms (depression, anxiety, irritability), and cognitive symptoms (difficulties in attention and memory). These symptom clusters can all amplify or adversely affect one another. For example, physical symptoms such as pain or sleep disturbance can worsen emotional symptoms (such as irritability and anxiety) and cognitive symptoms (such as attention and memory). Emotional symptoms can amplify physical symptoms and impair cognitive abilities. This dynamic interplay between the symptoms of mTBI becomes even more complicated when consideration is given to the interplay between symptoms of PTSD and mTBI.

The presence of PTSD can exacerbate cognitive and other postconcussive symptoms. In addition, PTSD patients with an associated TBI tend to have more prolonged cognitive symptoms. It is possible that patients with both PTSD and postconcussive symptoms may have headaches or dizziness amplified through a mechanism similar to that found with psychological factors affecting physical condition.

The difficulty is accentuated with mTBI in contrast to more severe injuries because the expected recovery course is on the order of days to weeks. By using the trajectory of noncombat mTBI in the absence of PTSD, continued postconcussive syndrome after 3 months postinjury is expected in only 10%–20% of cases, as previously discussed. At the time that symptoms of mTBI are expected to remit, symptoms of PTSD and other emotional conditions often persist or even increase. In the minority of mTBI cases that do not follow the typical course of recovery, persistent postconcussive syndrome can develop in which an increase in emotional or cognitive symptom expression at 6–12 months is characteristic. This may relate to increased levels of stress experienced when the individual resumes full activities. The coincident increase in PTSD symptom report at about this same time makes determining the etiology of these symptoms particularly challenging.

As a result of awareness of the problems with persistent symptoms, such as irritability, memory problems, headache, and difficulty concentrating, among many previously deployed OIF troops, the Department of Defense and the Department of Veterans Affairs implemented population-injury screening procedures for mTBI in addition to the population-screening efforts for PTSD, with the goal of addressing all potential problems in service members and veterans (Defense and Veterans Brain Injury Center 2010; Defense and Veterans Brain Injury Center Working Group 2006).

Biological Interface Between PTSD and TBI

There are a number of areas in which the biology of PTSD and that of TBI interface. This section examines genetic contributions, endocrine changes, neurochemical changes, and structural changes.

Genetic Interface

Increased prevalence of PTSD has been found in adult children of Holocaust survivors even though these children as a group did not have greater exposure to life-threatening events (Yehuda et al. 1998). In a twin study of DSM-III-R anxiety disorders (American Psychiatric Association 1987), PTSD was only found in co-twins of anxiety probands. This finding was twice as prevalent in monozygotic twins, being noted in 20% compared with only 7% in dizygotic twins (Seedat et al. 2001).

The most well-known study illustrating a link between PTSD and genetics is the Vietnam Era Twin Registry (True et al. 1993). This analysis adjusted for differences in combat exposure. There was no evidence that shared environment contributed to development of symptoms. The genetic contribution to variance of liability for each symptom cluster was found to be as follows: reexperiencing (13%–30%), avoidance (30%–34%), and arousal (28%–32%).

There are limited techniques of identifying genes using traditional genetic methods. No linkage studies and only two association studies have been performed. One of these studies identified an association between PTSD and the A1 allele of the dopamine type 2 receptor gene. The other study did not replicate this finding (Segman and Shalev 2003). Newer techniques are focusing on identifying biomarkers and attempting to find associations with genes specific to the biomarker, with the hope that there may be overlap with the actual genetic coding of the syndrome itself (Radant et al. 2001).

There have been several genetic observations in TBI. The most interesting of these observations involve the apolipoprotein E epsilon 4 allele (*APOE*E4*). Patients with TBI who also had the **E4* allele appeared to have more severe cognitive impairment and neurological deficits in one study with boxers (Jordan et al. 1997). Teasdale et al. (1997) demonstrated that *APOE*E4* was associated with a poorer outcome as measured by the Glasgow Outcome Scale 6 months postinjury. Millar et al. (2003) also demonstrated strong associations between the **E4* allele and a poor clinical outcome. This particular linkage to *APOE*E4* relates to pathophysiological changes and is likely to exert its effects through modification of protection/repair mechanisms. *APOE*E4* was traditionally linked to a higher risk of developing Alzheimer's disease. Head injury is also a known risk factor for Alzheimer's disease.

In summary, genetic studies of PTSD suggest that there may be a hereditary predisposition to vulnerability following a trauma in some cases. Similarly, possession of the *APOE*E4* allele may influence recovery following TBI (see Chapter 3, Genetic Factors).

HPA Involvement in PTSD and TBI

There have been many studies of cortisol levels observed in PTSD. These studies evaluate the axis between the hypothalamus, the pituitary gland, and the adrenal gland (HPA). A classic stress response has elevations in corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH), and cortisol. Cortisol mediates its effects by binding to glucocorticoid receptors. These receptors are decreased in chronic stress and depression.

PTSD subjects have alterations in their HPA axis, with low cortisol levels and high levels of CRF. Previously, the low level of cortisol was attributed to adrenal burnout, meaning that initial elevations with the acute trauma were eventually followed by burnout to lower levels. However, emergency room studies of acute measures of cortisol at 1–2 hours following a trauma show low to normal levels in patients subsequently diagnosed with PTSD (Resnick et al. 1995; Schnurr et al. 2004). Studies of PTSD subjects have demonstrated that these patients have both an increase in the quantity of glucocorticoid receptors and an increase in the sensitivity of these receptors. These receptor changes allow for enhanced negative feedback inhibition of cortisol at the pituitary gland with less ACTH released and the attenuation of cortisol. The chronically elevated levels of CRF in PTSD patients have been shown to alter pituitary responsiveness (Yehuda 2000).

Although most common after severe injury (Schneider et al. 2007), up to 50% of TBI (Tariverdi et al. 2006) patients have impaired neuroendocrine function. Of these, 20% have a combination of two or more deficiencies, many of which are transient. When the initial injury is severe enough to cause a panhypopituitary state, there is usually no recovery of pituitary function. The most common pituitary dysfunction associated with TBI is growth hormone deficiency, observed in 15% of subjects. This finding provides a diagnostic challenge as some of the symptoms may overlap with those of postconcussive syndrome (Aimaretti et al. 2004).

The pathophysiology of the pattern of TBI-related pituitary dysfunction is thought to suggest a hierarchy of vulnerability to trauma of pituitary cells. The most vulnerable cells include somatotrophs and gonadotrophs. These cells tend to be located in the lateral wings of the pituitary gland and to be supplied primarily by the long, hypophyseal portal system. This pathway is more vulnerable to trauma based on its trajectory through the diaphragm of the pituitary (Benvenga et al. 2000). More resilient cells include corticotrophs and thyrotrophs. These cells tend to be located in the central portion of the gland and are supplied by the short, hypophyseal portal systems.

In summary, PTSD and TBI are both associated with decreased function of the pituitary gland. In PTSD, this decreased function is based primarily on the increased sensitivity and number of glucocorticoid receptors causing increased negative feedback on the pituitary gland. TBI patients commonly have impaired function of the pituitary due to the decreased release of hormones, most commonly from the most vulnerable pituitary cells (somatotrophs and gonadotrophs).

Neurochemical Changes in PTSD and TBI

There is a dysregulation of many neurotransmitter and neurochemical pathways in PTSD. Of these, the most compelling evidence surrounds serotonin. This may account for the fact that selective serotonin reuptake inhibitors (SSRIs) appear to have the most efficacy for symptoms of PTSD (Pearlstein 2000). Some PTSD patients have their symptoms activated pharmacologically by the serotonin agonist *m*-chlorophenylpiperazine (m-CPP) (Hageman et al. 2001). SSRIs are known to modulate the locus ceruleus and the release of norepinephrine. Noradrenergic aspects of PTSD include prefrontal cortex inhibition of the amygdala, the startle response, and release with recollection of the traumatic event. These factors. lead to a positive feedback loop contributing to the overconsolidation of a traumatic memory. There is additional involvement with the downregulation of γ-aminobutyric acid (GABA) and an increase in the excitotoxic neurotransmitter, glutamate, which is implicated in the encoding of memory (Friedman 2000).

In the setting of TBI, there is a storm of neurotransmitter release. The increase in serotonin seen in TBI is thought to be associated with the depression of cerebral glucose utilization in areas damaged by the TBI. The areas that are most sensitive to serotonin include the limbic areas and the frontal-subcortical circuits. Noradrenergic neurotransmitter systems have also been found to be dysfunctional. Acetylcholine may have the most significant effects for cognitive symptoms due to support of function in the reticular formation (arousal and attention), entorhinal-hippocampal formation (declarative memory), and frontal-subcortical circuits (executive function). There is a resultant decreased synthesis as well as a loss of acetylcholine neurons (Schmidt and Grady 1995). Further support of the cholinergic contribution to cognitive aspects of TBI comes from studies of sensory gating, a parameter of attention that utilizes acetylcholine (Arciniegas and Topkoff 2004). Drugs such as rivastigmine may improve memory deficits in cases where depletion of limbic cholinergic activity is suspected (Silver et al. 2006).

Sometimes the cholinergic deficit causes noradrenergic dysfunction secondary to the lost modulation effect from acetylcholine. Other times, the absolute loss of noradrenergic projections is mild but the effects are exaggerated because of variations in the metabolism due to genetic variability of the catechol O-methyltransferase enzyme (Lipsky et al. 2005). There is also involvement of glutamate, the principal excitatory neurotransmitter that is thought to facilitate information processing. TBI is associated with persistent damage and dysfunction to areas dense in glutamate receptors (Miller et al. 1990); these are the neurotransmitters traditionally associated with excitotoxicity.

In summary, PTSD is associated with a number of neurochemical changes. Similar neurochemical changes have been observed as a direct result of injury in cases of TBI.

Structural Changes in PTSD and TBI

Major brain areas involved in the pathology of PTSD are the medial prefrontal cortex, anterior cingulate cortex, hippocampus, and amygdala (Kolassa et al. 2007). Biological models propose that PTSD involves an exaggerated response of the amygdala and resultant impairments in regulation by the medial prefrontal cortex (Rauch et al. 2006). The amygdala controls conditioned fear reactions. Studies

have shown that inhibition of these fear reactions involves the medial prefrontal cortex (Lanius et al. 2006).

TBI also often involves damage to the prefrontal cortex, ventral portions of the frontal lobe, and the anterior temporal lobe due to shearing forces of these brain areas against the skull. The capacity to regulate the fear reaction may be impaired after TBI in some individuals if the neural networks involved in the regulation of anxiety are damaged as a result of the TBI (Kennedy et al. 2007). For example, a case report illustrates just one of the ways in which a neurological consequence of TBI might induce an unusual variant of a PTSD reexperiencing symptom. This individual suffered continuous reexperiencing of one of the traumatic parts of the precipitating event over the course of 7–10 days. It was hypothesized that the presence of frontal dysexecutive impairment due to brain injury increased the perseverative nature of this reexperiencing phenomenon (King 2002).

The most compelling finding on structural and volumetric studies of PTSD patients is the observation of hippocampal atrophy. This is observed not only with volumetric studies but also with magnetic resonance spectroscopy studies in which reductions in *N*-acetyl aspartate correlate with reduced density or viability of neurons. There have been many volumetric studies of hippocampal atrophy in PTSD. This has been observed to be a right-sided phenomenon in combat veterans with an 18% decrease in the right hippocampus of Vietnam veterans (Pitman et al. 2001) and a left-sided phenomenon in women with childhood sexual abuse (Bremner et al. 1995). One study identified PTSD patients with bilateral hippocampal atrophy. This finding appears to correlate with neuropsychological studies in PTSD that demonstrate decreased short-term memory on formal testing (Elzinga and Bremner 2002). It is interesting that hippocampal atrophy in PTSD does not occur in children and is not seen in the first 6 months after trauma. The hippocampi and amygdala are located in the medial area of the temporal lobes. Therefore, the areas of the brain that are most vulnerable to TBI are also the same areas that are most involved with dysfunction in PTSD patients.

Emerging Technologies

Recent advances in diagnostic technologies are beginning to help us better understand the complicated comorbidity of TBI and PTSD. These technologies include advances in radiological techniques as well as advances in neurophysiological assessment. There are also ongoing efforts to develop serum biomarkers for both TBI and PTSD.

Chen et al. (2008) demonstrated the utility of functional magnetic resonance imaging (MRI) in evaluating the persistent psychiatric sequelae of depression in football players who sustained an on-field concussion. The results suggested that persistent depressed mood following a concussion may reflect an underlying pathophysiology consistent with a limbic-frontal model of depression. Similarly, positron emission tomography studies in patients with PTSD demonstrate hypoactivation in regions of the dorsal and rostral anterior cingulate cortices and the ventromedial prefrontal cortex, regions of the brain that are linked to regulation of emotion (Etkin and Wager 2007).

Recent studies in diffusion tensor imaging have demonstrated abnormalities in patients suffering from acute concussive symptoms. Wilde et al. (2008) demonstrated that the degree of abnormality correlated with the severity of symptoms in patients evaluated within 6 days of their concussion. For patients with persistent symptoms including associated psychological symptoms, computer-based MRI volumetric analysis was able to demonstrate statistically significant differences in brain volumes between those patients who had an mTBI with persistent symptoms and those control patients who did not have a history of mTBI. This technology has also been able to distinguish significant differences between mTBI patients and moderate-severe TBI patients.

Electrophysiological advances include the use of evoked potentials, quantitative electroencephalography, and magnetoencephalography (see Chapter 7, Electrophysiological Assessment). There are a number of research protocols currently under way to determine if these technologies can accurately assist in better understanding the complex relationships between PTSD and TBI.

There is a great deal of ongoing research evaluating the development of accurate biomarkers for both PTSD and TBI. The history of the development of biomarkers for psychiatric conditions has been a history of challenge as evidenced by the current lack of a serum biomarker for depression that is sensitive and specific enough to be used in clinical application. There have been some advancements in the development of a biomarker for severe TBI (N-100). Specificity challenges have been prominent in the context of polytrauma and combat injuries. Research and attempts to develop a reliable biomarker for mTBI are ongoing.

Treatment Implications

Understanding the full context of the interface between PTSD and TBI is vital to comprehensive management and treatment planning. Potential PTSD treatment approaches for those with comorbid TBI are listed in Table 12–2 (Bisson and Andrew 2008). The efficacy of traditional treatments for PTSD in the context of TBI has yet to be demonstrated. An Institute of Medicine report on treatment of PTSD did not identify any PTSD treatment research that recognizes factors of cognitive impairment in veterans returning from Iraq and Afghanistan.

Research results have shown that rehabilitation and outcome after TBI are hindered by the presence of PTSD. In a study of 96 patients with severe TBI who were evaluated 6 months after discharge from acute inpatient rehabilitation, the subgroup with diagnoses of PTSD, consisting of approximately one-quarter of the sample, reported poorer general health, lower levels of functional capacity, less satisfaction with life, and more depressive symptoms than those without PTSD (Bryant et al. 2001; Johansen et al. 2007). In cases of mTBI, symptoms and functional outcomes at 3–4 months postinjury relate to the presence and severity of PTSD symptoms (Hoge et al. 2008).

The main treatment implication is the demonstration that patients who have been involved in a TBI should be evaluated not only for residual physical, cognitive, and traditional emotional symptoms associated with TBI but

TABLE 12–2. Potential posttraumatic stress disorder treatment approaches for those with comorbid traumatic brain injury

Treatment	Description	Example
Trauma-focused cognitive-behavioral therapy (TFCBT)	Psychological treatment delivered individually that is based on trauma-focused cognitive or behavioral therapy	Exposure therapy
Stress management/relaxation	Psychological treatment delivered individually that is non-trauma-focused	
TFCBT group therapy	Trauma-focused cognitive or behavioral therapy delivered in a group setting	
Non-trauma cognitive-behavioral group therapy	Non-trauma-focused cognitive or behavioral therapy delivered in group setting	
Pharmacological treatment	Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine, sertraline, paroxetine
	Mood stabilizers	Lamotrigine
	Atypical antipsychotics	Olanzapine
	Other medications	Propranolol

also for the possibility of comorbid PTSD. There have been cases in which patients with residual symptoms of both TBI and PTSD were only treated for the PTSD symptoms, leading to worsening physical symptoms. Treatment plans should be developed using a multidisciplinary approach that encompasses evaluation and management of all potential symptoms from each TBI symptom cluster (physical, cognitive, and emotional) to assure maximal chance of recovery of all symptoms.

Conclusion

The majority of evidence refutes a paradigm proposing that the symptoms of TBI or concussion are all attributable to PTSD. This view does not incorporate an understanding of the data from different contexts of injury, including civilian and noncombat blast TBI. In fact, combat data indicate a higher incidence of PTSD in injuries with TBI compared with injuries without TBI.

An understanding of the biology and emerging technologies in this area further elucidates the complicated relationship between TBI and PTSD. Studies in these areas have illustrated how both athletic and combat injuries produce some of the same biological changes that are associated with postconcussive emotional symptoms. However, the paradigm that suggests that PTSD and TBI symptoms are completely independent also does not recognize the complicated relationships that emerge when both these conditions may converge in a single patient.

A number of longitudinal studies are under way to further understand this complicated relationship in the context of long-term prognoses. The paradigm that is most consistent with all available data illustrates an overlapping relationship in which the symptoms of PTSD and TBI affect one another.

KEY CLINICAL POINTS

- Posttraumatic stress disorder (PTSD) is characterized by persistent symptoms of reliving a traumatic experience (nightmares or intrusive memories), avoidance, and increased autonomic arousal (hypervigilance, sleep disturbance, irritability).
- Traumatic brain injury (TBI), in particular mild TBI, may increase the risk of developing PTSD.
- TBI and PTSD result in similar neurochemical abnormalities.
- Damage to the prefrontal cortex, ventral portions of the frontal lobe, and the anterior temporal lobe may be evident in cases of TBI and PTSD.
- The presence of PTSD may adversely affect recovery from TBI.

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CHAPTER 13

Personality Change

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"Silent epidemic" was a term first coined in the 1980s to reflect the frustration of clinicians, patients, and families with the lack of public awareness regarding the multiple hidden consequences of traumatic brain injury (TBI). Early this century, military actions in both Operation Iraqi Freedom and Operation Enduring Freedom in Iraq and Afghanistan created a new type of combat-related injury due to exposure to blasts from improvised explosive devices. TBI became the signature injury of these campaigns, and with that, news accounts of (neuro)behavioral problems among returning soldiers became commonplace. Studies of behavioral change after TBI over the past two decades show the substantial increase in lifetime risk of psychiatric disturbance following TBI in both children and adults. One significant risk lies in the development of personality changes. In recognition of this problem, on August 28, 2008, the Department of Defense issued Instruction Number 1332.14, which revised procedure in Enlisted Administrative Separations from military service. This directive specifically addressed concerns regarding discharge from military service due to "personality disorder" when a soldier was currently or formerly deployed to an imminent danger area. Such a change in military regulation reflected the recognition of the impact of TBI on personality alteration in those who manifest no external evidence of injury.

Studies of patients with TBI find that the most significant problems at 1, 5, and 15 years postinjury are personality changes (Livingston et al. 1985; Tomsen 1984; Weddell et al. 1980). At one extreme, subtle awareness on the part of the person and his or her most intimate friends of an attitudinal shift or interpersonal "clumsiness" can exist, whereas at the other extreme, there may be dramatic departures from socially acceptable norms of behavior. Such individual variation in personality creates substantial problems in quantifying these changes after TBI.

Personality changes have been conceptualized as exaggerations of premorbid traits in the face of the overwhelming anxiety of illness (Strain and Grossman 1975), although no definitive study exists. Clinical experience, such as the classic case of Phineas Gage, one of history's most famous brain-injury survivors, has supported the position that focal cerebral contusions may elicit a pattern of behaviors that initially suggest a personality change. In the course of extended interaction with the individual, it is often observed that these discrete areas exist in the context of the person's overall premorbid personality style. The manifestations of these personality changes vary as a function of fatigue, anxiety, sensory misperception, styles of the other individuals involved, and environmental cues. Development of chameleon-like or "as-if" attributes can create diagnostic confusion with patients who have disorders due to early disturbances of separation-individuation (Gunderson and Singer 1975; Mahler et al. 1975; Munro 1969). Patients may be diagnosed as having borderline personality disorder when they display the impulsivity, lack of empathy, lack of sense of self, and inability to self-monitor that are typical of frontal lobe dysfunction.

Confounding this issue further are the recent studies of impaired frontal lobe functioning in patients with the diagnosis of borderline personality disorder. Normal human growth and development over the life cycle mediate certain elements of personality change subsequent to TBI. An Eriksonian model provides a functional yardstick against which to measure such traits (Erikson 1950). The maturational arrests that are observed after TBI may, in part, arise from a critical insult that stalls subsequent developmental stages. Actions that are acceptable from a 15-year-old adolescent are not well received in a 35-year-old. Yet those who sustained their TBI in adolescence are caught in precisely this "time warp" that adversely affects their relationships. Dissection of these issues requires a strong therapeutic relationship between the physician and patient that allows coping strategies to be observed and assessed in multiple settings and under varying conditions. By

their very nature, personality changes show modest response to a crisis intervention approach to treatment. In this chapter, we review the complexities of these personality alterations.

Personality Change After TBI

In her classic 1978 paper, Muriel Lezak described alterations in personality after TBI as 1) impaired social perceptiveness, 2) impaired self-control and regulation, 3) stimulus-bound behavior, 4) emotional change, and 5) inability to learn from social experience (Lezak 1978). Alone or in combination, these deficits impair the ability of the patient to engage in a mature social interaction and create a high potential for alienation from others. Loss of self-monitoring capacities is overtly manifest as the externalization of responsibility for failed social interactions. As a result, this behavior can appear similar to a narcissistic disorder. Whether this lack of interpersonal awareness or insight represents an injury-derived agnosia (failure to recognize one's behavior) or is a result of a defensive use of denial is unclear (Sandifer 1946). The term *organic denial* has been proposed to describe this phenomenon. Subsequent attempts by Lezak and others to define correlates between brain lesions and behavior after TBI resulted in a reworking and refinement of her 1978 paper. Describing a population of individuals with frontal lobe injuries, Lezak (1982) identified the following attributes: 1) problems with initiation, 2) inability to shift responses, 3) difficulty stopping ongoing behavior, 4) inability to monitor oneself, and 5) profound concreteness. The clinician often observes the apathetic, abulic patient who, after experiencing a TBI, lacks sufficient motivation to get going (similar to bradykinesia).

Neuroanatomical and Neurophysiological Substrates of Personality

In 1868, Dr. John Harlow described a nineteenth-century railroad worker, Phineas Gage, who experienced a penetrating brain injury with a tamping rod and developed personality alterations described as apathy, disinhibition, lability, and loss of appropriate social behavior. Hibbard et al. (2000), using the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (First et al. 1997), found that two-thirds of their cohort of individuals with brain injury met criteria for a DSM-IV-TR (American Psychiatric Association 2000) personality disorder diagnosis after injury that was independent of injury severity, age at injury, or time since injury occurred. Such alterations are illustrative of the effects of both focal and diffuse changes that accompany TBI.

As a result of limits to the resolution of the scanning device, focal trauma to the tips of the temporal lobes, inferior orbital frontal regions, or frontal convexities may occur without neuroanatomical imaging evidence of injury and yet may have devastating consequences for the patient and the family (Jenkins et al. 1986; Langfitt et al. 1986; Wilson and Wyper 1992). Diffuse axonal injury results in the "unplugging" of neural networks from one another, with a decrease or loss of the associational matrix within the central nervous system (CNS) creating random networking lapses for the individual during functional activities. Lapses may vary from transient problems with initiation delaying one's ability to appropriately begin a pattern, such as a conversation or a problem-solving sequence, to more overt problems with stopping ongoing behaviors. Attempts to define the location of personality in the human brain include Wolford et al. (2000) identifying the left hemisphere as the locus of searching for patterns in events and Gazzaniga (1998) postulating the existence of a "hypothesis generator" in the left hemisphere (see Table 13–1 for a list of brain regions associated with personality traits). Research into the brain–behavior substrate for personality and judgment has continued to find hemispheric differentiation.

Alternatively, functional magnetic resonance imaging (fMRI) studies have demonstrated activation of the frontopolar cortex and medial frontal gyrus in judgment settings without emotional significance, whereas moral judgment activated regions in the right anterior temporal cortex, lenticular nucleus, and cerebellum as well (Moll et al. 2001). A review of fMRI findings in moral cognition by Young and Koenigs (2007) further supports the assertion that ventromedial prefrontal cortex (VMPC) mediates the interplay between emotion and moral cognition. Temporoparietal junction and medial orbitofrontal cortex activation on fMRI in an observed pain/empathy paradigm in normal control subjects has been identified (Lamm et al. 2007). Patients with VMPC lesions were more willing to judge personal moral violations as acceptable behavior in personal moral dilemmas and more quickly than control subjects (Ciaramelli et al. 2007). Whether this difference might reflect alteration in information acquisition in a multiattribute decision-making process (e.g., the degree of certainty vs. uncertainty) in those with VMPC injury has been suggested by one investigator (Fellows 2006).

Localization of personality to any one structure or set of structures in the CNS is a formidable task. The set of characteristic reactions and psychological defenses to an anxiety-inducing stimulus emerges from a complex interaction among limbic-mediated drive states, paralimbic cortical inhibition of certain of those states, contextual elements relating to pattern recognition of similar past events, and selection of a response pattern predicated on a cost-benefit analysis for the event in question. All of these cognitive events must occur subsequent to the sensory recognition of the triggering event. Diffuse injury that occurs in TBI can influence any of these events. Pathway reduplication and parallel systems in the CNS may contribute to the behavioral variability over time. This creates the potential for an irregular syndrome.

Nondominant parietal structures and frontal executive structures may define awareness of body in space and integration of sensory signals. The right middle inferior frontal gyrus shows activation in a self-evaluation task accompanied by embarrassment on fMRI (Morita et al. 2008). Further fMRI studies of self-awareness during speech processing that describe medial parietal and medial prefron-

TABLE 13–1. Brain regions associated with personality traits

Trait	Association
Aggression	Reduced cingulate cortex volume and activity
Conditioned memory storage	Cerebellum
Decision values	Central orbitofrontal activation
Dispassionate analysis	Increased anterior cingulate activity
Emotional bias in moral decisions	Ventromedial and orbitofrontal prefrontal cortices activation
Emotional memory storage	Amygdala
Empathy/self-reflection	Insula activation
Extroversion	Reduced dorsolateral prefrontal cortex, anterior cingulate, and thalamus activity
Goal values	Medial orbitofrontal activation
Insightful/"eureka" moments	Increased superior temporal gyrus activity
Mistrust/disbelief	Reduced insula activity
Novelty seeking	Increased hippocampus and striatum activity
Optimism	Increased amygdala and anterior cingulate activity
Personal awareness of mental state/character	Medial prefrontal cortex
Personal space boundaries	Motor, somatosensory, cingulate, and parietal cortices
Prediction errors	Ventral striatum (caudate-putamen) activation
Punctuality/subjective time sense	Substantia nigra, basal ganglia, and prefrontal circuits
Reflective/comparing past-present situations	Lateral prefrontal cortex activation
Self-monitoring/guiding behavior	Cingulate cortex
Social avoidance/fear/anxiety	Increased amygdala activity
Social comfort/safety	Increased striatal activity
Trust/belief	Increased ventromedial prefrontal cortex activity
Perceived unfairness	Increased insula activity

Source. Adapted from Carter et al. 2009.

tal activation in a "self-generated voice" condition with modulation of the inferior parietal lobule are needed to distinguish between speech production and speech listening situations (Jardri et al. 2007). Indeed, damage to parietal regions can result in a syndrome of guarded hypervigilance similar to a paranoid style (Devinsky 2009). Damage to temporal regions of the amygdala may alter the affective valence of an event. Rage and fear responses associated with these lesions are discussed in Chapter 14, Aggressive Disorders.

Basic science research in animal models and infants provides insights into the regional localization of temperament, inhibition, and impulsivity. Right frontal hemispheric influences are found in most of these processes. Intense defensiveness in rhesus monkeys, manifested by elevations in cortisol concentration (viewed as traitlike fear-related behaviors), occurs in those monkeys with extreme right frontal asymmetry (Kalin et al. 1998). Similarly, 4-month-old human infants also demonstrated greater right frontal electroencephalographic activity in direct proportion to level of inhibited behavior (Calkins et al. 1996). Conversely, impulsivity in a rat model has been correlated with selective lesions in the nucleus accumbens but not with lesions in the anterior cingulate or medial prefrontal cortices (Cardinal et al. 2001). Frontal reactivity as measured by event-related potentials (ERPs) is linked to sensation-seeking behavior. In this research, frontal P3 ERP amplitudes in a cohort of high-sensation seekers (i.e., skydivers) were larger than in control subjects. The implication that such large amplitudes reflect the capacity to improve automatic attentional processes has been suggested (Pierson et al. 1999).

The definition of frontal lobe syndromes has been the subject of multiple articles and a comprehensive work by Stuss and Benson (1986). Functional correlates of regional changes in these lobes are important with focal lesions such as arteriovenous malformations, neoplastic disease, and focal hemorrhagic events. However, caution is advised when ascribing definitive importance to frontal lesions in TBI when the critical neuropathological change is diffuse axonal injury. Nonetheless, some elements of frontal lobe localization may be evident after TBI. Orbital frontal lesions resulting from contusions of neural tissue against the floor of the anterior cranial vault can occur when an individual falls backward, striking the occiput against a firm surface. Unilateral dysfunction in olfaction (cranial nerve I) may be detected as a result of either complete avulsion from the cribiform plate or stretching of fibers on the inferior surface of the frontal lobes (Costanzo and Zasler 1992).

As described by Rolls (2004):

> The orbitofrontal cortex contains the secondary taste cortex, in which the reward value of taste is represented. It also contains the secondary and tertiary olfactory cortical areas, in which information about the identity and also

> about the reward value of odors is represented. The orbitofrontal cortex also receives information about the sight of objects from the temporal lobe cortical visual areas.... A somatosensory input is revealed by neurons that respond to the texture of food in the mouth, including a population that responds to the mouth feel of fat. In complementary neuroimaging studies in humans, it is being found that areas of the orbitofrontal cortex are activated by pleasant touch, by painful touch, by taste, by smell, and by more abstract reinforcers such as winning or losing money. Damage to the orbitofrontal cortex can impair the learning and reversal of stimulus-reinforcement associations, and thus the correction of behavioral responses when these are no longer appropriate because previous reinforcement contingencies change. The information which reaches the orbitofrontal cortex for these functions includes information about faces, and damage to the orbitofrontal cortex can impair face (and voice) expression identification. This evidence thus shows that the orbitofrontal cortex is involved in decoding and representing some primary reinforcers such as taste and touch; in learning and reversing associations of visual and other stimuli to these primary reinforcers; and in controlling and correcting reward-related and punishment-related behavior, and thus in emotion. (p. 11)

Orbitofrontal injuries are often accompanied by neurobehavioral alterations, including impulsivity, euphoria, and manic symptoms. Individuals with orbitofrontal injuries also have been described as "pseudosociopathic" because they have diminished capacity for introspection and self-awareness. Damage to the medial surfaces or the frontal convexities defines a syndrome of apathy, abulia, and indifference, as described earlier. These individuals present a "lobotomized" image, much as Jack Nicholson portrayed in the closing scenes of *One Flew Over the Cuckoo's Nest*. The term "pseudodepressed" has been applied to this population.

Reasoning and creativity have been defined as frontal lobe functions. Measurements of regional cerebral blood flow in anterior prefrontal, frontotemporal, and superior frontal regions define increases bilaterally on a divergent thinking task assessing creativity (Carlsson et al. 2000). The predictability of a task has implications as to the activation of frontal regions. Expected sequential tasks engage medial anterior prefrontal cortex and ventral striatum, whereas unpredictable tasks involve polar prefrontal and dorsolateral striatum (Koechlin et al. 2000). Functional neuroimaging studies reveal the frontal lobe as the site of accessing information previously encoded and required for problem solving. Fletcher and Henson (2001) found ventrolateral frontal cortex activation, with successful encoding and initial stage of retrieval of data from long-term stores into working memory. Data selection, manipulation, and monitoring activated the dorsolateral frontal cortex for complex encoding and analysis of relevance of information retrieved for use. Cortical activation anterior to the cephalad edge of the inferior frontal gyrus (anterior frontal cortex [AFC]) is seen with goal selection and data coordination function between the ventrolateral and dorsolateral frontal cortex. Online monitoring of goal-directed behavior and shifting cognitive sets also activates the AFC.

In an analysis of right hemispheric function by Devinsky (2000), awareness of physical and emotional self-constructs (e.g., body image, relation of body to environmental space, and social function) resided in the AFC. According to a review by Krawczyk (2002), orbitofrontal and ventromedial areas affect decisions based on reward values and provide affective information regarding decision attributes and options. Dorsolateral prefrontal cortex activity is recruited when decision making mandates evaluation of multiple sources of information and may recruit separable areas when making well-defined versus poorly defined decisions. Anterior and ventral cingulate cortex involvement is especially relevant in sorting among conflicting options, as well as signaling outcome-relevant information. Frontal activation on functional imaging studies occurs in localization studies of empathy, emotional distress, forgiveness, self-monitoring, and constructs of "the self." Imaging studies assessing social reasoning define activation of the left superior frontal gyrus, orbitofrontal gyrus, and precuneus in both empathy and forgiveness. Empathy-related activation is also found in left anterior middle temporal and left inferior frontal gyri. Forgiveness activates the posterior cingulate gyrus (Farrow et al. 2001). Frontal ERP measurement during an error-monitoring task defines amplitude variability inversely correlated to negative affect and emotionality in study subjects (Luu et al. 2000). Basal ganglia–thalamocortical circuits modulate generation, switching, and blending in executive functions (Saint-Cyr et al. 1995). Self-monitoring during a verbal inhibitory exercise activates the left dorsolateral prefrontal cortex (and, to a lesser degree, the anterior cingulate) (Chee et al. 2000). Nondominant frontal lobe dysfunction as measured by single-photon emission computed tomography has a strong correlation with loss of "self" (Miller et al. 2001). Implicit gender stereotyping and overlearned social knowledge link to ventromedial cortex function (Milne and Grafman 2001).

The neurochemical basis of personality attributes is emerging as an area of interest. Whereas models of dopamine receptor activity relating to vigilance, expectation, and reward have been postulated (Gershanik et al. 1983; McEntee et al. 1987), serotonin has been implicated in large-scale studies of hostility in those with type A personality (Tyrer and Seivewright 1988; Williams 1991). The correlation between high circulating levels of catecholamines and their metabolites and good outcome post-TBI (Clifton et al. 1981;Woolf et al. 1987) is notable. This laboratory finding supports the long-held clinical wisdom that the patient who is agitated and "hits the ground running" has a much better prognosis than a lethargic, apathetic counterpart.

Preinjury Factors and Personality

Controversy exists regarding the importance of premorbid personality in predicting the occurrence of TBI. "Clinical wisdom" initially suggested that TBI was not strictly a random event and tended to affect those with a proclivity for "living on the edge." Studies, however, have found no overrepresentation of risk takers or substance abusers in adolescents with TBI (Lehr 1990). Ruff et al. (1996) noted that those with significant dependency issues, grandiosity, overachievement, perfectionism, and borderline personal-

ity have a compromised outcome. Bigler (2001) noted no demonstrable impact of preinjury antisocial traits with frontal lobe injury. Studies by Cantu (1997) suggest an increasing risk of concussion in football-related injuries as the number of events increase: the first event creates a threefold increase in vulnerability to a second event, whereas a second event increases this to an eightfold statistical probability.

Studies of the neural basis of personality disorders suggest frontal lobe regional influences in impulsive and aggressive personality disorders (Siever et al. 1999). Reduction in metabolic function for serotonergic modulation in orbitofrontal, ventral medial, and cingulate cortices is implicated in this study. Studies of borderline personality disorder define reduced frontal cortex glucose metabolism on positron emission tomography in those meeting DSM-III-R (American Psychiatric Association 1987) criteria (Goyer et al. 1994). Populations at risk for frontal abnormalities at baseline, theoretically, may possess an increased vulnerability for personality dysfunction post-TBI.

Premorbid personality factors affect the type of defense mechanism used to cope or adapt with the stresses of TBI. The schema developed by Strain and Grossman (1975) for stresses of hospitalization, as shown in Table 13–2, can be adapted to focus on the stresses specific to the experience of TBI. The loss of self is a primary focus of individual psychotherapy, as discussed in Chapter 36, Psychotherapy.

Loss of sense of self pervades every aspect of life for those with TBI, resulting in significant anxiety. In an attempt to contain this anxiety, the patient uses the defenses that have provided the greatest past success in stress reduction. This exaggeration of premorbid style is identical to that described in a study of personality types in acutely ill medical patients (Kahana and Bibring 1964). These authors observed that these styles became exaggerated under stress. Because stress is reduced by the correction of Axis I or Axis III disturbances, the individual gradually returns to the pre-illness level of homeostasis. In the case of TBI, the level of stress becomes chronic because there is a seemingly permanent exaggeration of personality style.

TABLE 13–2. Manifestations of stress in hospitalized patients with traumatic brain injury

Threat to one's sense of self
Change in self-identity
Short-term memory impairment
Disorientation
Stranger anxiety
Short-term memory impairment
Loss of anticipatory capacity
Impaired visual memory or recognition
Visual field cuts
Inattention syndromes (anosognosia)
Separation anxiety
Disorientation
Loss of anticipatory capacity
Short-term memory impairment
Fear of losing love or approval
Social role disruption
Interpersonal intrusiveness
Loss of intimacy and approval
Impaired self-observational skills
Fear of losing control of developmentally mastered milestones
Loss of impulse control
Bowel or bladder incontinence
Motor dysfunction (apraxia)
Functional independence changes in activities of daily living
Language disturbances (aphasia, aprosodia, and alexia)
Fear of loss of or injury to body parts
Craniotomy scars
Percutaneous endoscopic gastrostomy tube sites
Tracheostomy scars
Urinary catheters
Fears of retribution, guilt, or shame
Retribution or expiation themes
Survivor guilt

Source. Adapted from Strain and Grossman 1975.

Assessment of Personality

Several population-based measures of personality have been used in the assessment of patients with TBI. These include the Minnesota Multiphasic Personality Inventory (MMPI)–2 (Butcher et al. 1989), Millon Clinical Multiaxial Inventory–III (Davis et al. 1999; Groth-Marnat 1997; Millon 1994), Personality Assessment Inventory (Morey 1991), Millon Behavioral Health Inventory (Millon et al. 1982), and Millon Behavioral Medicine Diagnostic (Millon et al. 2001). The limitations of these instruments in patients with TBI relate to problems with the length of the questionnaire and time for completion, the use of inappropriate comparison groups in the fundamental design of the instrument (i.e., medically healthy, psychiatric patients), and true neuromedical symptoms elevating scores on clinical scales, leading to a risk of overdiagnosis of conversion and other somatoform disorders.

Use of the MMPI in individuals with TBI has been specifically cited as having potentials for misdiagnosis (Levin et al. 1976). Foremost among these is its length even in the shortened 168-item version published in 1974 (Vincent et al. 1984). Slowed rate of information processing that occurs in TBI results in an inordinate time for proper administration of the MMPI. Patient impulsivity may generate invalid scores. Language-mediated problems, which affect up to 85% of individuals post-TBI, may preclude adequate reading, comprehension, or analytic skills, resulting in an inability to honestly answer the items (Groher 1977). At least one study (Kaimann 1983) has correlated elevations in MMPI scores with neuropathological findings on computed tomography scans. In this study, a high degree of correlation was noted between elevations of the Depression scale and nondominant temporal lobe lesions, elevations of the Psychoticism scale and periventricular lesions, and elevations of the Psychopathic Deviance scale and lesions of the frontal lobes. The Fake Bad scale has been criticized for its bias in gender-based symptoms as

well as neurological symptoms commonly experienced by those with TBI. Exclusive use of a population-based measure in lieu of a comprehensive clinical interview conducted by a skilled professional is to be absolutely avoided in the evaluation of individuals with TBI. Face-to-face interaction between examiner and patient is always indicated to allow the assessment of nonverbal elements of communication and the "process" aspects of the patient's style. Multiple problems with written and symbolic language found after TBI render pencil-and-paper analysis inadequate to evaluate intact communication pathways that may enable the patient to better communicate his or her strengths and weaknesses. Efforts to objectively quantify personality changes after TBI have relied on factor analysis of multicenter studies such as the National Traumatic Coma Databank (Levin et al. 1990).

One such instrument is the Neurobehavioral Rating Scale (Levin et al. 1987; Vanier et al. 2000), a 27-item, observer-rated scale that incorporates elements of the Brief Psychiatric Rating Scale (Overall and Gorham 1962) and provides a personality and behavior change profile that can demonstrate recovery over time. A companion assessment has been developed for the pediatric population that incorporates a more age-appropriate profile of memory changes (Ewing-Cobbs et al. 1990). Diagnostic categories for these changes in DSM-IV-TR (American Psychiatric Association 2000) are included in the section "Personality Change Due to a General Medical Condition." The elements are a persistent disturbance in previous personality characteristics, attributable to a nonpsychiatric medical condition, and the occurrence of marked distress or impairment in social or occupational functioning. Secondary personality change subtypes are described in Table 13–3.

TABLE 13–3. Secondary personality change subtypes by symptom presentation (DSM-IV-TR)

Labile type	Other type (e.g., associated with a seizure disorder)
Disinhibited type	
Aggressive type	Combined type
Apathetic type	Unspecified type
Paranoid type	

Source. American Psychiatric Association 2000, p. 188.

Clinical Elements of Personality Change After TBI

Loss of "Sense of Self"

Awareness of one's uniqueness as a person or "innate sense of self" results from the combined influences of experience, genetic endowment, defensive structure, and social reinforcers at any specified point in time. Changes in the environmental reinforcers play a major role in the regression observed in hospitalized patients without TBI (see Table 13–2). These same factors influence individuals with chronic medical illnesses such as TBI. Pressures to conform to an external set of demands in addition to the chameleon-like effect of TBI on personality further serve to confound the individual's sense of identity. This chameleon quality relates to the patient's adopting the behavioral characteristics of individuals in the immediate environment and underscores the need for placement in the least restrictive setting. A patient with brain injury may well act as one with a severe psychotic disorder when hospitalized on an acute admission unit or chronic care facility. Once returned to community-based supported living settings, dysfunctional styles improve. This issue has been the basis for numerous class action suits in Connecticut, Massachusetts, Maryland, and elsewhere to preclude commingling in state mental health facilities. When in the presence of more functional individuals, the patient shows a higher level of competence. Subtle deficits in executive function that accompany frontal lobe injuries in mild TBI may affect those individuals who rely on these skills for vocational or interpersonal success, such as lawyers, health care professionals, and entrepreneurs. Integrative deficits in visuospatial domains may undermine the confidence and skills of craftsmen whose jobs rely on these functions, such as welders, electricians, and artists. The chronic and enduring nature of these deficits requires a reworking of the internal representation of oneself, which may be hindered by the impairment in self-appraisal.

Childish Behavior

Childish behavior represents a constellation of changes following TBI involving language, cognition, and egocentricity. Pragmatic language deficits (Table 13–4; adapted from Ehrlich and Sipesk 1985) are implicated most frequently in childish behavior observed after TBI (Szekeres et al. 1987). Developmentally acquired skills such as turn taking, sharing, not interrupting, and inviting expansion on a conversational topic all require awareness of others and ongoing appraisal of the environment during social discourse. A childish style emerges when these elements are absent or diminished. Developmental arrests that result from hospitalization, as observed in excessive and inappropriate attachment with therapy staff or nurses, also may be perceived as childish.

One aspect of childish behavior relates to the Eriksonian stage of psychosocial development (Table 13–5) that is present at the highest risk period for the occurrence of TBI (15–24 years old). During this period, the stage of identity versus diffusion precedes the stage of intimacy versus isolation. A task of adolescence is to define oneself independent of one's parents, and then to share that self with another in an intimate relationship. In the setting of rehabilitation, the need for a strong therapeutic alliance between patient and therapist is critical and similar to that required for successful psychotherapy. The patient must trust the therapist and relinquish control for a period of time to permit the improvement of a dysfunctional process. Similarly, both activities require delaying gratification and becoming more vulnerable (physically and emotionally) to the therapist. The therapist, in both settings, must carefully avoid the creation of potentially damaging scenarios and misperceptions of the motivation behind the therapist's actions. Infatuations may arise out of a misguided enthusiasm for helping the patient, which is misinterpreted by the patient as a process that is more intimate than professional. A further complication arises from the demographics of the TBI patient and staff: The majority of

TABLE 13–4. Pragmatic language dysfunction after traumatic brain injury

Decreased intelligibility
Choppy rhythm
Impaired prosody
Limited gesturing with avoidant posturing
Limited affect and eye gaze
Constricted operational vocabulary
Use of ungrammatical syntax
Random, diffuse, and disjointed verbal style
Limited use of language with reliance on stereotypical uses
Abrupt shift of topic
Perseveration
Inability to alter message when communication failure occurs
Frequent interruptions of others
Limited initiation and/or listening

Source. Adapted from Ehrlich and Sipesk 1985.

TABLE 13–5. Erikson's stages of psychosocial development

Trust vs. mistrust
Autonomy vs. shame and doubt
Initiative vs. guilt
Industry vs. inferiority
Identity vs. diffusion
Intimacy vs. isolation
Generativity vs. stagnation
Integrity vs. despair

TBIs occur in young males, whereas the staff caring for these patients are typically younger female professionals. Avoidance of such childish responses rests in large measure on the active supervision of therapeutic staff by seasoned senior supervisors and the establishment of therapeutic limits early in the treatment process. Mental health professionals who have received psychotherapy supervision at some point in their training are often more aware of these transference–countertransference issues in the therapeutic process. Use of this unique expertise by the rehabilitation team can minimize staff and patient conflict.

Impaired Judgment and Social Awareness/ Inappropriate Behavior

Judgment may be impaired due to difficulty in accurately assessing a current situation on the basis of previously acquired information from past situations. Two neural networks have been implicated in this process: 1) a primitive network involving the basal ganglia–dopamine system that learns to make decisions slowly based on the relative probability rewards but has less sensitivity to recency or specific reward value, and 2) a more sophisticated network that accesses basal ganglia–orbitofrontal cortex networks to estimate the true expected value of decisions and more rapidly switches behavior when reinforcement contingencies change (Frank and Claus 2006). This requires the correct and efficient retrieval of information from long-term data banks and an active comparative process to assess similar and dissimilar elements of the setting. Difficulties in accurate scanning of the situation, assessing the relevant features of the situation, and distorted time sense may manifest as impairments in judgment. Inappropriate reactions to social cues may result from impaired prosodic language and failure to appreciate the gestalt of a situation. This demonstrates deficiencies with multitasking and nonverbal task analysis. These difficulties constitute neurolinguistic deficits associated with the pragmatics of language (see Table 13–4; see also Prutting and Kirchner 1983). A patient may accurately appraise a situation, effectively review past strategies for interaction, and still execute an inappropriate response due to a failure to coordinate propositional language with the intended prosodic component. This can occur when the patient misreads a sarcastic remark as one that is sincere. Studies have identified sleep loss as particularly disruptive to the ventromedial prefrontal regions of the brain that integrate affect and cognition in judgment and decision making (Kilgore et al. 2007).

Aggression/Irritability

Irritability and aggressive behavior reflect an inability to filter environmental "noise" combined with defective inhibitory capacity. Arousal or vigilance may range from heightened to impaired. Low-vigilance states are associated with a poorer prognosis for functional independence (Clifton et al. 1981; Woolf et al. 1987). These problems most frequently are correlated with reduction in dopaminergic activity (Feeney and Sutton 1988; Lal et al. 1988; Neppe 1988) or increases in cholinergic activity in the CNS (Nissen et al. 1987; Rusted and Warburton 1989). Hypervigilant states may portend a better clinical prognosis; however, the heightened arousal may predispose to aggressive behavior (Eichelman 1987). Serotonergic and noradrenergic mechanisms have been implicated in aggressive states. These behaviors may be observed to increase in frequency in response to fatigue, pain (both acute and chronic), autonomic arousal (such as seen in posttraumatic stress disorder), and confrontation with affectively critical settings.

Affective Lability/Instability

One's inability to modulate and control emotional expression is a result of impaired capacity to monitor volume combined with failure or inefficiency of inhibiting behavior. While most prevalent in injury to brainstem structures, less severe forms may emerge after even mild TBI. This may escalate in the context of either affectively charged or neutral subject matter or setting. Loss of affective resonance with subject content is found in prosodic dysfunction and "pseudobulbar" states. Frequently associated with fatigue and complex social settings, these alterations may be mistakenly ascribed to depressive disorder or Cluster B personality disorders. The use of dextromethorphan preparations, tricyclic antidepressants, and selective serotonin reuptake inhibitors may reduce such episodes.

Attention

Failure to attend to relevant environmental stimuli can result from sensory-perceptual imbalances, primary attention impairment, or a combination of both. Disorders of attention are a common consequence of TBI and may be overlooked by the casual observer (Stuss et al. 1985, 1989; Van Zomeren 1981). The inability to attend to one distinct stimulus may be manifest in any sensory domain, including visual, auditory, and tactile. Sensory-perceptual imbalance in bilateral systems such as vision and hearing may also present as attentional failure in settings where bilateral processing facilitates figure-ground discrimination, localization, or sustained sensory processing. These disorders are seen in central auditory processing deficits and in posttrauma vision syndrome in which ambient visual pathways are impaired. Clinically, this manifests as the reduced capacity to converse in noisy settings (e.g., parties, malls), impaired ability to read maps and blueprints, and problems interpreting simultaneous sensory events. When vestibular or peripheral labyrinthine damage results in visual dependency to sustain postural integrity, similar attentional impairment may be observed in the context of visually complex environments. In those settings, the overt discomfort may be misidentified as a primary anxiety disorder such as agoraphobia or avoidant behavior.

Language/Pragmatic Deficits

Language disturbance is observed in up to 85% of individuals following TBI (Groher 1977). Changes may include problems with verbal memory, auditory processing, integration and synthesis of linguistic information, word retrieval, and spelling. Foreign accent syndromes may also be seen. These problems most commonly arise from the combined effects of diffuse injury and focal cortical contusions. Loss of spontaneity of speech may occur in even the most trivial of injuries. Disturbances in the intonation of language (prosodic dysfunction) can influence the ability to convey affect in speech (motor aprosodia) and to perceive affect in speech (sensory aprosodia). Cortical regions in analogous position to Broca's and Wernicke's areas in the nondominant hemisphere are believed to subserve expressive and receptive prosodic speech, respectively. In motor aprosodia, the patient may be misdiagnosed as depressed with blunted affect or as thought disordered with flattened affect. The inability to impart tonal color to one's language often requires the use of either physical mannerisms (shaking fists or pounding the table) or invective to punctuate one's intended message clearly. Pure sensory (auditory and visual) prosodic dysfunction is rarely observed. Substantial regions of the nondominant hemisphere and the inferior surfaces of both temporal lobes are involved in sensory prosody, possibly due to the adaptive evolutionary advantage that exists in the capacity to visually recognize affect in others. More commonly after TBI, dysfunction of auditory sensory prosody is seen and is manifest as the inability to correctly interpret affect in situations in which visual cuing is absent. This typically would be encountered in telephone conversations and crowd settings where the capacity to lock on to one individual's face is compromised. In such situations, the individual may respond out of context to another's conversation predicated on his or her own mood state.

Evaluation of post-TBI neurolinguistic problems mandates a comprehensive speech-language assessment performed by a speech-language pathologist with experience in TBI. Attention to developmental language issues is required to adequately define the context in which the TBI changes occur. Audiometric evaluation may also be needed to diagnose occult peripheral hearing and processing deficits that may further worsen language capability.

Perception

Perceptual problems arise post-TBI due to diffuse damage to subcortical pathways responsible for interpretation of visual, auditory, kinesthetic, olfactory, and gustatory stimuli. Although end-organ damage may coexist to further compromise perception, deficient central processing occurs in most levels of TBI. Visual processing problems may be manifest by defects in visual organization, visual figure-ground awareness, three-dimensional perception, and visual tracking. These changes are often so subtle that the individual fails to recognize the existence of any problem. Rather, the presenting complaint is often anxiety that is situation specific or headache occurring after activities that stress the sensory network. For example, an interior designer decreased the complexity of wallpaper hung after the disastrous event of hanging an entire room's wallpaper upside down. In another situation, a seamstress pieced a pattern in such a manner that the sleeves were inside out. Auditory perceptual problems include auditory figure-ground, vigilance, localization, and attention disturbances. Although the individual may possess intact afferent pathways for hearing, central integrative deficits render the person functionally deaf (i.e., auditory agnosia or pure word deafness). Figure-ground deficits render the individual unable to accurately perceive one voice amidst a crowd of many, as may occur at a party or a mall. The inability to lock on to one stimulus source, again, is the underlying problem.

Olfactory disturbances may involve not only disruption of the olfactory nerve but also perceptual changes due to injury to the rhinencephalic cortex. Some association with sexual dysfunction exists in the literature, although no controlled study exists. These deficits have significant survival ramifications, as seen in the inability to smell smoke, food spoilage, or leaking natural gas. Adaptations to olfactory disturbances might include the use of smoke detectors, visual inspection of the contents of a container before ingestion, and gas alarms to warn of leakage.

Treatment

As shown in Chapter 4, Neuropsychiatric Assessment, comprehensive neuropsychological evaluation has been the mainstay of TBI intellectual assessment since the 1980s. The contributions of other rehabilitation professionals in the evaluation and treatment of neurocognitive and neurolinguistic deficits after brain injury have not consistently been appreciated (Levin et al. 1982, 1991; Prigatano 1986).

Although neurolinguistic experts and those with neurosensory integration backgrounds have been consulted in the area of treatment of TBI in children, a developmental approach has not been used in the evaluation and treatment of adults. In individuals who have sustained classic concussive injuries or mild TBI, the sensitivity of standardized neuropsychological testing batteries may miss the "higher" cognitive problems that require more facile manipulation of symbolic language. A comprehensive evaluation includes the assessments of the psychiatrist, neuropsychologist, occupational therapist, physical therapist, and speech-language pathologist. The clinical use of an Eriksonian model to identify the psychosocial stage of the patient in the rehabilitation setting provides an understanding of the emotional recovery from the traumatic event.

Development of basic trust in the form of a therapeutic alliance with the treatment team is the core necessity for successful outcome. Becoming increasingly independent in activities of daily living prepares the patient for the increasing complexity of group-based therapeutic activities. Competitive issues among group members arise at this stage, which require caution on the therapist's part to avoid unduly frustrating the patient. Gradually a sense of a new identity evolves, incorporating elements of the patient's preaccident style with the residua of the neurological damage. Attempts to seek intimacy with peers from the preinjury period may result in rejection due to antipathy for changes resulting from TBI or normal developmental maturation of those peers beyond the patient's current level. Creation of a productive enriching environment allows for continued growth and productivity, with the resulting personal satisfaction.

Therapeutic interventions combine the use of pharmacological manipulation with a series of structured exercises of graded difficulty. The use of splints and adaptive equipment supports maximal physical independence of the individual when recovery to premorbid functional levels would be impossible.

Just as TBI rarely results in an improved physical state, the patient's behavior is seldom improved after TBI. The goal of treatment is to return the person to his or her premorbid level of function. For the adult, the goal is to rehabilitate rather than habilitate.

Principles of Pharmacotherapy

Successful pharmacotherapy following TBI depends on the stability of basic physiological processes. Although some degree of relative improvement may be achieved without attention to the critical details discussed in this section, sustained improvement, avoidance of polypharmacy, and general health quality will be sacrificed. The following areas require investigation and stabilization (Table 13–6):

TABLE 13–6. Basic stabilization requirements to facilitate pharmacotherapy

Adequate hydration
Nutritional stability
Daily aerobic exercise
Restorative sleep
Hormonal stability
Adequate analgesia

1. *Hydration:* Inadequate water intake, either due to habit or loss of hypothalamic thirst drive, will compromise CNS function. Even relatively modest states of dehydration may affect fatigue, cognition, and attentional processes.
2. *Nutrition:* Failure to ingest adequate caloric requirements will reduce energy, contribute to agitation, and worsen distractibility. Hypothalamic factors may be involved with loss of hunger sensation; however, more typically, nutritional failures arise from the inability to effectively organize, plan, and execute the requisite menu planning, shopping, cooking, and time management on a daily basis. Overreliance on convenience foods or high-sugar snacks worsens affective and cognitive stability. Subtle alteration in olfaction will reduce the satisfaction derived from eating, resulting in either excessive or reduced intake.
3. *Exercise:* The role of regular aerobic exercise in improving the efficiency of brain metabolism has been well documented in those with TBI. A target of 45–60 minutes per day of exercise returns a five- to sevenfold increase in metabolic efficiency of the CNS.
4. *Sleep:* Sleep deprivation has a direct impact on judgment and problem solving. Preinjury sleep disorders must be defined and addressed. Abundant evidence exists of the impact of TBI on sleep architecture, REM entry, and restorative elements. Assessment for nocturnal hypoxemia using overnight pulse oximetry is warranted with referral for polysomnography as indicated. Percentage of sleep spent in slow-wave sleep (stages 3 and 4), REM latency, and the occurrence of central or obstructive apneic events must be defined. Laryngospasm related to reflux of stomach gorge may mandate dietary adjustment and use of proton pump antagonists. Nocturnal pain management, either through mechanical modification (sculpted foam pillows, wedges) or bedtime dosing of analgesic, is essential.
5. *Hormonal factors:* Central hypopituitary states following all levels of severity of TBI are well recognized (Schneider et al. 2007). Deficiencies of thyroxin, growth hormone, estrogen, and testosterone have been identified and affect mood, fatigue, and cognitive/executive efficiency. The importance of serial testing due to the potential conversion of normal endocrinological function to a deficient state is noted. Hormone replacement therapy, either temporary or permanent, is mandated.
6. *Pain management:* Adequate analgesia after the identification of all pain generators directly improves attention, multitasking, and executive functioning. In addition to nocturnal relief and improved sleep quality, the use of an extended-release/once-daily dosing

regimen reduces the risk of dyscompliance (failure to follow through because of neurocognitive issues).

Pharmacotherapy serves as a mechanism to provide a "splint" or "adaptive device" on the neurochemical milieu while the intrinsic healing of the CNS occurs. Selection of the agent is predicated on a cost-benefit analysis of desired therapeutic effects countered against the known side effects. This includes an awareness of the idiosyncratic responses observed in individuals after TBI (O'Shanick 1991). Indications and contraindications relate to those agents that can adversely impact the recovery of the CNS. These might include dopamine antagonists, which may inhibit recovery curves in the acute phase postinjury (Feeney et al. 1982). Anticholinergic agents may in high concentrations induce delirium or worsen cognitive performance (Nissen et al. 1987; O'Shanick 1991; Rusted and Warburton 1989). Agents that lower seizure threshold require careful monitoring to prevent seizure induction (O'Shanick and Zasler 1990). Any medication that shares metabolic degradation pathways with an anticonvulsant in use requires scrutiny of levels early in the course of therapy and regularly thereafter (O'Shanick 1987). A comprehensive review of pharmacological agents, indications, and caveats is found in Chapter 35, Psychopharmacology.

Psychotherapeutic Interventions

Verbal therapies with individuals with TBI require careful monitoring to ensure that auditory processing problems do not interfere with the therapeutic process. Short-term memory problems also may be mistaken for resistance in the setting of a traditional psychotherapeutic relationship. The use of a notebook or audiotape for the patient's benefit remedies this problem. A flexible treatment schedule that also includes a period with an involved outside observer provides corroborating data that may be unavailable to the patient because of frontal lobe injuries. It is important to exercise care with issues of a confidential nature that could compromise trust in the therapist. A close alliance with healthy family members can provide the therapist with a base of understanding of the system needs and tolerances.

Ylvisaker and Feeney (1996) described a model of supported cognition and self-advocacy to improve real-world executive functioning. Additional information concerning individual, behavioral, cognitive, and family therapies is given in Chapter 37, Cognitive Rehabilitation; Chapter 38, Behavioral Treatment; and Chapter 39, Complementary and Integrative Treatments.

KEY CLINICAL POINTS

- Clinically disruptive personality change following traumatic brain injury may mimic Cluster B personality traits, paranoia, or dependent/avoidant traits.
- When interviewing a patient with a suspected traumatic brain injury, one should stay alert for evidence of propositional language difficulties (e.g., hesitant or delayed responses, circumlocution, paraphasia, reduced expressive or receptive lexicon), pragmatic deficits (e.g., interruptions, impaired closure, impaired cohesion), and prosodic dysfunction (e.g., blunted inflection, inability to respond to humor/irony).
- Using both an open-ended style of interview ("Tell me about…") and a review of systems (yes-no format) to obtain the history will minimize underreporting due to impaired self-awareness.
- An interview with a collateral informant for complementary information on current and preinjury functioning is essential.
- Seventy percent of individuals with traumatic brain injury sustain injury to the frontal lobes.
- Impairment of auditory processing can mimic attention deficit disorder.
- Visual dependence to maintain balance can mimic avoidant, agoraphobic, or anxiety disorders.
- Treatment of personality change requires a comprehensive neurorehabilitation effort to reduce the anxiety generated by failure of preinjury sensory, cognitive, and executive capacities.

- Prior to pharmacological intervention, stabilization of hydration, nutrition, sleep, exercise, analgesia, and hormonal status must be addressed.

- An oral history and a mental status exam are not sufficient for examination of a patient with traumatic brain injury. A physical/neurological examination including testing of olfaction, auditory processing, visual-spatial integrity, and higher-level balance must be performed by the psychiatric physician.

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CHAPTER 14

Aggressive Disorders

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EXPLOSIVE AND VIOLENT BEHAVIOR HAS LONG been associated with focal brain lesions, as well as with diffuse damage to the central nervous system (CNS). Irritability and/or aggressiveness are major sources of disability to individuals with brain injury and sources of stress to their families. Agitation that occurs during the acute stages of recovery from brain injury can endanger the safety of the patients and their caregivers. Agitation may be predictive of longer length of hospital stay and decreased cognition (Bogner et al. 2001). Subsequently, low frustration tolerance and explosive behavior may develop that can be set off by minimal provocation or occur without warning. These episodes range in severity from irritability to outbursts that result in damage to property or assaults on others. In severe cases, it may be unsafe for affected individuals to remain in the community or with their families, and they often are referred to long-term psychiatric or neurobehavioral facilities. Therefore, it is essential that all psychiatrists be aware of neurologically induced aggression and its assessment and treatment so that they can provide effective care to patients with this condition and to their families.

Prevalence

It has been reported that during the acute recovery period, 35%–96% of individuals with traumatic brain injury (TBI) exhibit agitated behavior. After the acute recovery phase, irritability or bad temper is common. In follow-up periods ranging from 1 to 15 years after injury, these behaviors occurred in 31%–71% of patients who experienced severe TBI. Studies of mild TBI have evaluated individuals for much briefer periods of time: 1-year estimates of irritability, temper, or agitation from these studies range from 5% to 70%. There have been three prospective studies of the occurrence of aggression, agitation, or restlessness that has been monitored by an objective rating instrument, the Overt Aggression Scale (OAS) (Brooke et al. 1992; Rao et al. 2009; Tateno et al. 2003). Brooke and colleagues found that of 100 patients with severe traumatic brain injury (TBI) (Glasgow Coma Scale score <8, >1 hour of coma, and >1 week of hospitalization), only 11 patients exhibited agitated behavior. Only 3 patients manifested these behaviors for more than 1 week. However, 35 individuals were observed to be restless but not agitated. In a study of 89 patients assessed during the first 6 months after TBI, Tateno et al. (2003) found aggressive behavior in 33.7% of individuals with TBI, compared with 11.5% of patients with multiple trauma but without TBI. In a prospective study of 67 patients after TBI, Rao and colleagues (2009) found that 28.4% of the patients exhibited aggressive behavior, which, except for one of these patients, was exclusively verbal in nature.

In a study of psychiatric disorders in 100 self-referred individuals who had TBI several years earlier, Hibbard et al. (1998) found that 34% admitted to symptoms of irritability (i.e., having an increased number of arguments/fights, making quick, impulsive decisions, complaining, cursing at self, feeling impatient, or threatening to hurt self), and 14% admitted to aggressive behavior (i.e., cursing at others, screaming/yelling, breaking/throwing things, being arrested, hitting/pushing others, threatening to hurt others). In a survey of all skilled nursing facilities in Connecticut, 45% of facilities had individuals with a primary diagnosis of TBI who met the definition of agitation (Wolf et al. 1996). In a series of 67 patients admitted with mild to moderate TBI and rated prospectively, restlessness occurred in 40% and agitation occurred in 19% (van der Naalt et al. 2000). A small study of death row inmates found that 75% had a history of TBI (Freedman and Hemenway 2000). Carlsson et al. (1987) examined the relationship between the number of TBIs associated with loss of consciousness and various symptoms and demonstrated

that irritability increased with subsequent injuries. Of men who did not have head injuries with loss of consciousness, 21% reported irritability, whereas 31% of men with one injury with loss of consciousness and 33% of men with two or more injuries with loss of consciousness admitted to this symptom (P=0.0001). In an evaluation of 60 subjects in a county jail, those with TBI in the prior year had significantly worse anger and aggression and a trend toward poorer cognition and more psychiatric disorders (Slaughter et al. 2003). Finally, in a group of 458 research subjects, aggression was elevated as a function of TBI and personality disorder (Ferguson and Coccaro 2009).

Prediction of who will develop aggressive behaviors after brain injury is challenging. Risk factors may include irritability, impulsivity, and a preinjury history of aggression; neuropsychological test performance does not consistently predict propensity toward violence in those who have experienced brain injury (Greve et al. 2001). In a study of patients in the first 6 months after TBI, aggressive behavior was significantly associated with the presence of major depression, frontal lobe lesions, poor premorbid social functioning, and a history of alcohol and substance abuse (Tateno et al. 2003). In a group of 30 patients who developed major depression in the first year after TBI, 17 patients (56.7%) exhibited aggressive behavior (Jorge et al. 2004). In a group of 32 individuals who were over 2 years post-TBI with mild to moderate irritability (as measured by the Neuropsychiatric Inventory [Cummings et al. 1994]), irritability was significantly related to depression, social support, marriage quality, transportation, sleep, and fatigue (Hammond et al. 2006). In a study of 228 patients with moderate to severe TBI followed up to 5 years after injury, 25% were classified as aggressive by the OAS. The study found that depression was the most significant factor associated with aggression, and that depression was also associated with other traumatic complaints, younger age at injury, and low life satisfaction (Baguley et al. 2006). In a group of 287 patients with severe TBI, 134 patients exhibited aggressive behavior as rated on the Neurobehavioral Rating Scale (Wood and Liossi 2006). Individuals with aggressive behavior had increased disinhibition, social withdrawal, tiredness, poor drive/motivation, and poor sleep patterns. They were more likely to have a low IQ, lower socioeconomic status, and to be male. In addition, the aggressive group demonstrated more impairment in verbal memory and visuospatial abilities, suggesting more dominant hemisphere dysfunction. In the first 3 months after TBI, new-onset major depression, poorer social functioning, and increased dependency in activities of daily living were associated with verbal aggression but not a history of substance use (Rao et al. 2009).

Characteristics of Aggression After Brain Injury

In the acute phase after brain injury, patients often experience a period of agitation and confusion that may last from days to months. In rehabilitation facilities, these patients are described as "confused, agitated" (a Rancho Los Amigos Scale score of 4 [Hagen et al. 1972; see Table 4–6 in Chapter 4, Neuropsychiatric Assessment, p. 59]) and have characteristics similar to those associated with delirium (see Chapter 9, Delirium and Posttraumatic Confusion). Brooke et al. (1992) suggest that agitation usually appears in the first 2 weeks of hospitalization and resolves within 2 weeks. Restlessness may appear after 2 months and may persist for 4–6 weeks. In our clinical experience, after the acute recovery phase has resolved, continuing aggressive outbursts have typical characteristics (Table 14–1). These episodes may occur in the presence of other emotional changes or neurological disorders that occur secondary to brain injury, such as mood lability or seizures.

TABLE 14–1. Characteristic features of aggression after brain injury

Type	Features
Reactive	Triggered by modest or trivial stimuli
Nonreflective	Usually does not involve premeditation or planning
Nonpurposeful	Aggression serves no obvious long-term aims or goals
Explosive	Buildup is NOT gradual
Periodic	Brief outbursts of rage and aggression punctuated by long periods of relative calm
Ego-dystonic	After outbursts, patients are upset, concerned, and/or embarrassed, as opposed to blaming others or justifying behavior

Certain behavioral syndromes have been related to damage to specific areas of the frontal lobe. The orbitofrontal syndrome is associated with behavioral excesses (e.g., impulsivity, disinhibition, hyperactivity, distractibility, and mood lability). Outbursts of rage and violent behavior occur after damage to the inferior orbital surface of the frontal lobe and anterior temporal lobes. The diagnostic category in DSM-IV-TR is "personality change due to a general medical condition" (American Psychiatric Association 2000) (Table 14–2). Patients with aggressive behavior would be specified as "aggressive type," whereas those with mood lability would be specified as "labile type."

Pathophysiology of Aggression

Neuroanatomy of Aggression

Many areas of the brain are involved in the production and mediation of aggressive behavior, and lesions at different levels of neuronal organization can elicit specific types of aggressive behaviors. Van der Naalt (2000) found that more lesions, mainly localized in the frontotemporal region, were found in those patients manifesting restlessness and agitation (81% vs. 39%). Frontal lesions have been found to be associated with aggressive behavior by some groups (Tateno et al. 2003) but not by others (Rao et al. 2009). Several anatomic areas of the brain are important in the production (or lack of suppression) of "irritative aggression," that is, feelings of irritability with occasional

TABLE 14–2. DSM-IV-TR criteria for personality change due to a general medical condition

Diagnostic criteria for personality change due to a general medical condition

A. A persistent personality disturbance that represents a change from the individual's previous characteristic personality pattern. (In children, the disturbance involves a marked deviation from normal development or a significant change in the child's usual behavior patterns lasting at least 1 year.)

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder (including other mental disorders due to a general medical condition).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify type:

Labile Type: if the predominant feature is affective lability

Disinhibited Type: if the predominant feature is poor impulse control as evidenced by sexual indiscretions, etc.

Aggressive Type: if the predominant feature is aggressive behavior

Apathetic Type: if the predominant feature is marked apathy and indifference

Paranoid Type: if the predominant feature is suspiciousness or paranoid ideation

Other Type: if the presentation is not characterized by any of the above subtypes

Combined Type: if more than one feature predominates in the clinical picture

Unspecified Type

Source. Reprinted from the *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000. Used with permission. Copyright © 2000 American Psychiatric Association.

explosions. Table 14–3 summarizes the roles of key regions of the brain in mediating aggression. Many areas of the brain are involved in the production and mediation of aggressive behavior, and lesions at different levels of neuronal organization can elicit specific types of aggressive behaviors.

Hypothalamus

The regulation of the neuroendocrine and autonomic responses is controlled by the hypothalamus, which is involved in "flight or fight" reactions. Although stimulation of areas of the hypothalamus have produced aggressive behavior in animals and in patients with tumors, this is probably an infrequent cause for post-TBI aggression.

TABLE 14–3. Neuropathology of aggression

Locus	Activity
Hypothalamus	Orchestrates neuroendocrine response via sympathetic arousal, monitors internal status
Limbic system	Mediates impulses from prefrontal cortex, adds emotional content to cognition
Amygdala	Activates and/or suppresses hypothalamus, input from neocortex
Temporal cortex	Is associated with aggression in both ictal and interictal status
Frontal neocortex	Modulates limbic and hypothalamic activity, associated with social and judgment aspects of aggression

Limbic System

The limbic system, especially the amygdala, is responsible for mediating impulses from the prefrontal cortex and hypothalamus, and it adds emotional content to cognition and to associating biological drives to specific stimuli (e.g., searching for food when hungry) (Halgren 1992). Activation of the amygdala, which can occur in seizurelike states or in kindling, may result in enhanced emotional reactions, such as outrage at personal slights. Damage to the amygdaloid area has resulted in violent behavior (Tonkonogy 1991). Injury to the anterior temporal lobe, which is a common site for contusions, has been associated with the "dyscontrol syndrome." Some patients with temporal lobe epilepsy exhibit emotional lability, impairment of impulse control, and suspiciousness (Garyfallos et al. 1988).

Neocortex

The most recent region of the brain to evolve, the neocortex, coordinates timing and observation of social cues, often before the expression of associated emotions. Because of the location of prominent bony protuberances in the base of the skull, this area of the brain is highly vulnerable to traumatic injury. Lesions in this area give rise to disinhibited anger after minimal provocation characterized by an individual showing little regard for the consequences of the affect or behavior. Patients with violent behavior have been found to have a high frequency of frontal lobe lesions (Heinrichs 1989). Injury to the orbitofrontal region may put an individual at a particularly high risk for commission of violent acts (Brower and Price 2001). New et al. (2002) used positron emission tomography to assess regional metabolic activity in response to a serotonergic stimulus in patients (without TBI) who manifested impulsive aggression. They found that the patients did not activate the left anteromedial orbital cortex (as did nonaggressive control subjects), and the anterior cingulate was deactivated. The posterior cingulate was activitated in patients and deactivated in control subjects. Tateno et al. (2003) found that the frequency of frontal lobe lesions was significantly higher among aggressive patients, and those

with focal frontal lesions exhibited higher aggressive scores as measured by the OAS, but Rao et al. (2009) did not find a difference. Those individuals with TBI who were nonaggressive had a greater frequency of diffuse injury. Frontal lesions may result in the sudden discharge of limbic- and/or amygdala-generated affects—affects that are no longer modulated, processed, or inhibited by the frontal lobe. In this condition, the patient overreacts with rage and/or aggression on thoughts or feelings that would have ordinarily been modulated, inhibited, or suppressed. In healthy volunteers, imagined aggressive behaviors were associated with significant emotional reactivity and cerebral blood flow reductions in the ventromedial prefrontal cortex, suggesting that a functional deactivation occurs (Pietrini et al. 2000). We hypothesize that injury to this area causes a structural deactivation, which "deinhibits" limbic structures.

Neurotransmitters in Aggression

Many neurotransmitters are involved in the mediation of aggression. Among the neurotransmitter systems, serotonin, norepinephrine (NE), dopamine, acetylcholine, and the γ-aminobutyric acid (GABA) systems have prominent roles in influencing aggressive behavior. It is often difficult to translate studies of aggression in various species of animals to a complex human behavior. Multiple neurotransmitter systems may be altered simultaneously by an injury that affects diffuse areas of the brain, and it may not be possible to relate any one neurotransmitter change to a specific behavior, such as aggression. In addition, different transmitters affect one another, and frequently the critical factor is the relationship among the neurotransmitters. However, in reviewing the available research data, we can advance certain generalizations that have merit in helping researchers understand the neurobiology of aggression and provide treatment. The alterations in neurotransmitters after TBI are discussed elsewhere (see Chapter 35, Psychopharmacology). The possible role of these neurotransmitters in producing or modulating aggressive behavior is discussed later in this chapter.

Animal studies suggest that NE enhances aggressive behavior, including sham rage, affective aggression, and shock-induced fighting (Eichelman 1987). Humans who exhibit aggressive or impulsive behavior have been shown to have increased levels of the NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) (Brown et al. 1979). Stimulation of the amygdala produces sham rage and is associated with a decrease in brainstem levels of NE (indicative of NE release) (Reis 1972).

Lowered levels of serotonergic activity have been associated with increased aggression in a number of studies. Clinical studies have confirmed the role of decreased serotonin in the expression of aggressiveness and impulsivity in humans (Kruesi et al. 1992; Linnoila and Virkkunen 1992), particularly as it applies to self-destructive acts.

Some studies have shown an increase in 5-hydroxytryptamine type 2 (5-HT_2) receptor binding in the frontal cortex of suicide victims (Arango et al. 1990), although not all results are consistent with these findings (Cheetham et al. 1988). A link between the gene for tryptophan hydroxylase and levels of cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) in impulsive-aggressive individuals has been reported (Nielsen et al. 1994). The 5-HT_2 receptor antagonists, including antipsychotic drugs, have antiaggressive properties (Mann 1995). Other work looking at receptor subtypes in rats found multifaceted relationships between serotonin receptor type and aggression. Only 5-HT_2 agonists decreased defensive aggression, but agonists 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 all reduced offensive aggression (Muehlencamp et al. 1995). It has been reported that deleting the 5-HT_{1B} gene increases aggression (Hen et al. 1993).

Increases in dopamine may lead to aggression in several animal models (Eichelman 1987), and agitation is a common symptom in schizophrenia, often treated with antidopaminergic medications. Levodopa has been shown to cause aggression in animals, and personality changes in Parkinson's disease patients treated with this medication have also been reported (Lammers and van Rossum 1968; Saint-Cyr et al. 1993).

Monoamine oxidase inhibitor type A is important for the catabolism for dopamine, norepinephrine, and serotonin. Aggression, especially in response to provocation, is more common in subjects with low activity (McDermott et al. 2009). Thus, some individuals may be more predisposed genetically to aggression after experiencing TBI.

Acetylcholine has been reported to increase aggressive behaviors (Eichelman 1987). However, use of acetylcholinesterase inhibitors has been suggested as a treatment for disruptive patients with Alzheimer's disease (Kaufer et al. 1998).

GABA is an inhibitory neurotransmitter found throughout the brain. Although no studies have examined GABA levels after brain injury, it would be expected that injured neurons would produce less GABA. Increasing GABA via benzodiazepines results in reduced aggressive behavior in animals (Eichelman 1987).

Physiology of Aggression

Aggressive behavior may result from neuronal excitability of limbic system structures. For example, subconvulsive stimulation (i.e., kindling) of the amygdala leads to permanent changes in neuronal excitability (Post et al. 1982). Epileptogenic lesions in the hippocampus in cats, induced by the injection of the excitotoxic substance kainic acid, result in interictal defensive rage reactions (Engel et al. 1991). During periods when the cat experiences partial seizures, the animal exhibits heightened emotional reactivity and lability. In addition, defensive reactions can be elicited by excitatory injections to the midbrain periaqueductal gray region. Hypothalamus-induced rage reactions can be modulated by amygdaloid kindling.

Assessment

Differential Diagnosis

Individuals who exhibit aggressive behavior after sustaining TBI require a thorough assessment. Multiple factors may play a significant role in the production of aggressive behaviors in these patients. During the time period of

emergence from coma, agitated behaviors can occur as the result of delirium. The usual clinical picture is one of restlessness, confusion, and disorientation. (The assessment and treatment of delirium are discussed in Chapter 9, Delirium and Posttraumatic Confusion.) For patients who become aggressive after TBI, it is important to systematically assess the presence of concurrent neuropsychiatric disorders, because such assessment may guide subsequent treatment. Thus, the clinician must diagnose psychosis, depression, mania, mood lability, anxiety, seizure disorders, and other concurrent neurological conditions.

When aggressive behavior occurs during later stages of recovery, after confusion and posttraumatic amnesia (PTA) have resolved, it must be determined whether the aggressivity and impulsivity of the individual antedated, was caused by, or was aggravated by the brain injury. Those who have experienced a TBI may have a history of neuropsychiatric problems including learning disabilities, attentional deficits, behavioral problems, or personality disorders. A preinjury history of drug and substance abuse may be associated with aggressive behavior in the first 6 months after TBI (Tateno et al. 2003). Coexistent anxiety and depressive disorders are associated with increased aggression and irritability (Baguley et al. 2006; Hibbard et al. 1998; Rao et al. 2009; Tateno et al. 2003).

Because previous impulse dyscontrol and lability are exacerbated by brain injury, traits intensify after damage to the prefrontal areas and other brain regions that inhibit preexisting aggressive impulses. Many patients are able to differentiate between the aggressivity exhibited before brain injury and their current dyscontrol. One patient stated, "Before the accident, I engaged in hostile behavior when I wanted to and when it served my purpose; now I have no control over when I explode."

Drug effects and side effects commonly result in disinhibition or irritability (Table 14–4). By far, the drug most commonly associated with aggression is alcohol, during both intoxication and withdrawal. Patients who were using alcohol when they incurred a brain injury exhibit longer durations of agitation compared to those of patients with TBI with no detectable blood alcohol level at the time of hospitalization (Sparadeo and Gill 1989). Stimulating drugs, such as cocaine and amphetamines, as well as the stimulating antidepressants may produce severe anxiety and agitation in patients with or without brain lesions. Because patients with TBI have an increased occurrence of concomitant alcohol or substance abuse, the clinician must consider the effects of illicit substances in all TBI patients with irritability. Antipsychotic medications often increase agitation through anticholinergic side effects, and agitation and irritability usually accompany severe akathisia. Many other drugs may produce confusional states, especially anticholinergic medications that cause agitated delirium. Drugs such as the tricyclic antidepressants (e.g., amitriptyline, imipramine, and doxepin) and the aliphatic phenothiazine antipsychotic drugs (e.g., chlorpromazine and thioridazine) are well known to have potent anticholinergic effects. However, other drugs have anticholinergic properties that are usually not considered to have these effects. These drugs include digoxin, ranitidine, cimetidine, theophylline, nifedipine, codeine, and furosemide (Tune et al. 1992).

TABLE 14–4. Medications and drugs associated with aggression

Alcohol: intoxication and withdrawal states
Hypnotic and antianxiety agents (barbiturates and benzodiazepines): intoxication and withdrawal states
Analgesics (opiates and other narcotics): intoxication and withdrawal states
Steroids (prednisone, cortisone, and anabolic steroids)
Antidepressants: especially in initial phases of treatment
Amphetamines and cocaine: aggression associated with manic excitement in early stages of abuse and secondary to paranoid ideation in later stages of use
Antipsychotics: high-potency agents that lead to akathisia
Anticholinergic drugs (including over-the-counter sedatives) associated with delirium and central anticholinergic syndrome

TABLE 14–5. Common etiologies of aggression in individuals with traumatic brain injury

Medications, alcohol and other abused substances, and over-the-counter drugs
Delirium (hypoxia, electrolyte imbalance, anesthesia and surgery, uremia, and so on)
Alzheimer's disease
Infectious diseases (encephalitis, meningitis, pneumonia, urinary tract infections)
Epilepsy (ictal, postictal, and interictal)
Metabolic disorders (hyperthyroidism or hypothyroidism, hypoglycemia, vitamin deficiencies)

Patients with TBI are susceptible to developing other medical disorders that may increase aggressive behaviors (Table 14–5), and comorbidity must always be considered in the individual who exhibits agitation after TBI. The clinician should not, a priori, assume that the brain injury per se is the cause of the aggressivity but rather should assess the patient for the presence of other common etiologies of aggression. Because patients with neurological disorders are more susceptible to accidents, falls, and other sources of brain disorders, a neurological disorder may be the "underlying condition" that leads to the traumatic injury. In addition, when there are exacerbations or recurrences of aggressive behavior in a patient who has been in good control, an investigation must be completed to search for other etiologies, such as medication effects, infections, pain, or changes in social circumstances.

Studies of the emotional and psychiatric syndromes associated with epilepsy have documented an increase in hostility, irritability, and aggression interictally (Mendez et al. 1986; Robertson et al. 1987). Weiger and Bear (1988) describe interictal aggression in patients with temporal lobe epilepsy. They have observed that interictal aggression is characterized by behavior that is justified on moral or ethical grounds and may develop over protracted periods of time. This aggressive behavior is distinguished from the violent behavior that occurs during the ictal or postictal period, which is char-

acterized by its nondirected quality and the presence of an altered level of consciousness. Even in patients with temporal lobe epilepsy, there are many factors that influence aggression. In a retrospective survey of aggressive and nonaggressive patients with temporal lobe epilepsy, Herzberg and Fenwick (1988) found that aggressive behavior was associated with early onset of seizures, a long duration of behavioral problems, and the male gender. There was no significant correlation of aggression with electroencephalogram or computed tomography scan abnormalities or a history of psychosis. These findings are consistent with those of Stevens and Hermann (1981), who critically examined the scientific literature on the association between temporal lobe epilepsy and violent behavior. They concluded that the significant factor predisposing to violence is the site of the lesion, particularly damage or dysfunction in the limbic areas of the brain.

Psychosocial factors are important in the expression of aggressive behavior. Those who have experienced a TBI may be acutely sensitive to changes in their environment or to variations in emotional support. Poorer social functioning and more difficulty in activities of daily living are associated with aggressive behavior in the first few months after TBI (Rao et al. 2009). Social conditions and support networks that existed before the injury affect the symptoms and course of recovery (Brown et al. 1981). Factors such as higher levels of education, income, and socioeconomic status positively affect a person's ability to return to work after mild brain injury (Rimel et al. 1981). Certain patients become aggressive only in specific circumstances, such as in the presence of particular family members. This suggests that there is some maintained level of control over aggressive behaviors and that the level of control may be modified by behavioral therapeutic techniques. Most families require professional support to adjust to the impulsive behavior of a violent relative with organic dyscontrol of aggression. Frequently, efforts to avoid triggering a rageful or violent episode lead families to withdraw from a patient. This can result in a paradox: the patient learns to gain attention by being aggressive. Thus, the unwanted behavior is unwittingly reinforced by familial withdrawal.

Documentation of Aggressive Behavior

Before therapeutic intervention is initiated to treat violent behavior, the clinician should document the baseline frequency of these behaviors. There are spontaneous day-to-day and week-to-week fluctuations in aggression that cannot be validly interpreted without prospective documentation. In our study of over 4,000 aggressive episodes in chronically hospitalized patients, hospital records failed to document 50%–75% of episodes (Silver and Yudofsky 1987, 1991). This study and others also indicated that aggression—like certain mood disorders—may have cyclic exacerbations. It is essential that the clinician establish a treatment plan, using objective documentation of aggressive episodes to monitor the efficacy of interventions and to designate specific time frames for the initiation and discontinuation of pharmacotherapy for acute episodes and for the initiation of pharmacotherapy for chronic aggressive behavior.

The OAS is an operationalized instrument of proven reliability and validity that can be used to easily and effectively rate aggressive behavior in patients with a wide range of disorders (Silver and Yudofsky 1987, 1991; Yudofsky et al. 1986) (Figure 14–1). The scale includes items that assess verbal aggression, physical aggression against objects, physical aggression against self, and physical aggression against others. Each category of aggression has four levels of severity that are defined by objective criteria. An aggression score can be derived by obtaining the sum of the most severe ratings of each type of aggressive behavior over a particular time course. Aggressive behavior can be monitored by staff or family members using the OAS. Documentation of agitation can be objectively rated with the Overt Agitation Severity Scale (Yudofsky et al. 1997) (Figure 14–2). The Agitated Behavior Scale (Bogner et al. 1999), which rates 14 problematic behaviors, has been used in acute and long-term rehabilitation settings (Figure 14–3).

Treatment

Aggressive and agitated behaviors may be treated in a variety of settings, ranging from the acute brain injury unit in a general hospital, to a "neurobehavioral" unit in a rehabilitation facility, to outpatient environments including the home setting. A multifactorial, multidisciplinary, collaborative approach to treatment is necessary in most cases. The continuation of family treatments, psychopharmacological interventions, and insight-oriented psychotherapeutic approaches is often required. In establishing a treatment plan for patients with agitation or aggression, the overarching principle is that diagnosis comes before treatment. The history of the development of symptoms in a biopsychosocial context is usually the most critical part of the evaluation. It is essential to determine the mental status of the patient before the agitated or aggressive event, the nature of the precipitant, the physical and social environment in which the behavior occurs, the ways in which the event is mitigated, and the primary and secondary gains related to agitation and aggression (Corrigan et al. 1993; Yudofsky et al. 1998).

Although there is no medication that is approved by the U.S. Food and Drug Administration specifically for the treatment of aggression, medications are widely used (and commonly misused) in the management of patients with acute or chronic aggression. The reported effectiveness of these medications is highly variable, as are the reported rationales for their prescription. Some of these medications are offered to inhibit excessive activity in temporolimbic areas (e.g., anticonvulsants), to reduce "hyperactive" limbic monoaminergic neurotransmission (e.g., noradrenergic blockade with propranolol, dopaminergic blockade with haloperidol), or to augment orbitofrontal and/or dorsolateral prefrontal cortical activity with monoaminergic agonists (e.g., amantadine, methylphenidate, perhaps buspirone) or increase serotonergic input (i.e., selective serotonin reuptake inhibitors).

Unfortunately, there is a paucity of rigorous, double-blind, placebo-controlled studies (i.e., Level I studies) and even prospective cohort studies (i.e., Level II) to guide clinicians in the use of pharmacological interventions (Fleminger et al. 2006; Warden et al. 2006). Considering the difficult problem of aggression, the lack of well-controlled studies is concerning. The "best" evidence is for β-blockers, with little evidence to support any other medication, other

OVERT AGGRESSION SCALE (OAS)

Stuart Yudofsky, M.D., Jonathan Silver, M.D., Wynn Jackson, M.D., and Jean Endicott, Ph.D.

IDENTIFYING DATA

Name of Patient	Name of Rater
Sex of Patient: 1 Male 2 Female	Date / / (mo/da/yr) Shift: 1 Night 2 Day 3 Evening

☐ No aggressive incident(s) (verbal or physical) against self, others, or objects during the shift. (check here)

AGGRESSIVE BEHAVIOR (Check all that apply)

VERBAL AGGRESSION	PHYSICAL AGGRESSION AGAINST SELF
☐ Makes loud noises, shouts angrily ☐ Yells mild personal insults, e.g., "You're stupid!" ☐ Curses viciously, uses foul language in anger, makes moderate threats to others or self ☐ Makes clear threats of violence toward others or self (I'm going to kill you.) or requests to help to control self	☐ Picks or scratches skin, hits self, pulls hair, (with no or minor injury only) ☐ Bangs head, hits fist into objects, throws self onto floor or into objects (hurts self without serious injury) ☐ Small cuts or bruises, minor burns ☐ Mutilates self, makes deep cuts, bites that bleed, internal injury fracture, loss of consciousness, loss of teeth
PHYSICAL AGGRESSION AGAINST OBJECTS	**PHYSICAL AGGRESSION AGAINST OTHER PEOPLE**
☐ Slams door, scatters clothing, makes a mess ☐ Throws objects down, kicks furniture without breaking it, marks the wall ☐ Break objects, smashes windows ☐ Sets fires, throws objects dangerously	☐ Makes threatening gesture, swings at people, grabs at clothes ☐ Strikes, kicks, pushes, pulls hair (without injury to them) ☐ Attacks others causing mild–moderate physical injury (bruises, sprain, welts) ☐ Attacks others causing severe physical injury (broken bones, deep lacerations, internal injury)
Time incident began: _ _ : _ _ AM/PM	Duration of incident: _ _ : _ _ (hours/minutes)

INTERVENTION (check all that apply)

☐ None	☐ Immediate medication given by mouth	☐ Use of restraints
☐ Talking to patient	☐ Immediate medication given by injection	☐ Injury requires immediate medical treatment for patient
☐ Closer observation	☐ Isolation without seclusion (time out)	☐ Injury requires immediate treatment for other person
☐ Holding patient	☐ Seclusion	

COMMENTS

FIGURE 14–1. The Overt Aggression Scale.

Source. Reprinted from Yudofsky SC, Silver JM, Jackson W, et al.: "The Overt Aggression Scale for the Objective Rating of Verbal and Physical Aggression." *American Journal of Psychiatry* 143:35–39, 1986. Used with permission.

than small case series or reports. Because detailed review of the literature, including case reports, is found elsewhere (Fleminger et al. 2006; Silver et al. 2005; Warden et al. 2006; Yudofsky et al. 1998), only the more important studies will be mentioned in this chapter.

The approach we suggest starts with appropriate assessment of possible etiologies of these behaviors. Treatment is focused on the occurrence of comorbid neuropsychiatric conditions (e.g., depression, psychosis, insomnia, anxiety, delirium) (Figure 14–4), whether the treatment is in the acute (hours to days) or chronic (weeks to months) phase, and the severity of the behavior (mild to severe). The clinician must be aware that patients may not respond to just one medication but instead may require combination treatment, similar to the pharmacotherapeutic treatment for refractory depression.

OVERT AGITATION SEVERITY SCALE (OASS)

Yudofsky SC, Kopecky HJ, Kunik M, Silver JM, Endicott J

INTENSITY (I)	BEHAVIOR	FREQUENCY (F)					SEVERITY SCORE (SS) (IxF=SS)
A.	**Vocalizations & Oral/Facial Movements**	NOT PRESENT	RARELY	SOME OF THE TIME	MOST OF THE TIME	ALWAYS PRESENT	
1	Whimpering, whining, moaning, grunting, crying	0	1	2	3	4	=
2	Smacking or licking of lips, chewing, clenching jaw; licking, grimacing, spitting	0	1	2	3	4	=
3	Rocking, twisting, banging of head	0	1	2	3	4	=
4	Vocal perseverating, screaming, cursing, threatening, wailing	0	1	2	3	4	=
B.	**Upper Torso & Upper Extremity Movements**						
1	Tapping fingers, fidgeting, or wringing of hands, swinging or flailing arms	0	1	2	3	4	=
2	Task perseverating (e.g., opening and closing drawers, folding and unfolding clothes, picking at objects, clothes, or self, pulling at own hair)	0	1	2	3	4	=
3	Rocking (back & forth), bobbing (up and down), twisting, writhing of torso; rubbing or masturbating self	0	1	2	3	4	=
4	Slapping, swatting, hitting at objects or others	0	1	2	3	4	=
C.	**Lower Extremity Movements**						
1	Tapping toes, clenching toes, tapping heel, extending, flexing or twisting foot	0	1	2	3	4	=
2	Shaking legs, tapping knees and/or thighs, thrusting pelvis, stomping	0	1	2	3	4	=
3	Pacing, wandering	0	1	2	3	4	=
4	Thrashing legs, kicking at objects or others	0	1	2	3	4	=

Total OASS ☐

Subtract Baseline OASS ☐

Revised OASS ☐

Instructions for Completing Form

Step One: For each behavior, circle the corresponding frequency after 15 minutes of observation.

Step Two: For every behavior exhibited, multiply the Intensity score (I) by the Frequency (F) and record as the Severity Score (SS).

Step Three: For the OVERT AGITATION SEVERITY SCORE (OASS), total all severity scores and record as Total OASS.

Step Four: Does this patient have a Neuromuscular Disorder (i.e., Parkinson's Disease, tardive dyskinesia), affecting Total OASS? Yes No

Step Five: If yes, please establish a baseline OASS in non-agitated state and subtract from above Total OASS for Revised OASS.

COMMENTS:

DIAGNOSIS:_____ NAME OF RATER:_____

SEX OF PATIENT: MALE(1); FEMALE(2) TIME OF OBSERVATION:_____

AGE:_____ DATE:_____

CURRENT MEDICATION:		
Name:	Dose:	Frequency:
Name:	Dose:	Frequency:
Name:	Dose:	Frequency:
Name:	Dose:	Frequency:
Name:	Dose:	Frequency:

FIGURE 14–2. The Overt Agitation Severity Scale.

Source. Reprinted from Yudofsky SC, Kopecky HJ, Kunik ME, et al.: "The Overt Agitation Severity Scale for the Objective Rating of Agitation." *The Journal of Neuropsychiatry and Clinical Neurosciences* 9:541–548, 1997. Used with permission.

Patient _____ Period of Observation:
Observ. Environ._____ From:_____am/pm___/___/___
Rater/Disc. _____ To:_____am/pm___/___/___

At the end of the observation period, indicate whether the behavior described in each item was present and, if so, to what degree: slight, moderate, or extreme. Use the following numerical values and criteria for your ratings.

1 = Absent: the behavior is not present.
2 = Present to a slight degree: the behavior is present but does not prevent the conduct of other contextually appropriate behavior. (The individual may redirect spontaneously, or the continuation of the agitated behavior does not disrupt appropriate behavior.)
3 = Present to a moderate degree: the individual needs to be redirected from an agitated to an appropriate behavior but benefits from such cueing.
4 = Present to an extreme degree: the individual is not able to engage in appropriate behavior because of the interference of the agitated behavior, even when external cueing or redirection is provided.

DO NOT LEAVE BLANKS.

____ 1. Short attention span, easy distractibility, inability to concentrate.
____ 2. Impulsive, impatient, low tolerance for pain or frustration.
____ 3. Uncooperative, resistant to care, demanding.
____ 4. Violent and/or threatening violence toward people or property.
____ 5. Explosive and/or unpredictable anger.
____ 6. Rocking, rubbing, moaning, or other self-stimulating behavior.
____ 7. Pulling at tubes, restraints, etc.
____ 8. Wandering from treatment areas.
____ 9. Restlessness, pacing, excessive movement.
____10. Repetitive behaviors, motor and/or verbal.
____11. Rapid, loud, or excessive talking.
____12. Sudden changes of mood.
____13. Easily initiated or excessive crying and/or laughter.
____14. Self-abusiveness, physical and/or verbal.
____ Total Score

FIGURE 14–3. The Agitated Behavior Scale.
Source. Adapted from Bogner et al. 1999.

Acute Aggression

Antipsychotic Medications

Antipsychotics are the most commonly used medications in the treatment of aggression. Although these agents are appropriate and effective when aggression is derivative of active psychosis, the use of antipsychotic agents to treat chronic aggression, especially chronic aggression secondary to TBI, is often ineffective, and the patient may develop serious complications. Usually, it is the sedative side effects rather than the antipsychotic properties of antipsychotics that are used (i.e., misused) to "treat" (i.e., mask) the aggression. Often, patients develop tolerance to their sedative effects, and therefore require increasing doses. For the first-generation antipsychotic medications, this can result in extrapyramidal side effects (EPS) and anticholinergic-related side effects occur. Paradoxically (and frequently), because of the development of akathisia, the patient may become more agitated and restless as the dose of neuroleptic is increased, especially when a high-potency antipsychotic such as haloperidol (Haldol) is administered. The akathisia is often mistaken for increased irritability and agitation, and a vicious cycle of increasing neuroleptics and worsening akathisias occurs. Many of the second-generation antipsychotic medications may result in significant weight gain and metabolic syndrome.

There is some evidence from studies of injury to motor neurons in animals that have found that haloperidol decreases recovery. This effect was only seen when animals actively participated in a behavioral task and not when the animals were restrained after drug administration (Feeney et al. 1982). It is possible that the effect on decreasing dopamine and inhibiting neuronal function, which may be the mechanism of action to treat aggression, may have other detrimental effects on recovery. This effect may not be seen with the "atypical" antipsychotic medications. Olanzapine did not impair cognitive performance in rats, whereas haloperidol did (Wilson et al. 2003). Rao et al. (1985) found that patients treated with haloperidol in the acute period after TBI experienced significantly longer periods of PTA, although the acute rehabilitation outcome did not differ from that of those not treated with this medication. Whether this finding is generalizable to recovery in brain injury and with the atypical antipsychotics remains

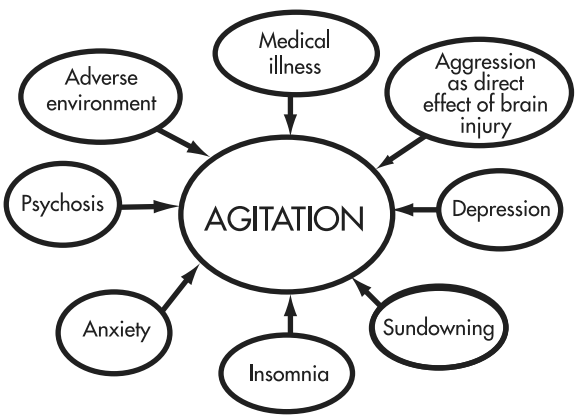


FIGURE 14–4. Neuropsychiatric factors associated with agitation and aggression.

unclear. However, the finding raises important potential risk/benefit issues that must be considered before antipsychotic drugs are used to treat aggressive behavior in patients with neuronal damage.

In patients with brain injury and acute aggression, we recommend starting an atypical antipsychotic medication such as risperidone at low doses of 0.5 mg orally with repeated administration every hour until control of aggression is achieved. If after several administrations of risperidone the patient's aggressive behavior does not improve, the hourly dose may be increased until the patient is so sedated as to no longer exhibit agitation or violence. Once the patient is not aggressive for 48 hours, the daily dosage should be decreased gradually (e.g., by 25% per day) to ascertain whether aggressive behavior reemerges. In this case, consideration should then be given to whether it is best to increase the dose of risperidone and/or initiate treatment with a more specific antiaggressive drug. Other atypical antipsychotic medications may be used, although there is only limited published experience with the use of quetiapine in TBI patients (Kim and Bijlani 2006).

Sedatives and Hypnotics

There is an inconsistent literature on the effects of the benzodiazepines in the treatment of aggression. The sedative properties of benzodiazepines are especially helpful in the management of acute agitation and aggression. Most likely, this is because of the amplifying effect of benzodiazepines on the inhibitory neurotransmitter GABA. Paradoxically, several studies report increased hostility and aggression and the induction of rage in patients treated with benzodiazepines, although this appears to be rare. Benzodiazepines can produce amnesia, and preexisting memory dysfunction can be exacerbated by the use of benzodiazepines. Brain-injured patients may also experience increased problems with coordination and balance with benzodiazepine use. For this reason, we prefer not to use benzodiazepines in the treatment of acute aggression in patients with TBI.

Chronic Aggression

If a patient continues to exhibit periods of agitation or aggression beyond several weeks, the use of specific antiaggressive medications should be initiated to prevent these episodes from occurring. Because no medication has been approved by the Food and Drug Administration for treatment of aggression, the clinician must use medications that may be antiaggressive but that have been approved for other uses (e.g., seizure disorders, depression, hypertension) (Yudofsky et al. 1998). Although the pathophysiology of aggression may not be similar in different neuropsychiatric disorders (e.g., dementia, mental retardation), we often have to extrapolate from data obtained in non-TBI studies.

Antipsychotic Medications

If, after thorough clinical evaluation, it is determined that the aggressive episodes result from psychosis, such as paranoid delusions or command hallucinations, then antipsychotic medications are the treatment of choice. There are no controlled studies of antipsychotic medications for treatment of aggression (or psychosis) after TBI.

Antianxiety Medications

Serotonin appears to be a key neurotransmitter in the modulation of aggressive behavior. In preliminary open case studies, buspirone, a 5-HT_{1A} agonist, has been reported to be effective in the management of aggression and agitation for patients with brain injury. In rare instances, we have found that some patients become more aggressive when treated with buspirone. Its advantage is ease of use and tolerability. We recommend that buspirone be initiated at low dosages (i.e., 7.5 mg twice daily) and increased to 15 mg twice daily after 1 week. Dosages of 45–60 mg/day may be required before there is improvement in aggressive behavior, although we have noted dramatic improvement within 1 week.

Clonazepam may be effective in the long-term management of aggression, although evidence is restricted to case reports. We use clonazepam when pronounced aggression and anxiety occur together, or when aggression occurs in association with neurologically induced tics and similarly disinhibited motor behaviors. Doses should be initiated at 0.5 mg twice daily and may be increased to as high as 2–4 mg twice daily, as tolerated. Sedation and ataxia are frequent side effects.

Anticonvulsant Medications

The anticonvulsant carbamazepine has been shown to be effective for the treatment of bipolar disorders and has also been advocated for the control of aggression in both epileptic and nonepileptic populations. Open studies have indicated that carbamazepine may be effective in decreasing aggressive behavior associated with developmental disabilities and schizophrenia and in patients with a variety of other organic brain disorders (Yudofsky et al. 1998). There have been several studies that have included individuals with TBI, but none have been controlled trials. In our experience and that of others, the anticonvulsant valproic acid may also be helpful to some patients with organically induced aggression, but there have been a limited number of open case reports published on patients with TBI. There is only one published case of lamotrigine for post-TBI aggression (Pachet et al. 2003).

For patients with aggression and epilepsy whose seizures are being treated with anticonvulsant drugs such as phenytoin and phenobarbital, switching to carbamazepine or to valproic acid may treat both conditions. Oxcarbazepine may be an alternative to carbamazepine, although there are no published reports on this use of oxcarbazepine at this time.

Antimanic Drugs

Although lithium is known to be effective in controlling aggression related to manic excitement, many studies suggest that it may also have a role in the treatment of aggression in selected, nonbipolar patient populations, including individuals with mental retardation who exhibit self-injurious or aggressive behavior, children and adolescents with behavioral disorders, prison inmates, and those with other organic brain syndromes (Yudofsky et al. 1998).

Individuals with brain injury may have increased sensitivity to the neurotoxic effects of lithium. Because of lithium's potential for neurotoxicity, we limit the use of lithium in patients whose aggression is related to manic effects and in patients whose recurrent irritability is related to cyclic mood disorders.

Antidepressants

The antidepressants that have been reported to control aggressive behavior are those that act preferentially (e.g., amitriptyline) or specifically (e.g., trazodone, sertraline, and fluoxetine) on serotonin.

Fluoxetine, a potent serotonergic antidepressant, has been reported to be effective in the treatment of aggressive behavior in a patient who experienced brain injury as well as in patients with personality disorders and depression and in adolescents with mental retardation and self-injurious behavior (Yudofsky et al. 1998). We have used selective serotonin reuptake inhibitors (SSRIs) with considerable success in aggressive patients with brain lesions. The dosages used are similar to those for the treatment of mood lability and depression.

We have evaluated and treated many patients with emotional lability who enact the full symptomatic picture of neuroaggressive syndrome (characterized by frequent episodes of tearfulness and irritability). These patients, whose diagnoses according to DSM-IV-TR would be "Personality Change, Labile Type, Due to Traumatic Brain Injury," have responded well to SSRI antidepressants. We suggest using an SSRI such as sertraline or citalopram as the initial medication from the antidepressant category.

Stimulants

There have been several studies that have examined the role of dopaminergic medications and stimulants in the treatment of agitation and aggression. Amantadine has shown efficacy in a single-site, double-blind, placebo-controlled trial in the treatment of irritability in 76 outpatients with TBI (Hammond, in press).

Mooney and Haas (1993) conducted a randomized, pretest and posttest, placebo-controlled single-blind study of the effect of methylphenidate, 30 mg/day for 6 weeks, on brain-injury-related anger in 38 individuals with "serious" TBI 6 months or more after their injuries. Although those receiving methylphenidate had a lower level of anger after treatment, they also had greater levels of pretreatment anger.

Antihypertensive Medications: Beta-Blockers

Since the first report of the use of β-adrenergic receptor blockers in the treatment of acute aggression in 1977, over 25 articles have appeared in the neurologic and psychiatric literature reporting experience in using β-blockers with over 200 patients with aggression (Yudofsky et al. 1998) and provide the strongest level of evidence of their efficacy in the treatment of post-TBI aggression (Warden et al. 2006). Most of these patients had been unsuccessfully treated with antipsychotics, minor tranquilizers, lithium, and/or anticonvulsants before treatment with β-blockers. The β-blockers that have been investigated in controlled prospective studies include propranolol (a lipid-soluble, nonselective receptor antagonist), nadolol (a water-soluble, nonselective receptor antagonist), and pindolol (a lipid-soluble, nonselective β receptor antagonist with partial sympathomimetic activity). The effectiveness of propranolol in reducing agitation has been demonstrated during the initial hospitalization after TBI in a double-blind, placebo-controlled study of 21 subjects with severe TBI (Brooke et al. 1992). Behavior was monitored using the OAS. The maximum intensity of episodes and the numbers of episodes were less after propranolol was given than they were after placebo was given. The authors of the study do not list the number of patients who dropped out at each time point during the study, thus diminishing the reliability of the conclusions. Greendyke et al. (1986) performed a double-blind, randomized, placebo-controlled crossover study of propranolol in 10 patients with aggression (mean dose, 520 mg). However, in the subgroup of five patients with TBI, the specific response to propranolol was not reported. This group (Greendyke and Kanter 1986) later performed a double-blind, randomized, placebo-controlled crossover study of pindolol (doses up to 60 mg/day) in 11 patients with behavioral problems, including aggression. It appears that most of these patients were in the earlier propranolol study. Only five of these patients had TBI. Although the group of patients demonstrated improvement in assaultiveness, hostility, and uncooperativeness, the authors of this chapter are unable to assess whether the TBI patients responded differentially. The study by Alpert et al. (1990) using nadolol was conducted with chronically hospitalized patients who did not have TBI. This literature suggests that β-adrenergic receptor blockers are effective agents for the treatment of aggressive and violent behaviors, particularly those related to organic brain syndrome.

Beta-blockers are started at a low dose (i.e., propranolol 60 mg/day) and can be increased every 3–4 days by that dosage with appropriate monitoring of pulse and blood pressure. Dosages of greater than 640 mg/day usually are not required. When a patient requires the use of a once-a-day medication because of compliance difficulties, long-acting propranolol (i.e., Inderal LA) or nadolol (Corgard) can be used. When patients develop bradycardia that prevents prescribing therapeutic dosages of propranolol, pindolol (Visken) can be substituted, using one-tenth the dosage of propranolol. Pindolol's intrinsic sympathomimetic activity stimulates the β receptor and restricts the development of bradycardia. However, patients may have decreased ability for aerobic exercise due to β-blockade.

The major side effects of β-blockers when they are used to treat aggression are a lowering of blood pressure and pulse rate. Because peripheral beta receptors are fully blocked in doses of 300–400 mg/day, further decreases in these vital signs usually do not occur, even when doses are increased to much higher levels. Despite reports of depression with the use of β-blockers, controlled trials and our experience indicate that it is a rare occurrence (Ko et al. 2002; Yudofsky 1992). Because the use of propranolol is associated with significant increases in plasma levels of thioridazine, which has an absolute dosage ceiling of

TABLE 14–6. Pharmacotherapy of agitation/aggression

Presentation/drug	Primary indication
Acute agitation/severe aggression	
High-potency antipsychotic drugs (haloperidol, risperidone)	Acute agitation/severe aggression
Benzodiazepines (lorazepam)	
Chronic agitation	
Atypical antipsychotics (risperidone, olanzapine, quetiapine, clozapine)	Psychosis
Valproic acid, carbamazepine	Seizure disorder, severe aggression
Serotonergic antidepressants (selective serotonin reuptake inhibitors, trazodone)	Depression, mood lability
Amantadine	Under investigation
Buspirone	Anxiety
Beta-blockers	Aggression without concomitant neuropsychiatric sequelae

800 mg/day, the combination of these two medications should be avoided whenever possible.

Table 14–6 summarizes our recommendations for the use of various classes of medications in the treatment of chronic aggressive disorders associated with TBI. Acute aggression may be treated by using the sedative properties of neuroleptics or benzodiazepines. In treating aggression, the clinician, when possible, should diagnose and treat underlying disorders and use, when possible, antiaggressive agents specific for those disorders. There are several factors that influence this decision. Because of the frequent association of depression and aggression/irritability, the antidepressants may often be the first-line medication. Buspirone, although the level of evidence is not strong, may be chosen because of the ease of use and minimal side effects.

When there is partial response after a therapeutic trial with a specific medication, adjunctive treatment with a medication with a different mechanism of action should be instituted. For example, a patient with partial response to β-blockers can have additional improvement with the addition of an anticonvulsant.

Behavioral Treatment

It is clear that aggression can be caused and influenced by a combination of environmental and biological factors. Because of the dangerous and unpredictable nature of aggression, caregivers—both in institutions and at home—have intense and sometimes injudicious reactions to aggression when it occurs. Behavioral treatments have been shown to be highly effective in treating patients with organic aggression and may be useful when combined with pharmacotherapy (see Chapter 38 in this volume for discussion).

Conclusion

Aggressive behavior after brain injury is common and can be highly disabling. Aggression often significantly impedes appropriate rehabilitation and reintegration into the community. There are many neurobiological factors that can lead to aggressive behavior after injury. After appropriate evaluation and assessment of possible etiologies, treatment begins with the documentation of the aggressive episodes. Psychopharmacological strategies differ according to whether the medication is for the treatment of acute aggression or for the prevention of episodes in the patient with chronic aggression. Although the treatment of acute aggression involves the judicious use of sedation, the treatment of chronic aggression is guided by underlying diagnoses and symptomatologies. Behavioral strategies remain an important component in the comprehensive treatment of aggression. In applying this comprehensive approach, aggression can be controlled with minimal adverse cognitive sequelae.

KEY CLINICAL POINTS

- Aggressive behavior and irritability are common after traumatic brain injury.
- Medical causes must be ruled out.
- Depression is the most common comorbid disorder.
- Monitoring of the frequency and severity of the behavior is helpful.
- Several medications can be effective.

Recommended Readings

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CHAPTER 15

Mild Brain Injury

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Severity of brain injury exists along a broad continuum (see Chapter 2, Neuropathology). Discerning the extent of injury neuropathology in humans is limited to examination of the brain either at autopsy or indirectly through neuroimaging. This has resulted in efforts to classify brain injury severity on the basis of clinical signs and symptoms evident at the time of injury or shortly thereafter. This approach does not take into account the forces that contribute to the injury, measures of associated neuropathology, or ultimate functional outcome. Thus, these efforts are at best an approximation of injury severity. Nevertheless, over the last several decades it has become the convention to categorize injury severity into three groups: mild, moderate, and severe, based on initial presentation. At the more severe end of the injury spectrum, the correlation between initial injury severity rating and various outcome measures is relatively robust (Rassovsky et al. 2006). At the milder end of the spectrum, this correlation is less tight, and over the last 100 years (Evans 1994) this has generated confusion with regard to the typical presentation, trajectory of recovery, and outcome of milder injuries. Interest in this topic has grown dramatically since the last edition of this book—about one-fifth of the papers published on mild traumatic brain injury (mTBI) in the past 60 years appeared in the last 5 years. This chapter presents an overview of issues pertinent to mild brain injury.

Definitions

The classification of injury severity focuses predominantly on three parameters: duration and depth of loss of consciousness (LOC) if any, the duration of memory disturbance associated with the event (retrograde and anterograde amnesia), and a simple measure of best speech and language, motor, and oculomotor function known as the Glasgow Coma Scale (GCS) (Teasdale and Jennett 1974) (see Table 15–1). These three parameters have been shown to correlate reasonably well with some outcome measures such as survival and major disability (Rassovsky et al. 2006), especially at the more severe end of the injury spectrum. However, even in Level I trauma centers, it can be very difficult to obtain reliable measures of these parameters. Accurate assessment requires expert observers repeating the measures at regular intervals in a longitudinal fashion (Tate et al. 2006), with agreed-upon ways of coding individuals who are sedated, intubated, or under the influence of pain medications, or who undergo surgical procedures for other injuries. With milder injuries, assessment of these parameters is often limited because injuries may be unwitnessed, consciousness may not be impaired at the time of presentation to the emergency department, and clinicians often focus on evaluating serious injuries to other body regions. Nevertheless, individuals with injuries in which the duration of unconsciousness is less than 30 minutes, the duration of posttraumatic amnesia (PTA) is less than 24 hours, and the GCS scores (Teasdale and Jennett 1974) are 13 or greater are usually considered to have had a mild brain injury. When initially seen, these patients may be confused or disoriented and appear lethargic (Table 15–1). Several efforts have been made to standardize the definition of mTBI. These efforts come from a variety of civilian, military, sports injury, and public health groups.

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TABLE 15–1. Clinical indicators of mild traumatic brain injury

Indicator	Duration	Comment
Loss of consciousness	0–30 minutes	If unwitnessed, must distinguish from posttraumatic amnesia. Difficult to assess when intubated, sedated, or intoxicated.
Disturbed consciousness	Momentary to several hours	Can fluctuate, wax, and wane. Individual may appear stunned, dazed, confused, and/or disoriented.
Retrograde amnesia	0–several hours	Often absent or very brief.
Anterograde amnesia (posttraumatic amnesia)	None–24 hours	Individual may report patchy recollections. Ends with return of continuous, sequential memory. Difficult to assess when intubated, sedated, or intoxicated.
Neurological signs	Typically transient	May have visual disturbance, language difficulty, impact seizure. Often no signs evident other than disturbance of consciousness and cognition.
Glasgow Coma Scale	Score of 13–15 thirty minutes after the event	Difficult to assess when intubated, sedated, or intoxicated.
Clinical symptoms	Variable	Individual may report headache, nausea, dizziness, sensitivity to light/noise, cognitive problems.

Civilian Definitions and Diagnostic Criteria

There are three generally accepted civilian definitions of mTBI: those from the Centers for Disease Control and Prevention (CDC) (2003), the World Health Organization (WHO) (Carroll et al. 2004), and the American Congress of Rehabilitation Medicine (ACRM) (Kay et al. 1993). These instruments overlap significantly (see Table 15–2), and their core elements have been used to develop military screening instruments. The critical common elements include agreement that mTBI can be diagnosed in the absence of LOC but the presence of altered or disturbed consciousness (e.g., manifested by incomplete memory of the event, or being confused or disoriented) and an upper limit of the duration of LOC (30 minutes). For example, the ACRM (Kay et al. 1993) defined mTBI as a traumatically induced disruption of brain function that results in LOC of less than 30 minutes duration or alteration of consciousness manifested by incomplete memory of the event or being dazed and confused; the period of PTA should not last longer than 24 hours, and the individual may or may not have focal neurological findings (Kay et al. 1993). The CDC and WHO definitions are quite similar (see Ruff et al. 2009) and allow for patient report/history in considering the diagnosis.

Military Screening Instruments

The U.S. Department of Defense (DoD) and Department of Veterans Affairs (VA) have also adopted screening instruments that implicitly include definitions of mTBI that overlap significantly with the civilian definitions. These screening instruments (e.g., the Military Acute Concussion Evaluation, the Brief Traumatic Brain Injury Screen, the VA screen, and the Post-Deployment Health Assessment and Reassessment screens; see Chapter 26, Traumatic Brain Injury in the Context of War) assess events often associated with mTBI (e.g., blast/explosions, falls, fragments, bullets, motor vehicle accidents, or other causes) and ask questions designed to assess the presence of the core critical elements of the civilian definitions of mTBI described above. It is important to note that these instruments were never designed to provide accurate diagnosis of mTBI but rather to identify a population at higher risk for such exposure who could then be further evaluated by expert clinicians.

Other Classifications

There are related definitions used in other settings. For example, the International Classification of Diseases, 9th Revision, Clinical Modification (American Medical Association 2005) includes a diagnostic category of concussion defined as "transient impairment of function as a result of a blow to the brain" and distinguishes between concussion without LOC (with mental confusion), brief LOC (<1 hour), and more prolonged LOC.

Efforts to categorize severity of brain injury have also been a focus in sports medicine (see Chapter 27, Sports Injuries; also Langlois et al. 2006). A variety of schemes have been proposed for the grading of concussions (see Echemendia and Julian 2001; McCrory et al. 2009; also Chapter 27 for reviews). Most individuals use the terms mTBI and concussion interchangeably, although the most recent consensus statement on concussion in sports (McCrory et al. 2009) opines that the terms describe different injury constructs and that structural imaging results following concussion are uniformly normal. It is not clear that this is a useful distinction.

DSM-IV-TR (American Psychiatric Association 2000) does not define *concussion* but did propose *postconcussional disorder* in an appendix of new categories in need of further research and clarification. The criteria include a "significant cerebral concussion" manifested by LOC, evidence of deficits in attention and memory, and at least three other symptoms that have lasted at least 3 months. The International Classification of Diseases, 10th Edition (ICD-10) defined a *postconcussional syndrome* when an individual reports three or more of eight common postconcussion symptoms after a TBI (World Health Organization 2007) (see Table 15–3). It is worth noting that these classification

TABLE 15–2. Definitions of mild traumatic brain injury

		Core symptoms				
Source	Etiology	Loss of consciousness	Alteration of consciousness	Memory	Neurological symptoms/signs	Other
American Congress of Rehabilitation Medicine (Kay et al. 1993)	A traumatically induced physiological disruption of brain function	Any loss of consciousness less than 30 minutes	Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused)	Any loss of memory for events immediately before or after the accident	Focal neurological deficit(s) that may or may not be transient	After 30 minutes, an initial Glasgow Coma Scale score of 13–15, posttraumatic amnesia not greater than 24 hours
Centers for Disease Control and Prevention (2003)	Injury to the head resulting from blunt trauma or acceleration or deceleration forces	Observed or self-reported loss of consciousness lasting 30 minutes or less	Observed or self-reported transient confusion, disorientation, or impaired consciousness	Observed or self-reported dysfunction of memory (amnesia) around the time of injury	Observed signs of other neurological or neuropsychological dysfunction, such as seizures acutely following head injury; among infants/very young children: irritability, lethargy, or vomiting	
World Health Organization (Carroll et al. 2004)	An acute brain injury resulting from mechanical energy to the head from external physical forces	Loss of consciousness for 30 minutes or less	Confusion or disorientation	Posttraumatic amnesia for less than 24 hours	Transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery	Glasgow Coma Scale score of 13–15 after 30 minutes must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries

schemes stray from the concept of an exposure to an event (i.e., an mTBI) and attempt to attribute current distress and symptoms to a remote mTBI. A few studies have explored the clinical differences and diagnostic validity of these different diagnostic schemes (Boake et al. 2004, 2005; McCauley et al. 2005; Ruff and Jurica 1999). As might be expected given the different thresholds, the criteria identify different populations (e.g., Boake et al. 2004 found agreement in only 46% of their cohort of 178 TBI patients) but not very different symptom or outcome patterns (McCauley et al. 2005; Ruff and Jurica 1999). Furthermore, Boake et al. (2005) compared 178 individuals with mild-moderate TBI with 104 individuals with extracranial injuries (i.e., "other injury group") on the DSM-IV-TR and ICD-10 criteria 3 months after injury. Specificity for both disorders was quite low, and in fact 40% of the extracranial injury group (without TBI) would have met ICD-10 criteria for postconcussional disorder. However, it is worth noting that a history of TBI is often missed even in Level I and II trauma centers (Powell et al. 2008) thus it is possible that some individuals included in the extracranial injury group also had suffered a TBI.

Using any of the common definitions of mTBI, the prognosis for this population is better than that for moderate and severe injury (Carroll et al. 2004; Levin et al. 1990; McCrea et al. 2009; Rees 2003; Rimel et al. 1982; Schretlen and Shapiro 2003; Sigurdardottir et al. 2009; Williams et al. 1990). However, the subgroup with abnormal initial neuroimaging findings (usually on computed tomography [CT] scans) may represent a different group (often referred to as complicated mild TBI) whose prognosis is similar to those with moderate TBI (Iverson 2006; Kashluba et al. 2008; Williams et al. 1990). For example, Iverson (2006) compared 50 individuals with complicated mTBI with 50 individuals with uncomplicated mTBI on a battery of cognitive tests obtained within 2 weeks of injury and found that the complicated mTBI group performed more poorly on several of the measures, although the effect sizes were not large. Kashluba et al. (2008) compared cognitive and functional outcomes in 102 individuals with complicated mTBI with 127 individuals with moderate TBI at the end of their acute rehabilitation period and 1 year after injury and found very few differences in either cognitive or functional outcome. Thus, the combination of clinical signs and symptoms shortly after injury and initial radiological findings may be a better scheme for predicting outcome.

Epidemiology

Most information about the incidence and prevalence of mTBI comes from studies of brain injury of all severities (e.g., see Table 15–4). For this reason the data are subject to

TABLE 15–3. Criteria for postconcussional syndromes and disorders

ICD-criteria for postconcussional syndrome

A history of TBI and the presence of three or more of the following eight symptoms:

- Headache
- Dizziness
- Fatigue
- Irritability
- Insomnia
- Poor concentration
- Memory difficulty
- Intolerance of stress, emotion, or alcohol

DSM-IV criteria for postconcussional disorder

A. History of TBI causing "significant cerebral concussion"

B. Cognitive deficit in attention and/or memory

C. Presence of at least three of the following eight symptoms that appear after injury and persist for 3 months:

- Fatigue
- Sleep disturbance
- Headache
- Dizziness
- Irritability
- Affective disturbance
- Personality change
- Apathy

D. Symptoms that begin or worsen after injury

E. Symptoms of sufficient severity to interfere with social role functioning

F. Symptoms not better explained by dementia due to head trauma and another disorder

Source. American Psychiatric Association 2000; World Health Organization 1992.

effects of the evolution in the definition and management of mTBI that has occurred over time. For example, there has been a dramatic decrease in the rates of hospitalization for mTBI, with a concomitant increase in the rates of emergency department discharges for mTBI (Rutland-Brown et al. 2006; see also Chapter 1, Epidemiology, in this volume), thus it is important to be aware of how and when incidence figures are ascertained. Most estimates of the percentage of injuries that are mild fall within the 60%–80% range (Rutland-Brown et al. 2006). It is important to point out that available data from either hospitalization rates or emergency department discharge rates underestimate the absolute number because not all injured individuals seek care, or they seek care at outpatient clinics not included in surveillance data (Langlois et al. 2006; Rutland-Brown et al. 2006; Zaloshnja et al. 2008).

Mirroring the demographic profile of TBI in general, mild injury occurs about twice as frequently in males, with increased incidence in the 15–24 and over-70 age groups (Rutland-Brown et al. 2006). Causes of mild brain injury are also similar to those of brain injury in general, with falls, motor vehicle accidents, struck or struck-by events, and assaults the most common causes (Kraus et al. 1994; Rutland-Brown et al. 2006). Assaults account for a higher percentage of mild brain injuries in some areas, especially in large urban centers (Sorenson and Kraus 1991). In military populations, blast injury is the most common etiology (see Chapter 1, Epidemiology, and Chapter 12, Posttraumatic Stress Disorder, in this volume). Falls account for a larger percentage in children younger than 10 years and adults older than 65 years (Goleburn and Golden 2001; Luerssen et al. 1988). The majority of sports-related mild brain injuries probably go unreported.

Estimates of the economic burden of mTBI are difficult to come by. Based on inflation-adjusted census data from 1995, the CDC estimated a total cost of $16.7 billion for mTBI (Rutland-Brown et al. 2006; Thurman et al. 1999). Again these estimates did not count those who do not seek care in hospitals or emergency departments, or at all. It also did not account for lost productivity to the individual or those caring for him or her (Rutland-Brown et al. 2006). Thus, in many respects, the term mild brain injury is a misnomer. Although the initial clinical picture may be mild relative to the spectrum of possible neuropathological and functional outcomes such as death or persistent minimally conscious state, the extent of the problem and the frequency and intensity of certain predictable sequelae make mild brain injury anything but a minor problem.

Pathophysiology

Neuropathological Evidence

There is evidence that neuronal damage can accompany mild brain injury. Animal models of brain injury using a variety of models across several species (fluid percussion, controlled cortical impact, combination models) (Jane et al. 1985; Morales et al. 2005; Povlishock and Coburn 1989; Thompson et al. 2005) suggest that the neuropathology of brain injury occurs along a spectrum and injuries at the mild end are similar qualitatively to more severe injuries, with evidence of axonal injury to subcortical white matter, hippocampus, thalamus, and cerebellum (e.g., Park et al. 2006). Axonal damage may range from stretching, with associated poration that if not severe can seal over, to axotomy (Farkas and Povlishock 2007). Axotomy may occur at the time of injury if strain forces are sufficient or may evolve over hours to days. Delayed injury is believed to occur subsequent to initial changes in the permeability of the axonal membrane and disruption of elements of the cytoskeleton, particularly axonal neurofilaments. This in turn can lead to loss or disruption of axonal transport, axonal distortion (for review, see Farkas and Povlishock 2007), and eventual separation of the proximal and distal portion of the axon. Secondary deafferentation (structural changes and sometimes neuronal death due to loss of synaptic input) in target areas of the affected axon can follow (Povlishock and Christman 1995). These changes in axon structure evolve over a 12- to 24-hour period and can be seen in the absence of structural damage to neighboring supportive or vascular tissue. Subsequent Wallerian degeneration can take place over the subsequent 2–60 days (Povlishock and Christman 1995).

TABLE 15–4. Frequency and distribution (percent) of traumatic brain injury (TBI) in South Carolina by severity and level of care, 1996–2000

	Level of care		
Injury severity	Emergency departments only	Hospitalization	Total
Mild TBI	41,734 (85%)	7,365 (15%)	49,099 (100%)
Moderate and severe TBI	—	7,681 (100%)	7,681 (100%)
Total	41,734 (74%)	15,046 (26%)	56,780 (100%)

Source. Centers for Disease Control and Prevention 2003. Data from Selassie A: 1996–2000 South Carolina Department of Health Traumatic Brain Injury Surveillance Program.

A critical question is how accurately animal models reflect the human condition. Assessing for neuropathological changes after mTBI in humans is largely limited to convenience samples of individuals who sustain an mTBI, die shortly thereafter of other causes, and come to autopsy. For example, Oppenheimer (1968) reported destruction of myelin, axonal retraction bulbs (beadlike structures at the proximal end of a ruptured axon), and aggregates of small reactive glial cells (indicating recent tissue injury) in a variety of brain regions in five patients with minor or trivial injuries. One such patient had been knocked down by a motor scooter and had no LOC but was described as "stunned." PTA lasted approximately 20 minutes. Blumbergs et al. (1994), using immunostaining for amyloid precursor protein as a marker for axonal injury, reported multifocal axonal injury in five individuals who had sustained mild injuries with periods of unconsciousness as brief as 1 minute. Bigler (2004) described subtle neurocognitive and neuropathological abnormalities in a 47-year-old man who died 7 months after an mTBI of unrelated causes (Bigler 2004).

In addition to the microscopic structural changes described above, both animal and human studies suggest that mTBI can disrupt the normal balance between cellular energy demand and energy supply (see Marcoux et al. 2008). Under normal circumstances, energy consumption roughly matches energy supply at the neuronal level, and alterations in energy demand (i.e., increased neuronal metabolic activity) can be accommodated initially by utilization of intracellular stores and subsequently by increasing blood flow to facilitate the supply of oxygen and glucose. However, mTBI can result in significant changes in intracellular and extracellular concentrations of potassium, sodium, calcium, and magnesium ions. Restoration of the normal intracellular and extracellular gradients of these ions requires a significant increase in energy expenditure that is initially met by hyperglycolysis. Ongoing energy demand requires an increase in blood flow, however. Coupling of increased energy demand to increased energy supply can be disrupted after mTBI (Bergsneider et al. 2000; Giza and Hovda 2001; Junger et al. 1997; Lee et al. 1999; Strebel et al. 1997).

Neuroimaging Evidence

The limitations inherent in obtaining human brain tissue after mTBI have driven interest in other avenues to detect neural injury, such as neuroimaging. A wide array of neuropathological processes can be involved in TBI, including changes in bone (e.g., a skull fracture), tissue density and water content (edema), blood flow, white matter integrity and pathway connectivity (diffuse axonal injury), and subtle changes in the neuronal and extracellular biochemical milieu. No single imaging technique is thus capable of addressing all of these processes (for reviews, see Belanger et al. 2007; Levine et al. 2006).

Clinically, CT scanning is the most common imaging modality used in the management of mTBI, but results are normal in the majority of individuals. Three large cohort studies (Borczuk 1995; Haydel et al. 2000; Miller et al. 1997) assessed predictors of surgical lesions and abnormal CT scan results in mTBI patients with GCS scores of 15 representing more than 4,000 patients. The findings suggest that in individuals with very mild TBI (GCS scores of 15), 5%–10% have abnormal CT scans. Individuals who have GCS scores of 13 or 14 have a higher frequency of abnormal findings on CT scans, ranging from 20% to 35% (Harad and Kerstein 1992; Schynoll et al. 1993; Shackford et al. 1992; Stein and Ross 1992).

Methods based on magnetic resonance imaging (MRI), particularly using more recent image acquisition techniques such as susceptibility weighted imaging (Chastain et al. 2009) and diffusion tensor imaging (DTI) (e.g., Kraus et al. 2007; Niogi et al. 2008a), are more sensitive in detecting the diffuse axonal injury and small hemorrhages generally believed to be the neuropathology associated with mTBI (Belanger et al. 2007; Chastain et al. 2009). The type of lesion and the interval from injury to imaging affect the sensitivity of a given sequence.

DTI may be of particular use in demonstrating abnormalities of white matter pathways and connectivity (Arfanakis et al. 2002; Inglese et al. 2005; Kraus et al. 2007). This technique capitalizes on the fact that the diffusion of water is nonrandom (shows anisotropy) because it is more rapid along the long axis of an axon or set of axons (tracts). This allows the mapping of major white matter pathways and can show areas of change in white matter integrity (e.g., regions of reduced anisotropy). Of note is that changes in DTI parameters have been shown both acutely (Arfanakis et al. 2002) and chronically (Kraus et al. 2007). Furthermore some of the abnormalities in mTBI have been shown to correlate with cognitive performance (memory, attention, reaction time) (Niogi et al. 2008a, 2008b).

Functional imaging techniques also show promise in clarifying the underlying pathophysiology of mTBI (see Chapter 5, Structural Imaging, this volume). Several studies have explored the utility of single-photon emission computed tomography (SPECT) in TBI (e.g., Hattori et al. 2009; Jacobs et al. 1994; Roper et al. 1991). Most studies conclude that abnormalities in cortical perfusion can be

shown even in the absence of structural abnormalities, and flow deficits observed with SPECT may more accurately reflect the size or extent of damaged tissue than CT (Choksey et al. 1991; Mitchener et al. 1997; Silverman et al. 1993). The clinical significance of perfusion deficits demonstrated on SPECT has not been clearly demonstrated.

Some literature exists on the use of positron emission tomography in TBI, although many of these studies have been conducted in patients with moderate and severe TBI (Alavi and Newberg 1996; Kato et al. 2007; Kawai et al. 2008; Ruff et al. 1989a). Several groups have reported abnormal findings in small cohorts of mTBI patients with persistent postconcussive complaints (Chen et al. 2003; Gross et al. 1996; Humayun et al. 1989; Ruff et al. 1994), although given the frequent comorbidities present in such patients, it is unclear what these abnormalities mean.

Another imaging modality that shows some promise in clarifying some of the underlying symptoms of TBI is functional MRI (fMRI). McAllister and colleagues (McAllister et al. 1999, 2001, 2006) have used fMRI to show that individuals with mTBI within 1 month of their injury show different patterns of activation of working memory circuitry. Although cognitive performance was not different from that of healthy control subjects, the groups with mTBI reported significantly more cognitive and memory complaints. This suggests the possibility that the mTBI group may have problems with the allocation of memory processing resources and may label this as memory trouble.

Magnetic resonance spectroscopy also informs on the effects of TBI, related to detection of changes in metabolites such as *N*-acetyl aspartate (NAA), total creatine (CRE), and choline-containing compounds (Ashwal et al. 2006; Garnett et al. 2000; Gasparovic et al. 2009; Nakabayashi et al. 2007). For example, Gasparovic et al. (2009) studied 10 individuals with mTBI 10 days after injury. They found lower glutamate-glutamine concentrations in gray matter and elevated levels of CRE in white matter in the mTBI group. The levels of CRE predicted executive function performance and emotional distress levels in the mTBI group. Vagnozzi et al. (2008) found reduced NAA/CRE ratio in 13 individuals studied within 3 days of a sports concussion. The abnormality persisted at 15 days but was largely resolved 30 days after injury except in 3 athletes who sustained a second concussion and had a longer recovery trajectory.

The literature mentioned above suggests that brain injury considered mild on the basis of the degree and duration of altered consciousness at the time of the event can be associated with neural injury starting at the moment of impact and evolving over several hours to days and longer. The types of injuries seen, both macroscopically and microscopically, are similar in quality and location to those seen with moderate and severe degrees of brain injury. The question is whether these changes are associated with symptomatic and functional problems, and what is the trajectory of recovery.

Sequelae of mTBI

The sequelae of mTBI remain a topic of intense interest and strong opinion. In considering this topic, it is helpful to focus on the following questions: 1) What are the typical subjective and objective problems shortly after the injury? 2) What is the typical trajectory of recovery in the majority of individuals? 3) Are there individuals who deviate from this typical recovery trajectory? and 4) What are the factors that contribute to this outcome variance? Perhaps most important, it is critical to distinguish between a history of a mTBI (exposure) and attribution of current symptoms to that event. With that in mind, this section is divided into sequelae that are seen shortly after the injury and sequelae that may persist months or even years after the event. For the purposes of this chapter, short-term has been somewhat arbitrarily defined as up to 3 months after injury.

Short-Term Sequelae

Cognitive Sequelae

Most investigators agree that individuals with mild brain injury can be distinguished from healthy control subjects on measures of speed of information processing, attention and memory, and performance consistency in the first week or so subsequent to the injury (Carroll et al. 2004; Heitger et al. 2006; Levin et al. 1987; McMillan and Glucksman 1987; Ruff et al. 1989b). Even individuals who are asymptomatic several days after a mild concussion with no LOC can have impaired processing speed (McCrea et al. 2003, 2009; Warden et al. 2001). The usual course of recovery is fairly rapid. Studies of cognitive testing 1 month and 3 months after injury tend to show progressive diminution of group differences in cognition, although when differences persist they are also usually in the domains of memory, attention, and processing speed (Bohnen et al. 1993; Carroll et al. 2004; Dikmen et al. 1986a, 1986b; Gentilini et al. 1989; Gronwall 1989; Heitger et al. 2006; Ruff et al. 1989b). Studies of elite athletes (McCrea et al. 2003) suggest that for certain populations (young, healthy individuals highly motivated to return to play), the vast majority are symptom free and by certain cognitive screening measures have returned to their previous baseline function within 7–10 days. Insofar as fatigue may impair cognitive performance or elicit symptoms, the enhanced physical fitness of this group may contribute to their rapid recovery. By contrast, recovery can take much longer for populations seen in emergency departments. For example, Heitger et al. (2006) found deficits in verbal learning in 37 individuals with mTBI compared with matched controls at both 3 and 6 months after injury. Although there were no group differences in cognition 12 months after injury, the mTBI group showed persistent abnormalities in motor function and postconcussive symptoms. Furthermore, even in the NCAA study approximately 10% of the athletes did not recover fully within the typical 1-week time frame (McCrea et al. 2003), and Ellemberg et al. (2007) found evidence of poorer cognitive function 6–8 months after a single concussion in a small sample of collegiate female soccer players compared with nonconcussed teammate controls.

Behavioral Sequelae and "Postconcussive Symptoms"

In addition to the cognitive sequelae, a variety of significant emotional and behavioral sequelae are associated with mild brain injury. These sequelae take two broad forms: 1) neuropsychiatric distress immediately or shortly

after the injury that can be considered part of the natural course of injury, and 2) an increased vulnerability to psychiatric disorders during and subsequent to the acute recovery period (van Reekum et al. 2000; Whelan et al. 2000). The latter (vulnerability to psychiatric illness) will be discussed after the short- and long-term sequelae, because it is arguably less clearly related to time from injury.

A cluster of symptoms that occur after brain injury of all severities (as well as other conditions) have acquired the unfortunate label of "postconcussive symptoms." The most common of these symptoms can be grouped into three categories: cognitive complaints (decreased memory, attention, and concentration), somatic complaints (headache, fatigue, insomnia, dizziness, tinnitus, and sensitivity to noise or light), and affective complaints (depression, irritability, and anxiety). The symptoms are commonly reported subsequent to brain injury of varying severity and should not be considered synonymous with mild brain injury (Deb et al. 1998; Dikmen et al. 2010; Hinkeldey and Corrigan 1990; McKinlay et al. 1981; van Zomeren and van Den Burg 1985). A variety of instruments have been developed to assess these symptoms. Figure 15–1 shows one such instrument, the Rivermead Post Concussion Symptoms Questionnaire (King et al. 1995), that is frequently used to track such symptoms.

The Rivermead Post Concussion Symptoms Questionnaire

After a head injury or accident some people experience symptoms which can cause worry or nuisance. We would like to know if you now suffer from any of the symptoms given below. As many of these symptoms occur normally, we would like you to compare yourself now with before the accident. For each one, please circle the number closest to your answer.

0 = Not experienced at all
1 = No more of a problem
2 = A mild problem
3 = A moderate problem
4 = A severe problem

Compared with before the accident, do you now (i.e., over the last 24 hours) suffer from:

Headaches	0	1	2	3	4
Feelings of dizziness	0	1	2	3	4
Nausea and/or vomiting	0	1	2	3	4
Noise sensitivity, easily upset by loud noise	0	1	2	3	4
Sleep disturbance	0	1	2	3	4
Fatigue, tiring more easily	0	1	2	3	4
Being irritable, easily angered	0	1	2	3	4
Feeling depressed or tearful	0	1	2	3	4
Feeling frustrated or impatient	0	1	2	3	4
Forgetfulness, poor memory	0	1	2	3	4
Poor concentration	0	1	2	3	4
Taking longer to think	0	1	2	3	4
Blurred vision	0	1	2	3	4
Light sensitivity, easily upset by bright light	0	1	2	3	4
Double vision	0	1	2	3	4
Restlessness	0	1	2	3	4

Are you experiencing any other difficulties?

1. _____	0	1	2	3	4
2. _____	0	1	2	3	4

FIGURE 15–1. Rivermead Post Concussion Symptoms Questionnaire.

Source. Reprinted, with kind permission of Springer Science & Business Media, from King N, Crawford S, Wenden F, et al.: "The Rivermead Post Concussion Symptoms Questionnaire: A Measure of Symptoms Commonly Experienced After Head Injury and Its Reliability." *Journal of Neurology* 242:587–592, 1995.

In the immediate postinjury period, 80%–100% of mild brain injury patients describe one or more symptoms (Dikmen et al. 2010; Levin et al. 1987), although significant differences from control groups are not always found (Dikmen et al. 1986b). McLean et al. (1983) found that 65% of their 20 patients complained of persistent fatigue, 40% of decreased memory, and 45% of decreased concentration 1 month subsequent to their mild brain injury. Forty-five percent of these individuals had not returned to their previous major daily activities and rated their overall level of function as significantly more impaired than control subjects.

Even at 3 months after injury, many studies suggest surprisingly high rates of symptoms. Rimel et al. (1981), in a widely quoted study of 424 individuals with mild brain injury (GCS ≥13, LOC <20 minutes), found that 78% complained of headache, 60% complained of decreased memory, and 50% and 25% either complained of decrease in financial status or were unemployed, respectively, at 3 months after their injury. Thirty-one percent of this population had a history of prior brain injuries. In the Levin et al. (1987) multicenter study, 47%, 22%, and 22% of the individuals continued to complain of headache, decreased energy, and dizziness, respectively. Others have found similarly high symptom rates but have not reported base rates in control groups (Bohnen et al. 1993; Ingebrigtsen et al. 1998). Lundin et al. (2006) found that 49% of their cohort of mTBI patients reported at least one symptom on the Rivermead questionnaire. Although this did not differ from the control group, the intensity rating of the symptoms was higher in the mTBI group. Regardless of the exact percentage of individuals who are symptomatic 3 months after injury, it is apparent that there is a discrepancy between the message typically given to the individual with an mTBI in the emergency department ("You had a very mild injury or concussion. You will be fine…") and the reality that many experience.

Long-Term Sequelae

Cognitive Sequelae

The long-term cognitive sequelae of mild brain injury are a subject of ongoing discussion. Some of this hinges on the definition of long-term, which typically ranges from 6 months to 12 months or more after injury. Most studies suggest that assessment of group-level data yields little evidence of long-term deficits attributable to a single mTBI 1 year or more after injury (Dikmen et al. 1986a, 1995a). Several meta-analyses have addressed the question of long-term cognitive deficits after mTBI (Belanger et al. 2005; Binder 1997; Binder et al. 1997; Frencham et al. 2005; Iverson 2005; Schretlen and Shapiro 2003). These reviews are consistent in concluding that at a group level, most spontaneous cognitive recovery after mTBI is complete by 3 months postinjury. For example, Binder and colleagues (Binder 1997; Binder et al. 1997), in a meta-analysis of data from eight studies of long-term (3 months to many years after injury) effects of mTBI, found a small effect size on measures of attention and, in a review of additional studies, reported that approximately 8% of individuals remained symptomatic chronically and 14% had work-related disability. For studies using other-injury control subjects in the follow-up interval of 1 year after injury, the effect size attributable to TBI was in the range of 0.1 (Schretlen and Shapiro 2003) to 0.35 (Frencham et al. 2005) for mTBI and 0.6–0.9 for moderate to severe TBI (Schretlen and Shapiro 2003).

Two systematic reviews also speak to this issue. The WHO report on mTBI (Carroll et al. 2004) reviewed 427 studies of prognosis after mTBI (both children and adult studies were included) and deemed 120 of those of sufficient scientific merit to include in their final report. On the basis of these studies (see Table 15–5), they concluded that there was strong evidence for cognitive dysfunction shortly after injury (days to 1 week) and that there was strong and consistent evidence that these deficits resolve at the group level by 3 months after injury. In a more recent Institute of Medicine (2009) report on brain injury, the authors reviewed 6 primary studies and 17 secondary studies that met their criteria for addressing the question of long-term (in this instance defined as 6 months or more after injury) cognitive deficits after mTBI and concluded that there was insufficient evidence to determine whether there is an association between mTBI and long-term cognitive deficits given contradictory findings.

This literature is helpful when considering group-level data and is reassuring that for the majority of individuals a single mTBI does not result in long-term cognitive deficits. What these data do not address are such issues as the effects of multiple mTBI and the prediction of individuals who do not show the typical recovery trajectory. Studies of individuals with persistent symptoms after mTBI are less encouraging (Guilmette and Rasile 1995; Leininger et al. 1990). For example, Guilmette and Rasile (1995) found significant deficits in tests of verbal memory and learning in a sample of individuals with mTBI (LOC <30 minutes, PTA <24 hours) but with persistent complaints. Arciniegas et al. (2000a, 2001b) studied a cohort of individuals with persistent cognitive complaints after mTBI and showed high rates of deficient sensory gating. Furthermore, the gating disturbance was associated with reduced hippocampal volume and response to cholinergic agents. On the other hand, Stulemeijer et al. (2007) found that approximately 40% of a cohort of 79 mTBI patients had significant cognitive complaints 6 months after injury but their cognitive performance did not differ from those without such complaints. These studies suggest that additional information is needed about the subgroup of individuals with persistent complaints.

The overall impression from these studies is that mild brain injury results in measurable deficits in speed of information processing, attention, and memory in the immediate postinjury period. Recovery from these deficits is the rule, occurring over a variable period ranging from 4 to 12 weeks. For a minority of patients, recovery may occur much more slowly or remain incomplete.

Postconcussive Symptoms

Although the frequency and intensity of postconcussive symptoms generally improve with time, careful assessment often reveals a surprisingly high rate of symptoms. McCullagh et al. (2001) found significant rates of persis-

tent symptoms 5–6 months after mTBI, with virtually 50% of the 57 subjects reporting dizziness and headache and approximately 75% reporting fatigue. Furthermore, 50%–60% of those with GCS scores of 13–15 met General Health Questionnaire (Goldberg and Hebber 1979) criteria for psychiatric "caseness" indicative of significant psychological distress. Kraus J et al. (2005) in a carefully designed dual cohort study (mTBI and matched other-injury control group) found that 83% of the mTBI cohort reported at least one complaint 6 months after injury and had a mean of 4.3 complaints. Headaches, dizziness, vision difficulties, memory or learning problems, and alcohol intolerance occurred at higher rates in the mTBI cohort.

Even after 1 year, several studies have suggested a surprising rate of symptoms after mTBI, especially in populations seen in emergency departments as opposed to those from sports injury cohorts (Deb et al. 1998, 1999). Dikmen et al. (2010), combining data from several of their previous studies of TBI, reported that 44% of hospitalized cases in the mTBI group without CT abnormalities or prolonged PTA (i.e., longer than 24 hours) noted three or more symptoms that were new or worse since the injury. Although not significantly different from an other-injury control group, only 24% of the latter had three or more symptoms. Fifty percent of their complicated mild group reported three or more symptoms, and this did differ significantly from the control group. A somewhat more encouraging picture is found if one limits the inquiry to those with uncomplicated mTBI (Alves et al. 1993). Attributing the cause of symptoms or cognitive impairment to an mTBI must be done with caution. As Satz et al. (1999) and others (Dacey et al. 1991; Dikmen et al. 1995a, 1995b; Stulemeijer et al. 2006) have pointed out, it is important to consider the effects of other system injuries as well as the base rate of typical "postconcussive symptoms" in the general population. Ideally, studies looking at the longitudinal course of mTBI-related symptoms would include two control groups: one with another mild injury (not to the brain) and a noninjured group (Satz et al. 1999).

Is There a Postconcussive Syndrome?

A good deal of confusion surrounds the use of the term *postconcussive syndrome*. Some clinicians use it to describe any combination of one or more symptoms experienced at any time point after an mTBI. Others use the term to describe individuals who have persistent complaints after an mTBI that they (or someone) attribute to that injury event. The issue is further confounded by the ICD-10 diagnosis of postconcussion syndrome (World Health Organization 1992), the DSM-IV-TR provisional diagnosis of postconcussional disorder as noted earlier in this chapter, and the observation that postconcussive symptoms are not specific to TBI and have been found to occur at high rates in the general population (e.g., Iverson and Lange 2003). Furthermore, in emergency department populations, mTBI does not predict postconcussion syndrome within a week of the injury (Meares et al. 2008). This lack of specificity of symptoms should not necessarily lead to the conclusion that they are not caused by the mTBI. There are numerous examples in medicine in which symptom clusters can be caused by many different factors. This does not invalidate the symptom, rather it serves as a caution that attribution of symptoms is not always straightforward, and the further removed one is from the putative initiating or causal event, the more difficult it is to be certain.

It may be more useful to distinguish different symptom patterns. For example, an individual who experiences intermittent headache and dizziness for several months after an mTBI may have a different problem than an individual who presents 1–2 years after an astonishingly mild injury completely disabled by complaints of poor memory, fatigue, chronic pain, and balance problems. In fact, it is not at all clear that there is a postconcussive "syndrome" per se, or rather common symptoms that occur to greater or lesser degrees in a given individual as a function of a particular injury and relevant premorbid factors. It may not be helpful to view the sequelae of TBI or mTBI as a syndrome because it may adversely affect treatment. If one considers multiple symptoms to be a syndrome with a common underlying mechanism (be it neural damage, depression, or compensation seeking), one tends to attribute multiple symptoms to a single etiology (i.e., "postconcussive syndrome") and to look for treatments that will ameliorate the syndrome. If one views the symptoms as having many different mechanisms (albeit the same initiating event), then one tends to take a more careful look at the typology of each symptom and is better positioned to properly diagnose and treat the different sources of distress (e.g., dizziness related to labyrinthine trauma or headache due to cervical muscle strain). Common clinical experience suggests that individuals who experience multiple symptoms shortly after an injury can show improvement in all, some, or none of the symptoms over time, suggesting at the very least that the symptoms are not always tightly linked and can be uncoupled.

Predictors of Incomplete Recovery

It is difficult to ascertain what percentage of individuals actually fall into the poor outcome category. The literature often suggests that 10%–15% of individuals will have persistent or chronic problems based on a study by Rutherford et al. (1979). However, as Greiffenstein (2009) pointed out, this study may overestimate the number of individuals with persistent symptoms in that several of those with persistent symptoms were felt to be malingering when initially seen 6 weeks after the injury. Furthermore, the definition of poor outcome or delayed recovery varies. Some define poor outcome as persistent troubles at 3 months, some at 6 months, others at more than 1 year. One must also clarify the indicator of "poor outcome." If one defines poor outcome in terms of self-reported symptoms and distress, the above literature suggests that roughly 40%–50% of some samples will have problems at 3 months (Lundin et al. 2006; Rapoport et al. 2002), a similar percentage at 6 months (Kraus et al. 2005; Stulemeijer et al. 2008), and even at 12 months (Dikmen et al. 2010). Although the

TABLE 15–5. Summary of studies of cognitive effects of mild traumatic brain injury

Authors	Setting and subjects	Follow-up	Prognostic factors/outcomes	Design and findings
Dikmen et al. 1995a	Cases: adults, hospitalized, any LOC or PTA 1 hour, able to follow commands <1 hour from injury (n=161) Controls: other injuries (n=121)	1 year	Prognostic factors: type of injury Outcomes: cognitive functioning	Phase I cohort: No cognitive test deficits at 1 year.
Gentilini et al. 1985	Cases: ages 13–75 years, GCS 13–15, LOC 20 minutes, normal neurological exam, hospitalized<3 days (n=50) Controls: spouse, friend, relative, schoolmate of cases (n=50)	None	Prognostic factors: none Outcomes: cognitive tests	Cross-sectional: No differences at 1 month.
Heitger et al. 2006	37 mTBI patients (GCS 13–15; PTA<24 hours, no CT scan), 15–56 years of age, 37 matched controls	1 week, 3, 6, 12 months	Prognostic factors: none Outcomes: oculomotor, visuomotor, cognitive testing and the Rivermead	Cohort study: mTBI group performed worse on most measures at 1 week, verbal learning worse at 3 and 6 months, visuomotor/ oculomotor impaired at 12 months.
Iverson et al. 2000	Adults admitted to trauma hospital with GCS 13–15 with altered consciousness, normal imaging, and no neurological deficits (n=195)	None	Prognostic factors: LOC present, absent or equivocal Outcomes: acute cognitive functioning	Cross-sectional: Within 1 week, no differences between groups on most tests. Equivocal LOC had worse scores on trials B than positive or negative LOC groups (no explanation given).
Lovell et al. (1999)	Admitted to trauma center, GCS 14–15, no skull fracture or intracranial abnormality (n=383)	Up to 7 days	Prognostic factors: certain, uncertain, or no LOC Outcomes: cognitive testing	Phase I cohort: Mild deficits in speed of information processing, attention, and memory but not related to LOC.
Macciocchi et al. 1996	Cases: football players, concussion with LOC up to 5 minutes (n=183) Controls: matched students (n=48)	1, 5, 10 days, 12 weeks	Prognostic factors: concussion Outcomes: cognitive tests and symptoms (for cases)	Phase I cohort: Cases had initial test deficits. At 10 days, no differences in tests, no headaches, but some dizziness and self-reported memory problems in cases.
Maddocks and Saling 1996	Cases: Australian rules football players, sports concussion (n=10) Controls: age and education matched umpires (n=10)	5 days	Prognostic factors: concussion and preinjury test scores (for cases) Outcomes: symptoms and cognitive tests	Phase I cohort: Headache and nausea had resolved at 5 days but cases had mild cognitive deficits.
Matser et al. 1999	Cases: Three teams of amateur soccer players (n=33) Controls: runners and swimmers (n=27) Concussions self-reported	N/A	Prognostic factors: athlete engaging in sport with or without head blows Outcomes: cognitive tests	Cross-sectional: Cases had impaired planning and memory.

TABLE 15–5. Summary of studies of cognitive effects of mild traumatic brain injury *(continued)*

Authors	Setting and subjects	Follow-up	Prognostic factors/outcomes	Design and findings
Matser et al. 2001	Professional soccer players (volunteers). Players had median 500 headers (10th percentile=70; 90th percentile=1,260) in a season and a median of 1 concussion (90th percentile was 12) during career (n=84)	None	Prognostic factors: number of headers, concussions, adjusted for age, education, alcohol, history of general anesthesia, nonsoccer concussions Outcomes: cognitive tests	Cross-sectional: Number of headers was associated with deficits in focused attention and visual/verbal memory, number of soccer-related concussions associated with deficits in sustained attention and visuoperceptual processing.
McCrory et al. 2000	Australian rules football players with concussion, defined as transient altered consciousness or disturbance of vision or equilibrium (n=23)	15 minutes postinjury and to return to play	Prognostic factors: preinjury scores Outcomes: number, type and duration of symptoms and Digit Symbol Substitution Test	Phase I cohort: 100% had headaches (40% of these lasted longer than 15 minutes). Slowed Digit Substitution Test at 15 minutes; 43% returned to play same day and all returned within 2 weeks.
McMillan and Glucksman 1987	Admissions to hospital Cases: mTBI with LOC and PTA 1–24 hours (n=24) Controls: adults with orthopedic injuries (n=24)	Follow-up after discharge for up to 7 days	Prognostic factors: type of injury Outcomes: cognitive tests and symptoms	Phase I cohort: mTBI cases showed impaired information processing speed and self-perceived memory deficits.
Ponsford et al. 2000	Presentations to emergency room Cases: GCS 13–15, LOC 30 minutes, PTA 24 hours, no focal neurological signs, no need for surgery (n=136) Controls: minor other injuries not requiring surgery (n=71)	3 months	Prognostic factors: type of injury, sociodemographic, and premorbid characteristics Outcomes: cognitive and behavioral or psychological functioning	Phase II cohort: At 1 week, cases had more symptoms and slowed informational processing. At 3 months, symptoms had resolved in most and no differences in cognitive functioning. Continued problems in cases unrelated to mTBI severity, but related to prior head injury, prior health or psychiatric problems, life stressors, being students, female, and injured in motor vehicle collision.
Richardson and Snape 1984	Men, admitted to hospital after injury, ages 16–64 years Cases: mTBI (n=16 cases had coma 10 minutes; n=22 cases had PTA 24 hours) Controls: orthopedic injuries, matched on age and gender (n=60)	None	Prognostic factors: type of injury Outcomes: free recall of abstract and concrete words	Cross-sectional: At 24 hours after resolution of PTA, cases showed deficit in recall of concrete material.
Richardson and Barry 1985	Men ages 16–64 years, admitted to hospital after injury Cases: mTBI with PTA 7 hours; those on medications at time of testing excluded (n=18) Controls: orthopedic injuries, similar to cases on age, socioeconomic status, and injury/testing interval (n=48)	None	Prognostic factors: type of injury Outcomes: recognition memory for faces, free oral recall of visual stimuli, free recall of concrete and abstract words	Cross-sectional: At 24 hours after resolution of PTA, no differences in recognition memory or recall of visual stimuli, but deficit in memory of words when imagery instructions not provided. Suggests that in the acute phase, mTBI patients do not spontaneously use imagery to improve recall of verbal material.

TABLE 15–5. Summary of studies of cognitive effects of mild traumatic brain injury *(continued)*

Authors	Setting and subjects	Follow-up	Prognostic factors/outcomes	Design and findings
Teasdale and Engberg 1997	Population-based Danish men in archive of Danish draft board Cases: hospitalized with concussion (ICD code 850) as sole diagnosis (n=1,220)	3 to >200 days	Prognostic factors: time between injury and testing Outcomes: cognitive test scores	Phase I cohort: Increased risk of cognitive deficits at 3–6 days (RR=2.45, 95% CI 1.23–4.9); no increased risk up to 100 days; after 100 days (RR=1.3,0(95% CI 0.87–1.93) and after 200 days (RR=1.19, 95% CI 1.02–1.38).
Williams et al. (1990)	Ages 16–40 years, admitted to neurosurgery. Mild TBI defined as GCS 13–15, normal CT, may include linear or basilar skull fracture. Mild complicated TBI defined as GCS 13–15 with focal brain lesion, depressed skull fracture, or both (n=215 with 23%–48% loss to follow-up for cognitive testing)	1–3 months for cognitive testing, 6 months for Glasgow Outcome Scale	Prognostic factors: mTBI complications Outcomes: cognitive tests, Glasgow Outcome Scale	Phase I cohort: Mild better than mild complicated on mean verbal fluency (35.35, SD=28.26 vs. 23.61, SD=22.36), information-processing rate (0.56, SD=0.24 vs. 0.41, SD=0.19), and recognition memory (86.50, SD=7.51 vs. 80.55, SD=12.37); 97.10% mTBI without and 83.78% with complications had good recovery.

Note. CI=confidence interval; CT=computed tomography; ICD=International Classification of Diseases; GCS=Glasgow Coma Scale; LOC=loss of consciousness; mTBI=mild traumatic brain injury; N/A=not applicable; PTA=posttraumatic amnesia; RR=relative risk; SD=standard deviation.

Source. Adapted from Carroll et al. 2004.

TABLE 15–6. Factors associated with delayed recovery/poor outcome

Indicator	Representative reference(s)	Comment
Increased age at injury	Dikmen et al. (2001)	True of all injury severities.
Premorbid psychiatric illness	Kashluba et al. (2008); Lange et al. (2007)	
Development of psychiatric illness after injury (e.g., depression, posttraumatic stress disorder)	Dikmen et al. (2004); Gfeller et al. (1994); Jorge and Starkstein (2005); Mooney et al. (2005); Rapoport et al. (2006)	Fairly consistent association between Axis I diagnosis and increased levels of postconcussive symptoms and other outcome measures.
Compensation/litigation	Belanger et al. (2005); Binder and Rohling (1996); Feinstein et al. (2001); Paniak et al. (2002)	Not a universal finding. Association should not be misinterpreted as causation.
Repetitive injuries	Beaumont et al. (2009); McKee et al. (2009); Rimel et al. (1981)	Evidence is somewhat indirect and tentative—comes from both sports injury literature and early emergency department populations (Rimel et al. 1981). See Institute of Medicine (2009) for discussion.
Selected polymorphic alleles (e.g., *ANKK1, APOE*E4*)	McAllister (2005, 2008; Chapter 3, Genetic Factors, this volume)	Several large ongoing studies should shed further light on this.
Abnormal acute neuroimaging	Iverson (2006); Kashluba et al. (2008); Williams et al. (1990)	"Complicated mild TBI" has outcomes more similar to moderate TBI.
Expectation of poor outcome	Mittenberg et al. (1992); Whittaker et al. (2007)	Expectation of poor outcome or severity of complications associated with poor recovery.
Extracranial injuries and high initial symptom load	Stulemeijer et al. (2008)	Extracranial injuries may prolong need for treatment and delay return to work but not necessarily increase "postconcussive symptoms" (Stulemeijer et al. 2006).

Note. TBI=traumatic brain injury.

symptoms are not specific to TBI, and acknowledging that those who suffer other injuries also have high rates, the fact remains that the burden of symptoms is high. However, if one defines poor outcome in terms of performance on arguably more objective measures (e.g., neurocognitive tests), the effect of mTBI at a group level is quite small and can be overwhelmed by other factors such as age and other medical or psychiatric disorders (Dikmen et al. 2001). Limiting conclusions from most of these studies is the fact that preinjury baseline data are typically not available and thus the most definitive data, change scores, are not available. Samples that have preinjury data, such as athlete samples, differ in several important respects from emergency department populations (see previous Cognitive Sequelae section) with respect to being young, healthy, motivated to minimize symptoms, and perhaps exerting less effort on preseason testing so as to minimize any apparent effects of a concussion during the season. Perhaps more important, given the large number of individuals who do not seek medical attention after mTBI (Langlois et al. 2006), one does not really know what the denominator is.

Certain factors appear to predict a poorer prognosis (see Table 15–6). For example, in early studies, Barth et al. (1983) and Rimel et al. (1981) found significantly poorer outcomes in their studies that included a large percentage of individuals with a prior history of brain injury compared with studies (such as Dikmen et al. 1986b) that excluded those with a prior history of TBI. The presence of psychiatric conditions (Mooney and Speed 2001; Mooney et al. 2005) are particularly important factors. Recent work in military populations suggests that the presence of depression and posttraumatic stress disorder (PTSD) may account for much of the distress in individuals who also suffered an mTBI and have persistent symptoms (Hoge et al. 2008; Schneiderman et al. 2008). Age at time of injury appears to play a role in terms of both symptoms and neuropsychological function (Dikmen et al. 2001, 2010). Intuitively, it would seem that repetitive injuries would be associated with persistent symptoms, and certainly studies of contact athletes suggest that for some groups this holds true (McKee et al. 2009). Furthermore, it seems that novel or more difficult cognitive tasks, or tasks performed under mild degrees of physiological stress, can negatively influence the performance of patients with mild injury (Ewing et al. 1980; Gentilini et al. 1989; Gronwall 1989; Hugenholtz et al. 1988). Injury often occurs in the context of environmental and psychosocial upheaval, and such factors may increase the risk for persistent sequelae after mTBI (Fenton et al. 1993). It is possible that specific genetic profiles contribute to response to neurotrauma and cognitive outcomes (see Chapter 3, Genetic Factors, in this volume; see also McAllister et al. 2005, 2008).

A theme in the literature is that compensation seeking plays a role in adverse outcome. Some of the studies on this topic are drawn from largely medicolegal referral practices (e.g., Miller 1961). Other studies have failed to confirm any significant linkage between compensation or litigation and frequency or severity of postconcussive symptoms either prior to or after settlement (Keshavan et al. 1981; Merskey and Woodforde 1972; Rimel et al. 1981). For example, Rutherford (1989) reported on a series of patients with mild brain injury involved in litigation. In this sample, over 40% of those involved in litigation had no symptoms at the time of their medical-legal evaluation approximately 1 year after the injury. Approximately one-third of those who had symptoms at that time did not have

symptoms at the time of settlement approximately 1 year later, and virtually all of the patients who were symptomatic at the time of settlement remained symptomatic 1 year later. Thus, for many patients, improvement can occur before medical-legal evaluation, during the interval between evaluation and settlement, and may remain long after compensation issues have been settled.

This is not to say that compensation claims do not influence the clinical presentation of some individuals with persistent symptoms after an mTBI. Litigation and compensation proceedings are frequently highly adversarial, prolonged ordeals, and it would be naive to expect that this kind of psychosocial stress would not affect symptom presentation. Feinstein et al. (2001) prospectively studied the role of litigation on symptoms in 97 consecutive individuals with mTBI seen approximately 6 weeks after injury. Even this early in the process, those involved in litigation were experiencing significantly more anxiety and social dysfunction and had poorer outcomes on the Glasgow Outcome Scale and the Rivermead Head Injury Follow-Up Questionnaire (Crawford et al. 1996) than did nonlitigants. The two groups did not differ demographically or with respect to other putative poor prognostic factors such as prior TBI, substance abuse, or premorbid psychiatric illness. Paniak et al. (2002) found higher symptom rates shortly after injury as well as 3 and 12 months after injury in those seeking compensation compared with those who were not. Rees (2003) suggested that these issues may well cause sufficient stress to the hypothalamic-pituitary-adrenal axis to prolong or maintain symptoms. Kashluba et al. (2008) found higher rates of compensation seeking at 3 months after injury in their group with more symptoms compared with their low-symptom group. Meta-analyses (Belanger et al. 2005; Binder and Rohling 1996) have suggested that compensation factors are associated with symptoms. For example, Belanger et al. (2005) in their meta-analysis of moderating effects on neurocognitive outcome found that effect sizes of mTBI did not decrease with time in those seeking compensation versus those not seeking compensation. Of interest, this was true in studies that looked at measures of effort as well as those that did not. Carroll et al. (2004) in the WHO report concluded that compensation and litigation were consistent predictors of delayed outcome. Unfortunately, many seem to conclude from these associations that the interest in being compensated for an injury causes the symptoms, an assertion that does not follow from a simple association.

Other motivational factors may also play a role in functional level and cognitive performance. Keller et al. (2000) compared performance on a test of divided attention in 12 individuals with mTBI, 10 with more severe injuries, and 11 healthy control subjects before and after being told that test performance might affect ability to drive safely. The mTBI group did significantly better, and in fact test performance was within the published normal range with driving as a motivator. However, the healthy control subjects also improved and still outperformed the mTBI group.

A variety of tests have been developed to help with the assessment of effort (for discussion, see Iverson and Binder 2000). Many of these tests are based on a forced-choice format in which performance that is significantly worse than chance, or, in some cases, scores lower than norms obtained from populations with known severe neurological disorders, suggest a negative response bias (Iverson and Binder 2000; Meyers et al. 1999). For example, Stulemeijer et al. (2007) found indicators of poor effort in about a quarter of their cohort of 110 mTBI patients tested 6 months after injury. Poor effort was associated with poor neurocognitive performance, lower educational attainment, and change in work status but not litigation. However, there are numerous reasons that may account for apparent poor effort or negative response bias on tests of cognitive function, and malingering should not be immediately assumed. Inconsistent performance must be interpreted within the context of such factors as fatigue, medication effects, and medical or comorbid psychiatric conditions. With respect to the latter, somatoform disorders, depression, and factitious disorders need to be sorted out. For example, in a study of VA patients, Campbell et al. (2009) found high rates of poor effort in their cohort of individuals with comorbid PTSD/TBI but not in those with either PTSD or TBI alone. The reasons for this are not clear. Individuals with mTBI are subject to the influences of stress and complex motivations. Performance variation under various different conditions or worsening of symptoms in the context of heightened stress such as adversarial litigation is "normal" and should not be construed as evidence of malingering or of "real injury" not being present.

Other contributors to the distress after an mTBI may include the lack of education and information available to the public about mild injury, as well as the lack of consensus about the etiology and maintenance of symptoms among professionals who care for these individuals. Confusion exists among professionals as well (Evans 1994). Two surveys (Harrington et al. 1993) done some 20 years apart suggest that the training and clinical practice of different specialists strongly influence views of the etiology of postconcussive symptoms and, thus, the message that a physician is likely to communicate to his or her patients, increasing the chances of mixed messages. A Harris Poll (2000) and several studies have shown that the lay public is ignorant about the nature and effects of mTBI and that simple psychoeducational approaches aimed at adjusting expectations about common symptoms and the course of recovery, along with regular monitoring of clinical status, can reduce symptoms after injury (Minderhoud et al. 1997; Mittenberg et al. 1996; Paniak et al. 1998; Wade et al. 1997, 1998). Related to this, some have suggested that the expectation of symptoms might play a role in outcome (Mittenberg et al. 1992; Whittaker et al. 2007). However, if one expects something to happen and then it does, this in no way should suggest that the symptoms are not physiologically based. By this argument, because one might expect pain from hitting oneself with a hammer, the pain experienced is caused by that expectation rather than the stimulation of pain fibers brought about by crushed tissue and related hemorrhaging and edema.

Although many correlation or association studies have explored the role of a particular factor on a specific outcome after mTBI, there are relatively few comprehensive attempts to model outcome. However, Stulemeijer et al. (2008) assessed a large number of potential predictor variables at time of injury in a cohort of 201 individuals with

TABLE 15–7. Mild traumatic brain injury and subsequent psychopathology

Syndrome	Comment
"Emotional distress"	General symptom inventories generally elevated in minor TBI. Mixed symptom picture.
Affective disorders	
Depression	Depression scales generally elevated after TBI (Busch and Alpern 1998; Dikmen et al. 2004; Jorge and Starkstein 2005 for review; Pagulayan et al. 2008; Schoenhuber and Gentilini 1988).
	Mobayed and Dinan (1990) found 20% of sample met DSM-III criteria.
	Federoff et al. (1992) and Jorge et al. (1993a, 1993b, 1994; Jorge and Robinson 2002) found 25%–30% of their 66 patients depressed at 1 month and 1 year. Overall, almost 50% depression of some form in first year. Similar to Fann et al. (1995).
	Depression associated with poorer social and functional outcome.
	Increased risk of depression and suicide associated with TBI (Hibbard et al. 1998; Silver et al. 2001).
Mania	May occur after very mild TBI, even without loss of consciousness (Bracken 1987; Nizamie et al. 1988; Pope et al. 1988; Riess et al. 1987; Zwil et al. 1992, 1993).
	Increased relative risk of bipolar disorder (van Reekum et al. 2000).
	May have increased frequency of "irritable mania."
Psychotic disorders	Relatively rare complication. Can be associated with TBI-induced affective disorders.
	In genetically vulnerable individuals, even mild TBI associated with increased risk of psychotic disorders (Malaspina et al. 2001).
Anxiety disorders	Symptoms consistent with anxiety often endorsed, but may not be more frequent than in general population (Schoenhuber and Gentilini 1988). Generalized anxiety disorder found in roughly 25% (Fann et al. 1995). Increased rate of generalized anxiety disorder (van Reekum et al. 2000).
Posttraumatic stress disorder	Posttraumatic stress disorder seen in up to 20%–30% (Bryant and Harvey 1999a, 1999b; Mayou et al. 2000), higher in some military combat populations (Hoge et al. 2008; Schneiderman et al. 2008).

Note. TBI=traumatic brain injury.

mTBI. Full return to work and low levels of postconcussive symptoms 6 months after injury were the primary outcome variables. Sixty-four percent of the cohort had complete recovery using those indicators. Individuals with low initial concussive symptoms, no preinjury physical problems, and no PTSD symptoms had a 90% chance of having few or no postconcussive symptoms, and those with 11 years of education, no nausea or vomiting at time of injury, no extracranial injuries, and low levels of pain after injury had a 90% chance of full return to work at 6 months.

Association With Psychiatric Illness

TBI in general, including mTBI, increases the risk for developing a variety of psychiatric disorders that can contribute to significant disability after the injury (Table 15–7) (see Chapters 10, Mood Disorders; 11, Psychotic Disorders; and 12, Posttraumatic Stress Disorder, in this volume; Deb et al. 1998, 1999; Hibbard et al. 1998, 2000; Silver et al. 2001; and Whelan-Goodinson et al. 2009). The presence of these disorders can serve to accentuate or increase the degree of distress associated with lingering symptoms, and successful treatment of comorbid conditions can result in significant reduction of postconcussive symptoms (Fann et al. 2000, 2001).

Depression

Depressive symptoms are a common complication of brain injury including TBI (see Busch and Alpern 1998; Dikmen et al. 2004; Jorge and Starkstein 2005 for review; Pagulayan et al. 2008; and Chapter 10, Mood Disorders, in this volume). There are fewer studies of mTBI specifically. However, Merskey and Woodforde (1972), in their study of 27 patients with mild brain injury, found that 7 patients had "endogenous" depression, 9 others had a mixture of anxiety and depression, and another 4 had "reactive" depression in combination with a variety of other behavioral problems. Others have also found high rates of depression or depressive symptoms in mTBI (Mobayed and Dinan 1990; Schoenhuber and Gentilini 1988). Several other studies of mixed TBI severity that included significant numbers of mTBI participants have also found high rates of depression (Fann et al. 1995; Federoff et al. 1992; Jorge et al. 1993a, 1993b). Many postconcussive symptoms such as subjective slowing, irritability, fatigue, and sleep disturbance can be consistent with a depressive syndrome, even when patients may not endorse explicit items such as "depressed mood." Gfeller et al. (1994) found a relationship between depression, increased rates of postconcussive symptoms, and impaired performance on some cognitive measures in their sample of 42 individuals with mTBI and headache. Pagulayan et al. (2008) studied the link between depressive symptoms and injury-related difficulties in a population with varied injury severity followed 1 year after injury. In this sample, early depressive symptoms did not predict subsequent injury difficulties, whereas early and current injury difficulties did predict depressive symptoms.

Mania

Mania can occur after mTBI (Bracken 1987; Nizamie et al. 1988; Pope et al. 1988; Riess et al. 1987; Zwil et al. 1993).

The phenomenology of mania after TBI may differ somewhat from primary or idiopathic mania in having a higher rate of relapse (Hoff et al. 1988) and a higher percentage of irritable and violent behavior (Shukla et al. 1987). Quite commonly, patients have both personality changes secondary to their injury and a manic syndrome (Zwil et al. 1992). The latter can present as a periodic worsening of the irritability and impulsivity characteristic of the former. This periodicity may be mistaken for an integral part of the personality changes and may account for the lower frequency of mania diagnosed in these patients (Hale 1982; Stewart and Hemsath 1988).

Psychosis

Psychotic syndromes similar in presentation to those seen in schizophrenia and the affective disorders do occur subsequent to brain injury (see Chapter 11, Psychotic Disorders, in this volume; see also Harrison et al. 2006; Vaishnavi et al. 2009), although they are thought to be rare after mild brain injury.

Anxiety

Few studies have examined anxiety syndromes that occur after mild brain injury (Moore et al. 2006). As with depression, there is an overlap between some postconcussive symptoms and generalized anxiety disorder (GAD) symptoms. For example, many patients endorse complaints of headache, dizziness, blurred vision, irritability, and sensitivity to noise or light after mild brain injury (Dikmen et al. 1986b; Dikmen et al. 2010; Levin et al. 1987). It is less clear how many patients actually experience anxiety and how many have diagnosable anxiety disorders. Fann et al. (1995) reported that 24% of their sample (the majority of whom had mTBI) evaluated 2–3 years after injury met criteria for GAD. Hibbard et al. (1998) also found high rates of several different anxiety disorders (PTSD, 19%; obsessive-compulsive disorder, 15%; panic disorder, 14%; GAD, 9%) in their sample of individuals with mixed injury severity.

Posttraumatic Stress Disorder

There is an increasing awareness of the relationship between PTSD and brain injury in both civilian and military populations. Although it might at first seem strange that those with LOC could develop PTSD with intrusive memories, it has been suggested that the intrusive memories are of events immediately before or after the accident, or there may be patchy amnesia with some islands of preserved memory. It is not uncommon in clinical practice to see patients with a history of mild brain injury who manifest signs and symptoms suggestive of PTSD. These may include sleep disturbance, recurrent nightmares, exaggerated startle responses, daytime flashbacks, and avoidant behaviors such as refusing to drive or leave home. Lishman (1973), in his review of the psychiatric sequelae of brain injury, referred to PTSD-like symptoms, noting that "the circumstances of the accident may recur vividly in dreams, maintain states of anxiety, or become the focus for obsessional rumination or conversion hysteria" (p. 306). He suggested that these and other "neurotic disabilities" may be more likely to occur in milder degrees of injury, especially in the absence of PTA.

Bryant and Harvey (1998, 1999a, 1999b) reported a series of studies of individuals hospitalized after motor vehicle accidents, some with and some without mTBI. They showed that rates of acute stress disorder 1 month after an accident are comparable in the two groups and that acute stress disorder is a good predictor of those who go on to develop PTSD 6 months after injury (Bryant and Harvey 1998; Harvey and Bryant 1998a, 1998b). For example, they studied 46 individuals admitted to a hospital after an mTBI (LOC with PTA less than 24 hours) and 59 survivors of motor vehicle accidents without evidence of TBI 6 months after their accidents (Bryant and Harvey 1999a, 1999b). Twenty percent of the TBI group and 25% of the non-TBI group had PTSD. The TBI group had more postconcussive symptoms than did the non-TBI group. Furthermore, the TBI group with PTSD was significantly more symptomatic than the TBI group without PTSD. This suggests that PTSD can amplify postconcussive symptoms after an mTBI and complicate recovery. In their mTBI sample (LOC less than 15 minutes), Mayou et al. (2000) found that an astonishing 48% of those with definite LOC had PTSD 3 months after injury, and one-third of their subjects with mTBI had PTSD 1 year after injury.

The conflicts in Iraq and Afghanistan have spurred an interest in the relationship between psychological and biomechanical trauma, particularly in military populations (e.g., see Chapter 26, Traumatic Brain Injury in the Context of War, this volume; see also McAllister 2009; Stein and McAllister 2009; Vasterling et al. 2009). Although both TBI and PTSD are quite prevalent in military personnel involved in the current conflicts (Tanielian and Jaycox 2008), two more recent studies highlight the complex interaction. Hoge et al. (2008) found that 44% of Iraq war returnees reporting a TBI with LOC met criteria for PTSD, compared with 27% of those reporting altered mental status, 16% with other injuries, and 9% with no injury. Much of the variance observed in these groups with respect to physical health outcomes and symptoms could be accounted for by the presence of PTSD and/or depression. It is important to point out that participants were assessed 3–4 months after deployment and thus reflect individuals with persistent symptoms. Schneiderman et al. (2008) found that combat-incurred mTBI approximately doubled the risk for PTSD and that a PTSD diagnosis was the strongest factor associated with persistent postconcussive symptoms.

Studies such as these should not be construed as minimizing the effects of mTBI. Rather, they highlight the critical nature of the permissive or gateway effect that mTBI serves in terms of increasing the relative risk for psychiatric disorders. First, as the above review points out, the civilian literature has emphasized for a decade or more that one of the causes of persistent symptoms after mTBI (which is what the Hoge and Schneiderman papers address) is the development of a psychiatric disorder such as depression or PTSD. Further, it is important to distinguish a history of exposure to mTBI from attribution of current symptoms to that event. If one conceptualizes persistent symptoms as a "postconcussive syndrome" or "chronic

TBI," one risks missing the diagnosis of a comorbid psychiatric disorder that could be quite responsive to appropriate treatment (McAllister 2009). Second, careful consideration of the confluence of psychological and biomechanical trauma suggests a possible neural substrate for the high rates of comorbid mTBI and PTSD in this particular cohort. The brain regions thought to play a role in the genesis of PTSD (e.g., hippocampus, amygdala, medial and orbital frontal cortices) overlap considerably with brain regions vulnerable to injury associated with typical biomechanical trauma (hippocampus, frontal cortex, and frontal subcortical white matter) (Stein and McAllister 2009). In a cohort of military personnel exposed to high rates of mTBI in association with relentless exposure to combat trauma, it does not seem at all mysterious to find high rates of comorbidity.

Functional Disability

Long-term functional disability caused by mild brain injury depends on the injury to assessment interval and the outcome measure used. Early studies suggested cause for concern. In a widely quoted study by Rimel et al. (1981), 34% of 310 patients gainfully employed before their mild brain injury were unemployed 3 months after the injury, and 15% of the patients noted difficulty with common household chores. Dikmen et al. (1986b) found significant impairment in many common daily activities such as work, sleep or rest, home management, and ambulation at 1 month after the injury. Only 4 of 19 subjects had returned to their major role (work, home management, studies) and leisure activities without limitations. However, much of this disability was not necessarily related to the brain injury per se but was associated with injury to other body areas, a finding similar to that of Stulemeijer et al. (2006). Ruffolo et al. (1999) studied return to work in 50 consecutive individuals hospitalized with mTBI sustained in motor vehicle accidents who were employed premorbidly, had no significant other injuries, and had no prior TBI, neurological disease, or psychiatric illness requiring hospitalization. When assessed at a mean of 7 months after injury, 42% had returned to work of some sort; however, only 12% had returned to their premorbid level of employment. Twenty percent of those returning to modified employment reported cognitive limitations, and 80% reported physical limitations. Binder et al. (1997), in a review of several studies of mTBI, reported a 14% rate of work-related disability. Studies of military personnel also suggest possible long-term effects of exposure to mTBI. Vanderploeg et al. (2007, 2009) assessed a cohort of community-dwelling Vietnam-era veterans and found increased rates of headaches, fainting, as well as problems with memory, sleep, and self-assessed disability in veterans who reported a history of mTBI compared with those who had nonhead injuries and those without injuries. Thus, it would seem that rates of overall disability mirror those of cognitive and behavioral dysfunction after mild brain injury, being quite high within the first 1–3 months and showing a significant drop over the subsequent 3–12 months. Again, it must be noted that a small percentage of patients continue to experience significant degrees of disability in various areas (cognitive, behavioral, psychosocial) at the 1-year mark and beyond.

Treatment Issues

In general, treatment interventions can be organized as those designed to prevent the development of persistent symptoms and those that target specific symptoms or disorders that have become evident after an mTBI (for review, see Comper et al. 2005). The former typically involve psychoeducational interventions, the latter may consist of medication or cognitive-behavioral interventions. At the risk of stating the obvious, however, the foundation of the approach to patients with mild brain injury is a proper evaluation.

Evaluation

Significant effort must be expended to clarify premorbid history. In particular, one must look for a prior history of brain injury, which can be seen in as many as 30% of patients (Institute of Medicine 2009; Rimel et al. 1981), as well as substance abuse and other psychiatric disorders that are risk factors for TBI (Deb et al. 1998, 1999; Hibbard et al. 1998, 2000; Silver et al. 2001; Whelan-Goodinson et al. 2009). Interviews with significant others can be invaluable in gaining a clearer picture of these issues.

Signs and symptoms attributed to the injury must be clearly defined, as should any changes in symptom picture as a function of time from the injury. The profile of the injury itself must be outlined, including the type of injury, the presence or absence of LOC and its duration, and the presence, absence, and duration of any retrograde and anterograde amnesia. Corroborative information, including accounts from observers, emergency medical technicians, ambulance and emergency department personnel, and inpatient hospital records, can be invaluable. In these records, however, phrases such as "normal mental status" without sufficient documentation do not eliminate the possibility that cognitive changes occurred. This is particularly true when the emergency team is distracted by trauma to other parts of the body (Powell et al. 2008). The presence and location of complications such as depressed skull fractures, cerebral contusions, and hematomas should be noted because of potential prognostic implications. The neurodiagnostic tests done and the timing in relation to the injury should be clarified and the reports or actual studies obtained. If they have not been performed, an MRI and a careful neuropsychological evaluation may be considered. Such studies, however, are not always abnormal in the presence of brain injury especially if performed well after the event. Furthermore, even when abnormal, these studies may not reveal abnormalities that are pathognomonic for mild brain injury. Because few patients have these tests performed both before and after their injury, it is difficult to be certain that such abnormalities were caused by the traumatic event in question. As Binder et al. (2009) pointed out, it is normal to perform poorly on some number of tests administered as part of a battery.

All of the above information can then be integrated with findings from the clinical interview to determine the extent to which the history and examination are consistent with the known sequelae of mild brain injury. This process should determine the presence or absence of one or more of the specific syndromes outlined above, including postconcussive symptoms, depression, mania, anxiety syndromes (including PTSD), and psychotic syndromes. Treatment should then follow rationally from this diagnostic scheme.

Psychoeducation

Often, the most effective prevention of poor recovery or intervention in patients with active neurobehavioral sequelae is a careful explanation of the pathophysiology, typical sequelae, and time course of recovery associated with minor brain injury (Bell et al. 2008; Comper et al. 2005; Minderhoud et al. 1997; Mittenberg et al. 1996; Paniak et al. 1998; Ponsford 2005; Wade et al. 1997, 1998). Problems with slowing, attention, and memory, especially in the first 3–6 months, should be described. The potential for longer-term difficulties should be mentioned but not overemphasized. The overall tone should be that of expectant recovery. This should be done soon after the injury and is best done in the presence of family, friends, or significant others. The realistic setting of goals for return to major activities is a difficult process that must be individualized for each patient. Unfortunately, clinicians often become involved in the later stages of the process, by which time there is often an unpleasant dynamic in which one or more individuals (family, friends, employers, insurance carriers, health care workers) may be questioning the validity of complaints on the basis of the seemingly "minor" nature of the injury and the patient's healthy appearance. Validating the complaints of the patient without undue fostering of illness behavior can be a difficult and lengthy process. Attempts to take a more problem-based approach seem to have been less successful to date (Elgmark Andersson et al. 2007; Ghaffar et al. 2006).

Medication Approaches

Medication approaches to the sequelae of mTBI have generally taken three broad approaches: 1) amelioration of psychiatric complications, 2) amelioration of specific symptoms (e.g., sleep disturbances, headaches, and dizziness; see Chapters 20, 21, and 22 in this volume), and 3) approaches to cognitive complaints. Several general principles should be borne in mind when prescribing psychotropic agents in the population with mTBI. Most important, the vast majority of individuals with mTBI will recover without the need for medication, and there have been no studies in mTBI populations to determine if a given medication alters the rate of recovery. Thus most individuals should be reassured and encouraged to let recovery occur over time. If medications are warranted, the clinician should bear in mind that many of these individuals seem to be more sensitive to common psychotropic side effects such as sedation, psychomotor slowing, and cognitive impairment (such as impairments of recent memory and attention). Although there are few actual data, most clinicians working with patients with TBI note this tendency toward increased side effects and a resultant narrowing of the benefit-to-toxicity ratio. In general, it is prudent to use lower starting and (often) final doses and prolong the titration intervals (see Chapter 35, Psychopharmacology, in this volume; see also Arciniegas et al. 2000b; Silver et al. 1992; Warden et al. 2006).

With respect to amelioration of psychiatric complications, the same general approaches taken in the noninjured population are typically used, although therapeutic efficacy studies are lacking in this group (Warden et al. 2006). Psychotropic use is complicated by enhanced sensitivity to side effects, a mixed and atypical clinical picture (which can complicate assessment of target symptoms and drug response), and, perhaps, a reduced efficacy of certain standard agents, although the evidence for this is tentative (Silver et al. 2009).

The treatment of postconcussive cognitive symptoms is even less clear-cut. Work since the 1980s has focused on the role of catecholaminergic and cholinergic mechanisms as mediators of the attentional and memory domains vulnerable to injury in TBI (Arciniegas et al. 2008; McAllister and Arciniegas 2002). Catecholaminergic mechanisms, particularly through dopaminergic (DA) and alpha-2 adrenergic systems, appear to play important roles in memory function, particularly working memory function both in healthy individuals and individuals with TBI (see Arnsten 1998; McAllister et al. 2004). Several DA agonists, including bromocriptine and stimulants, particularly those with DA agonist properties such as methylphenidate, amphetamine, and levodopa, have been used to treat various cognitive and behavioral sequelae of TBI and other acquired brain injuries (Arciniegas et al. 2000b; Dobkin and Hanlon 1993; Glenn 1998; McAllister and Arnsten 2008; McAllister et al. 2004; Powell et al. 1996).

Another hypothesis relates cognitive impairment after TBI to acute and long-term alterations in cortical cholinergic function (Arciniegas 2003). Multiple studies have demonstrated that cholinergic augmentation, generally using one of several cholinesterase inhibitors (e.g., physostigmine or donepezil), can improve TBI-induced memory deficits even in the late postinjury period (longer than 1 year) in some TBI survivors (Aigner 1995; Cardenas et al. 1994; Eames and Sutton 1995; Tayerni et al. 1998; Whelan et al. 2000). Arciniegas and colleagues have advanced the theory that cholinergic mechanisms play a critical role, particularly in certain attentional deficits after TBI (Arciniegas et al. 1999), and have reported successful use of donepezil in some individuals with TBI (Arciniegas et al. 2001a). Thus, there appears to be increasing evidence, both theoretical and clinical, that suggests that the cautious, empiric use of cholinergic and catecholaminergic agents is warranted for the treatment of chronic memory and attentional deficits.

KEY CLINICAL POINTS

- Well over a million people experience a mild traumatic brain injury (mTBI) in the United States each year.
- Limited human data and more extensive animal data suggest that mild brain injury produces neuropathological changes to a lesser extent than but of similar quality and location to those seen in more severe brain injury.
- Mild brain injury is associated with impairments in speed of information processing, attention, and memory. These deficits are most pronounced in the initial days to weeks after the injury. Most patients show a rapid, progressive improvement over the subsequent 1–3 months. A small percentage of patients have demonstrable long-term sequelae.
- A variety of predictable cognitive, somatic, and behavioral complaints, known as postconcussive symptoms, are seen subsequent to brain injury of all levels of severity. These symptoms occur predictably after mTBI but also after more severe injury and in other injury settings, and thus they are not specific to mTBI.
- After mild brain injury, most patients show progressive resolution of these symptoms over the subsequent 1–6 months. A small but significant percentage has persistent symptoms 12 months or longer.
- Several factors may be associated with poor outcome or delayed recovery, including a history of prior brain injury, increased age at time of injury, certain complications (such as depressed skull fracture or computed tomography evidence of cerebral contusions or hemorrhages), preexisting psychiatric illness or postinjury development of psychiatric illness, injury to other body systems, and certain psychosocial factors.
- Mild brain injury has been associated with the new onset of discrete psychiatric disorders, including depression and posttraumatic stress disorder. The brain injury may result in atypical clinical presentations, heightened sensitivity to standard psychotropic agents, and a somewhat more refractory course, although these observations must be considered tentative.
- Treatment of the neuropsychiatric sequelae involves careful assessment of premorbid function, psychosocial context, and injury profile. Psychoeducational strategies, supportive psychotherapy, and judicious use of appropriate psychotropic agents can be beneficial.

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CHAPTER 16

Posttraumatic Epilepsy

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RECOVERY FROM A TRAUMATIC BRAIN INJURY (TBI) involves dealing with problems that can be physical, cognitive, and psychological in nature. The development of posttraumatic epilepsy further complicates recovery by means of the physical and psychological consequences of seizures as well as the medications used for their treatment. Whereas most posttraumatic symptoms show gradual improvement of variable degree over time, epilepsy is unique in recurring suddenly and unexpectedly, leading to a physical and psychological setback that can negatively affect recovery and that has been shown to worsen functional outcome after TBI (Asikainen et al. 1998).

Epidemiology of Posttraumatic Epilepsy

Trauma is one of the most common identifiable etiologies for the development of epilepsy, responsible for 20% of symptomatic epilepsy (Agrawal et al. 2006). Young adults and those with military injuries have the highest incidence of posttraumatic epilepsy (Agrawal et al. 2006).

The term *posttraumatic epilepsy* should rightfully be reserved for two or more unprovoked seizures occurring after brain trauma, though in many studies a single seizure is considered synonymous with epilepsy. Whereas a true "contact" seizure may occur at the moment of injury, "concussive convulsions," which are akin to convulsive syncope, may occur and be confused with seizures even though they are benign in nature (McCrory and Berkovic 1998).

Timing of Posttraumatic Seizures

The timing of occurrence of seizures after brain trauma is important in prognostication and has been classified in studies as immediate, early, and late. Immediate seizures occur within the first 24 hours of injury, early seizures within the first week, and late seizures beyond 1 week (Agrawal et al. 2006). Immediate seizures, including contact seizures at the moment of injury, are often not included in epidemiological studies of posttraumatic epilepsy. Children are particularly likely to experience immediate seizures, with up to 94% of those who experience seizures having them in the first 24 hours (Hahn et al. 1988). Such seizures have generally been considered not to carry a high risk of the development of epilepsy. However, Kollevold (1978) reported that both immediate and early seizures increased the risk of late seizures. Children also have a 50%–100% greater risk of early seizures than adults with comparable injuries (Annegers et al. 1998; Kollevold 1978). Most studies have reported a similar elevation of epilepsy risk with the occurrence of early seizures, with a lifetime incidence of epilepsy as high as 25% (Jennett 1975; Temkin 2003). However, Annegers et al. (1998) reported that in multivariate analysis early seizures were not predictive of later epilepsy (see below). Similarly, Jennett (1975) did not find an increased risk of late seizures after early seizures of children under age 16 with only focal early seizures. In virtually all studies late seizures carry a much higher risk of epilepsy (Agrawal et al. 2006; Annegers et al. 1998; Jennett 1975).

In terms of timing, approximately 90% of posttraumatic seizures occurring within the first month will occur in the first week (Jennett 1975). Such seizures may be due to perioperative events, edema, and metabolic factors (Agrawal et al. 2006). Of those who develop posttraumatic epilepsy, 80% experience their first seizure within the first year and 90% by the end of the second year (Da Silva et al. 1992). However, 15%–20% of patients may experience their first seizure beyond 2 years (Agrawal et al. 2006), and the risk of a first seizure remains elevated for 10 years after a moderate head injury and more than 20 years after a severe injury (Annegers et al. 1998; Temkin 2003). These observations highlight the fact that there may be a significant

lag time to the development of epilepsy following a brain injury. In a recent extension of the Vietnam Head Injury Study, 12.6% of patients experienced their first seizure more than 14 years after injury (Raymont et al. 2010). Haltiner et al. (1997) found that of patients with one late posttraumatic seizure, 86% had a second seizure within 2 years, 52% had at least five late seizures, and 37% had 10 or more seizures.

Clinical Factors Related to Risk

Over the years numerous authors have examined the clinical factors related to head injury and the subsequent development of posttraumatic epilepsy. Virtually all studies have demonstrated a higher epilepsy risk with greater severity, cortical damage, and hemorrhage, and, therefore, with penetrating injuries. Jennett (1975) reported that 5% of patients with closed head injuries develop posttraumatic epilepsy, as opposed to 30%–50% of those with an open injury.

Annegers et al. (1998) published the largest and longest prospective longitudinal study of posttraumatic epilepsy among 4,541 patients in Olmsted County, Minnesota, from 1935 to 1984, with an additional 10 years of follow-up. Rates of seizures were compared with the general population. Head injuries were classified as mild (loss of consciousness or posttraumatic amnesia <30 minutes), moderate (loss of consciousness or posttraumatic amnesia >30 minutes or the presence of a skull fracture), or severe (loss of consciousness or posttraumatic amnesia >1 day or the presence of a subdural hematoma or contusion). The 30-year cumulative incidences were 2.1%, 4.2%, and 16.7% for mild, moderate, and severe injury, respectively. The risk of seizures was elevated for 5, 10, and more than 20 years for mild, moderate, and severe injuries, respectively. Thus, severity correlated not only with the overall epilepsy risk but also with the length of the period of risk. Contusions and subdural hematomas were the strongest risk factors for late seizures, and age greater than 65 years was also a major risk. However, skull fractures were less of a risk, and a loss of consciousness or posttraumatic amnesia had prognostic significance only when it lasted more than 24 hours. Early seizures, which increased epilepsy risk in univariate analysis, lost significance in a multivariate analysis.

In a recent Danish population-based study of posttraumatic epilepsy in children and young adults, Christensen et al. (2009) reported on 78,572 patients with TBI, of whom 1,017 developed epilepsy. The risk of epilepsy was doubled after mild injury or a skull fracture and seven times higher after a severe injury. Risk was highest in the first year but remained high for more than 10 years after mild and severe injuries. The risk of epilepsy also increased with age at the time of injury and in those with a family history of epilepsy.

Temkin (2003) reported on 783 high-risk patients in two drug prophylaxis studies. There was a 25% risk of early seizures with a depressed fracture, intracerebral hematoma, or subdural hematoma and a 28% risk for those with immediate seizures. The risk of late seizures was elevated with surgically evacuated subdural or intracerebral hematomas, early seizures, Glasgow Coma Scale score 3–8, time to following commands of a week or more, depressed fractures not surgically treated, dural penetration by injury, at least one nonreactive pupil, and parietal lesions on computed tomography (CT) scans. Epilepsy risk does not appear to be elevated with subarachnoid, intraventricular, and punctate hemorrhage, as well as extradural hematomas not requiring evacuation (Agrawal et al. 2006).

Etiology/Pathophysiology

Pathological changes resulting from TBI vary with the specific circumstances of injury. In cases of closed head injury, there can be diffuse axonal injury and neuronal shearing, as well as focal hemorrhage and contusion. With penetrating injuries, there can be bone and missile fragments, as well as the formation of a cicatrix on the cortical surface.

Early seizures may be related to physical and metabolic changes in the damaged cortex, such as edema, ischemia, and the release of excitatory amino acids such as glutamate, as well as cytokines, bioactive lipids, and other toxic mediators (Diaz-Arrastia et al. 2009). However, late seizures appear related to cortical iron deposition from hemoglobin breakdown to hemosiderin (Willmore 1996). Breakdown of hemoglobin results in free radical formation that causes the peroxidation of lipid membranes, resulting in cell wall disruption, cell death, and subsequent gliosis. Iron may also contribute to the formation of an epileptogenic focus via decreased nitric oxide synthase activity (Agrawal et al. 2006). The occurrence of seizures may also be fostered by an increase in excitatory neurotransmitters and decrease in inhibitory neurotransmitters, such as GABA (γ-aminobutyric acid) (Willmore 1996). Excitotoxicity at *N*-methyl-D-aspartate receptors may be followed by the formation of a chronic focus (Agrawal et al. 2006). Mesial temporal sclerosis is seen in posttraumatic epilepsy and was originally felt to be rare and seen only when TBI occurred at an early age, though it may also be seen with later trauma (Diaz-Arrastia et al. 2009).

Posttraumatic Seizure Types

Seizures occurring as a result of brain injury are necessarily an expression of partial epilepsy, though they often present clinically as a generalized tonic-clonic seizure. Partial seizures may be as frequent as generalized seizures (Salazar et al. 1985), and up to 52% of posttraumatic seizures may be nonconvulsive in nature (Vespa et al. 1999). Children, the elderly, and those with the most severe injuries may have a higher proportion of partial seizures (Da Silva et al. 1992). Of note, children under age 5 are particularly likely to present with status epilepticus (Jennett 1975).

Recognizing epileptic phenomena in TBI is of paramount importance in assuring optimal rehabilitation. Posttraumatic symptoms are often categorized along three dimensions: cognitive, psychiatric, and somatic. Epileptic phenomena masquerade in each of these dimensions and can be misdiagnosed. With complex partial or tonic-clonic

TABLE 16–1. Partial seizure manifestations

Frontal	Cephalic sensations, motor phenomena, forced thoughts or actions
Temporal (mesial)	Fear, sensation of somebody behind, déjà vu, jamais vu, rising epigastric sensation, autonomic manifestations (flushing, piloerection), illusions, hallucinations, depersonalization, derealization
Temporal (lateral)	Aphasia, vertigo, simple auditory hallucinations
Parietal	Simple or complex somatosensory phenomena, pain (rare)
Occipital	Simple or complex visual hallucinations (less experiential than temporal hallucinations), vomiting

TABLE 16–2. Psychic phenomena during partial seizures

Cognitive	"Dreamy state," derealization, depersonalization, dissociation, mystical/religious experience, forced thinking, altered speed of thoughts, distortion of time, distortion of body image
Dysphasic	Speech arrest, nonfluent speech, paraphasias, comprehension deficit, repetitive utterances, dyslexia, agraphia
Dysmnesic	Déjà vu, jamias vu, selective memory impairment, forced recollection
Affective	Fear, depression, anger, pleasure, laughter, crying
Visual, auditory, olfactory	Illusions and hallucinations

seizures, clinical manifestations are usually obvious to the observer. However, during simple partial seizures (i.e., auras) that do not progress, the manifestations are often subjective, and their diagnosis as seizures is further complicated by the fact that the majority of such seizures, even with gross clonic motor activity, are not associated with ictal electroencephalogram (EEG) changes (Luciano 1993). The key to diagnosis in such cases is an awareness of what ictal manifestations may be expected from various cortical regions. Table 16–1 lists some clinical manifestations of partial seizures arising in various lobes. Also crucial in proper diagnosis is an awareness that seizures are usually brief (1–2 minutes) and are characteristically stereotypic, having virtually identical duration and phenomenology with each occurrence in a given patient. Other physiological and behavioral episodes tend to demonstrate greater temporal and phenomenological variability.

Given the great number of deceleration injuries, injury to the frontotemporal regions is particularly common in TBI, as are seizures arising in these regions. Because partial seizures arising in these regions may be purely subjective or at times seemingly bizarre in manifestation, it is important to be aware of the clinical features of such seizures and question patients about such phenomena, as they may not be aware that their experiences represent seizures. Diagnosis is made even more difficult by the fact that the regions damaged, such as the orbitofrontal and anteromesial temporal cortices, are deep, and surface EEG may not demonstrate epileptiform activity even during seizures in many patients. In some cases misdiagnosis may lead to referral to other specialists, such as psychiatrists, cardiologists, or gastroenterologists.

Temporal Lobe Seizures

The anteromesial temporal regions are exquisitely sensitive to injury and produce certain ictal phenomena with relatively high frequency. These phenomena reflect the fact that the mesial temporal cortex houses the hippocampus, amygdala, and entorhinal cortex, which are important in memory, autonomic function, emotional processing, and olfactory function.

The most common auras in temporal lobe epilepsy are epigastric sensations, which can occur in isolation. This often involves a rising abdominal sensation such as is experienced when going over the top of a roller coaster (Luciano 1993). Other autonomic manifestations include tachycardia, hypertension, respiratory arrest, peristalsis, pallor, piloerection, sweating, urinary incontinence, and mydriasis (Luciano 1993). Dangerous bradyarrhythmias with prolonged asystole can also occur, particularly with right temporal/insular onsets, but are exceedingly rare (Nadkarni 2006). Ictal vomiting (ictus emeticus) can occur and is almost exclusively right temporal in origin (Luciano 1993).

A multitude of psychic manifestations can also occur as partial seizures, predominantly from the temporal lobe (Table 16–2). It should be noted that there are many symptoms listed that can be confused with primary psychiatric disorders. States such as depersonalization and derealization can be confused with anxiety neuroses. Fear is the most common ictal emotion and arises from the region of the amygdala (Luciano 1993). It may be differentiated from panic disorder by its unprovoked occurrence, maximal fear at the moment of onset, and brief duration more typical of a seizure (Luciano 1993; Luciano and Alper 2000). Another amygdaloid seizure manifestation is the sensation that somebody is standing behind one's shoulder, often on the contralateral side (Luciano and Alper 2000). One of the authors (D.L.) has treated two patients with TBI whose only ictal manifestations were such sensations, and both patients were erroneously diagnosed and treated for paranoid disorders.

Ictal psychosis also arises from temporal lobe seizures (Sengoku et al. 1997) and can arise from frontal seizures as well (Luat et al. 2008). In inpatient settings, psychosis as a purely ictal manifestation is underdiagnosed (Luat et al. 2008). Illusions and hallucinations, primarily visual, are most commonly produced by temporal lobe seizures (Luciano 1993). Olfactory hallucinations, usually of a foul odor, may arise from the region of the uncus or basal forebrain (Luciano 1993).

Frontal Lobe Seizures

Deceleration injuries selectively injure frontopolar and orbitofrontal cortices at higher rates than other brain regions as a result of inertial propulsion of the brain into the bony cranial vault with sudden deceleration. Auras are less frequent in

frontal than temporal lobe seizures (Luciano 1993). They can occur in isolation, are often nonspecific, and can involve a vague cephalic sensation; vague autonomic sensations; forced, crowded, or obscure thinking; and, rarely, forced actions akin to a compulsive disorder (Luciano 1993).

Motor phenomena, either focal or generalized, are prominent in frontal epilepsy, and many will express as generalized tonic-clonic events that are clinically obvious. Of greater diagnostic concern are frontal complex partial seizures, often arising from the orbital or mesial frontal cortex. Such seizures often occur nocturnally and may have strong affective expression with screaming or cursing, intense axial thrashing movements that appear bizarre, pelvic thrusting, complex automatisms such as bicycling or boxing, and irregular or desynchronized movements, leading many to misinterpret them as nonepileptic psychogenic seizures, particularly because as many as 25% may have no associated ictal EEG changes (Luciano 1993).

Confusional States

Intermittent confusion and disorientation is often seen in brain injury and postconcussive states (Sherer et al. 2009). This may manifest in particularly stressful situations, as in the need to filter many stimuli or life stress, or at the end of the day with prominent "neuro-fatigue." It is important to distinguish this from nonconvulsive status epilepticus (NCSE) due to complex partial or localization-related seizures that often presents with an altered sensorium and confusional state without prominent motor manifestations (Riggio 2006). NCSE can also involve bizarre behavior, sedation, or stupor. Many of these symptoms can result directly from the underlying brain injury in the absence of seizures, and there is a bias to ascribe such phenomena to sequelae of the injury itself.

Failing to recognize and treat NCSE can have grave consequences, including persistent confusion, kindling of epileptic foci, and perhaps superimposed injury leading to ongoing and persistent memory or other cognitive deficits (Drislane 2000; Profitlich et al. 2008). The incidence of NCSE in brain injury is not well known but is likely higher than recognized if inpatient studies of coma may be used as proxies (Bauer and Trinka 2009).

Subclinical Seizures

Subclinical seizures are ictal EEG discharges that do not have associated clinical manifestations. In one report such seizures were more common than overt seizures and were more common in penetrating injuries (Sarah 2004). These seizures do not obviously interrupt functioning but can act to markedly diminish cognitive functioning and potential for cognitive rehabilitation (Binnie et al. 1987).

Diagnosis

The diagnosis of epilepsy is primarily clinical in nature, and the direct observation of a seizure is invaluable. The EEG has been the gold standard of epilepsy diagnosis, but sensitivity is low, and a routine EEG will be normal in 59% of patients with definite epilepsy (Desai et al. 1988). Performing sleep deprivation in a patient with epilepsy with a normal routine EEG significantly increases the likelihood of finding an epileptiform abnormality. Sleep may also be captured during such a study, and a sleep EEG is much more likely to demonstrate an abnormality (Tucker 2005).

Ambulatory EEGs are convenient for the patient and can increase yield by virtue of a much longer recording time as well as capturing periods of sleep. Epileptiform activity on ambulatory EEGs was reported in 34.6% of patients in the first week after TBI and in 50% of patients between 6 and 12 months after injury (Kazibutowska et al. 1992). Finally, inpatient video EEG monitoring can be performed, during which antiepileptic medication can be tapered and sleep deprivation performed to increase the likelihood of capturing interictal abnormalities and also precipitating clinical seizures while in a safe monitored setting. It is important to realize that even during an event the majority of simple partial seizures and many frontal complex partial seizures are not associated with ictal EEG changes (Luciano 1993).

In general, in cases of brain trauma the EEG may help determine the localization and severity of injury but not the risk of developing posttraumatic epilepsy. Jennett and Van De Sande (1975) found that EEG abnormalities were more common in those with severe injuries, but the EEG did not improve the accuracy of prediction beyond that provided by clinical factors. Similarly, Salazar et al. (1985) studied 421 Vietnam veterans with penetrating injuries. Seizures had occurred in 53% of the veterans, but only 12% of those who had seizures had epileptiform activity on EEG. However, Angeleri et al. (1999) reported that the development of an EEG focus 1 month after injury increased the risk for seizures 3.49 times. Jabbari et al. (1986) performed EEGs on 515 Vietnam veterans after penetrating injuries and found that 42% of the EEGs were abnormal, but only 9% showed epileptiform activity. Notably, however, all patients with anterior temporal or central spikes had experienced seizures. Collectively, these results may suggest, as in the general partial epilepsy population, that a nonepileptiform EEG is not helpful diagnostically, but the presence of epileptiform abnormalities may be predictive of seizures.

One of the most powerful predictors of posttraumatic seizures is the presence of focal hemorrhagic brain damage on CT scans (Agrawal et al. 2006). Magnetic resonance imaging (MRI) is more sensitive for detecting white matter abnormalities, as well as hemosiderin deposits on T2-weighted images. Such deposits may be especially predictive of seizures when associated with surrounding gliosis (Kumar et al. 2003). In addition, diffusion tensor imaging with MRI has shown that patients with TBI who develop seizures may have a greater degree of cellular disruption than those who do not (Gupta et al. 2005). Interictal single-photon emission computed tomography (SPECT) scans lack sensitivity, though ictal SPECT scans, performed in epilepsy monitoring units, can identify an ictal focus in 70%–80% of cases (Tucker 2005).

Antiepileptic Drug Prophylaxis

The decision to treat with antiepileptic drugs (AEDs) is an obvious one once late unprovoked seizures have occurred.

The role of AED prophylaxis has been less clear. A number of studies have been performed over the years and, overall, the results suggest an antiepileptic effect of phenytoin and carbamazepine for early seizures only (Temkin 2009). There has been no suggestion of greater suppression of late seizures with such medications, let alone a truly prophylactic effect, preventing the development of epilepsy. In a relatively recent study, levetiracetam was as effective as phenytoin in seizure prophylaxis in cases of severe TBI, although the levetiracetam group had more epileptiform activity on EEG (Jones et al. 2008). This suggests a possible role for newer and safer AEDs, though further study is needed.

The American Academy of Neurology recommends that patients with severe TBI be given prophylactic phenytoin for 1 week only (Chang and Lowenstein 2003). This is particularly true for those at high risk and will prevent complications and further brain damage in the early phase due to elevated intracranial pressure, increased metabolic demand, and the excess release of excitatory neurotransmitters (Agrawal et al. 2006). Prophylactic treatment beyond this point is not indicated, which prevents many patients who will not experience seizures from experiencing the potential side effects of AEDs. This is particularly important in the TBI population given the potential for cognitive or behavioral side effects, which can further hinder recovery. Those with an early seizure may have AED treatment continued for a period of months if their risk is high, such as those with dural penetration, multiple contusions, or subdural hematomas requiring evacuation (Agrawal et al. 2006). The risk of recurrence following late seizures is high, and treatment is usually indicated for a minimum period of 2 years. However, AEDs other than phenytoin should be considered because this agent has been shown to have negative cognitive effects when used prophylactically in patients with severe TBI (Dikmen et al. 1991).

Several other prophylactic substances have been studied. Though effective in animal models, the administration of glucocorticoids after severe trauma did not decrease the occurrence of late posttraumatic seizures (Watson et al. 2004). Early infusions of magnesium also did not show a positive effect on seizures or functional outcome (Temkin et al. 2007). Antiperoxidants and free radical scavengers have prophylactic effects in experimental models but have not been studied in a controlled fashion in humans (Pagni and Zenga 2005).

Antiepileptic Drug Treatment

There are no specific AEDs for use in posttraumatic epilepsy, and the choice of an agent should be based on the same factors considered in patients with epilepsy of other etiologies, such as efficacy, side effect profile, and the potential treatment of comorbidities. Virtually all of the older and newer AEDs are efficacious in partial epilepsy, and the choice of an agent may be based more on these latter factors. In general, newer AEDs may be preferable given greater systemic safety and much less potential for drug interactions. In addition, in the brain-injured population one should generally avoid sedating drugs as well as drugs that can cause or worsen cognitive dysfunction and behavior. Although most AEDs can have cognitive side effects, they are most common with topiramate, followed by zonisamide, phenytoin, and oxcarbazepine (Arif et al. 2009). Conversely, lamotrigine may enhance cognitive function and health-related quality of life (Aldenkamp and Baker 2001).

Although many AEDs can have deleterious effects on mood, many have mood-stabilizing and anxiolytic properties and, occasionally, even stimulant properties. In some cases the aim of therapy may be balancing these effects. Table 16–3 lists potential psychotropic side effects of AEDs, beneficial and deleterious. Of the newer AEDs, levetiracetam may have the highest rate of psychiatric side effects, and such effects are more common in those with a psychiatric history (Weintraub et al. 2007). The two newest AEDs, lacosamide (Vimpat) and rufinamide (Banzel), do not yet have enough exposure for their psychotropic effects to be assessed.

The clinician must ideally attempt to control seizures while improving as many other posttraumatic symptoms as possible. A patient with depression, trouble focusing, or daytime somnolence may benefit from lamotrigine, which may have antidepressant and stimulating properties. In a population of severely brain-injured patients, lamotrigine enhanced alertness and cognition and resulted in more patients being discharged to the community (Showalter and Kimmel 2000). A patient with mood lability may benefit from carbamazepine, oxcarbazepine, valproate, or lamotrigine. Alternatively, a patient who has syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to TBI should avoid carbamazepine and oxcarbazepine given their potential to cause or exacerbate hyponatremia. Valproate may be helpful in the control of aggressivity, which is common in the TBI population, or coexistent bipolar disorder. A patient with either neuropathic pain or anxiety may find gabapentin or pregabalin helpful. Although topiramate may worsen cognition in some patients, it may be helpful in the control of headache and weight gain.

Surgical Treatment

In cases of posttraumatic epilepsy refractory to medical treatment, epilepsy surgery may be considered. However, TBI often results in bilateral and multifocal pathology and ictal onset zones that are poorly localized, resulting in a poorer surgical outcome (Agrawal et al. 2006). Results may be better if a resectable focal region of encephalomalacia can be identified as the source of seizures. Greater surgical success is seen in cases of posttraumatic mesial temporal sclerosis as opposed to neocortical epilepsy (Agrawal et al. 2006).

Psychiatric Aspects of Epilepsy

Mood and Anxiety Disorders

There is a substantially elevated prevalence of psychiatric disorders in epilepsy. The more than fourfold risk of a psychiatric disorder among people with epilepsy indicated by an analysis of two decades of Danish national health statistics provides an estimate of the substantial size of this effect (Christensen et al. 2007). Among psychiatric comor-

TABLE 16–3. Beneficial and harmful psychotropic effects of antiepileptic drugs

Antiepileptic drug	Beneficial effects	Harmful effects
Barbiturates	Anxiety, mood stabilization, sleep	Aggression, impaired cognition and attention, depression, irritability, sexual function and desire
Carbamazepine	Aggression, mania, mood stabilization	Irritability, impaired attention
Ethosuximide		Aggression, confusion, depression, insomnia
Gabapentin	Anxiety, insomnia, social phobia, mood stabilization	Irritability/agitation (usually in children with disabilities)
Lamotrigine	Depression, mood stabilization, mania	Insomnia, irritability (usually in children with disabilities)
Levetiracetam	Data not available	Anxiety, depression, irritability (all appear more common in children)
Phenytoin	Mania	Depression, impaired attention
Tiagabine	Mania, mood stabilization	Depression, irritability
Topiramate	Binge eating, mania, mood stabilization, ethanol dependence	Depression, impaired cognition (word finding, memory) and attention, irritability
Valproate	Agitation, aggression, irritability, mania, mood stabilization	Depression
Zonisamide	Mania	Aggression, emotional lability, irritability

bidities in epilepsy, depression is the most common, with reported estimates of prevalence commonly in the range of 20%–50%. Depression is a stronger determinant of quality of life than seizure control, but despite its clinical importance it is underdiagnosed and undertreated. Depression in epilepsy is related to stressors such as disability, memory problems, being denied a driver's license, stigmatization, and perceived loss of control. Biological effects are also likely involved, as indicated by a substantial body of preclinical and clinical evidence for altered serotonergic transmission in epilepsy (Alper et al. 2007).

The association between epilepsy and depression is reportedly bidirectional, with evidence indicating that depression may itself be a causal risk factor for the development of epilepsy. A prior history of depression is a risk factor for incident unprovoked seizures (Hesdorffer et al. 2006) and for the development of posttraumatic epilepsy following TBI (Ferguson et al. 2010), suggesting that depression itself is associated with decreased seizure threshold (Alper et al. 2007). Path analysis, which models causality using regression techniques, also indicates a bidirectional causal relationship between epilepsy and depression, and that depression is the ultimate mediating factor in the association of stress and anxiety with seizure frequency (Thapar et al. 2009). Additional evidence for an effect of psychiatric disorders themselves on seizure threshold includes the data from clinical trials indicating a substantially higher incidence of seizures in placebo-treated patients than the reported incidence of unprovoked seizures in the general population (Alper et al. 2007) and an association among family histories of epilepsy, family histories of mood disorders, and the incidence of postictal psychosis in probands with partial epilepsy (Alper et al. 2008).

Comprehensive meta-analyses, which include publications extending back to the early 1960s, indicate that the incidence of suicide is up to eight times greater in people with epilepsy compared with the general population (Pompili et al. 2006). However, more recent estimates indicate the rate may be lower. In the study on Danish national health statistics referenced earlier (Christensen et al. 2007), the overall relative risk of suicide in epilepsy was 3.17, compared with 1.99 in individuals with epilepsy without a history of psychiatric disorder and 13.7 in individuals with comorbid epilepsy and psychiatric disorders. These findings suggest that diagnosable, and likely treatable, psychiatric disorders determine much of the risk of suicide in epilepsy and underscore the imperative for recognition and treatment of psychiatric disorders, which are most commonly mood disorders, in epilepsy. Suicide rates declined over the period of the study from 1981 to 1997, which was suggested to be related in part to the decreased use of phenobarbital in view of its association with depressed mood as well as its lethality, and the relative frequency of overdose as a method of attempting suicide in the epileptic population. In addition to mood disorders, a prior history and a family history of suicide attempts are other important correlates of suicidal risk.

Since late 2008 the U.S. Food and Drug Administration (FDA) has issued a warning that all antiepileptic medications may cause suicidal behavior. However, many feel that this is too broad a generalization, and a study utilizing the United Kingdom General Practice Research Database suggested that risk for self-harm or suicidal behavior is not a general class effect of AEDs, but instead was associated with a specific subset of drugs regarded as having a high potential to cause depression, consisting of levetiracetam, tiagabine, topiramate, and vigabatrin (Andersohn et al. 2010).

Epilepsy may modulate the clinical presentation of depression, which has potentially important implications regarding its diagnosis and treatment. Item content of diagnostic criteria or rating scales for depression used in general psychiatry, such as impairment of attention and concentration or changes in sleep or appetite, may overlap with nonspecific cognitive deficits or adverse events related to the use of AEDs. A multicenter study identified features of depression presenting in epileptic patients for the purpose of developing a rating scale of items distinct to

depression in epilepsy, with diagnostic agreement with the major depressive disorder module of the Structured Clinical Interview for DSM-IV (First et al. 1997) as the validating measure (Gilliam et al. 2006). The study yielded a brief six-item scale with core content relating to anhedonia, frustration, and hopelessness that correlated well with a diagnosis of DSM-IV-TR (American Psychiatric Association 2000) major depression.

Anxiety disorders are less frequently studied but contribute independently to the decrement of quality of life in epilepsy (Johnson et al. 2004). Anxiety disorders also contribute to the risk of suicide in a manner that is independent and additive to the risk associated with mood disorders, and the assessment of symptoms of anxiety should be included in the evaluation of suicidal risk (Hesdorffer and Kanner 2009). Epilepsy can be associated with deficits of impulse control or cognitive operations related to the processing of anxiety, which may disinhibit anxiety-driven perseverative behaviors that may manifest as "viscosity," or it can be misidentified as compulsive rituals and result in inappropriate diagnosis of obsessive-compulsive disorder.

Psychosis

Postictal psychosis (PIP) is a common and clinically significant problem that is defined as the occurrence of psychotic symptoms after a seizure or seizure cluster without an alternative explanatory causative factor (Logsdail and Toone 1988). Psychosis can occur immediately after a seizure or following a period that has been termed a "lucid interval," with duration of up to a week. The reported incidence of PIP in consecutive series from video EEG monitoring studies is on the order of 7% (Kanner et al. 1996). PIP is associated with increased mortality (Logsdail and Toone 1988), which is mediated by epilepsy severity, as well as an increased incidence of suicide, particularly involving violent means. Risk factors for PIP include seizures with extratemporal or ambiguous localization, family history of mood disorders and seizures, abnormal interictal EEG activity, and encephalitis (Alper et al. 2008). PIP has been associated with temporal lobe epilepsy and hypothesized to result from temporal limbic dysfunction. However, it is partial epilepsy rather than localization to the temporal lobe per se that may mediate the association with psychosis. Psychosis is reportedly more frequent in patients with partial than idiopathic generalized epilepsy, and the apparent association with the temporal lobe may simply reflect the generally greater prevalence of temporal versus extratemporal onsets in partial epilepsy.

Interictal psychosis (IIP) is characterized by persistent psychotic symptoms and reportedly may result from progression due to recurrent episodes of PIP (Kanner and Ostrovskaya 2008; Tarulli et al. 2001). Although IIP has been regarded as the most common psychotic syndrome in epilepsy, PIP has been more common in some more relatively recent series. One difficulty regarding the epidemiology of IIP is the difficulty in distinguishing IIP from schizophrenia because of the increased prevalence of epilepsy in schizophrenia, as well as the uncertainty with regard to the sequence of the respective onsets of psychotic symptoms and seizures.

Nonepileptic Seizures

Nonepileptic seizures (NES) are paroxysmal behavioral events that resemble seizures but lack EEG changes or other clinical evidence of a physiological seizure. NES are common, with a reported frequency of up to 25% of admissions to specialized tertiary care epilepsy services, with a lower rate in outpatient settings. Diaz-Arrastia et al. (2009) reported that 33% of cases of intractable epilepsy related to TBI who underwent video EEG monitoring were found to have nonepileptic psychogenic seizures.

NES most frequently present as a conversion disorder, distinct from other categories of psychiatric disorders that may feature paroxysmal behavioral features or disturbances of attention such as anxiety, schizophrenia or other psychotic disorders, or attention deficit disorder (Alper et al. 1995). Conversion disorder involves intentional motor behavior that the patient is not consciously aware of producing and is linked to psychological factors such as trauma, conflict, bereavement, or disparity between the idealized and actual self. In DSM-IV-TR, conversion is classified as a somatoform disorder and is distinguished from other disorders that feature intentional symptom production on the basis of the patient's awareness of the intentional nature and motivational basis for producing the symptoms. Patients with conversion are not aware that their production of symptoms is intentional or why they do it. In contrast, patients with factitious disorder are consciously aware of intentionally producing symptoms but are not aware of the psychological basis of their motivation to be in the sick role. Malingerers are aware of both the conscious nature of their symptom production and the agenda it serves.

There is a reportedly a higher prevalence of histories of childhood abuse (Sharpe and Faye 2006) and greater severity of abuse (Alper et al. 1993) in patients with NES. A comprehensive meta-analysis reported that across all of the controlled studies included in the review, the prevalence of a history of sexual abuse was 35.7% and 16.6% in NES and control subjects, respectively (Sharpe and Faye 2006). The generally higher prevalence of abuse in women may explain in part the female gender predominance of approximately 75% in reported samples of patients with NES. NES are reportedly associated with a higher prevalence of symptoms of mood, anxiety, and personality disorders. Although reported rates of comorbidity of epileptic and nonepileptic seizures vary, these conditions co-occur at a rate that is greater than expected on the basis of chance. Mild TBI has been associated with NES (Kotsopoulos et al. 2005; Westbrook et al. 1998). On one hand, the association of TBI and NES may be viewed as consistent with other evidence for association conversion symptoms with neurobiological abnormality, including anoxic injury, as well as structural lesions and EEG abnormalities, and an effect of lateralization of abnormal structure or function implicating the right hemisphere. In some cases of TBI, NES may represent an expression of a posttraumatic stress disorder. On the other hand, a reported association of litigation and disability compensation with mild TBI in NES also suggests a possible effect of secondary gain in the association of TBI and NES. However, a patient focused on litigation as an identity in the psychological

context of a pervasive sense of deprivation and narcissistic injury may be operating in the domain of primary and not exclusively secondary gain.

NES can carry significant morbidity, including side effects of unneeded medications, acute treatments of ongoing "seizures" leading to intensive care stays and possible mortality, and loss of work and disintegration of social supports. NES can only be definitively diagnosed on a continuous video EEG monitoring unit, and once the diagnosis is made, appropriate treatment hinges on establishing rapport with the patient with a nonjudgmental and empathic stance and close collaboration between the psychiatrist and neurologist.

Psychotropic Medications

Important considerations regarding the selection of psychiatric drugs for use in epilepsy include the avoidance of excessive sedation, pharmacokinetic interactions, and possible effects on seizure threshold. Many people with epilepsy are already coping with sedation due to AEDs, and psychiatric drugs should be selected to minimize this problem. Examples of reported pharmacokinetic interactions of psychiatric drugs with AEDs include decreased levels of the antipsychotic drugs ziprasidone and aripiprazole due to the induction of CYP3A4 by carbamazepine, and increased levels of phenytoin due to the inhibition of CYP2C19 by fluvoxamine (Perucca 2006). A particularly important interaction between AEDs is the inhibition of the glucuronidation of lamotrigine by valproate, resulting in increased lamotrigine levels and liability toward Stevens-Johnson syndrome. Citalopram, escitalopram, mirtazapine, venlafaxine, and desvenlafaxine appear to have particularly weak microsomal enzyme interactions.

The prescribing information for most antidepressants includes a generic statement that advises caution in patients with epilepsy or who are otherwise at risk for seizures. However, there is a substantial body of clinical and preclinical evidence for anticonvulsant effects of antidepressant drugs (Alper et al. 2007). The preclinical literature indicates that antidepressants have anticonvulsant effects in animal models of epilepsy and that genetically epilepsy-prone animals have deficits of serotonergic and noradrenergic transmission. Analysis of clinical trials of psychotropic drugs approved between 1985 and 2004 indicated an anticonvulsant effect of most antidepressants, including the serotonin and serotonin-norepinephrine reuptake inhibitors (Alper et al. 2007). The clinical evidence for an anticonvulsant effect of antidepressants also includes open-label trials of fluoxetine or citalopram in which reduced seizure frequency was observed in epilepsy patients with or without depression.

Bupropion and the tricyclic antidepressants (TCAs) are associated with seizure risk that appears to be significantly related to pharmacokinetic factors. The warning regarding seizure threshold that is routinely included in the prescribing information for most antidepressants has likely contributed to the undertreatment of depression in epilepsy. This warning is based mainly on reports of seizures associated with supratherapeutic levels of TCAs (Preskorn and Fast 1992). More than three decades after the introduction of imipramine in 1960 as the first TCA approved in the United States, and at the end of the era of TCAs as first-line antidepressant monotherapy, Preskorn and Fast (1992) stated there were no case reports in the literature of TCA-induced seizures at therapeutic concentrations. An older literature indicates an anticonvulsant effect of imipramine at relatively low serum levels and includes a double-blind crossover study (Fromm et al. 1978). However, one study of patients with severe TBI treated with TCAs reported a 19% incidence of seizures in which the TCA was regarded as a probable etiological factor (Wroblewski et al. 1990). Unfortunately, TCA levels were not included in the study design.

Clinical trials of bupropion indicate an association of seizure risk with the immediate-release (IR) but not sustained-release (SR) formulation (Alper et al. 2007), which has been attributed to lower peak plasma concentrations with the SR form, suggesting the importance of pharmacokinetic factors (Jefferson et al. 2005). Among bupropion and its metabolites, seizure risk appears most strongly associated with hydroxybupropion (Silverstone et al. 2008), which is reportedly increased in slow CYP2D6 metabolizers who are administered bupropion (Pollock et al. 1996) and who might be expected to be at increased seizure risk, particularly in view of the absence of the availability of therapeutic drug monitoring. The prescribing information for all formulations of bupropion lists epilepsy as a contraindication, which appears to be a general inference based on data regarding the IR form in depressed patients without epilepsy and not on data obtained from prospective evaluation of patients with epilepsy. The apparently only published study on bupropion in patients with epilepsy reported an increase in myoclonus in 1 patient with uncontrolled myoclonic and absence seizures; increased simple partial seizures in 2 patients; and complex partial seizures in another in a total sample of 28 patients (Resor and Resor 2003). In this study bupropion was given in the SR form in divided doses of up to 300 mg/day. The authors concluded that the decision to use bupropion in patients with epilepsy should be evaluated in the context of the risk of untreated depression and the possibility that bupropion might offer relatively distinctive benefit to some patients who have not responded to trials of other antidepressants.

Stimulants, particularly methylphenidate, are used for the treatment of cognitive deficits and apathy in TBI (Silver et al. 2009). A retrospective study of 30 patients with epilepsy and severe TBI reported no increase in seizures in the first 3 months after starting methylphenidate compared with the preceding 3-month baseline (Wroblewski et al. 1992). A review of the use of stimulants in pediatric patients with epilepsy found no increase in seizures in association with treatment with methylphenidate (Torres et al. 2008) but noted low baseline seizure rates, small numbers of subjects, and short observation periods as factors that have limited the power of existing studies to detect change in seizure risk.

A currently important issue regarding the behavioral effects of AEDs is the question of their possible association with suicidality. The FDA has mandated warnings regarding risk of suicidality (defined as suicidal thoughts or behavior) in the prescribing information for AEDs on the basis of a meta-analysis of clinical trial data that indicated

a 1.8 times greater incidence of suicidality in patients treated with AEDs (Hesdorffer and Kanner 2009). The relative risk of suicidality was greater in patients treated with AEDs for epilepsy than in patients treated for psychiatric indications. The FDA's analysis and conclusions have been questioned with regard to statistical methodology, the attribution of an overall class effect that subsumed 11 different AEDs, and the relative weighting of the risks of uncontrolled seizures versus a small risk of suicidality (Hesdorffer and Kanner 2009). As is generally the case with adverse behavioral effects associated with AEDs, individual and family histories of psychiatric disorders appear to be significant determinants of risk.

Management of Aggressive Behavior and Agitation

Antipsychotic agents appear to be useful in postictal psychosis or delirium. Ziprasidone and aripiprazole have not been associated with an apparent lowering of seizure threshold in clinical trials (Alper et al. 2007). In addition to being dopamine type 2 (D_2) and 5-hydroxytryptamine type 2A (5-HT_{2A}) receptor antagonists, which is a common attribute of S_2D_2 or atypical antipsychotics, these drugs are also 5-HT_{1A} receptor agonists, which might contribute to their clinical efficacy in aggressive or agitated states. The anxiolytic 5-HT_{1A} agonist buspirone is sometimes effective in nonpsychotic aggressive patients with TBI (Levy et al. 2005), which suggests that the treatment effect may in part be addressing a disinhibited expression of the tension and irritability associated with anxiety. One useful behavioral principle in managing acute postictal delirium is to try to avoid the use of restraints. Postictal, confused patients who want to ambulate will often do so briefly and eventually accept guidance back to the bed. This is strongly preferable to a common occurrence in settings with less experience with epileptic patients when a confused or delirious postictal patient is unnecessarily restrained, resulting in an avoidable vicious cycle involving further escalation of agitation and further application of restraints (Alper et al. 2002).

Prognosis

The prognosis for patients with epilepsy is generally good, with approximately 70% achieving remission in the general population (Hauser and Hesdorffer 1990). In the posttraumatic epilepsy population, approximately 50% may be in remission 15 years after trauma (Walker and Erculei 1970; Willmore 1996). Those with frequent seizures in the first year have a lesser chance of obtaining an extended remission (Salazar et al. 1985).

Studies suggest that the development of posttraumatic epilepsy does not affect neuropsychological outcome, rehabilitation goals, or employment, but it does result in greater psychiatric problems as well as reduced general health and functional and social outcome (Agrawal et al. 2006). In some cases these problems may be related to the potential cognitive and behavioral effects of antiepileptic drugs, as well as psychosocial consequences of epilepsy such as the restriction of driving privileges.

KEY CLINICAL POINTS

- Seizures occurring 1 week or more after trauma (late seizures) carry a much higher risk of epilepsy than those occurring the first week (early seizures).
- The risk of a first seizure remains elevated for as long as 20 years after a severe traumatic brain injury.
- Greater degrees of cortical damage and hemorrhage increase the risk of developing posttraumatic epilepsy.
- Partial seizures from the temporal and frontal regions may not produce ictal electroencephalographic changes and may be confused with psychiatric disorders.
- Nonconvulsive status epilepticus must be differentiated from posttraumatic coma or confusion.
- A routine electroencephalogram may be normal in up to 59% of patients with definite epilepsy.
- Prophylactic antiepileptic medication, particularly phenytoin, is indicated only in the first week following severe traumatic brain injury.

- Antiepileptic drug treatment should be individualized and should ideally attempt to treat multiple problems.
- Depression is the most common psychiatric comorbidity in epilepsy.
- Fifty percent of those with posttraumatic epilepsy will be in remission after 15 years.

Recommended Resources

http://en.wikipedia.org/wiki/Post-traumatic_epilepsy
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1363374
http://professionals.epilepsy.com/wi/print_section.php?section=head_trauma
http://www.searchmedica.com/search.html?q=Post-Traumatic+Epilepsyanduseraction=searchandss=defLinkandfr=trueandc=ps

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Part III

NEUROPSYCHIATRIC SYMPTOMATOLOGIES

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CHAPTER 17

Cognitive Changes

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COGNITIVE CHANGES ARE OFTEN THE MOST SALIENT feature following closed traumatic brain injury (TBI) at any level of severity. Years after severe TBI, patients and families cite impaired cognition and neurobehavioral function as the greatest source of difficulty, contributing more to persisting disability than physical symptoms (DeGuise et al. 2008).

The extent of these changes after TBI reflects a number of factors, the most important being 1) the severity of diffuse axonal injury (DAI), as indexed by the depth and duration of coma, the length of posttraumatic amnesia, and the extent of generalized atrophy; and 2) the location and depth of focal cerebral lesions (Bigler 2007; Katz 1997). Other critical factors include the patient's age, preexisting morbidities, and the occurrence of significant extracranial or systemic injury (e.g., hypoxia or hypotension). Genetic factors may also contribute (Jordan 2007), although evidence concerning the apolipoprotein E genotype is somewhat mixed. Over the course of recovery, complications in relation to mood, pain, and sleep disturbance can also be expected to influence cognitive status.

Despite a wide range of potential deficits after TBI, there is a degree of consistency as to the nature and frequency of difficulties observed following TBI. This occurs because the damage incurred—both focal and diffuse—is concentrated in the anterior regions of the brain (Gentry et al. 1988; Wilde et al. 2005). As DAI becomes more severe, axonal damage is more widespread, with greater disruption of critical cortical-subcortical pathways. Injury to more central regions is also observed, such as the rostral brain stem. While discrete focal lesions may produce classic neurobehavioral syndromes such as aphasia, these are commonly superimposed on the more global dysfunction resulting from diffuse injury.

This chapter emphasizes four separate (but interrelated) cognitive domains that are commonly impaired after closed TBI: attention, memory, executive function, and language/communication. Particular implications for rehabilitation and psychosocial/functional recovery are associated with impairments in each area. The similarity between mild and more severe brain injury is also considered, as the two represent different locations on a continuum of cerebral involvement (Levine et al. 2008; Reitan and Wolfson 2000). However, the former has a much better prognosis. The chapter ends with a review of the evidence supporting pharmacological interventions to enhance cognitive function after TBI.

Impairments of Attention

Impaired attentional processes are very prevalent, if not universal, after TBI at all levels of severity (Gronwall 1987; Ponsford 2008; Table 17–1). During posttraumatic amnesia, patients may demonstrate impaired awareness and wandering attention, whereas inability to concentrate for more than a few minutes and distractibility characterize the early phases of recovery (Katz 1997). At later stages, impairments may only be revealed with rigorous testing. Because attention underpins all aspects of cognition, even mild impairments can restrict other processes such as the capacity for new learning. Commonly reported symptoms include mental slowing, trouble following conversation, loss of train of thought, and difficulty attending to two things at once.

Attention is not a unitary phenomenon; it can be subdivided using a commonly described taxonomy that includes selective, sustained, and divided components, as well as information processing speed and supervisory or executive aspects (see Table 17–1). These elements reflect the interactions of several widely dispersed networks (Raz and Buhle 2006). For example, a network for selective attention has been described that includes the posterior parietal, dorsolateral frontal, and cingulate regions, acting in concert with components of the thalamus, basal ganglia, and midbrain. These cortical regions may, respectively, contribute sensory, motor-exploratory, and limbic-motivational inputs to guide the targeting of attention. The brainstem reticular formation

supports the overall attentional tone or degree of responsiveness to stimuli. A greater role for the right hemisphere in alertness and sustained attention has been postulated, whereas the left hemisphere appears more closely linked to selective or focused attention (Ponsford 2008).

It is thus apparent that focal or diffuse injury during TBI may disrupt these circuits, potentially impairing different aspects of attention. Although there is some debate as to the precise nature of the deficits after TBI, the greatest unanimity exists with respect to reduced information processing speed. This frequent complaint corresponds with robust psychometric findings after TBI. Compared with control subjects, TBI patients demonstrate a slowing of reaction time that is proportional to task complexity. Choice reaction time paradigms, which require decision making among a number of alternative responses, have proved very sensitive to brain injury (Gronwall 1987; Mathias and Wheaton 2007). Choice reaction time tasks can discriminate between grades of TBI severity and demonstrate improvement over time, although persisting deficits in patients with severe TBI are observed at 2 years or more (van Zomeren and Brouwer 1994). Although it taps a number of cognitive processes, the Paced Auditory Serial Addition Task (Gronwall 1987) has been used extensively to study processing efficiency after TBI. In this task, subjects are presented with a series of single-digit numbers verbally and instructed to add each new digit to the one immediately preceding it. Task difficulty is varied by adjusting the time interval between the items presented. Performance on this measure has been shown to correlate with injury severity, to track recovery of attentional capacities, and to predict return to vocational activities (Lezak et al. 2004). Reduction in processing speed is thought to result from diffuse white matter dysfunction incurred during TBI (Lezak et al. 2004).

In addition to cognitive slowing, deficits have been examined with respect to selective, sustained, and divided attentional components. Results are at times contradictory and may differ with regard to the precise mechanisms underlying a particular deficit (Rios et al. 2004). For example, some investigators have hypothesized that slowed processing after TBI may explain many of the other attentional difficulties that are observed (Mathias and Wheaton 2007).

Abnormalities of selective attention (i.e., the ability to inhibit processing of irrelevant stimuli, or distractions) and sustained attention (i.e., the ability to maintain performance over extended periods, or vigilance) have been reported in patients with moderate to severe TBI (Mathias and Wheaton 2007; Ponsford 2008). In a simulated classroom setting, Whyte et al. (2000) found that TBI patients demonstrated a greater rate of "off-task" behavior compared with control subjects when completing a task in the face of distracting stimuli.

The findings are quite consistent in the case of divided attention (Park et al. 1999; Zoccolotti et al. 2000), which is also a frequent subjective complaint. Impairments in this area appear to characterize TBI patients at all levels of severity (Pare et al. 2009; Zoccolotti et al. 2000). The assessment of divided attention under dual-task conditions (i.e., performing simultaneous tasks) has proved to be a sensitive means to probe deficits that may otherwise go undetected. Using paradigms that control for slowed processing, several dual-task studies point toward limitations of executive or "supervisory control" aspects of attention

TABLE 17–1. Aspects of attention potentially impaired after traumatic brain injury

Arousal/alertness: general receptivity to sensory information and readiness to make a response
Selective attention: ability to select target information from a broad field of stimuli and inhibit irrelevant stimuli
Sustained attention: ability to sustain attention toward a source of information or task over a prolonged period (i.e., vigilance)
Divided attention: ability to share or divide attention between two or more sources of information or task demands at the same time
Information processing speed: rate at which information is processed within the central nervous system to allow cognitive activities to occur
Executive or "supervisory control" aspects: top-down coordination of lower-level attentional processes to perform complex, nonroutine tasks consistent with drives and intentions; the allocation of limited attentional resources is an essential feature at this level

Note. "Components" of attention, as with other cognitive domains, are hypothetical constructs devised to integrate clinical observations, neuropsychological test results, and theoretical models of cognition. As such, they refer to interrelated rather than discrete processes and also overlap with other domains such as memory.

This component of the attentional system is hypothesized to govern lower-level attentional processes and includes the allocation of attentional resources, target selection, interference control, switching between tasks, monitoring, and so forth (Rios et al. 2004). It is conceived as a limited-capacity component that is involved in the effortful or strategic processing of nonroutine tasks, as opposed to those in which information is processed automatically. Thus, TBI patients perform significantly worse than control subjects when two tasks place demands on working memory (see next section, Impairments of Learning and Memory), also considered an important component of controlled attentional processing (Park et al. 1999).

On balance, the weight of evidence clearly supports abnormalities in a number of aspects of attention, irrespective of TBI severity. Thus, even in patients with mild TBI, deficits in information processing and attention are considered principal features of the early postconcussional phase (Frencham et al. 2005; Lezak et al. 2004). Nonetheless, studies of uncomplicated mild TBI demonstrate that resolution of cognitive deficits within 1–3 months is the norm (Frencham et al. 2005). This is not the case after more severe injuries, in which residual deficits of attentional functions can be expected.

Impairments of Learning and Memory

Memory dysfunction is a cardinal feature after TBI (Table 17–2). It is most dramatically apparent during the early intervals of retrograde amnesia and posttraumatic amnesia, the duration of which strongly predicts eventual outcome. In the postacute stage and beyond, it remains perhaps the most common subjective complaint (Levin and Hanten

TABLE 17–2. Aspects of learning and memory potentially impaired after traumatic brain injury

Anterograde memory
The ability to learn new information; anterograde amnesia refers to a deficit in the conscious, deliberate recall of information first learned after brain insult
Retrograde memory
The retrieval of information that is already stored; retrograde amnesia involves impaired retrieval of memories acquired prior to a brain insult, typically autobiographical in nature
Explicit (or declarative) memory
Episodic memory: memory for specific personal experiences or "autobiographical" events
Semantic memory: memory for general facts and concepts, including knowledge of objects
Implicit memory[a]
Procedural memory: perceptual and motor skill learning; learning of rules and sequences
Priming effect: the enhancement in test performance as a result of previous exposure to stimuli
Classical conditioning
Aspects of memory related to executive functions
Working memory: the temporary storage and manipulation of information relevant for cognitive operations; via ongoing rehearsal, the duration of immediate or short-term memory (which would otherwise decay in a few seconds) is extended
Strategic memory: the application of active organizing and elaborative strategies to enhance encoding and retrieval
Source memory: memory regarding the context in which an episodic memory is formed; where and when an experience occurred; includes memory for temporal order and recency of presentation
Prospective memory: remembering to perform a task in the future at a specific time or following a certain event
Metamemory: awareness and knowledge regarding one's memory capabilities

[a]This aspect of memory appears much less vulnerable to the effects of traumatic brain injury (see Vakil 2005 for discussion).

2004; Vakil 2005). Objective memory dysfunction may persist in those with moderate to severe injuries even after IQ scores have normalized (Levin and Hanten 2004). During assessment, one must consider other domains potentially affecting memory function, such as attention, processing speed, and executive function.

Memory can be broadly divided into two components: *explicit memory,* which can be consciously, deliberately recalled; and *implicit memory,* which is acquired without conscious mediation or recollection. Explicit memory is further divisible into *episodic memory* for personal events and *semantic memory* for general facts about the world. In contrast, implicit memory refers to a range of abilities such as procedural learning, conditioning, and priming effects (Baddeley 2004).

Impaired episodic memory is a hallmark feature after TBI, the magnitude of which generally corresponds to injury severity (Levin and Hanten 2004). It is typically examined using standardized learning tests, such as the repeated presentation of a (supraspan) list of unrelated words. After moderate to severe injuries, such testing often reveals deficits of immediate and delayed recall, slower rates of learning, and recall errors (intrusions). Although recognition memory may be relatively intact, it too can be affected (Levin and Hanten 2004). Similar impairment may be evident in the visual domain. Some investigators report dysfunction at all stages of episodic processing, including encoding, consolidation, and retrieval (Curtiss et al. 2001), whereas others posit deficits at specific stages (Vanderploeg et al. 2001). However, differing patterns of memory deficits can be expected among individuals, owing to the significant pathological heterogeneity. A consistent finding is the failure to spontaneously apply organizing strategies when learning, such as clustering words according to semantic category (e.g., as "fruit" or "tools") (Curtiss et al. 2001). In general, tasks that require deliberate, controlled, and generally conscious processing, as opposed to automatic processes occurring unconsciously, show the greatest degree of disruption. Thus implicit memory is relatively spared after TBI (Vakil 2005). The semantic or general knowledge base also remains largely intact, although problems with inefficient access and retrieval can impede recall (McWilliams and Schmitter-Edgecombe 2008). Cases of relatively selective deficits with a specific aspect of memory have been described, such as marked semantic memory loss or disproportionate autobiographical memory alteration, yet these are rare and reported in the setting of severe injury (Levin and Hanten 2004; Vakil 2005).

Other aspects of memory closely associated with executive processing are vulnerable to injury. TBI commonly disrupts *working memory,* considered a temporary, limited-capacity storage system that facilitates complex processes such as language, problem solving, and the guidance of behavior (Baddeley 2004). Working memory is thought to comprise 1) a set of "slave" systems for the "online" maintenance of verbal and visuospatial information via rehearsal and 2) a "central executive" that further processes and manipulates the information being held. The central executive is closely linked with the dorsolateral prefrontal region and also serves to update stored information, inhibit unwanted thoughts, and switch focus between the slave systems, enabling the division of attention when necessary (Baddeley 2004). TBI preferentially affects the control/manipulation processes rather than the passive storage/rehearsal aspects, a finding supported by both neuropsychological (Vallat-Azouvi et al. 2007) and activation neuroimaging studies (Turner and Levine 2008). Thus performance at reversed digit span, requiring the active manipulation of information, is typically more impaired than digits forward.

A related construct known as *prospective memory,* or the ability to remember one's future intentions, is frequently impaired after TBI (Vakil 2005). Forgetting to take medications, attend appointments, or make bill payments can potentially jeopardize one's capacity for independent living. Prospective memory involves a set of processes including the initial storage of one's intentions, monitoring the passage of time and relevant circumstances, and the ability to initiate a new activity while inhibiting others.

TBI patients often regard their memory function as better than that suggested by reports of caregivers, pointing to

a deficit of *metamemory,* or self-awareness of memory capabilities. Moderate-to-severe TBI patients show reduced ability to gauge their performance during formal memory testing when compared with control subjects (Kennedy and Yorkston 2000). These deficiencies may be critical in influencing one to use compensatory strategies to enhance memory function or agree to participate in rehabilitation. A more accurate picture of everyday memory may be obtained using a measure such as the Rivermead Behavioural Memory Test (Wills et al. 2000), which includes naturalistic analogues of day-to-day tasks such as remembering to deliver a message, a route, people's names, and so forth.

Neuroimaging studies provide a basis for understanding memory impairments post-TBI. The consistent magnetic resonance imaging (MRI) findings of hippocampal atrophy and the marked sensitivity of this structure to the various types of injury incurred during TBI strongly implicate hippocampal involvement in explicit memory dysfunction following TBI. Yet only modest correlations between hippocampal size and reduced memory function are found (Bigler 2007), pointing to the significance of injury elsewhere. Diencephalic and basal forebrain structures are obvious candidates, given their substantial involvement in episodic memory. Frontal lobe contributions to mnemonic function are also implicated, based on mounting evidence for their involvement in encoding and retrieval processes, a role described as "working with memory" (Simons and Spiers 2003). Similarities between the pattern of memory deficits following TBI and that of patients with focal frontal lobe lesions have been frequently emphasized (Levin and Hanten 2004; Vakil 2005).

In addition, a major contribution from diffuse injury, with disruption of wider memory networks, is suggested by the fact that memory deficits tend to show stronger associations with severity indicators such as posttraumatic amnesia duration and Glasgow Coma Scale scores than with the presence of specific focal lesions on neuroimaging (Levin and Hanten 2004). In a study of patients with MRI-confirmed "pure DAI," Scheid et al. (2006) found that mnemonic dysfunction was the most striking disturbance, present at a moderate to severe level in 50%. Although attention and executive dysfunction were also frequent, they were relatively less severe. The memory impairments were attributed to disruption of both frontal-subcortical and memory-specific temporal networks, based on the observed patterns of cognitive impairment.

In mild TBI, prospective studies demonstrate that as with attention, initial impairment on standard memory tests tends to resolve within 1–3 months (Belanger et al. 2005). However, a discrepancy is often noted between normalized test results and persisting subjective complaints, particularly when cognitively demanding tasks are performed. It is possible that residual cognitive inefficiency contributes to a perception of forgetfulness that is not tapped by standard tests of memory. A functional MRI (fMRI) study of working memory by McAllister et al. (2001) supports this idea. Despite test performance similar to that of controls, mild TBI patients examined at 1 month postinjury showed more extensive cerebral activation as working memory load increased. The authors theorized that mild TBI patients may need to work harder to maintain premorbid levels of cognitive performance.

TABLE 17–3. Aspects of executive functions potentially impaired after traumatic brain injury

Goal establishment, planning, and anticipation of consequences
Initiation and inhibition of responses; temporal sequencing of behavior
Generation of novel response alternatives (vs. perseverative or stereotyped responses)
Mental flexibility/ease of mental and behavioral switching
Transcending of the immediately salient aspects of a situation (vs. stimulus-bound behavior or environmental dependency)
Conceptual/inferential reasoning; problem solving in novel or complex circumstances
Decision making
Working memory
Executive attentional and memory processes
Self-monitoring and self-regulation, including emotional responses
Social adaptive functioning: perspective taking, use of social feedback, adherence to social norms

In contrast to the spontaneous recovery seen in mild TBI, longitudinal studies of moderate-to-severe TBI confirm that memory disturbance often remains a prominent feature over the long term (Draper and Ponsford 2008).

Impairments of Frontal Executive Functions

The term *executive functions* refers to a set of higher-order capabilities that are considered the domain of the frontal lobes and their projections. They engage and direct other mental activities such as attention, memory, language, and motor behavior in the mediation of real-world problems. Specific frontal executive functions include establishing relevant goals and planning, initiating and sequencing goal-directed behavior, inhibiting competing actions and stimuli, conceptual reasoning, decision making, as well as the activities of self-monitoring and self-regulating (Stuss and Levine 2002; see Table 17–3).

Deficits in executive function are a critical determinant of functional outcome after TBI (Crepeau and Scherzer 1993). Historically, a parallel has been noted between the pattern of deficit seen after severe TBI and that resulting from focal frontal lobe damage (Stuss and Gow 1992). This association is strengthened by the fact that TBI has a strong predilection for the anterior portions of the brain, with polar and ventral frontal and temporal regions being particularly prone to contusional damage. Additionally, although DAI is observed throughout the neuraxis, it too is more concentrated in the anterior regions (Gentry et al. 1988; Levine et al. 2008).

In a review of executive function after TBI, Cicerone et al. (2006) identified four distinct categories of function that can be linked with specific prefrontal regions (see also Stuss and Alexander 2009). This approach is adopted here and outlined in Table 17–4. Notably, three of the proposed

domains—associated with the dorsolateral, superior medial, and ventromedial prefrontal regions—map onto the three behaviorally relevant frontal-subcortical circuits, as elaborated by Cummings and Miller (2007) in a model that highlights the widespread links between the prefrontal cortex (PFC) and virtually all other cortical and subcortical regions. Each of these four domains is briefly reviewed, followed by a discussion of social cognition, an important facet of human cognition that also has a strong association with executive processes.

Dorsolateral Prefrontal Cortex and Executive Cognitive Functions

Executive cognitive function (ECF) refers to a specific category of function that is reliant on the dorsolateral PFC and its connections. Difficulties with attention, working memory, planning, and reasoning may arise from focal damage to this area. Cognitive processes falling under this rubric include those assayed by commonly used measures of executive function. For example, verbal fluency tasks require efficient self-generation, retrieval strategies, monitoring, and suppression of inappropriate responses, whereas the Trail Making Test (Part B) requires divided attention and the alternation of mental set. Category-sorting tasks assess conceptual reasoning and the ability to maintain or shift response sets and to make use of feedback (Stuss and Levine 2002). As is evident, ECF involves multiple cognitive processes, and thus several tests are typically used to assess its integrity.

Studies among those with moderate to severe TBI have often found deficits of concept formation/flexibility on the Wisconsin Card Sorting Test (Benge et al. 2007), control aspects of working memory (Turner and Levine 2008), the application of strategic memory (Vakil 2005), planning ability (Cazalis et al. 2006), and executive attentional functions (Zoccolotti et al. 2000). In a meta-analysis of verbal fluency, Henry and Crawford (2004) found that TBI patients showed comparable declines in both phonemic and semantic fluency, a pattern similar to individuals with focal frontal lesions due to varying etiologies. Furthermore, the fluency deficits were found to be independent from slowed mental processing and general cognitive decline, as indicated by verbal IQ. When contrasted with other measures, phonemic fluency was among the more sensitive ECF tests to the presence of TBI. Although particularly sensitive to left dorsolateral PFC dysfunction, fluency tasks may also be affected by disturbance of right or left medial PFC function (Stuss and Levine 2002).

Studies have tended to show stronger associations between ECF deficits and indicators of diffuse injury (e.g., coma depth, generalized atrophy) than with the presence or absence of a demonstrable frontal lesion. Findings such as these point to the impact of diffuse injury on the extensive cortical and subcortical connections to the dorsolateral PFC (Anderson et al. 1995; Bigler 2007); they also show that the absence of frontal lesion does not imply intact ECF. Fork et al. (2005) compared the cognitive profiles of patients with high-resolution computed tomography–confirmed DAI, who were without contusions, with a group with frontal contusions but no features of DAI. Although the groups performed quite similarly within the first few weeks postinjury, at 5–8 months those with DAI had greater deficits on measures of ECF and memory in contrast to the frontal lesion group. Scheid et al. (2006) obtained similar results when examining a group with MRI-confirmed pure DAI on a range of measures at 9 months postinjury. Forty percent of their group had at least moderate deficits on measures of ECF. (Their memory difficulties were also substantial.) This research highlights the important contribution of diffuse injury to ECF impairment observed following TBI.

There is evidence for ECF disturbance in mild TBI, with reduced verbal fluency a frequent finding (Belanger et al. 2005). As noted earlier, deficits of higher-order functions may only become apparent under conditions of increased demand or task complexity (e.g., during dual-task conditions; Pare et al. 2009). In these situations, effective performance appears to be sustained at a cost (including mounting fatigue and the sacrifice of performance speed for accuracy).

TABLE 17–4. Categories of frontal executive function

Executive cognitive functions: dorsolateral PFC
Spatial, temporal, and conceptual reasoning (assessed by traditional tests of "executive function")
Activation-regulating functions: superior medial PFC
Initiating and maintaining mental processes
Monitoring response conflict
Behavioral self-regulation functions: ventromedial PFC
Emotional processing
Mediation of stimulus-reward associations
Metacognitive processes: frontal polar regions
Higher-order integrative aspects of personality, self-awareness, and social cognition
Prospective memory; complex multitasking

Note. PFC=prefrontal cortex.

Source. Adapted from Cicerone et al. (2006) and Stuss and Alexander (2009).

Superior Medial Prefrontal Cortex and Activation-Regulating Functions

The superior medial frontal regions provide an important activating or energizing function to initiate and sustain mental processes at a level required for goal-directed activity (Cicerone et al. 2006). Superior medial frontal damage can produce marked apathy or abulia (i.e., "without will"), and in the extreme, akinetic mutism, resulting from bilateral lesions. Stuss and Alexander (2009) noted that lesser degrees of this deficit may be revealed by slowing on reaction time tasks, as reduced output on verbal fluency tasks (most notably in the first 15 seconds), or as slowed responses/errors during the conflict trial of the Stroop color-naming test.

While isolated superior medial PFC damage is unlikely in the setting of closed TBI, these regions are vulnerable to both diffuse injury and localized effects, such as transfalcine herniation. Both gray and white matter

atrophy of the superior medial frontal region are observed in volumetric MRI studies of moderate and severe TBI (Levine et al. 2008; Wilde et al. 2005).

In addition to structural changes, evidence of functional impairment in this region is provided by findings from imaging studies using positron emission tomography (Fontaine et al. 1999) and fMRI (Soeda et al. 2005), as well as electrophysiology research examining event-related potentials that signal response conflict (Larson et al. 2007).

The importance of this work is based on the robust neuroimaging finding that superior medial prefrontal regions are engaged whenever a cognitive task becomes more difficult and performance monitoring demands increase (Gazzaniga et al. 2009). The superior medial regions—and the anterior cingulate in particular—appear to make a critical contribution to cognitive control by monitoring for potential response conflicts, such as may occur in novel or difficult situations (or elicited in Stroop-like tasks) (Gazzaniga et al. 2009). Performance errors, the result of extreme response conflict, similarly activate the superior medial PFC. In contrast, an absence of such activation following conflict or errors may contribute to an apathetic state (Cummings and Miller 2007). Superior medial regions thus contribute an evaluative function to cognitive control, signaling a need for increased activation of regulatory processes, which are in turn implemented within lateral PFC regions. As an example, superior medial regions may energize or strengthen task representations within working memory to enhance task performance. Medial and lateral PFC may thus work in tandem to mediate cognitive control and reduce performance decrements (Larson et al. 2007). These interactions may also help explain the similarities among some of the clinical features of superior medial and dorsolateral PFC dysfunction.

Evidence for dysfunction among networks supporting conflict monitoring and cognitive control has clear implications for patients with TBI. Compromised performance monitoring may warrant a specific emphasis within rehabilitation; it may also contribute to impairments in deficit awareness (Larson et al. 2007).

Ventromedial Prefrontal Cortex and Behavioral Self-Regulation

Traditional ECF measures may fail to capture the substantial deficits in real-life decision making and interpersonal function that often follow severe TBI (Reid-Arndt et al. 2007). These vital aspects of behavior are linked to the integrity of the ventromedial PFC, which includes the orbitofrontal cortex and the adjacent ventral aspects of the medial PFC. Together they comprise the limbic sector of the PFC, with similarities in cytoarchitecture and robust connections both among themselves and with other limbic structures (Price 2006). These regions typically bear the brunt of TBI-related damage, showing vulnerability to both diffuse and focal effects (Gentry et al. 1988; Wilde et al. 2005). The famous case of Phineas Gage over 150 years ago and subsequent reports illustrate the range of difficulties that may be observed following focal ventromedial PFC lesions: lack of insight, impaired planning and decision making, social impropriety, lack of empathy, and both dampened and poorly modulated emotional responses (Beer 2007; Stuss and Levine 2002). Patients with focal ventromedial PFC lesions may also show a striking dissociation between preserved intellectual ability on standard cognitive tests and the failure to apply such knowledge in unstructured situations.

The ventromedial PFC plays a prominent role in emotional processing and in the mediation of stimulus-reward associations, both of which contribute to inappropriate decisions and self-regulation. Using the Iowa Gambling Task, a novel measure designed to simulate real-world decision making, Bechara et al. (2000) showed that patients with focal ventromedial PFC lesions persist at making disadvantageous choices despite continuing to lose money. The patients also showed diminished emotional arousal prior to making risky decisions, leading the authors to propose that the failure to choose advantageously arose from an inability to process emotion-related bodily sensations (gut feelings) that would normally bias cognition and guide decisions. As a result, these patients appear to be insensitive to future consequences.

An alternative explanation for this aberrant behavior has been suggested. It may result from a more basic defect in adjusting behavior in response to feedback. Thus patients with ventromedial PFC lesions have been shown to perform poorly at reward-reversal learning tasks, continuing to respond to cues that are no longer associated with a reward (Fellows and Farah 2005). Based on a study of TBI patients, Rolls et al. (1994) argued that this particular form of affective perseveration lies at the root of the socially inappropriate, maladaptive behavior that follows ventromedial PFC damage.

While novel measures are proving sensitive to ventral frontal dysfunction, the utility of these tests among unselected TBI patients awaits further study (Fujiwara et al. 2008). In contrast, assessment of olfactory function remains among the most sensitive and specific tests of ventromedial PFC integrity (Fujiwara et al. 2008; Zald 2006). It also must be emphasized that a careful review of a patient's real-world function, based on interviews with family members and care providers, remains a critical source of information regarding the presence of a self-regulatory deficit. Standardized questionnaires that survey the range of behavioral symptoms associated with frontal lesions are available, such as the Frontal Systems Behavioral Scale (Malloy and Grace 2005), which has proved sensitive among TBI patients (Reid-Arndt et al. 2007).

Frontal Poles and Metacognitive Processes

The frontal polar region is uniquely positioned to fulfill a specialized, integrative role in relation to other PFC regions (Stuss and Alexander 2009). This stems from its unique cytoarchitecture and its pattern of reciprocal connections, which are almost exclusively with higher-order association cortices located in the PFC and elsewhere (Burgess et al. 2007). As such, it receives highly processed, abstract information from other supramodal areas and appears to bridge higher-order EFC functions with those related to emotion, drive, and self-regulation (Cicerone et al.

2006; Stuss and Alexander 2009). It is associated with metacognition (the knowledge of one's abilities), awareness of one's internal states, as well as with episodic (autonoetic or self-knowing) memory. The region is also thought to process future plans and goals, as well as more abstract rewards, thus contributing to prospective memory function and complex, real-world multitasking (i.e., holding an overarching goal in mind while working through independent tasks) (Burgess et al. 2007; Stuss and Alexander 2009). Although limited, TBI data pertaining to this region are of considerable interest given its vulnerability to traumatic injury.

Social Cognition

Although reflecting activity within a range of frontal and temporal distributed subsystems, a more recent discussion of frontal lobe function has focused on social cognition, a term encompassing the abilities required to interpret the behavior of others; make inferences about their feelings, beliefs, and intentions (termed *perspective taking* or *theory of mind*); conceptualize one's relationship with another; and use this information to guide behavior (Rankin 2007). Studies among TBI patients have emphasized unique contributions from the ventromedial PFC region to this aspect of cognition.

Stone et al. (1998) found that TBI patients with selective ventromedial PFC damage, in contrast to lesions elsewhere, showed an impaired ability to appreciate a social faux pas, considered an aspect within theory of mind. Shamay-Tsoory et al. (2005) extended this work using three theory-of-mind tasks that required varying levels of emotional processing. Again, patients with ventromedial PFC lesions were impaired in appreciating the affective component of another's mental state. The authors considered this to reflect a critical factor in the reduced ability to display empathy noted among patients with ventromedial PFC damage. Beer (2007) and colleagues hypothesized that the ventromedial PFC may play a specific role in relation to "self-conscious emotions," such as embarrassment, shame, and pride. In a series of experiments, they showed that while patients with ventromedial PFC lesions were able to experience self-conscious emotions, these feelings tended to reinforce their problematic social behavior rather than correct it (e.g., displaying pride after excessive teasing, or alternately, excessive embarrassment that was unwarranted).

The literature pertaining to social cognition in TBI patients with more widespread cerebral pathology has been summarized by Bornhofen and McDonald (2008). A consistent finding is of deficiencies in the perception of affective information conveyed by facial expression, voice, bodily gestures, and social context observed in a significant proportion of those with severe injury. Evidence also suggests that the perception of negative emotions, such as anger, disgust, sadness, and fear, may be most affected, in contrast to positive emotions. The neuropsychological profile from which emotion-processing deficits arise in TBI is a complicated one, largely reflecting the heterogeneous nature of the injuries (Bornhofen and McDonald 2008). TBI may affect neural systems mediating the perception and experience of affective states at multiple levels. In addition, contributions from nonsocial cognitive processes within TBI patients may be quite significant (Bornhofen and McDonald 2008). Difficulties with attention, processing speed, working memory, and other aspects of executive cognitive functioning can be expected to yield reductions in the accuracy and efficiency with which emotional signals are perceived, interpreted, and acted upon.

TABLE 17–5. Aspects of language/communication potentially impaired after traumatic brain injury

Language impairment
Classic aphasia syndromes: anomic aphasia; Wernicke's aphasia; other forms rare
"Subclinical" aphasia or language processing deficits: object naming, verbal associative fluency, comprehension of complex commands, writing to dictation
Discourse and pragmatic use of language
Less productive, less efficient speech; greater fragmentation
Difficulty initiating/maintaining topic of conversation, meeting a listener's needs, interpreting indirect communication
Other speech disorders
Mutism, stuttering, echolalia, palilalia
Dysarthria

Impairments of Language and Communication

Whereas subjective complaints related to word finding are frequent after any TBI, objective disturbance of language and communication more typically attends moderate and severe TBI (Levin and Chapman 1998). For example, relatives of severely injured patients identified difficulty speaking in 50% of cases reviewed at 7 years post-TBI (Oddy et al. 1985). The ability to communicate, or transmit and exchange information, is a fundamental determinant of psychosocial well-being. It reflects the complex interplay of primary receptive/expressive language functions, other nonlinguistic cognitive processes, and higher-order executive functions. The neural substrate involves distributed networks linking dominant prefrontal, perisylvian, and parietal language areas as well as other cerebral regions that mediate broader aspects of communication, such as the nondominant hemisphere. The vulnerability of communicative functions to both diffuse and focal injury incurred during TBI is thus apparent (Table 17–5).

Classic aphasia syndromes are intermittently seen among consecutive samples of TBI patients (Levin and Chapman 1998). Anomic aphasia is the most frequent type, manifesting as a fluent aphasia with marked inability to identify objects and proper names, frequent paraphasias and circumlocution, and preserved comprehension and repetition. Wernicke's, or receptive, aphasia is also observed; other forms are rare (Richardson 2000). The prognosis following acute aphasia syndromes is reasonably good. In 21 patients examined at 8 months postinjury, full

recovery of linguistic ability occurred in 43% of patients, whereas 29% had a deficit confined to a single language function, predominantly anomia (Levin et al. 1981). Additional speech disorders such as mutism, stuttering, and echolalia have been occasionally observed (Levin and Chapman 1998). In contrast, dysarthria is relatively common after severe TBI and may persist after resolution of other language deficits (Richardson 2000).

Although frank aphasia is uncommon, impairment of basic language functions has been repeatedly demonstrated using standard psychometric tests. These impairments include deficits of word retrieval, verbal associative fluency, and comprehension of complex auditory information (Levin and Chapman 1998). However, such measures are insufficiently sensitive to the broader difficulties experienced by many patients after TBI. Patients may appear functionally intact based on results from an aphasia battery, despite the presence of a variety of communication difficulties. Indeed, it has been noted that TBI patient appear to "talk better than they communicate," in contrast to aphasic patients who may "communicate better than they talk" (Coelho 2007).

A more recent emphasis has been on the examination of naturalistic language production, or discourse, such as retelling a story or describing how to perform a task. Patients with severe TBI demonstrate less productive and efficient speech, convey less content with longer utterances, and use fewer cohesive ties, which leads to fragmented discourse (Coelho 2007). Additional work examining interactive conversation has disclosed difficulties in the pragmatic use of language, including problems initiating and maintaining a topic of conversation, meeting the needs of a listener, and interpreting or using indirect communication such as sarcasm and humor (Coelho 2007).

As with other cognitive domains, it will be apparent that communicative functions cannot be viewed in isolation. Associated relationships among basic linguistic faculties and attention, working memory, and, in particular, frontal control functions are germane. Stuss and Levine (2002) summarized that left prefrontal injury is associated with simplified, repetitive, and impoverished discourse. In contrast, right prefrontal lesions may produce amplification of detail, insertion of irrelevant elements, and a tendency toward socially inappropriate discourse.

In the case of mild TBI, deficits chiefly comprise impaired word retrieval within the early recovery period. Although short-lived, such impairment may nonetheless affect one's overall communicative ability. In a meta-analysis of cognitive outcomes following mild TBI, Belanger et al. (2005) confirmed that the impact on verbal fluency within the first 90 days postinjury was specific and relatively large when compared with a number of other cognitive domains.

Treatment of Cognitive Impairments

Attempts to ameliorate cognitive impairments after TBI have focused broadly on neurocognitive rehabilitation, including a combination of restorative and compensatory approaches for damaged or lost functions (see Chapter 37, Cognitive Rehabilitation). Increasingly, these efforts have included pharmacological strategies to augment rehabilitation and influence functional recovery (Table 17–6). In this section, the literature supporting such interventions is surveyed. When possible, studies that used at least some degree of experimental control are highlighted. Specific details regarding the prescription and monitoring of these agents is provided in Chapter 35, Psychopharmacology.

The rationale for treatment derives from two principal sources. First, there is evidence for disruption of multiple neurotransmitter pathways after brain injury, both focal and diffuse. These neurotransmitters have widespread neuromodulatory effects and are known to play a role in attention, memory, and executive function (Arciniegas and Silver 2006; McAllister and Arnsten 2008). This suggests that agents with known effects on these neurotransmitter systems may have an important role in facilitating recovery.

Second, some of the neurobehavioral features after TBI show considerable resemblance to those in other neuropsychiatric conditions for which there are well-established treatments. These include deficiencies of concentration in attention-deficit/hyperactivity disorder, memory in Alzheimer's disease, alertness/arousal in narcolepsy, and mental speed in Parkinson's disease. Such similarities have led to the use of drugs in TBI patients that have shown benefit in the treatment of analogous neuropsychiatric syndromes, despite the lack of comprehensive research in the area.

Two other areas of pharmacotherapy should be mentioned, although they are beyond the scope of this chapter. Much research has been aimed at reducing the damage resulting from the initial injury, for example, by administering agents such as glutamate antagonists or free radical scavengers to limit the initial neurotoxic cascades. The interested reader is referred to McAllister and Arnsten (2008) for review. Another potential application for drug therapy is in the promotion of recovery from coma and minimally responsive states. Despite being a frequent intervention, there has been only limited research in this area.

Cholinergic Medication

The importance of cortical acetylcholine in attention, memory, and other cognitive processes is well established; procholinergic agents are currently the mainstay of treatment in patients with Alzheimer's disease. Animal models and human data support the rationale that cholinergic augmentation after TBI might be of benefit (Arciniegas 2003).

A growing clinical literature, which comprises single-case reports, open-label trials, and controlled studies with varying methodology, provides support for cholinergic augmentation. Among the controlled trials, some degree of improved cognition has been reported with physostigmine, an acetylcholinesterase inhibitor (Cardenas et al. 1994), and cytidine 5′-diphosphocholine, a choline precursor (Leon-Carrion et al. 2000; Levin 1991). The usefulness of physostigmine is limited, however, by the risk of systemic cholinergic toxicity.

TABLE 17–6. Medications reported to improve cognition after closed traumatic brain injury

Cholinergic agents
Physostigmine (not recommended)
Cytidine-5′-diphosphocholine
Cholinesterase inhibitors (donepezil, rivastigmine, galantamine)
Catecholaminergic agents
Psychostimulants (methylphenidate, dextroamphetamine)
Amantadine
Bromocriptine
Levodopa
Selegiline
Other agents
Tricyclic antidepressants
? Other antidepressants (SSRIs, SNRIs, bupropion)
? Atomoxetine (selective norepinephrine reuptake inhibitor)
? Pergolide, pramipexole, ropinirole (dopamine receptor agonists)
? Guanfacine (selective α_{2A}-adrenergic agonist)
? Lamotrigine
? Memantine (*N*-methyl-D-aspartate receptor antagonist)

Note. SNRIs=serotonin-norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors. "?" indicates potentially useful agents that have very limited or no support within the clinical traumatic brain injury literature. See text for details.

Since its approval for Alzheimer's disease treatment, the selective acetylcholinesterase inhibitor donepezil has been the subject of several reports. Improvement has been noted on cognitive measures such the Wechsler Adult Intelligence Scale—Revised IQ (Whelan et al. 2000), memory (Masanic et al. 2001; Whitlock 1999), and attention/speed of information processing (Khateb et al. 2005). Notably, Whitlock (1999) described an adverse behavioral reaction in 2 patients (agitation and aggression) requiring drug discontinuation. Another open-label study of 10 patients by Kaye et al. (2003) is of interest because 6 patients had experienced mild TBI (mean, 1.2 years postinjury). Although objective change on memory testing was not shown, patients were rated as globally improved by the investigators.

Three controlled studies of donepezil in TBI patients have been published. Morey et al. (2003) used a within-subjects design to evaluate seven patients with severe TBI and persisting memory dysfunction in the late recovery or chronic phase. Treatment phases included donepezil (titrated rapidly to 10 mg) for 6 months, a subsequent 6-week washout period, and a second 6-month treatment trial at 5 mg. Significant benefit on a visual memory measure was observed in the 10-mg phase only. No other effects were found, including measures tapping other aspects of memory. Nor did the improvement in visual memory appear to correlate with the patients' self-report on a memory complaints questionnaire. Those choosing to continue taking donepezil at the end of the study cited nonspecific cognitive benefits that could not be fully characterized.

Walker et al. (2004) obtained negative results using a retrospective case-control design among 36 patients with severe TBI within an acute rehabilitation setting (mean, 34.5 days postinjury). Eighteen patients receiving donepezil were contrasted with control subjects, matched for age and severity of injury. No difference was found on the primary outcome tool, the Functional Independence Measure—Cognitive Scale. As the authors noted, however, this measure may be insufficiently sensitive to drug-induced changes. In addition, only 25% of the treatment sample achieved a dose of 10 mg over the relatively short study period (mean 33.8 days).

Zhang et al. (2004) examined 18 patients with moderate to severe TBI (mean, 4–5 months postinjury) using two indices of immediate memory (verbal and nonverbal subtests from the Wechsler Memory Scale—Revised) and the Paced Auditory Serial Addition Task (as described in the section Impairments of Attention). Patients were randomly assigned to receive donepezil (increased rapidly to 10 mg) or placebo. After a 4-week washout phase, patients were crossed over to the alternate condition. Significant differences in favor of donepezil on all measures were observed, indicating improvement of immediate memory and attention/processing speed. Whether these test improvements led to functional gains or clinical improvement was not examined in the study.

Some studies have looked at other cholinesterase inhibitors and their efficacy in TBI patients. Silver et al. (2006) undertook a 12-week randomized, double-blind, placebo-controlled study with rivastigmine (3–6 mg/day) in a sample of 157 patients at least 12 months postinjury and found no significant treatment effects with respect to performance on the Hopkins Verbal Learning Test (HVLT) or a measure of rapid visual information processing. However, when the analysis was confined to a subset of patients with moderate to severe baseline memory impairment (n=81; defined as ≥ 25% impairment on the HVLT), cognitive benefits were noted in the rivastigmine but not the placebo group. The medication was also well tolerated. Silver et al. (2009) described a subsequent open-label extension study that followed their placebo-controlled trial. All of the study participants were offered rivastigmine for an additional 26 weeks. Notably, the results of the initial placebo-controlled trial were replicated, in that a subgroup of ex-placebo patients with greater baseline memory impairment (as defined above) again showed greater cognitive improvement during treatment with rivastigmine. In contrast, patients who initially received active treatment for 12 weeks demonstrated no further gains on the various measures of efficacy.

Limited data are available for galantamine. No improvement was noted in a single patient with acute TBI who was treated with this agent (Johnson et al. 2007). However, the patient also had a history of alcohol abuse and two prior brain injuries. Marginally more informative are the results from an open-label study of 111 patients with chronic TBI who were given donepezil, rivastigmine, or galantamine and then asked to subjectively rate their response (Tenovuo 2005). Almost two-thirds of patients reported improved vigilance and attention, and no differences were noted between the three drugs. The absence of objective cognitive markers and a placebo group introduces a note of caution when interpreting these findings.

In summary, although promising, the data with respect to cholinergic agents after TBI remain somewhat equivo-

cal. Nonetheless, there does appear to be evidence supporting cognitive improvement in some patients.

Catecholaminergic Agents

There is accumulating evidence that both norepinephrine and dopamine have a powerful influence on cognitive activities, particularly those tasks associated with the PFC (McAllister and Arnsten 2008).

Psychostimulants

Psychostimulants include methylphenidate and dextroamphetamine, considered indirect sympathomimetic agonists in that they do not act directly on receptors but rather increase the synaptic release and reuptake of catecholamines. Rationale for their use after TBI was initially based on their efficacy for conditions such as attention-deficit/hyperactivity disorder, narcolepsy, and depression/apathy attending medical conditions. There were only a handful of published cases in the TBI population. Since the 1980s, however, several controlled studies of methylphenidate have been reported.

There is evidence that a single dose of methylphenidate may have short-term cognitive benefits. In a double-blind, placebo-controlled trial of 18 subjects with chronic TBI and mild cognitive impairment, Kim et al. (2006) reported that 20 mg of methylphenidate enhanced the speed and accuracy with which subjects accessed working memory 2 hours and 48 hours after treatment. Whether more sustained dosing has the same effect is, however, open to debate. To date, results have been equivocal with the interpretation of findings compromised by methodologies of variable rigor. This notwithstanding, there is emerging evidence that methylphenidate may improve attention post TBI, particularly in relation to mental processing speed (Whyte et al. 2002).

In an effort to circumvent the shortcomings of earlier work, Whyte's group (Whyte et al. 1997, 2004) systematically explored the domain of attention in two studies of patients with residual cognitive complaints (almost all severe TBI and in the chronic phase of recovery). Both studies used a controlled, randomized, double-blind protocol. Results for the two studies were similar, showing significant positive effects on measures tapping information processing speed but not other facets of attention, such as susceptibility to distraction or sustained attention. The second study also found a reduction in off-task behavior in a simulated classroom setting, as well as on caregiver ratings of attention, suggesting that better test scores may translate into demonstrable functional improvements (Whyte et al. 2004). It is notable, however, that despite positive results, treatment effect sizes were relatively modest.

In a more recent study, Willmott and Ponsford (2009) examined attentional task performance among 40 moderate to severe patients in the early phase of recovery (mean, 68 days postinjury) using a randomized, double-blind crossover design. Compared with placebo, short-term treatment with methylphenidate significantly enhanced information processing speed but had no appreciable impact on more complex tasks placing higher demands on working memory and strategic control over attention. Of interest is the fact that the greatest medication response was observed in those with more severe head injuries, as indexed by lower Glasgow Coma Scale scores and slower baseline processing speed.

The literature on dextroamphetamine treatment for cognitive sequelae after TBI has been limited to single-case studies (Bleiberg et al. 1993; Evans et al. 1987), which indicate positive results. This agent has been of particular interest due to evidence that it may enhance the rate and extent of recovery if given early after ischemic stroke, perhaps by modulating central noradrenergic transmission (Goldstein 2003). This suggests a temporal window for the administration of treatment to optimize long-term benefit. Similar studies with dextroamphetamine have yet to be done in TBI patients; however, Plenger et al. (1996) examined persisting effects of methylphenidate in the acute setting. Although some benefits were noted at 30 days after drug discontinuation (improved vigilance and procedural learning), these effects were not sustained at 90 days.

Further data are needed to carefully delineate the role of psychostimulants in treating cognitive impairment. It is unknown whether enhancement of processing speed translates into improvement in other cognitive domains (e.g., memory), or whether a window of treatment opportunity exists for dextroamphetamine, as in some studies of outcome after stroke.

Amantadine and Memantine

Amantadine is frequently used in the TBI population, although more commonly in the setting of reduced arousal or marked behavioral disturbance after severe TBI (Gualtieri et al. 1989). It appears to have effects on both pre- and postsynaptic dopamine transmission and is also an *N*-methyl-D-aspartate (NMDA) antagonist. In a number of uncontrolled case reports and case series, improvements with respect to attentional processes and speed of processing (Andersson et al. 1992; Nickels et al. 1994), behavioral initiation (Nickels et al. 1994; van Reekum et al. 1995), verbal fluency, and mental flexibility (Kraus and Maki 1997b) have been noted.

The validity of these findings is boosted by an open-label study that combined treatment with amantadine and functional brain imaging. Kraus et al. (2005) gave 400 mg/day of amantadine to 22 patients with chronic TBI of varying severities (mild, moderate, and severe). Neuropsychological testing was undertaken pre and post 12 weeks of treatment. Six subjects also underwent a positron emission tomography scan. Significant improvements were noted in executive functioning but not in attention or memory. An increase in glucose metabolism in the left PFC accompanied the executive improvements.

However, two controlled studies have shown contrasting results. Schneider et al. (1999) studied 10 TBI patients of mixed severity in early recovery (time unspecified) using measures of attention, memory, and executive function. A randomized, placebo-controlled crossover design was used to evaluate a 2-week trial of amantadine. Although all patients generally improved over time, there was no difference in the rate of improvement between amantadine and the placebo condition.

In a second study, Meythaler et al. (2002) examined 35 severe-TBI patients within 6 weeks of injury who were randomly assigned to receive either amantadine or placebo for 6 weeks. Crossover to the alternate condition occurred for a second 6-week period. Patients showed more rapid improvement when taking amantadine versus placebo on both screening cognitive tests and measures of functional ability, although not all comparisons reached statistical significance. Of note, the exact timing of active treatment (i.e., whether patients received amantadine in the first 6 weeks vs. the second) had no impact on the ultimate level of recovery. Thus, at 3 and 6 months there were no differences between the groups on any measure, lending no support to the notion of a treatment window within the first 3 months postinjury.

As with other agents, data regarding amantadine require confirmation as well as extension to different phases of recovery and levels of severity. The limited research in the early recovery phase cannot rule out general improvements in arousal or behavioral improvements in initiation or agitation as alternative explanations for the apparent cognitive improvement. Nor can the research fully separate out the effects of spontaneous recovery.

Memantine is an uncompetitive NMDA receptor antagonist that is of theoretical interest in relation to the prevention of traumatically induced glutaminergic excitotoxicity. Nonetheless, clinical reports of its use among human TBI patients are lacking. As with amantadine from which it is derived, it also appears to improve dopaminergic function and could enhance postinjury cognitive function through this means (Arciniegas and Silver 2006).

Other Dopaminergic Agents

Direct dopamine agonists, the dopamine precursor levodopa, and selegiline may also be of benefit. Several case reports describe the use of the selective D_2 agonist bromocriptine after TBI, as summarized by Muller and von Cramon (1994), who also described seven TBI cases of their own. They reported that bromocriptine led to clear benefit in some patients and proposed that reduced responsiveness and initiation in markedly apathetic states (i.e., akinetic mutism) may be the principal applications after acquired cerebral trauma. In their series, the authors did not, however, observe consistent improvement on standard measures of attention, memory, or problem solving with bromocriptine, and also they noted that relatively high doses might be required.

Two subsequent reports provide additional support for this treatment. Powell et al. (1996) described a series of 11 postacute patients with abulia (8 with TBI, 3 with subarachnoid hemorrhage), all of whom improved while taking bromocriptine with respect to abulia, as well as on measures of digit span, verbal list learning, and fluency. In one of the two controlled trials to date, McDowell et al. (1998) examined the impact of low-dose bromocriptine on cognition in 24 patients who were generally in the postacute phase after severe TBI. In contrast to earlier reports, these patients were not selected on the basis of apathy. Drug treatment was found to enhance performance on tests of executive function and a dual-task paradigm, although not on measures tapping basic processes such as information processing speed.

The results of a second study paint a different picture (Whyte et al. 2008). Twelve adults with moderate to severe TBI in the postacute phase of recovery took part in a 6-week double-blind, placebo-controlled crossover study with the doses of bromocriptine increased to 5 mg twice daily. Cognitive indices focused on measures of attention, including measurement of performance in real-world situations such as a distracting environment. Not only did patients on bromocriptine perform more poorly than the placebo group on some attentional measures, but blood pressure decreased as well, leading the authors to abandon plans for a larger replication study. This negative study leaves the topic in some flux, the earlier positive reports negated to a degree by this more recent report. It would be premature, however, to conclude that bromocriptine lacks therapeutic efficacy. It is possible that benefits accrue at a lower dose, and moreover one that limits side effects. The results of further research are awaited here.

Despite preclinical evidence for a unique contribution of the D_1 receptor to working memory (McAllister and Arnsten 2008), the potential role of pergolide, a mixed D_1/D_2 agonist, has not been explored in cognitively impaired TBI patients. The newer dopamine agonists pramipexole and ropinirole—which act preferentially at the D_3 and D_2 receptors, respectively—may also prove useful but have not yet been tried. These latter two agents may offer additional neuroprotective benefit.

Other dopaminergic agents have shown positive results, according to case reports. Lal et al. (1988) gave levodopa to 12 TBI patients who had plateaued in their recovery after severe TBI. Improved arousal, attention, and initiation were noted. Kraus and Maki (1997a) reported enhanced cognition in a severe TBI patient when levodopa was added to amantadine treatment. Selegiline, a selective monoamine oxidase-B inhibitor, may also mitigate some of the cognitive impairment in TBI patients (Newburn and Newburn 2005; Zhu et al. 2000).

Antidepressants and Other Drugs

Antidepressants of the tricyclic class have been reported to display stimulant-like effects on arousal and initiation in two case series (Reinhard et al. 1996; Wroblewski et al. 1993). The authors attributed the positive effects to the enhancement of catecholaminergic transmission. In contrast, the selective serotonin reuptake inhibitor class has shown mixed results. Sertraline failed to improve cognition in 11 patients treated 2 weeks after severe TBI (Meythaler et al. 2001). Horsfield et al. (2002) reported improvement on a single working memory task, but not on other measures, in a series of 5 patients treated with fluoxetine in the late recovery phase. However, all the patients had been referred concerning mental health problems and improved with respect to depressive symptoms over the study period. Moreover, the notion that working memory might specifically be enhanced by selective serotonin reuptake inhibitor treatment appears to conflict with research showing working memory decrements in volunteers given either tryptophan, a 5-hydroxytryptamine (5-HT) precursor, or fenfluramine, a 5-HT agonist (Luciana et al. 2001). The role of the 5-HT system in opposing certain dopamine-mediated cognitive functions, such as working memory, was cited to explain these findings.

It is therefore informative to view the results of a three-way comparison between sertraline, methylphenidate, and placebo in a 4-week double-blind parallel group trial in patients (n=10 in each group) with mild to moderate TBI (Lee et al. 2005). Although sertraline and methylphenidate were equally effective treating depressed mood, only methylphenidate was associated with cognitive improvement and with the maintaining of daytime alertness. Methylphenidate was also better tolerated.

Two reports have indicated positive effects of lamotrigine on cognition after TBI. This agent alters neuronal excitability by modulating ion channels and inhibits the release of glutamate. It has also been noted to improve alertness in those with seizure disorders. Showalter and Kimmel (2000) noted greater than expected cognitive improvement in 9 of 13 patients with a persistently reduced level of arousal at 3 months postinjury (6 with severe TBI; 5 with subarachnoid hemorrhage). A single case study described pronounced improvement on the cognitive dimensions of two functional assessment measures at 6 months after severe closed TBI (Pachet et al. 2003). However, in each of these reports, lamotrigine was initially prescribed as an add-on treatment for posttraumatic seizures. This raises the question of whether the apparent cognitive benefit could have derived from better seizure control.

Conclusion

Patients with TBI may exhibit diverse neurobehavioral impairments as a consequence of injury to the cerebral cortex, subcortical structures, and connecting white matter pathways that mediate complex adaptive behavior. This chapter addresses the cognitive changes that are frequently observed across the range of TBI severity. Certain aspects of cognition, such as mental processing speed and working memory, are particularly susceptible to disruption after TBI. Although at times these impairments may be readily appreciable during an office or bedside interview, formal neuropsychological assessment is typically necessary to elicit and carefully map out the deficits. Similarly, a speech-language pathologist is often required to assess the extent of communication impairments. Additional work is needed to fully characterize the impact of TBI on complex cognitive constructs such as executive control processes, behavioral self-regulatory functions, and social cognition. A better understanding of these brain-behavior relationships will in turn generate improved treatment strategies. Remediation of cognitive impairment after TBI remains of critical importance because it is often associated with enduring disruption of social and vocational function.

The literature provides support for a number of pharmacological interventions that can potentially enhance rehabilitative efforts. Despite methodological shortcomings, the accumulated data indicate fairly clear benefit in some individuals with respect to alertness, mental processing speed, and memory. However, the extent to which frontal executive functions can be shown to improve with drug therapy remains unclear. It has been difficult to demonstrate enhancement of these higher-order functions, in part because they are not readily isolated from processes such as attention, working memory, and learning. In addition, because most of the agents used influence neurobehavioral parameters such as arousal, motivational tone, and psychomotor activation, as well as affective lability and mood, it is clear that a multifaceted approach to assessment will be necessary to clarify which aspects of cognition and behavior respond to a specific intervention. Through such an approach, the relationship between improved mood or apathy and enhanced cognitive function can be carefully explored. Finally, the ecological validity of all these studies remains to be determined. The extent to which improvements noted in the laboratory translate into real-world benefits remains one of the most pressing unanswered questions.

KEY CLINICAL POINTS

Cognitive Changes After TBI

- Cognitive and neurobehavioral changes are often the most salient features following traumatic brain injury (TBI) at any level of severity. Mild and severe brain injuries represent different locations on a continuum of cerebral involvement.
- Discrete focal lesions may produce classic neurobehavioral syndromes such as aphasia, but these are commonly superimposed on more global dysfunction arising from diffuse injury.
- Impairments of attention are among the most prevalent findings after TBI. The most robust finding is a reduction in processing speed; abnormalities of divided attention are also consistently noted.

- Memory dysfunction is another cardinal finding after TBI, with impaired episodic memory a hallmark. Executive contributions to memory dysfunction are often implicated, such as a failure to apply organizing strategies when learning, as are impairments of working memory, prospective memory, and metamemory.

- Frontal executive functions are higher-order capabilities that control other mental activities, such as attention, memory, and motor behavior, and critically influence functional outcome after TBI.

- Four categories of executive function are proposed: executive cognitive, activation-regulating, behavior-regulating, and metacognitive functions.

- Social cognition is an important facet of cognition with strong links to executive processes. Studies in TBI patients have emphasized unique contributions from the ventromedial prefrontal cortex region to social cognitive function.

- Impairments of language and communication after TBI may include classic aphasia syndromes; many more individuals have impairments of basic linguistic functions, such as word retrieval, verbal fluency, and auditory comprehension of complex information. Dysarthria is relatively common and may persist.

- The assessment of naturalistic language production or discourse may reveal deficits such as less productive, less efficient speech. Deficits in pragmatics, or the use of language, are also frequently evident and include reduced ability to meet the needs of a listener and to perceive sarcasm.

Treatment of Cognitive Deficits

- During brain injury, disruption occurs within multiple neurotransmitter systems—namely, the systems known to mediate attention, memory, and executive function.

- The clinical literature provides support for a number of pharmacological interventions that can potentially enhance rehabilitative efforts, particularly in relation to cholinergic and catecholaminergic agents.

- Despite methodological shortcomings, the accumulated data indicate frequent benefit with respect to alertness and mental processing speed. Memory improvement has at times been shown. However, the extent to which complex executive functions may improve with drug therapy remains unclear.

- Additional research is needed to determine the extent to which improvements noted on laboratory measures translate into real-world benefits that enhance the daily function of individuals with TBI.

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CHAPTER 18

Disorders of Diminished Motivation

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MOTIVATION IS ESSENTIAL TO ADAPTIVE FUNCTIONING and quality of life. This is as much true for individuals with traumatic brain injury (TBI) as it is for those with stroke, dementia, or any other neuropsychiatric illness. Clinicians understand intuitively the importance of motivation. They know that without motivation, individuals with TBI will fail to keep appointments, stay on their medications, devote themselves to friends and family, or return to their jobs. Motivational loss handicaps physical rehabilitation and coping skills and is an important source of burden for families of individuals with TBI.

Western psychology has long recognized the place of motivation in human behavior. Motivation is an ever-present, essential determinant of behavior and adaptation. Motivation, like attention, emotion, and other state variables, is not a single function of the brain. Psychologically and biologically, motivation is a complex of capacities, and the neural systems that subserve it are themselves both delimited and distributed, integrated and interdependent.

In this chapter, we present an approach to motivational impairments in TBI. We provide definitions of motivation and disorders of diminished motivation (DDMs) and descriptions of their assessment and management that are based on a biopsychosocial approach to the causes of motivational loss. We then discuss the neural mechanisms of motivation and the ways in which DDMs reflect selective dysfunction of these systems. Readers should expect the clinical material to be familiar in some ways—because neuropsychiatric assessment of motivation builds on everyday clinical skills and experiences—and unfamiliar in others—because most clinicians are not in the habit of making explicit their intuitive understanding of motivation in clinical practice. As we proceed, we reference the modest literature that addresses diminished motivation and its mechanisms in TBI.

Motivation

Motivation refers to the characteristics and determinants of goal-directed behavior. Theories of motivation are intended to account for the "direction, vigor, and persistence of an individual's actions" (Atkinson and Birch 1978, p. 4)—that is, for how behavior "gets started, is energized, is sustained, is directed, is stopped and what kind of subjective reaction is present in the organism when all this is going on" (Jones 1955, p. vii).

Disorders of Motivation

Disorders of motivation are a "third domain of psychopathology" (Marin 1996a); disorders of cognition and emotion are the other two. Disorders of motivation may be classified by an increase, decrease, or dysregulation of motivation, as well as anergias typified by Lyme disease, chronic fatigue, and psychomotor retardation. Increased motivation is exemplified by the hyperconnection symptoms of interictal personality in temporal lobe epilepsy and by appetitive disorders such as aggression and hyperphagia. Dysregulation of motivation is exemplified by impulse control disorders, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder. Disorders of diminished motivation include akinetic mutism, abulia, and apathy, which are the focus of this chapter.

The essential feature of apathy, abulia, and akinetic mutism is diminished motivation. Literature (Marin 1997) places them on a continuum of motivational loss, with apathy at the minor pole and akinetic mutism at the major pole of severity.

Cases of *akinetic mutism* follow bilateral lesions of the anterior cingulate cortex that form from the cognitive region posteriorly to the skeletomotor division of the cingulate (Bonelli and Cummings 2007). Akinetic mutism is characterized by profound apathy; a wakeful state with no spontaneous movement or verbalization; indifference to pain, thirst, or hunger; and lack of response to prompts and questions. Intact visual tracking is essential for the diagnosis; its presence excludes more extensive damage involving the brain stem. Conditions that may contribute to akinetic mutism include cerebrovascular disease, craniopharyngiomas, and tumor. TBI may cause akinetic mutism, although there are few reported cases in the TBI literature.

The term *abulia* refers to a less dramatic psychomotor syndrome than akinetic mutism. Vijayaraghavan et al. (2002) studied the concept of abulia in a group of British neurologists and psychiatrists and concluded that the following features characterize abulia: profound apathy, lack of purposeful and spontaneous movements, poverty and latency of speech, and reduced interest in usual pastimes and social engagement. Abulia shades into akinetic mutism when it worsens and into apathy when it improves.

Apathy indicates diminished motivation that occurs in the presence of normal consciousness, attention, and mood. Patients with apathy are generally able to initiate and sustain behavior; describe their plans, goals, and interests; and react emotionally to significant events and experiences. However, these features are less common, less extensive, less intense, and shorter in duration than they are in individuals who are not apathetic.

Recognition

How does one recognize DDMs? Because motivation is the psychological domain concerned with goal-directed behavior, the detection of diminished motivation requires examining goal-related aspects of overt behavior, cognition, and emotion. Thus, DDMs present with diminution in each of these three aspects. One can say that diminished motivation is present if a patient with intact level of consciousness, attention, language, and sensorimotor capacity presents with a simultaneous decrease in the overt behavioral, cognitive, and emotional concomitants of goal-directed behavior. This is an operational definition of diminished motivation and thus is a guideline for identifying the features that define DDMs and differentiate them from other disorders.

Differential Diagnosis

Differential diagnosis of DDMs depends on the acuity and severity of the TBI. For acute and severe cases, differential diagnosis focuses on TBI complications that produce profound impairment in level of consciousness, attention, speech, or motor capacity (Celesia 1997). Chronic or less severely impaired patients should be evaluated for depression and dementia as well as for frontal-subcortical syndromes that affect personality and executive cognitive dysfunction.

Patients with diminished motivation all show diminished activity. Inactivity—whether motor, cognitive, or emotional—may result from changes in virtually any domain of mental status. Attentional changes associated with coma, stupor, or mild delirium suggest diminished motivation because they are often associated with diminished activity. Memory loss may suggest diminished motivation when there is increased latency of response or when patients have poverty of speech because they have poverty of recall. Perceptual changes—illusions, hallucinations, and reduplicative phenomena—may lead to bewilderment and preoccupation, which also may bring apathy and abulia to mind. Mood changes operate similarly. In addition, complications of depression—for example, psychomotor retardation or catatonia—also resemble diminished motivation because motor activity, speech, and emotional expressivity are often reduced. Disorder of thought content and form may be particularly misleading. Psychotic thought content may lead to autistic or self-absorbed presentation of self. Thought blocking, circumstantiality, and impaired coherence of thought may appear as reduced goal-directedness or drive.

In light of these factors, the two groups of disorders to distinguish in differential diagnosis are those in which the following occur:

1. *Diminished activity suggests diminished motivation but is actually due to other impairment.* In stupor and coma, the essential impairment is diminished level of consciousness. Delirium may involve a diminished level of consciousness but is primarily a disorder of attention accompanied by some other cognitive, perceptual impairment. Aprosodia is a disorder of emotion information; diminished motivation is not a feature. Aprosodia may be confused with apathy because they both may be associated with truncated emotional responses. Catatonia and psychomotor retardation resemble DDMs because of the presence of reduced motor and speech activity. Slowing of thought and activity, the essential features of psychomotor retardation, may occur in many disorders, including DDMs. Akinesia is a disorder of movement rather than motivation, though it may be associated with apathy.
2. *Diminished activity is associated with diminished motivation, but both are due to some other disorder.* Depression is a disorder of mood. By definition, it is a dysphoric state. Consequently, one suffers from depression. By contrast, one does not suffer from apathy or other DDMs. However, motivational symptoms are commonplace in depression; it is dysphoria and negative thought content that distinguish depression. Demoralization, like depression, is a dysphoric state. Demoralization is distinguished by a sense of futility, resignation, or powerlessness to realize some goal that is still desired. Dementia is, by definition, a disorder of intellect. Memory, executive capacity, or other cognitive impairments are essential to diagnosis.

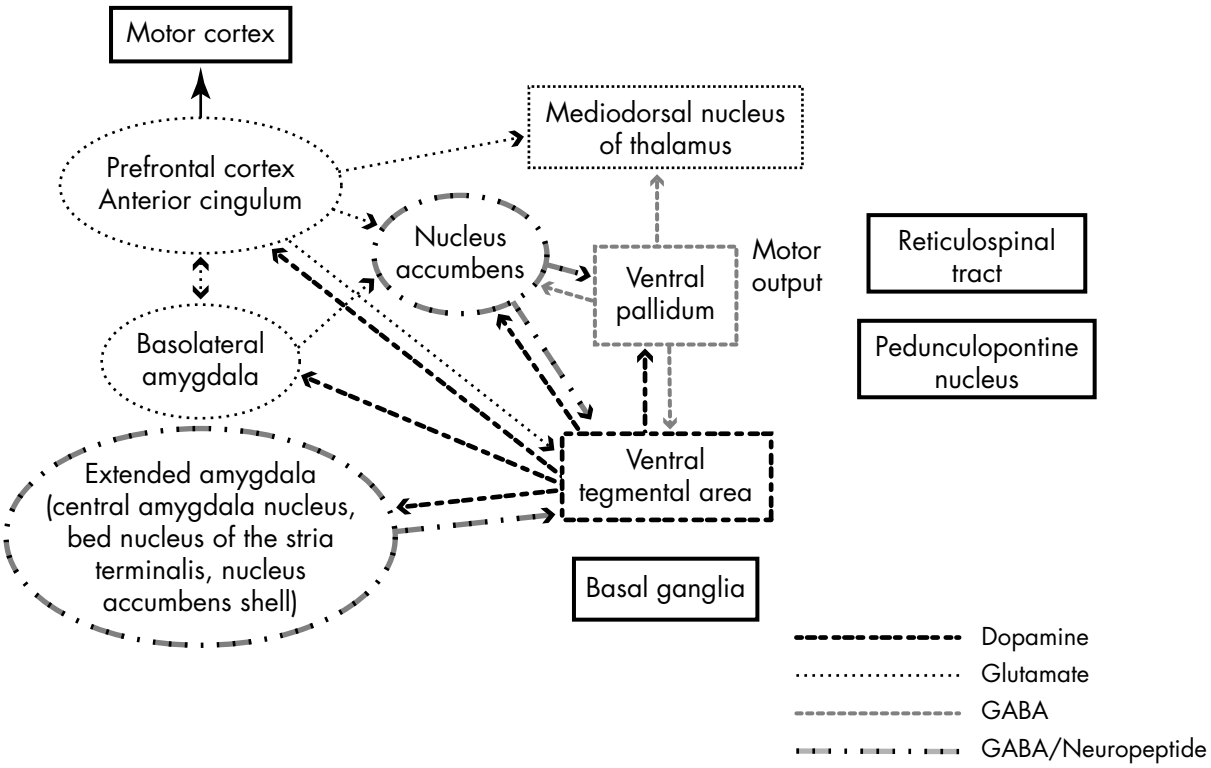


FIGURE 18–1. Motivational circuitry.

The core circuit that mediates the activation of behavior consists of the prefrontal cortex (PFC), basolateral and extended amygdala, and nucleus accumbens (NA). This circuit consists of glutamatergic interconnections among the amygdala, NA, and PFC and dopaminergic afferents from the ventral tegmental area. Three additional components include the γ-aminobutyric acid (GABA) and neuropeptide projections from the accumbens to the ventral pallidum, and the GABA/neuropeptide projections from the extended amygdala, a cluster of nuclei including the central amygdala nucleus, bed nucleus of the stria terminalis, and shell of the nucleus accumbens. The last component is a series subcircuit composed of GABAergic projections from the ventral pallidum to the mediodorsal thalamus and a reciprocal glutamatergic projection between the thalamus and PFC. This component serves to recapture information exiting the circuit back to the PFC. Output is via the motor cortex, basal ganglia, reticulospinal tract, and pedunculopontine nucleus. The flow of information within and through the circuits permits the translation of motivation into action.

Source. Adapted from Kalivas PW, Churchill L, Klitenick MA: "The Circuitry Mediating the Translation of Motivational Stimuli Into Adaptive Motor Responses" in *Limbic Motor* Circuits *and Neuropsychiatry.* Edited by Kalivas PW, Barnes CD. Boca Raton, FL, CRC Press, 1993, pp. 237–288. Modified with permission from CRC Press, LLC, and Taylor & Francis.

Mechanism of Motivation

A model for the mechanism of motivation aids in the assessment and treatment of DDMs. It also provides a framework for defining research questions and acts as a template for novel therapeutic targets. The antecedents of motivated behavior define the neural substrates that "activate" the behavior by attaching salience (importance) to a specific environmental or interoceptive stimulus and "directing" the activated stimulus to a specific behavioral response (Kalivas and Volkaw 2005). Figure 18–1 illustrates the neural substrates that are associated with both the perception of reward and the initiation of motor behaviors. The interconnections between the substrates form a circuit known as the *motive circuit* (Kalivas et al. 1993), which is involved in the translation of biologically relevant environmental and pharmacological stimuli into adaptive motor responses. The figure shows the topography of the interconnections between subnuclei of the circuit and illustrates how information may progress from the limbic system (motive circuit) to the extrapyramidal and pyramidal motor systems.

Three brain regions mediate the activation of behavior: the amygdala, prefrontal cortex (PFC), and nucleus accumbens (NA). The PFC evaluates the motivational importance of a stimulus and determines the intensity of the behavioral response. The amygdala and NA evaluate the emotional valence (positive or negative) of the stimulus. The essential feature of the model presented here is the neuronal circuit consisting of glutamatergic interconnections among the amygdala, NA, and PFC and dopaminergic afferents to all three regions. Three additional circuits include: 1) GABA (γ-aminobutyric acid) and neuropeptide projections from the NA to the ventral pallidum (VP) that mediate the expression of motivated behavior; 2) GABA/neuropeptide projections from extended amygdala (central amygdala nucleus, bed nucleus of the stria terminalis, and nucleus accumbens shell) that serve as a conduit for environmental and interoceptive stimuli; and 3) GABA projections from the VP to the mediodorsal thalamus and a reciprocal glutamatergic projec-

tion between the thalamus and PFC that mediates the return of information exiting the circuit back to the PFC.

The NA is subdivided into a more medially located shell region, primarily affiliated with limbic inputs to the core circuit, and a more lateral core region, affiliated in its connectivity with output regions in the basal ganglia and brain stem. The VP and ventral tegmental area (VTA) show similar functional differentiation into limbic-motive and motor-output regions. Projections from the VTA release dopamine throughout the circuit in response to a motivational stimulus. Dopamine signals the circuit to initiate behavioral responses to the stimulus and facilitates cellular changes that form learned associations (neuroplasticity) with the event. Motivationally relevant events are integrated through the anterior cingulate and ventral orbital cortices in the PFC and mediate not only whether a behavioral response will occur but also the intensity of the response. Interactions between the basolateral and central amygdala nucleus include autonomic and endocrine associations via projections from the central nucleus to the brain stem and hypothalamus and to dopamine neurons in the VTA. The glutamatergic projections from the basolateral amygdala to the PFC and NA mediate how learned associations influence complex behavioral responses. The NA shell is interconnected with the hypothalamus and VTA and is central to regulating ingestive behaviors, whereas the NA core associates with the anterior cingulate and orbitofrontal cortex and appears, through glutamatergic afferents from the PFC, to mediate learned behaviors in response to motivationally relevant stimuli.

The means by which the direction of behavior is determined has not been clearly demonstrated. Studies have shown that activation of the PFC precedes and stimulates behavioral output through prefrontal glutamatergic efferents to accumbens-thalamocortical circuitry (Badre and Wagner 2004; Haber 2003). VTA firing also precedes behaviors cued by reward-predictive sensory stimuli and scales with the magnitude of the reward (Fields et al. 2007). Additional evidence shows that different NA neurons respond differentially to distinct motivational stimuli (Carelli and Wondolowski 2003) and that NA dopamine regulates effort-related processes involved in overcoming response costs (Salamone 2007). NA dopamine depletions decrease spontaneous, stimulant-induced, and food-induced motor activity, with commensurate decreases in food-seeking behavior as response requirements of the task increase (Salamone et al. 2007). In rat studies of lesions of frontal cortical areas, lesions or inactivation of the anterior cingulate cortex (Schweimer and Hauber 2005), as well as inactivation of basolateral amygdala (Ghods-Sharifi et al. 2008), altered effort-related choice in T-maze tasks and produced effects similar to those shown for the administration of low-dose haloperidol and nucleus accumbens dopamine depletions (Salamone et al. 2007). Stimulation of GABA and adenosine A_{2A} receptors in the VP also produces behavioral effects similar to those produced by accumbens dopamine depletion (Farrar et al. 2008). Although there has been rapid growth in the evolution of our understanding of brain circuitry involved in the activation of behavior and the direction of behavioral output, it remains uncertain which brain areas are involved in the exertion of effort, the perception of effort, or the decisional process (Salamone et al. 2007). Identification of neural substrates involved in regulating behavioral activation and effort-based choice will provide additional insight into the pathogenesis of DDMs.

It is also important to note that there are several ways in which the motivational significance of an event is influenced by nonmotivational processes. First, determining *what* and *where* requires integrity of the sensory apparatus and the peripheral nervous system. If one is unable to perceive what is there, one's appraisal of its motivational significance suffers or, at least, is altered. Sensorimotor capacity also modifies behavior because motivation depends on the individual's subjective assessment of the likelihood that behavior will lead to goal attainment. This applies equally to patients adapting to hip fracture, hemiparesis, or executive cognitive impairment: motivation suffers if the individual judges that effort will be fruitless.

Clinical Pathogenesis

Neurobehavioral Mechanisms

Understanding the pathogenesis of DDMs requires considering the location, behavioral function, and neurochemistry of the neural systems that mediate them (Marin 1996b). The anatomical and physiological changes that affect these systems after trauma are a result of complex mechanical and physiological events. Gross pathology, such as contusion and hemorrhage, or more subtle changes, such as diffuse axonal injury, hypoxia, and microvascular changes, may damage cortical, subcortical, or deep parenchymal structures. There are also secondary injury mechanisms, including delayed brain damage due to the release of excitatory neurotransmitters, or derangements in neurotransmitter function (Kraus 2007).

Pathogenesis of TBI symptoms also may be understood in terms of the neurochemistry of the motivational circuitry, as described earlier, since disruption of this circuitry undermines all the major motivational functions. Severe dysfunction leaves patients unable to establish or modify motivational state, select among alternative response options, or initiate behavior. Therefore, severe dysfunction presents as akinetic mutism or abulia. If less severe—either because the initial insult is less severe or because a patient with severe injury is improving—the patient shows apathy. Such cases of apathy may be described as *pure* or affective apathy, because motivation is lost without impairment of extrapyramidal motor or executive cognition. This interpretation of pathogenesis is supported by clinical reports of apathy in association with coarse brain disease affecting the orbital-medial PFC, ventral striatum, and ventral pallidum (Levy and Dubois 2006).

If dysfunction simultaneously affects motivational circuitry and the striatonigral system, motivational loss and extrapyramidal symptoms occur together. This presents as akinesia or *motor apathy*, depending on whether the extrapyramidal or motivational symptoms predominate, respectively. *Cognitive apathy*, the association of motivational loss with executive cognitive dysfunction, may have a neurological or behavioral mechanism, as described in the following sections.

A functional analysis of patients with diminished motivation suggests several ways in which loss of behavioral ca-

pacity may contribute to motivational loss. Clinical observations have long suggested that DDMs may result from dysfunction of dorsolateral circuits (Marin 1996a, 1997; Stuss et al. 2000). Cognitive apathy may be due to simultaneous damage to the dorsolateral cortex and the associated territory within the basal ganglia, for example, the dorsal caudate nucleus (Levy and Dubois 2006). However, the association of dorsolateral circuit dysfunction with apathy may have another explanation: it may be a psychological response to the perceived inability to organize behavior.

These are not the only neurobehavioral mechanisms for motivational loss in DDMs. Loss of awareness of impairment, another symptom of prefrontal cortical damage, is predictive of return to work in individuals with TBI (Nakase-Richardson et al. 2007). Although not yet demonstrated empirically, impaired awareness is thought to mediate these functional problems at least in part because of its impact on motivation. Incentive motivation, a symptom of striatopallidal damage, is a process that translates an expected reward into behavioral activation. This can be operationalized by a behavioral paradigm that measures the effect of financial incentive on the speed of performing a simple psychomotor task (Schmidt et al. 2008). Novelty seeking in Alzheimer's disease has been shown to discriminate between patients with and without apathy (Daffner et al. 1999). The validity of novelty seeking as a neurobehavioral mechanism for apathy is strengthened by physiological observations: apathy in patients with frontal lobe damage was associated with diminished amplitude of P3 event-related potentials, which are correlates of stimulus novelty (Daffner et al. 2000).

Neurochemical Mechanisms

Neurochemical sequelae of TBI provide another way to understand DDMs. There is some evidence (Wagner et al. 2005) that dopaminergic activity is affected in TBI. This is of particular importance given the essential role of dopamine systems in behavioral activation, incentive motivation, instrumental learning, and other elements of motivated behavior (Salamone et al. 2007). Several other biochemical changes have been described in TBI, including changes in levels of glutamate, acetylcholine, serotonin, norepinephrine, neuropeptides, and oxygen free radicals. Their direct or indirect participation in the motivational circuitry provides a theoretical basis for them to alter motivation in TBI. This, in turn, provides a rationale for other pharmacological therapies in the treatment of DDMs.

Assessment of Diminished Motivation

The assessment of patients with diminished motivation depends on knowledge of the etiology of diminished motivation and the confluence of biological, psychosocial, and socioenvironmental factors that control motivated behavior. Table 18–1 lists conditions associated with apathy, abulia, and akinetic mutism (Marin 1996a; Stuss et al. 2000). When less severe, the diseases that cause akinetic mutism cause abulia and apathy. In addition, many psychiatric disorders and psychosocial conditions produce apathy. The assessment of patients with diminished motivation requires comprehensive and systematic neuropsychiatric assessment, which includes careful evaluation of the patient's social and physical environment. Differential diagnosis of diminished motivation, as discussed in the earlier section Differential Diagnosis, guides the clinician in distinguishing among these possibilities.

The psychosocial history indicates the baseline level of motivation (Marin 1996a) and pre- and postmorbid coping skills (Finset and Andersson 2000) that characterize adult personality. This is particularly important in evaluating patients with subtle motivational loss. The clinician estimating an individual's premorbid or "normal" motivation must also consider cultural factors, preinjury psychopathology, and diverse personal qualities. Personal loss, psychological trauma, and phase-of-life events may alter motivation. Occasionally, apathy is the primary symptom of an adjustment disorder (e.g., an empty-nest syndrome or retirement reaction) or the primary means for dealing with anxiety (i.e., a defense mechanism). The clinician should evaluate symptoms of personality disorder as well, keeping in mind the dynamics of motivation.

Interactions of medical, psychological, and neurological variables are particularly relevant in elderly patients because they often have multiple clinical problems. There is an extensive list of drugs whose use may alter motivation. Dopaminergic agents—agonists or antagonists—are most familiar as mediators of motivational change. But equally important are serotonergic, cholinergic, and adrenergic agents because of their interaction with dopamine systems. Pharmacokinetic variables, especially facilitation and inhibition of P450 enzymes, are an independent influence on motivation. For example, there are case reports suggesting that fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) may dispose to apathy (Benoit et al. 2008). Furthermore, SSRIs, particularly fluoxetine and paroxetine, are potent 2D6 inhibitors. Therefore, if an irritable patient with TBI is treated with haloperidol and then, because apathy is misdiagnosed as depression, treated with one of these two SSRIs, motivation may worsen for two reasons: the SSRI may induce apathy directly, and haloperidol-induced motor apathy may worsen because the SSRI increases levels of haloperidol.

The neurological disorders affecting motivation and its neural machinery should direct the clinician's attention to several aspects of the neurological examination. Because frontal and diencephalic diseases figure prominently in the differential diagnosis of DDMs, it is important to know whether olfactory function, visual acuity, and visual fields are intact. Frontal release signs and paratonic rigidity (gegenhalten) are relevant for the same reason. Extrapyramidal motor signs clarify the evaluation of motor subtypes of DDMs. For example, chorea, micrographia, loss of associated movements, or loss of vertical eye movements suggests that diminished motivation may be due to Huntington's disease, Parkinson's disease, or progressive supranuclear palsy. Neuropsychological assessment clarifies the cognitive subtypes of motivational loss, often in intricate and unexpected ways. For example, the results of executive cognitive assessment may suggest that lack of activity in one patient reflects impairment in sequencing, whereas in another patient it reflects loss of verbal fluency and initiation.

A word is in order about formal rating of motivational loss. Clinicians, especially those unfamiliar with DDMs,

TABLE 18–1. Conditions associated with apathy, abulia, and akinetic mutism

Neurological disorders

Frontal lobe
- Frontotemporal dementia
- Anterior cerebral artery infarction
- Ruptured anterior communicating artery
- Tumor
- Hydrocephalus
- Trauma

Right hemisphere
- Right middle cerebral artery infarction

Cerebral white matter
- Ischemic white matter disease
- Multiple sclerosis
- Binswanger's encephalopathy
- HIV

Basal ganglia
- Parkinson's disease
- Huntington's disease
- Progressive supranuclear palsy
- Carbon monoxide poisoning

Diencephalon
- Degeneration or infarction of thalamus
- Wernicke-Korsakoff disease

Amygdala
- Klüver-Bucy syndrome

Multifocal disease
- Alzheimer's disease (apathy may be mediated by damage to prefrontal cortex, parietal cortex, amygdala)

Medical disorders
- Apathetic hyperthyroidism
- Hypothyroidism
- Pseudohypoparathyroidism
- Lyme disease
- Wilson's disease
- Chronic fatigue syndrome
- Testosterone deficiency
- Debilitating medical conditions (e.g., malignancy, renal or heart failure)

Drug-induced conditions
- Neuroleptics, especially typical neuroleptics
- Selective serotonin reuptake inhibitors
- Marijuana dependence
- Stimulant (cocaine, amphetamine) withdrawal
- Cocaine-related subcortical strokes

Socioenvironmental effects (lack of reward, loss of incentive, lack of perceived control)
- Role change
- Institutionalism

Environmental effects
- Motor vehicle accident
- Falls (particularly among elderly)
- Sports-related injury
- Combat-related injury

Note. Akinetic mutism results from stroke, obstructive hydrocephalus, trauma, tumor, degenerative disease, or toxins (carbon monoxide) affecting the anterior cingulate gyrus (bilaterally) or paramedian structures of the diencephalon and midbrain (ascending reticular formation, median forebrain bundle, ventral pallidum). When improving or less severe, such cases present as abulia or apathy.

may find it helpful to rate the severity of motivational loss. The rating process familiarizes one systematically with the clinical signs of motivation and its loss. Furthermore, ratings may aid differential diagnosis. For example, if a clinician is unsure whether a patient with psychomotor retardation is apathetic or depressed, it may be helpful for the clinician to discover that ratings show high levels of apathy and low levels of depression. This would suggest psychomotor retardation is better characterized as bradykinesia and akinesia. If so, the next clinical step may be to perform a neurological examination and obtain a magnetic resonance image of the head rather than to have the patient start taking an antidepressant.

Several rating methods are available for quantifying loss of motivation. Construct validity is strongest for the Apathy Evaluation Scale (AES; Figure 18–2) (Marin et al. 1991), an 18-item scale that can be administered as a self-rated scale, a caregiver pencil-and-paper test, or a clinician-rated semistructured inventory. The Apathy Scale was developed as an abridged version of the AES and validated in patients with Parkinson's disease (Starkstein et al. 1992). Lueken et al. (2007) developed a short version of the AES specifically adapted for nursing home residents with dementia. Correlation of this scale with the original full-length AES was high (r=0.97), with no loss in internal consistency or construct validity. Clarke et al. (2007) examined the psychometric properties of the clinical version of the AES and found it to be a reliable and valid measure for the characterization and quantification of apathy. The Lille Apathy Rating Scale (Dujardin et al. 2008) informant and caregiver versions are based on the conceptual principles of the AES and were validated in Parkinson's disease subjects. The Children's Motivation Scale (Gerring et al. 1996), also derived from the AES, uses developmentally appropriate behavioral anchors to permit rating of apathy in children and adolescents. Strauss and Sperry (2002) developed the Dementia Apathy Interview and Rating to evaluate changes in motivation, emotional responsiveness, and engagement in patients with dementia. The Neuropsychiatric Inventory (NPI) (Cummings et al. 1994) is a multidimensional instrument administered to caregivers. It was developed specifically to assess noncognitive symptoms of dementia and devotes 1 of 10 item domains to apathy. Robert et al. (2002) developed the Apathy Inventory, an extension of the NPI, that assesses emotional blunting, lack of initiative, and lack of interest apart from the global NPI score. Pedersen et al. (2008) validated the Unified Parkinson's Disease Rating Scale, section 1, as a screening and diagnostic instrument for apathy. Instruments (Reichman and Negron 2001) derived from the Schedule for the Assessment of Negative Symptoms have also been presented to estimate negative symptoms in dementia by using information from caregiver interviews. Observations of patient participation by clinical staff also have been used to index motivation (al Adawi et al. 1998).

Treatment

Diminished motivation can cause a range of impairment, from subtle to serious, in biopsychosocial functioning. Physical rehabilitation, functional capacity, socialization,

Instructions: Rate each item based on an interview of the subject. The interview should begin with a description of the subject's interests, activities, and daily routine. Ratings are based on both verbal and nonverbal information. Ask the subject to base responses on the previous 4 weeks. For each item, ratings should be judged.

Not at all characteristic	*Slightly characteristic*	*Somewhat characteristic*	*Very characteristic*
1	*2*	*3*	*4*

___ 1. She/he is interested in things.

___ 2. She/he gets things done during the day.

___ 3. Getting things started on his/her own is important to him/her.

___ 4. She/he is interested in having new experiences.

___ 5. She/he is interested in learning new things.

___ 6. She/he puts little effort into anything.

___ 7. She/he approaches life with intensity.

___ 8. Seeing a job through to the end is important to her/him.

___ 9. She/he spends time doing things that interest her/him.

___ 10. Someone has to tell her/him what to do each day.

___ 11. She/he is less concerned about her/his problems than she/he should be.

___ 12. She/he has friends.

___ 13. Getting together with friends is important to him/her.

___ 14. When something good happens, she/he gets excited.

___ 15. She/he has an accurate understanding of her/his problems.

___ 16. Getting things done during the day is important to her/him.

___ 17. She/he has initiative.

___ 18. She/he has motivation.

Scoring: The Apathy Evaluation Scale (AES) rating is the total score for the AES after recoding time. Items are recoded so that higher score on the AES indicates higher levels of apathy. Therefore, all positively worded items must be recoded so that 1=4, 2=3, 3=2, and 4=1. *Thus, all items must be recoded except #6, #10, #11.*

Interpretation: The minimum score of the AES is 18. A score of 36 suggests mild apathy. However, the AES is not well standardized. Age, social environment, diagnosis, and other factors should be considered in evaluating results. The author recommends users develop their own norms using appropriate controls.

FIGURE 18–2. Apathy Evaluation Scale (Clinician Version).

Note. The Apathy Evaluation Scale was developed by Robert S. Marin. Development and validation studies are described in Marin et al. 1991. Administration instructions may be obtained from Dr. Marin (marinr@upmc) or from "The Apathy Evaluation Scale" in *Handbook of Psychiatric Measures* (Washington, DC, American Psychiatric Publishing, 2000).

Source. Reprinted from Marin RS, Biedrzycki RC, Firinciogullari S: "Reliability and Validity of the Apathy Evaluation Scale." *Psychiatry Research* 38:143–162, 1991. Used with permission.

and family involvement all suffer when motivation falters. Therefore, treating DDMs requires psychosocial and biological interventions that are based on comprehensive assessment. This is as true for DDMs as it is for any other neuropsychiatric complication of TBI. The growing interest in apathy and related DDMs is leading to novel approaches to understanding coping impairments and pathogenetic neuropsychological losses (al Adawi et al. 1998) of patients with apathy. These and other new approaches are likely to lead to new nonpharmacological therapies for DDMs.

Treatment of akinetic mutism and abulia is primarily pharmacological. Patients with apathy may require pharmacological interventions; however, their preservation of cognitive and communicative capacity calls increasingly for psychological and social interventions. Such interventions are based on careful and ongoing characterization of the patient's motivational and neuropsychological status. Regardless of severity, treatment must consider the physical and psychosocial environment. Therefore, modifying the overall environment and attending to family and professional caregivers are elementary but crucial dimensions of treatment for DDMs.

As a preliminary step, treating DDMs requires optimizing the patient's general medical condition. This may mean controlling seizures or headaches, arranging physical or cognitive rehabilitation for cognitive and sensorimotor loss, or ensuring optimal hearing, vision, and speech. These are elementary steps for any treatment plan. However, they also increase motivation because improved physical status may enhance functional capacity, drive, and energy and thereby hope and optimism—in other words, increase the patient's expectation that initiative and effort will be successful.

Environmental Interventions

The purpose of environmental interventions is to increase the reward potential of the environment. Adaptive devices, such as motorized wheelchairs or voice-activated computers, compensate directly for the sensorimotor and neurological impairments that deny patients the full benefit of the environment. Apathetic TBI patients in the intensive care unit or on general medical floors are particularly vulnerable to sensory deprivation, social isolation, and perceived loss of control. Sensory deprivation may be addressed by improving lighting, normalizing the diurnal pattern of lighting, and minimizing the impact of white noise and electrical devices. Social isolation and socialization may be improved by extending visiting hours and improving access to areas where patients gather for dining, groups, and informal socialization.

Psychological Interventions

General psychological status contributes to motivation in the same way that general medical condition does. Goal-directed behavior depends not only on motivation but also on other state variables: arousal, attention, mood, and cognition. Therefore, the psychological treatment for DDMs goes hand in hand with the treatment of conditions—for example, stupor, delirium, depression, dementia—that lead to these disorders. Such treatments may include a variety of behavioral techniques (Giles and Manchester 2006) or specialized cognitive rehabilitative approaches to accomplish, for example, enhancement of attention or performance speed (Gracey 2002). Psychoeducation, vocational counseling, and psychotherapy should not be overlooked. Psychotherapy may focus on injury-related loss, interpersonal problems, or family stressors.

Behavioral Interventions

The clinician should introduce behavioral interventions methodically, making clear the tasks and skills required of the patient. Goals should be developed collaboratively to strengthen engagement and enhance the patient's sense of control and expectation of success. Once goals are developed, staff should be careful to follow through on the treatment plan.

General supportive measures are obviously valuable for patients with DDMs. However, these general supportive measures have specific aims in patients with diminished motivation. These aims include improving diminished initiative, impersistence, lack of ambition, lack of awareness, diminished response to reward, perceived lack of control of environment, and absence of goals. Supportive therapy can be provided in many forms. Examples include encouraging, reassuring, helping the patient identify and maintain short-term objectives, providing reward for positive outcomes, and reframing the patient's goals as achieving an objective "for yourself" or "for your family's sake."

Finally, there is the integration of neuropsychological assessment with the treatment of motivational loss. Accurate assessment provides the template for developing an individualized plan for psychological treatment. The treatment can be thought of as a psychological or motivational prosthesis because it is precisely molded to the pattern of abilities lost as a result of injury. The principle of a psychological prosthesis is, of course, not specific to DDMs. It can be applied to other problems that contribute to motivational loss. Memory aids help the amnestic patient and may enhance motivation in the process. These may be used by the patient directly, provided that memory problems are not simply due to forgetfulness. In either case, caregivers can devise methods to remind the patient of goals and plans, keeping the patient on track with short-term objectives and long-term goals. Organizational skills help the patient with attentional and working-memory impairment. Here, too, increasing the subjective sense of competency may improve motivation.

Pharmacological Treatment

There are four steps to pharmacological treatment: 1) optimize medical status; 2) diagnose and treat other conditions more specifically associated with diminished motivation (e.g., apathetic hyperthyroidism, Parkinson's disease; 3) eliminate or reduce doses of psychotropics and other agents that aggravate motivational loss (e.g., SSRIs, dopamine antagonists); and 4) treat depression in the most efficacious way possible.

Because more is known about treating depression than DDMs, treating depression usually takes preference when symptoms of both disorders are present. When apathy is associated with depression, consider using more activating antidepressants (e.g., sertraline, bupropion). Venlafaxine also may be useful, particularly at higher doses that are associated with noradrenergic as well as serotonergic reuptake inhibition. In some patients, a monoamine oxidase inhibitor may be indicated for treatment of depression. If so, tranylcypromine sulfate may be preferable to other monoamine oxidase inhibitors because of its stimulant or amphetamine-like property.

When apathy or another DDM is the primary clinical problem, agents that potentiate dopamine release and/or delay dopamine reuptake in the central nervous system appear to be the most promising. Among these, stimulants, dopamine agonists, and atypical antipsychotics are often used (Table 18–2). In a small clinical study, Newburn and Newburn (2005) reported improvement in the AES scores as well as functional improvement in TBI subjects given selegiline. There is a developing literature (Figiel and Sadowsky 2008) suggesting that cholinesterase inhibitors (i.e., donepezil, galantamine, rivastigmine) may benefit patients with apathy as well as other noncognitive behavioral symptoms. Given their relatively low risk for serious toxicity, cholinesterase inhibitors may have a place in the treatment of TBI patients with apathy and, conceivably, more severe DDMs.

With stimulants, atypical antipsychotics, and dopamine agonists, treatment is initiated at minimal doses. Once benefit begins, improvement is usually dose dependent. Therefore, slowly increasing the dose is indicated until the patient is clearly functioning better or until concerns about drug toxicity limit dose increases. When impairment is clear-cut and risk factors for treatment are few, higher doses should be considered.

There is little knowledge of how to manage stimulants, antipsychotics, and dopamine agonists once optimal benefit is achieved. The response to missed doses or discontinuation is variable. In some patients, treatment must be continued indefinitely because discontinuation precipitates recurrence of symptoms. In other patients, a gradual taper and discontinuation may be feasible, presumably reflecting neural plasticity or other processes that are part of recovery. Even when successful, the discontinuation may not be possible until after a year or more of treatment. In addition to ongoing risks of side effects, financial costs may obligate the physician to consider dose reduction.

Patients with apathy perhaps may be treated with methylphenidate or amphetamine. There is a modest literature describing significant and sometimes dramatic benefit of bromocriptine (Campbell and Duffy 1997) and intramuscular olanzapine (Spiegel et al. 2008) in the treatment of abulia and akinetic mutism. Presumably other dopamine agonists have comparable potential. All of the dopaminergic drugs dispose to behavioral toxicity, including psychosis, motor activation, restlessness, sleep disturbance, and delirium. With stimulants, care should be taken to monitor pulse and blood pressure, although serious problems are unusual. Evidence for benefit from amantadine in patients with apathy has been mixed (Moon 2000). In those patients who do benefit, however, amantadine's nonspecificity—it alters dopaminergic and glutamatergic receptors—may be a clinical advantage because DDMs are not due only to lack of dopaminergic activity. In older patients, amantadine dosing must be adjusted for decreased creatinine clearance.

DDMs associated with extrapyramidal motor symptoms (i.e., motor apathy) are treated with the same agents, including amantadine. What is distinctive in treating motor apathy is the goal of treatment: to manipulate dopaminergic function for the sake of motivation, not just to improve walking or speech. Overlooking this point may compromise outcome in the end, because the benefit of improved mobility is undercut by lack of motivation.

Newer psychotropic medications may be helpful for DDMs. Modafinil, introduced recently for the treatment of narcolepsy, has stimulating or arousing effects that may prove useful in some patients. Modafinil may cause headache and gastrointestinal symptoms but otherwise seems relatively free of major toxicity. Growing knowledge of glutamate systems raises the possibility that glutamatergic agents may prove useful as well (Goff and Coyle 2001).

TABLE 18–2. Drugs used in the treatment of apathy, abulia, and akinetic mutism

Agent	Usual daily dose,[a] mg (range)
Stimulants	
Dextroamphetamine	20 (5–60)
Methylphenidate	20 (10–60)
Activating antidepressants	
Bupropion	200 (100–400)
Protryptyline	40 (20–60)
Tranylcypromine sulfate	45 (30–90)
Venlafaxine	150 (100–450)
Dopamine agonists (selective and mixed)	
Amantadine	200 (100–300)
Bromocriptine	10 (5–90)
Levodopa/carbidopa	25/100 tid–25/250 qid
Pergolide	2 (1–5)
Selegiline	10 (5–40)[b]
Atypical antipsychotics	
Olanzapine	10 (2.5–20)
Quetiapine	150 (50–800)
Risperidone	2 (0.5–6.0)
Ziprasidone	80 (20–160)
Other psychotropics	
Donepezil	5 (5–10)
Galantamine	8 bid (4–8 bid)
Modafinil	50 (400)
Rivastigmine	3 bid (1.5–6 bid)

[a]May be divided.
[b]Requires diet low in tyramine, especially at doses above 10 mg; lower doses may produce serotonin syndrome if administered with agents that slow selegiline metabolism.

KEY CLINICAL POINTS

- Motivation is fundamental for adaptive behavior. The major disorders of diminished motivation (DDMs) are apathy, abulia, and akinetic mutism.
- Depending on its etiology, a DDM may be the primary clinical disturbance, a symptom of some other disorder, or a coexisting second disorder requiring independent diagnosis and management. This makes assessment complicated and challenging.
- Differential diagnosis usually focuses on delirium, dementia, depression, demoralization, akinesia, catatonia, and aprosodia.
- Motivation implies both an activation of behavior and a directed behavioral response. The neurology of motivation focuses on the amygdala, prefrontal cortex, and nucleus accumbens, as well as a neuronal circuit consisting of glutamatergic interconnections among the amygdala, prefrontal cortex, and nucleus accumbens and dopaminergic afferents to all three.
- Current knowledge permits an approach to assessment and treatment of DDMs through an understanding of these systems.
- Treatment of DDMs includes the full range of biomedical, psychological, and socioenvironmental approaches available in neuropsychiatry. Treating DDMs is an essential part of traumatic brain injury (TBI) care, offering individuals with TBI a way to improve their functional abilities and quality of life.
- Because the neuropsychiatry of motivation is so new, there is limited knowledge for guidance. However, experience has shown that individuals with TBI and their families may benefit in many and sometimes dramatic ways from the treatment of DDMs.

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CHAPTER 19

Awareness of Deficits

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INDIVIDUALS WHO EXPERIENCE A TRAUMATIC BRAIN injury (TBI) may have multiple medical, physical, and cognitive limitations. They may also have reduced awareness of these deficits. Up to 45% of individuals with moderate to severe TBI demonstrate awareness deficits (Freeland 1996; Hart et al. 2009). Deficits that are clearly evident to family or therapists are often not "seen" by the individual, are judged to be inconsequential, or are discounted. Such unawareness is often permanent and can be an enormous impediment to successful rehabilitation and a significant indicator of failure to return to work (Shames et al. 2005). Furthermore, deficits in awareness can be function specific. Some individuals with TBI can accurately assess their physical status (e.g., hemiplegia) but are less reliable in their assessment of their capacity for sound judgment, cognitive skills, interpersonal skills, and other aspects of social behavior (Trahan et al. 2006). In fact, this lack of awareness of neurobehavioral sequelae is commonly observed in moderate to severe TBI, and the resulting behavior is frequently the most troublesome to families and caregivers and presents the most significant barrier to returning to a more normalized existence after an injury.

Definition of Lack of Awareness

Awareness of capabilities, or the absence of such awareness, is not a straightforward, unitary concept. Many terms are used in the scientific literature and in common parlance to convey different aspects of this concept. It is important to keep these different terms, characteristics, and distinctions in mind as one considers the literature addressing awareness, not only in patients with TBI but also in other forms of central nervous system (CNS) insults. Terms such as *agnosia, anosognosia, unawareness,* and *denial* are often used interchangeably, and examination of the manner in which they are used often suggests various meanings, depending on the author or context. This is further complicated by the tendency to attribute awareness deficits to different mechanisms such as neurological impairment, psychological denial of disability, or some combination of the two (Katz et al. 2002). For clarification, we briefly define a number of related terms in Table 19–1.

Dimensions of Awareness

To better understand the concept of lack of awareness, it is helpful to conceptualize several different dimensions to the problem. We have previously described a schema (David 1990; Flashman 2002; Flashman et al. 1998) proposing three distinct dimensions related to awareness. The first dimension is whether an individual has knowledge of a specific deficit or difficulty. For example, it is common for individuals who have had a TBI to have problems in several domains, including sensorimotor function, cognition, and behavior. Although some individuals may accurately describe their postinjury changes, others

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TABLE 19–1. Terms and definitions used when describing lack of awareness

Agnosia	An impairment in recognition that cannot be explained on the basis of primary motor or sensory impairment; failure to recognize the significance of objects (e.g., visual agnosia).
Anosognosia	A lack of knowledge about a deficit. Usually used to describe an apparent loss of recognition or awareness of left hemiplegia after an abrupt brain insult (Babinski 1914). Currently used to describe the occurrence of frank denial of a neurological deficit. It is often used to refer to the inability to truly recognize one's strengths and deficits after a traumatic brain injury.
Denial of illness	Redescription of anosognosia (Weinstein and Kahn 1955). Implies a psychological or psychodynamic level of explanation—that is, patients with anosognosia are thought to be motivated to block distressing symptoms from awareness by using a defense mechanism (denial).
Lack of insight	Describes a spectrum of concepts, ranging from a psychological defense mechanism to a lack of cognitive skills that permit understanding of deficits; generally considered to be a multidimensional construct.
Anosodiaphoria	The absence of concern, or indifference to an acknowledged deficit or illness.

with similar deficits may argue persuasively that they are no different from their preinjury state despite dramatic evidence to the contrary. The second dimension is the emotional response that an individual manifests to his or her difficulties or deficits. In patients who are aware of a given deficit, responses can range from complete indifference (anosodiaphoria) to bitter complaint. Similarly, patients unaware of their deficits can manifest responses ranging from indifference to angry denial when attempts are made to convince them of their impairment. The third dimension is the ability to comprehend the impact or consequences of a deficit in day-to-day life. For example, some patients are aware that they have significant deficits (e.g., memory impairment) and are concerned about them but believe that they can function at their premorbid level without difficulty.

The manner in which an individual accounts for admitted difficulties or deficits is a separate but related issue. Causal attribution of a particular deficit or difficulty requires two things: first, that a person acknowledges a deficit; and second, that the person attributes it to the injury to a degree sufficient to have the trauma become part of his or her self-definition (Gordon et al. 1998). For example, many individuals acknowledge difficulties in certain areas but attribute those difficulties to factors other than their brain injury (e.g., to stress or tension). Although these individuals have some awareness of a deficit, their inability to attribute the deficit to their injury can result in problems overcoming those deficits and engaging in specific therapeutic activities.

Awareness in Healthy Individuals

It is important to note that even healthy individuals engage in inaccurate self-representation at times, not always deliberately or consciously. This is a different phenomenon from *impression management,* which has been defined as an intentional or deliberate form of socially desirable responding. The cognitive distortions displayed by healthy individuals are believed to represent a normal pattern of functioning and have been shown to be positively linked to well-being, positive effectivity, and self-esteem (Tournois et al. 2000). In addition, positive forms of self-deception (i.e., self-deceptive enhancement) may help serve to orient a person favorably toward the future (Trivers 2000). Research has suggested that self-deception is maximized when there is a lack of concrete information (i.e., making predictions about the future or recalling certain information from the past) and the motivation to self-deceive is high (i.e., a wish to make a good impression on someone or strong belief in one's own abilities and capabilities). Sackeim and Wegner (1986) examined aspects of self-evaluation in patients with depression and schizophrenia and in healthy control subjects. They found that the latter two groups used "self-serving biases" in their appraisals of their behaviors and outcomes, whereas the depressed patients did not. The self-serving biases were characterized as follows: "If an outcome is positive, I controlled it, I should be praised, and the outcome was very good. If an outcome is negative, I did not control it (as much), I should not be blamed, and it was not so bad anyway." Although individuals with TBI also use this schema of causal attribution, or what some term a defense mechanism, in everyday life, we suggest that the unawareness of symptoms manifested as part of their brain damage is a distinct, neurologically driven phenomenon.

Lack of Awareness in Other Neuropsychiatric Disorders

Bearing in mind differences in meaning, terminology, and methodology, we review what is known about the different aspects of lack of awareness in other neurological disorders, as it can inform our understanding of the problem in individuals with TBI.

Anton's Syndrome

One of the more dramatic examples of awareness deficits in CNS injury occurs in Anton's syndrome. Individuals with this syndrome are cortically blind, usually from damage to the occipital cortex, optic radiations involving primary visual or visual association cortex, or both (Anton 1898; Heilman 1991). They are unable to describe objects placed before them and stumble into walls or furniture when attempting to walk but, remarkably, believe that they can see. A variety of mechanisms have been proposed to account for this (see Heilman 1991 for full discussion), including associated confusion and memory loss, an inability to monitor visual input, and a disconnection of

visual processing from speech and language areas. Heilman (1991) suggested another scheme in which visual imagery and visual processing compete for attention and "representation on a visual buffer" (p. 57). Destruction of visual processing results in unimpeded display of visual imagery, which is misinterpreted by the individual as the ability to see and may relate to the confabulated responses frequently noted.

Anosognosia Related to Hemiplegia and Hemianopia

Another dramatic example of lack of awareness of deficits can be seen in individuals with sudden hemiplegia (loss of motor function on one side of the body) and hemianopia (loss of vision in either the left or right side of the visual field), most commonly of vascular origin, and typically in the nondominant hemisphere. Functionally, these individuals are unable to move the contralateral limb (usually the arm) or perceive stimuli in the contralateral hemifield, yet they proclaim that they are well and unimpaired in these functions. When the deficits are pointed out, their emotional responses can range from denial (anosognosia, often associated with confabulated explanations for the observed facts) to bland acceptance (anosodiaphoria). Most evidence suggests that involvement of the nondominant inferoparietal cortex is required (Critchley 1953; Gerstmann 1942); however, lesions apparently restricted to the frontal lobes have also been described (Zingerle 1913). Anosognosia related to left hemiplegia and left hemianopia with both cortico-subcortical lesions and lesions confined to deep structures has also been reported (Bisiach et al. 1986; Gerstmann 1942; Healton et al. 1982; Watson and Heilman 1979). A meta-analysis (Pia et al. 2004) indicated that anosognosia for hemiplegia most frequently occurs in association with unilateral right-sided or bilateral lesions of several different brain areas (cortical and/or subcortical). It seems to be equally frequent whether the damage is confined to frontal, parietal, or temporal cortical structures, and it may also emerge as a consequence of subcortical lesions. The probability of anosognosia occurring is highest when the lesion involves parietal and frontal structures in combination, relative to other combinations of lesioned areas. Notably, not all hemiplegic and hemianopic patients with large lesions involving the inferoparietal cortex develop anosognosia. The data suggest the existence of a complex cortico-subcortical circuit underlying awareness of motor acts that, if damaged, can give rise to the anosognosic symptoms.

A related but separate phenomenon is that of neglect, which refers to the lack of attention directed to part of the body (usually one side, commonly the nondominant side), space, or both. This can take the form of failure to orient to stimuli originating from the neglected region or the selective extinguishing of competing stimuli originating from different regions (e.g., left body and right body). Neglect is also more commonly seen after nondominant hemispheric injury, but not exclusively so. Neglect is often seen in patients with anosognosia, but in some individuals these phenomena do not co-occur (Bisiach and Geminiani 1991; Heilman 1991).

Anosognosia in Aphasia

Anosognosia has been reported to accompany jargon aphasias (e.g., Wernicke's aphasia, anomic aphasia, conduction aphasia, transcortical sensory aphasia). Jargon aphasia is characterized by long, rambling sentences, meaningless utterances, phonemic or semantic paraphasias, and neologisms. Typically, patients with jargon aphasia do not appear to monitor their own utterances, and they make few hesitations, pauses, or self-corrections. The patients' behaviors generally suggest that they are unaware both that listeners do not understand them and that they themselves do not comprehend what is said to them. Although some researchers have suggested that many patients appear to have at least some awareness of their speech and language deficits (e.g., Cohn and Neumann 1958), it should be noted that in published cases of jargon aphasia, the degree of awareness of aphasia varies markedly.

The anatomical substrate of the lack of awareness associated with jargon aphasias is not clear. Weinstein et al. (1966) compared patients with jargon aphasia with those with aphasia without jargon. All of the patients with jargon aphasia had bilateral damage, whereas the remaining 24 patients with aphasia without jargon had mostly unilateral brain lesions. In addition to being seemingly unaware of their language deficits, the patients with jargon aphasia tended to deny other deficits such as hemiparesis or hemianopia. The authors concluded that jargon aphasia requires a left hemisphere lesion accompanied by further neurological damage, which is also required for anosognosia. Although Brown (1981) also reported bilateral lesions in patients with jargon aphasia, Gianotti (1972) found that 30% of his patients with Wernicke's aphasia with anosognosia had only left hemisphere damage, indicating that while bilateral involvement may be conducive to anosognosia in aphasia, it is not necessary.

Awareness of Deficits in Other Neuropsychiatric Disorders

Although the preceding syndromes provide the most dramatic examples of awareness deficits after CNS injury, other neurological disorders are frequently associated with more subtle awareness deficits. For example, many patients with Alzheimer's disease fail to recognize the cognitive impairments caused by their illness, as well as the impact that their deficits have on their lives and those who care for them. Awareness in patients with Alzheimer's disease also appears to be related to the outcome of rehabilitation (Clare et al. 2004). Although the degree of deficit awareness varies considerably among patients (Neary et al. 1986), some findings (Feher et al. 1991; Reisberg et al. 1985; Santillan et al. 2003) suggest that the lack of insight in these patients increases with severity of dementia (Lopez et al. 1994; Starkstein et al. 2006) and correlates with degree of memory impairment (Kazui et al. 2006) and executive dysfunction (Lopez et al. 1994). There does appear to be a relationship between higher levels of depression and anxiety and greater awareness of deficit (Aalten et al. 2006), although the relationship may be somewhat complex. For example, one study (Spitznagel et

al. 2006) indicated that cognitive reserve as well as its interaction with depressive symptoms is associated with awareness, with depressive symptoms correlated with awareness in high, but not low, cognitive reserve groups. Higher levels of awareness have been reported to be associated with better cognitive rehabilitation outcomes in individuals with Alzheimer's disease (Clare et al. 2004). Anatomically, unawareness in dementia may be associated with hypoperfusion of the right dorsolateral frontal lobe (Reed et al. 1993), increased senile plaque density in the right prosubiculum (Marshall et al. 2004), and decreased perfusion of the bilateral inferior, medial, and orbital frontal lobes (Hanyu et al. 2008; Harwood et al. 2005; Salmon et al. 2006; Shibata et al. 2008), anterior cingulate gyri (Hanyu et al. 2008), and medial temporal structures (Salmon et al. 2006). Unawareness in dementia has also been identified as a multidimensional construct (Clare and Wilson 2006; Howorth and Saper 2003).

Individuals with schizophrenia also frequently demonstrate a lack of awareness of the deficits caused by their illness and its impact, which has a significant effect on medication compliance (Amador et al. 1991; McGlynn and Schacter 1989; Olfson et al. 2006). Lack of awareness of illness in schizophrenia is not typically associated with epidemiological variables, neurological signs, or positive and negative symptoms (Amador and Strauss 1993; Cuesta and Peralta 1994; David et al. 1995; Peralta and Cuesta 1994). The relationship between severity of illness and lack of awareness of illness remains unclear. Although a number of reports have suggested they are independent of each other (e.g., Amador et al. 1994; Bartko et al. 1988; David et al. 1995; McGlashan 1981), more recent studies have indicated a relationship between symptoms and symptom severity and unawareness in patients with schizophrenia (Sevy et al. 2004) and in first-episode patients with psychosis (Keshavan et al. 2004). Several dimensions of unawareness have been identified in schizophrenia, reflected in the literature and in the items included in the various instruments used to assess unawareness in this disorder (Amador et al. 1994; David et al. 1992; Flashman et al. 1998; McEvoy et al. 1981; Ritsner and Blumenkrantz 2007).

The literature suggests that lack of awareness of illness is not simply a function of global cognitive deficits but perhaps is more related to frontal-executive dysfunction including set shifting and error monitoring (Aleman et al. 2006; Cuesta and Peralta 1994; Cuesta et al. 1995; David et al. 1995; Lysaker and Bell 1994, 1998; McEvoy et al. 1989; Mohamed et al. 1999; Young et al. 1993) or memory skills (Keshavan et al. 2004), although this finding is not always replicated (e.g., Arduini et al. 2003; Jovanovski et al. 2007). Metacognition (i.e., the knowledge and experiences one has about one's own cognitive processes) has also been identified as a potential mediator between cognitive deficits and unawareness of illness in even first-episode patients with schizophrenia (Koren et al. 2004). Our own work has suggested that lack of awareness in schizophrenia is associated with selective structural brain changes, including smaller brain size, and selective atrophy of certain subregions of the frontal lobes (Flashman et al. 2000, 2001). There is also a growing literature demonstrating anatomic correlates, including frontal, prefrontal, and parietal regions, of unawareness of illness in individuals with schizophrenia (Laroi et al. 2000; Morgan et al. 2002; Pia and Tamietto 2006; Sapara et al. 2007; Shad et al. 2004, 2006, 2007). A negative correlation between the score for the severity of "lack of insight and judgment" and gray matter concentrations in the left posterior and right anterior cingulate, as well as bilateral temporal regions, was reported (Ha et al. 2004), suggesting the important roles of paralimbic structures and the involvement of the perceptual and monitoring systems in the mechanism of insight.

It seems clear, then, that a variety of CNS disorders are commonly associated with deficits in awareness, that unawareness is a multifactorial construct, and that deficits in unawareness are more a final common pathway for certain profiles of brain damage than a problem unique to those with TBI. Next, we review what is known about awareness deficits in TBI and discuss how the profile of injury commonly seen in TBI fits with the disorders described in preceding sections to assist in understanding the neuroanatomical substrate of lack of awareness.

Lack of Awareness After TBI

As noted in the beginning of this chapter, lack of awareness is a common and disabling sequela of TBI (Freeland 1996; Hart et al. 2009). Furthermore, it has become clear that certain deficits are more commonly acknowledged than others after an injury. Several investigators (e.g., Ford 1976; Miller and Stern 1965; Ota 1969) have noted that in contradistinction to those who care for them, individuals with TBI are much less likely to complain of changes in judgment, personality, and/or behavior. Fahy et al. (1967) evaluated ratings of 32 patients with severe TBI and their relatives (mean, 6 years postinjury). They found that while patients exhibited some awareness of their intellectual, memory, and speech deficits, they rarely acknowledged changes in personality or behavior such as irritability, impulsivity, and affective instability that were reported by relatives. Others have also reported less patient awareness of changes in personality in the context of at least some awareness of cognitive deficits (McKinlay and Brooks 1984; Thomsen 1974). Hart et al. (2004) found that individuals with TBI were most likely to rate themselves as less impaired than clinicians in the behavioral domain and were least likely to rate themselves as more impaired in the physical domain, with cognitive self-ratings falling in the middle. Hoofien et al. (2004) studied unawareness of cognitive deficits and their relationship to functional outcomes among individuals with TBI and found that awareness of deficits is not differentially distributed along a concrete-abstract continuum of cognitive domains. That is, despite the fact that concrete deficits (i.e., physical problems) are more commonly acknowledged than more abstract deficits (i.e., personality changes) after an injury, awareness of specific cognitive deficits does not vary on the basis of whether the skills are more concrete (e.g., memory abilities) or more abstract (e.g., verbal comprehension). Notably, awareness in this sample was significantly related to psychiatric symptomatology, with those who overestimated their cognitive performance also endorsing higher rates of psychiatric symptoms and rated as having more behavioral disturbances by their family members.

Furthermore, it has been reported that individuals with unawareness of their deficits may not acknowledge, or may minimize, the severity of these deficits for up to several years after the injury (Groswasser et al. 1977; Prigatano 2005). For example, Groswasser et al. (1977) reported that all patients who demonstrated unawareness of behavioral problems at 6 months postinjury continued to be unaware of these changes at a 30-month follow-up. In fact, self-awareness after brain injury has been described as a useful prognostic index of neuropsychological, psychopathological, and functional status (Noe et al. 2005). In their study of 62 patients with acquired brain injury (41 with TBI) studied 295±525 days after injury, Noe et al. (2005) reported that 30 patients had high levels of self-awareness and 32 had impaired self-awareness. Patients with accurate awareness of their deficits showed less psychopathological symptoms and had better neuropsychological function and higher functional independence than those with impaired self-awareness. Both groups improved, but with different patterns, after rehabilitation (multivariate analysis of variance, $P<0.05$).

Tyerman and Humphrey (1984) assessed self-concept in 25 severely brain-injured patients at 7 months postinjury by evaluating their ratings of anxiety, depression, and attitude toward physical disability. They reported that although patients with TBI were aware of numerous changes in themselves compared with before their accidents (i.e., viewed themselves as quite different from their "past self"), the majority of subjects reported that they expected to recover completely within a year. In fact, ratings of their "present self" did not differ significantly in most domains from ratings of "a typical person" and were generally more positive than their ratings of "a typical head-injured person." This suggests that despite awareness of some degree of change resulting from their TBI, patients were somewhat unrealistic about their prospects of recovery, as most severely brain-injured patients continue to have some degree of impairment.

Port et al. (2002) noted that most studies investigating self-awareness after TBI are conducted at least 2 years after the injury. They examined awareness deficits in 30 patients with moderate to severe TBI who were less than 2 years postinjury, using ratings provided by the patients and their significant others on the Awareness of Deficit Questionnaire, which examines various domains of daily functioning. Although the researchers found substantial agreement between the patients and their significant others, the patients with TBI were less likely to acknowledge problems in executive functioning. This finding suggests that awareness is impaired even in the early recovery stages, which has significant implications for rehabilitation. Bach and David (2006) examined self-awareness after both acquired and traumatic brain injury and found that lack of social self-awareness predicted behavioral disturbance independent of cognitive and executive function. A possible role for metacognition and affective processes in social self-awareness deficits was posited. Sawchyn et al. (2005) found evidence that emotional adjustment plays a significant role in patients with TBI and their awareness of neurobehavioral difficulties, and that the emotional adjustment (including helplessness, confusion, bizarre behavior, and general psychopathology) of patients with TBI was more strongly related to their level of awareness than was the severity of their injury.

Measurement of Awareness

It is also important to consider the methodology used to assess awareness. A number of strategies have been used to attempt to quantify awareness of deficits in patients with TBI. The most common strategy is comparison of patients' self-report of their function with another more objective measure. That is, comparisons can be made on the difference between patients' ratings and those made by their families and by rehabilitation staff or by comparing patients' estimates of their abilities with actual performance measures. Additionally, self-report questionnaires have been used to gather quantitative data on other measures of function. The most frequently used of these questionnaires are described briefly in Table 19–2. Attempts have been made to correlate some of these measures with each other and with cognitive measures (Bogod et al. 2003; Sherer et al. 2003b). An alternative means of quantitative assessment is use of structured interview questions, in which responses are scored by the interviewer according to a rating scale. In this case, the clinician is rating the patient's accuracy of self-perception (e.g., Ezrachi et al. 1991; Fleming et al. 1996; Levin et al. 1987).

These methods have several limitations. The use of questionnaires and structured interviews to quantify awareness of deficits relies predominantly on patients' ability to understand verbal questions and to verbalize their understanding of their deficits. Because of speech and language disorders, a number of patients therefore are unable to be assessed with such methods. Literature has suggested that relatives also may deny disability (McKinlay and Brooks 1984; Romano 1974), another confounding variable to obtaining accurate information regarding changes after TBI. In addition, it has been noted that there are certain circumstances in which participants may rate themselves as having more difficulty than does their informant, who may simply not be familiar enough with the behavior to be aware of difficulties (Leathem et al. 1998). Finally, when ratings are made by rehabilitation or other clinical staff, information regarding how the person was before the TBI may not be available to the raters; this information could be important in accurately completing the objective assessment. Giacino and Cicerone (1998) used an open-ended interview with patients in which they assessed the nature of the patients' responses to confrontation, feedback, or both regarding these deficits. They suggested that this may provide additional information about the basis of the unawareness. They also suggested that it may be possible to characterize individuals' reactions to objective performance feedback according to their cognitive response, their affective response, and the manner in which feedback is used.

In general, however, individuals with TBI have been shown to underestimate the severity of their cognitive and behavioral impairments when compared with family members' ratings, clinician ratings, and their performance on neuropsychological testing. These difficulties in accurately assessing strengths and weaknesses have a significant negative

TABLE 19–2. Rating scales frequently used to assess unawareness of illness in traumatic brain injury

Scale name	Authors	Purpose
Patient Competency Rating Scale	Prigatano and Fordyce 1986	Evaluates competency to perform various behavioral, cognitive, and emotional tasks, as well as providing insight into the level of awareness; 30 items scored on a 5-point Likert scale; informant and patient versions.
Awareness Questionnaire	Sherer et al. 1998b	Assesses awareness of motor/sensory, cognitive, and behavioral/affective deficits after traumatic brain injury; 18 items scored on a 5-point Likert scale; rated by patients and family/significant others or clinician.
Head Injury Behaviour Scale	Godfrey et al. 1993	Rates 20 behavioral items on a 4-point Likert scale; generates two scores: number of problems and distress score; patient and relative versions.
Functional Self-Appraisal Scale	Newman et al. 2000	Rates abilities in functional areas related to physical, cognitive, and emotional capabilities; 12 items rated on a 4-point scale; can be self-administered or used in a structured interview format; patient and rehabilitation staff member versions.
Barrow Neurological Institute Screen for Higher Cerebral Functions	Prigatano et al. 1995	Samples a wide range of neuropsychological functions; scores range from 3 to 50 (all items passed successfully); provides quantitative and qualitative information.
Self-Awareness of Deficits Interview	Fleming et al. 1996	Obtains both qualitative and quantitative data on self-awareness (of deficits, functional implications, and ability to set realistic goals); interview style with responses rated on a 4-point scale.
Self/Other Rating Form	Sohlberg et al. 1998	Rates cognition, social/emotional issues, daily living skills, physical abilities, and leisure time management; 24 items rated on a 5-point scale; patient and caregiver versions, interview format used.
Self-Regulation Skills Interview	Ownsworth et al. 2000	Assesses key metacognitive or self-regulation skills reflecting the theoretical model of Crosson et al. (1989); semistructured interview with 6 questions applied to a main area of difficulty identified by the participant that require some degree of intellectual awareness.

impact on overall outcome by decreasing motivation for treatment. Clinicians working to rehabilitate individuals with TBI report that unawareness is a major factor in determining long-term functional recovery (Gerstmann 1942; Trudel et al. 1996), including eventual return to employment, level of vocational achievement, and independent living status. Several studies have investigated the association between impaired awareness and functional outcome after TBI (Cavallo et al. 1992; Ezrachi et al. 1991; Fordyce and Roueche 1986; Rattok et al. 1992; Sherer et al. 1998a, 2003a; Trudel et al. 1996; Walker et al. 1987). These findings are summarized in Table 19–3 and provide strong, though not unqualified, evidence of a positive association between accurate self-awareness and favorable employment outcome after TBI.

Newman et al. (2000) studied self-awareness in 37 patients with TBI in an acute rehabilitation program using the Functional Self-Appraisal Scale, which compares patient and staff ratings of patient performance on tasks relevant for acute rehabilitation. There was a significant difference between ratings near admission, consistent with previous findings in acute settings that individuals with TBI tend to overestimate their abilities relative to other raters (Allen and Ruff 1990; Prigatano et al. 1990; Sherer et al. 1995, 1998b). By time of discharge, there was no significant difference between patient and staff ratings. However, it was suggested that this convergence of ratings was due primarily to patient improvement on the rehabilitation tasks rather than a reflection of increased awareness—that is, staff ratings changed from time 1 to time 2 assessments, whereas patient ratings did not. The authors noted that the difference between patients' and staff's ratings did not correlate with neuropsychological performance on admission and suggested that this supports the notion that awareness early in the recovery process is a distinct construct.

Overview of the Neuroanatomical Substrate of Awareness

On the basis of the study of cognitive processes in patients with various unawareness syndromes, a variety of models have been proposed to explain how individuals are aware of deficits and how they respond to them. Most of the models suggest several key features are necessary to the proper functioning of these cognitive processes. These include intact primary stimulus processing (e.g., visual or other sensory input) and the ability to monitor properly the input (compare it with known templates), formulate a response or choose from a menu of responses, monitor the response chosen, and compare the anticipated response with the actual response. For example, Heilman (1991) suggested that the reason many patients with Wernicke's aphasia do not self-correct is that they are unable to monitor their verbal output; they are thus unaware that what they say makes no sense and can become quite frustrated when others fail to understand what they are saying. In the instance of hemiplegia and associated anosognosia, Heilman (1991) sug-

TABLE 19–3. Studies investigating the relationship between impaired awareness and functional outcome after TBI

Study	Participants	Findings
Fordyce and Roueche 1986	Twenty-eight patients, severity unknown; three groups: one with ratings similar to clinicians; one rating themselves as less impaired; and one rating themselves as less impaired at admission but consistent with clinicians at discharge	No group differences in vocational outcome at follow-up. Reanalysis by Sherer et al. (1998a) found that final self-ratings indicating accurate awareness were more predictive of favorable vocational outcomes.
Walker et al. 1987	Twenty-five patients, severity unknown; compared patient self-ratings with ratings of family/significant others at admission to day treatment program	At follow-up, patients whose initial self-assessments agreed with assessments of family members were more productive than patients who rated themselves as less impaired.
Ezrachi et al. 1991	Fifty-nine patients with moderate or severe TBI	Accuracy of self-appraisal was predictive of vocational status 6 months after discharge. Awareness and acceptance were most favorable predictors of successful return to work.
Cavallo et al. 1992	Thirty-four patients with mild to severe TBI; compared patient ratings with ratings of family/significant others	Accuracy of awareness ratings did not affect return-to-work rates.
Trudel et al. 1996	Compared patient and therapist ratings	Direct relationship between the size of discrepancy in ratings and poorer outcome. Awareness was primary predictor of vocational and independent living status.
Sherer et al. 1998a	Sixty-six individuals with mild to severe TBI; two ratings of awareness (direct clinician rating of patients' accuracy and comparison of patient ratings with those of family/significant other)	Positive relationship between accurate self-awareness of functioning after TBI and favorable long-term employment outcome, regardless of awareness rating used.
Sherer et al. 2003b	One hundred twenty-nine patients with TBI seen for inpatient rehabilitation; ratings of awareness and employability made by patient and clinician at time of discharge	Clinician ratings of patient functioning were positively correlated with employability, whereas patient self-ratings of awareness showed a trend toward a negative relation to employability.
Fischer et al. 2004	Sixty-three patients with brain injuries of various etiologies admitted consecutively to an inpatient rehabilitation center; ratings included direct clinician ratings and difference between patient and staff ratings	Self-awareness appeared related to goal-setting ability and outcome in a long-term rehabilitation process but less in short-term experimental tasks.

Note. TBI=traumatic brain injury.

gested a different mechanism, namely that the usual right hemisphere lesion that produces the hemiplegia in some instances also disables the motor intention system. In the normal course of events, the motor intention circuits prepare the motor system for action and along with that the "expectation" that movement will take place. This expectation is subsequently compared with the actual results (i.e., movement does or does not take place in accordance with expectation), a function Heilman termed "the comparator." In the presence of a disabled motor intention system, there is no intention fed into the comparator, no expectation of movement setup, and thus no discrepancy noted by the comparator when no movement takes place. When confronted by the absence of movement and the observation by an observer that thus the arm must be paralyzed, the patient interprets the absence of such a discrepancy or mismatch as an intact motor system. In the case of the Wernicke's patient, the error is one of inadequate feedback; in the instance of the motor anosognosia, the error is improper "feedforward" (Heilman et al. 1998).

Stuss (1991b; Stuss and Benson 1986) suggested that frontal systems play a critical role in the maintenance of full awareness, whereas the knowledge of function, or conversely the knowledge of specific deficits, is associated with posterior brain functions. Lesions in specific posterior regions can lead to specific primary deficits (e.g., Anton's syndrome, neglect, and anosognosia). As noted in the section Lack of Awareness in Other Neuropsychiatric Disorders, patients with these disorders can have knowledge of some deficits and absence of knowledge about other deficits. This has been termed modality-specific awareness. Cases of modality-specific awareness argue against a central awareness mechanism. Rather, such cases suggest that the substrate underlying knowledge or awareness of specific deficits may be linked to modality-specific posterior (probably nondominant) brain regions. Thus, for example, awareness of visual deficits would involve posterior regions, probably in the visual association cortex. On the basis of the anosognosia associated with hemiplegia findings, awareness of contralateral motor function has been linked to the region of the inferior parietal lobule.

The response to acknowledged deficits may well involve several different brain regions. The response to deficits most closely linked to lack of awareness is relative

indifference (anosodiaphoria). An important component of this response may be selective inattention or neglect. Watson et al. (1981), for example, reported a patient with a right medial thalamic stroke who demonstrated contralateral neglect. He acknowledged his neurological deficits, including hemiparesis, but was quite unconcerned about the deficits. Watson et al. (1981) suggested that several interconnected regions, including the midbrain reticular formation, selected thalamic nuclei, and frontal cortex, facilitate attention and preparation of the brain for action (motor intention). Lesions in these areas may result in problems with neglect or the motor intention system, or both, and could result in an individual appearing somewhat unconcerned by obvious deficits. The frontal lobes also may be important, because they play a role in the affective response to a given stimulus. Individuals with dorsolateral frontal injury often display muted, bland, apathetic responses to significant stimuli. This may well tie into the anosodiaphoria, or indifference to deficits, that brain-injured patients can manifest.

Stuss (1991a, 1991b; Stuss and Benson 1986) suggested that frontal systems generate self-awareness, self-reflectiveness, and self-monitoring. Because frontal systems also play a critical role in the modulation of key social skills and behaviors (e.g., initiation, motivation, problem solving, and affective modulation), frontal lobe damage can affect the ability to understand the impact that deficits have on day-to-day function and future function and how to apply that knowledge to a current situation. In individuals with TBI, this dimension is frequently the focus of concern. Irritability, disinhibited outbursts, childishness, and intrusiveness are extremely common behavioral traits, yet are often not recognized by individuals with TBI (Ford 1976; McAllister 1992; Miller and Stern 1965; Oddy et al. 1985; Ota 1969; Prigatano 1991). One frequently sees the malignant combination of severe social skills deficits and an inability to understand the ramifications of these deficits. Even when the individual admits to some difficulties, he or she is often unable to predict the implications of these deficits in current or future social situations.

In a cognitive model of anosognosia, medial temporal dysfunction might impair the ability to compare current cognitive information with personal knowledge, whereas orbitofrontal damage may not allow individuals to accurately monitor their errors (O'Keeffe et al. 2004) or update the qualitative judgment associated with their impaired cognitive abilities (Salmon et al. 2006). Parietal lobe abnormalities might result in impairment of the network subserving perspective taking (Salmon et al. 2005). Ghajar and Ivry (2008) proposed that shearing of white matter connections between the prefrontal cortex, parietal lobe, and cerebellum leads to a fundamental defect in TBI affecting the anticipatory neural system. These fiber tracts are part of a neural network that generates predictions of future states and events, which are required for optimal performance, focused behavior, and accurate feedback. The authors hypothesized that after a TBI, impairment resulting from shearing injury results in the brain shifting from a predictive to a reactive mode, resulting in working memory deficits, distractibility, loss of goal-oriented behavior, and impaired awareness.

The neuroanatomical substrate of properly attributing the cause of various acknowledged deficits or difficulties to the traumatic brain injury is not known. Table 19–4 presents a summary of this information.

Relationship of the Typical Profiles of TBI Pathology to the Circuitry of Awareness

Given the preceding, it is not surprising that awareness deficits of various types are a common and challenging problem in individuals with TBI. As described by Gennarelli and Graham (1998), the typical profile of brain injury in acceleration-deceleration injuries includes contusions in the orbitofrontal region, the anterior and inferior temporal regions, and beneath or contralateral to the site of impact (coup or contrecoup). Intracerebral hemorrhages are seen in a variety of regions, including the basal ganglia. In moderate and severe TBI, diffuse axonal injury occurs. Such diffuse injury is often particularly evident in the corpus callosum, the superior cerebellar peduncle, the basal ganglia, and the periventricular white matter.

As DeKosky et al. (1998) pointed out, not all injury occurs at the time of impact. "Secondary injury," or that injury that is set in motion by the primary impact but evolves over the subsequent minutes, hours, or even days, also plays a crucial role in the postinjury sequelae. The various cascades involved in secondary injury can result in significant and far-reaching sequelae removed in location and time from the primary injury (see Chapter 2, Neuropathology).

Thus, there is significant overlap between the brain regions that play a role in awareness (broadly defined) and those regions most commonly injured in the typical TBI. There is a direct relationship between increased degree of diffuse axonal injury and injury severity; thus, it is not surprising that there is a correlation between injury severity and lack of awareness (Freeland 1996). The frontal lobes, both the dorsolateral and orbitofrontal areas, and related circuitry (subcortical white matter, basal ganglia, and thalamus) are also vulnerable to TBI. The known roles these regions play in cognition and behavior, self-monitoring, self-awareness, and other metacognitive processes make it readily apparent why challenging behaviors, along with failure to acknowledge the significance of those behaviors, inappropriate response to the behaviors, and difficulty comprehending the implications of these behaviors and other deficits, are such a common and vexing problem in individuals with TBI.

Impact of Lack of Awareness on Treatment and Rehabilitation

Individuals with TBI and impaired awareness can be very challenging for both rehabilitation workers and families. Evidence suggests that individuals with TBI are more likely to be aware of residual physical disabilities and

TABLE 19–4. Putative brain circuitry associated with components of unawareness

Component	Putative brain mechanisms or neural circuitry	Sample references
Lack of knowledge of deficits	Posterior modality-specific primary sensorimotor cortex (e.g., impaired visual cortex in Anton's syndrome)	Anton 1898; Heilman 1991; Stuss 1991a; Stuss and Benson 1986
Performance monitoring	Unknown; hypothesized "comparator" region that monitors fit between intention and action/output (e.g., people with Wernicke's aphasia unable to monitor own verbal output)	Heilman 1991; Stuss 1991a; Stuss and Benson 1986
Response to deficits	Loop involving midbrain reticular activating system, medial thalamus, and medial and dorsolateral prefrontal cortex	Stuss 1991a; Stuss and Benson 1986; Watson et al. 1981
Generalizability/application of knowledge to other contexts	Dorsolateral and mesial frontal-striatal-thalamic-frontal circuits	Cummings 1993; Stuss 1991a; Stuss and Benson 1986
Attribution/cause of deficits	Unknown	

often have a reduced appreciation of their limitations and impairments in the cognitive, functional, and psychosocial domains (Bond 1975; Brooks 1991; Fischer et al. 2004; Trahan et al. 2006).

It has also been reported that in some circumstances significant others and family members are less aware of cognitive problems than some individuals with TBI (Cavallo et al. 1992; Heilbronner et al. 1989; Hillier and Metzer 1997). Similarly, although family members may be less aware of more internal problems such as fatigue or pain, they are more likely than individuals with TBI to report personality and behavioral problems (Hillier and Metzer 1997). This demonstrates that there can be a wide divergence of perceptions between the three groups of individuals—patients with TBI, family members, and clinical staff—involved in the recovery and outcomes after TBI, and this can cause significant conflict that can affect the course of rehabilitation. In fact, failure to recognize cognitive, emotional, and behavioral barriers may be one of the most disabling effects of TBI and represents the greatest impediment to rehabilitation.

Giacino and Cicerone (1998) suggested that the existence of different types of unawareness after TBI may have implications for prognosis and rehabilitation because unawareness of deficits is related to rehabilitation outcome. In their view, patients with unawareness of deficits secondary to impairment of cognitive subsystems, such as attention, memory, or reasoning, appear capable of increasing their awareness when they are provided with relevant feedback and information about their disability, in parallel with improvements in these cognitive domains. Patients with unawareness secondary to psychological denial are unlikely to modify their behavior and are likely to demonstrate reduced motivation and resistance to treatment with attempts to increase their awareness. Finally, patients with unawareness secondary to breakdown of a supraordinate monitoring system may also be incapable of modifying their behavior, despite intact intellectual knowledge of possible deficits.

A study by Anson and Ponsford (2006) investigated several variables associated with change in psychological adjustment following a 10-session cognitive-behavioral therapy group for individuals who sustained a TBI. Age at injury, time since injury, injury severity, awareness, cognitive functioning, and affective status were examined. Results indicated that better outcomes following intervention were primarily associated with greater self-awareness of injury-related deficits prior to beginning therapy. It is noteworthy that self-awareness of deficits related to brain injury contributed the greatest unique proportion of the variance to change in depression following the intervention, and the authors proposed that these individuals may be more receptive to adaptive coping strategies discussed in the group and more likely to implement them in their daily activities. Goverover (2004) found that categorization, deductive reasoning, and self-awareness of individuals with TBI are good predictors of functional performance and can help in planning appropriate treatment interventions.

Finally, a study by Roberts et al. (2006) found that scores of unawareness, as well as scores on two of three mood measures, decreased significantly after individuals met with a neurologist to review the findings of their brain scans and possible neurobehavioral outcomes. The improvement in scores was maintained at a 2-week follow-up.

There are various strategies for working with patients with unawareness of deficits secondary to TBI (Deaton 1978), although little empirical evidence exists to demonstrate their effectiveness (Fleming et al. 1996). From a theoretical standpoint, approaches generally can be categorized as those that address awareness as an overarching deficit that must be considered before change can occur and those that nest the treatment of awareness deficits in a broader, integrative program designed to maximize functional capacity (see Table 19–5). For example, some clinicians argue that neither a prerequisite level of awareness nor awareness training is an essential ingredient for behavior change (e.g., Sohlberg et al. 1998). That is, individuals with TBI can be trained to use compensatory strategies even when they do not understand why or believe that they do not need them. However, the fact that behavior can change without changed awareness does not imply that increased awareness cannot change behavior. As Kent (1999) pointed out, the deeper and more comprehensive an individual's awareness becomes, the more that person is able to apply his or her understanding to new and different situations. Although one can behaviorally train a person to use compensatory strategies, without some increase in the person's awareness of the need for these strategies, it is difficult to get that person to continue to use the strategies or generalize them to other situations.

TABLE 19–5. Treatment approaches for brain injury rehabilitation

Focus: *Lack of awareness regarded as an overarching deficit that must be addressed before change can occur*	**Focus:** *Treatment of awareness deficits nested in comprehensive-integrative programs designed to maximize functional capacity*
Holistic milieu-oriented neuropsychological programs	Educational sessions and functional training sessions
Compensatory and facilitatory approaches	Cognitive therapy (individual and/or group)
Structured experiences	Cognitive-behavioral therapy (individual and/or group)
Confrontational techniques	Coping skills groups
Cognitive interventions (individual and/or group)	Emotion-focused treatments
Provision of feedback of brain-imaging findings	Combined cognitive and emotion-focused therapy
Behavioral interventions (individual and/or group)	Matching intensity of the services to the severity of the disability and time since injury
Community activities highlighting limitations and barriers	
Videotaping and provision of feedback	
Instructional game format	
Occupation-based intervention program	

Many different approaches have been attempted to increase the level of awareness in individuals with brain injury, including holistic milieu-oriented neuropsychological programs, compensatory and facilitatory approaches, structured experiences, direct feedback, confrontational techniques, and therapies including cognitive, group, and behavioral interventions (Fleming et al. 2006). Other programs involve education regarding the consequences of brain injury (Fordyce and Roueche 1986), community activities designed to highlight limitations and barriers (Barin et al. 1985), videotaping individuals with brain injury and providing feedback regarding their behavior (Alexy et al. 1983), and development of an instructional game format (Zhou et al. 1996). For example, Chittum et al. (1996) used an individualized training package (educational discussion) in conjunction with the board game format to teach awareness of behavioral and cognitive difficulties to three adults with acquired brain injury. All three participants responded favorably to the training, which was assessed by percentage of questions answered correctly during the game sessions and in pre/postgeneralization probes in both domains. Fleming et al. (2006) used an occupation-based intervention program in four individuals after acquired brain injury. In this 10-week individualized program, a facilitative approach used techniques to improve self-awareness in the work context. Results of this pilot study indicated support for the effectiveness of the program in facilitating participants' self-awareness; notably, increased anxiety was found to accompany improvements in self-awareness for all participants. Cheng and Man (2006) found significant improvement in level of awareness in a group of TBI patients after an intensive awareness intervention program, relative to a group of patients who received a conventional rehabilitation program; however, there were no differences in functional outcomes between the two groups. The intervention was delivered on an individual basis for two sessions per day, 5 days per week, for 4 weeks, with both educational sessions and functional training sessions. Intervention strategies included the use of concrete feedback, education about brain injury and the patient's deficits (educational sessions), and self-performed prediction and goal-setting activities though practice (functional training sessions).

In general, a distinction can be made between intervention approaches for unawareness due to neurocognitive factors and approaches for unawareness due to psychological factors. Considerations in the development of appropriate rehabilitation programs that directly address unawareness include the need for individually tailored interventions, differing individual responses according to the nature of the unawareness deficit, and the risk of eliciting emotional distress in some individuals (Fleming et al. 2006).

As noted, others argue for what they conceptualize as a more comprehensive integrative model. This model of treatment involves developing and working toward goals in several areas of everyday life. Patients work toward goals in a gradual, stepwise fashion. Each step involves increasingly greater levels of independence, with the overall goal being the highest level of functional independence for each individual. Significant changes have been reported in the vocational status and living situation of even severely injured TBI patients after several months of treatment (Ben-Yishay et al. 1987; Malec et al. 1993; Prigatano et al. 1984). Although it is not clear which aspects of the program are most crucial to successful outcome, level of awareness has been identified as an important component (Bergquist and Jacket 1993; Ezrachi et al. 1991; Malec and Degiorgio 2002; Prigatano et al. 1990). Other criteria for successful rehabilitation, regardless of type, include matching intensity of the services to the severity of the disability and time since injury (Malec and Degiorgio 2002). Cognitive and emotion-focused treatments, as well as both in conjunction, have been used appropriately and successfully with individuals who demonstrate impaired awareness after acquired brain injury (Mateer et al. 2005).

We would argue that there are several components of any successful approach that should be attended to, including assessment, neuropsychological evaluation, development of a therapeutic alliance, supportive group and family therapy, and education of the patient and his or her support system. These components are outlined in Table 19–6 and discussed briefly in the following paragraphs.

First, it is helpful to delineate the extent and profile of the awareness deficit. One should clarify whether the problem is more a deficit in knowledge, an inappropriate response to an acknowledged deficit (e.g., anosodiaphoria), or an inability to understand the impact or consequences that the deficits will have on areas of day-to-day

TABLE 19–6. Components of the treatment process

Component	Goal	Likely problems
Assessment	To delineate the extent and profile of the awareness deficit.	Deficits in knowledge. Inappropriate response to acknowledged deficit. Inability to understand impact/consequences of deficits on function.
Neuropsychological evaluation	To determine to what extent awareness deficits are related to cognitive deficits.	Frontal-subcortical system impairment. Right parietal lobe dysfunction.
Development of a therapeutic alliance	To develop a relationship in which therapists can validate individuals' self and worldview without fostering unrealistic hopes/expectations. Individuals with TBI may comply with rehabilitation even when they do not agree they have deficits.	Individuals may become alienated from therapist and rehabilitation process if they feel assistance is being forced on them.
Education of individual with TBI	To provide individuals with some idea of the treatment goals.	Poor motivation in individuals who do not agree with identified problems. Difficulty with generalizing knowledge to real-life situations.
Group therapy	To provide individuals with TBI feedback from others who are or have been in similar circumstances.	Resistance to identifying with others as "similar."
Education of support system (family/significant others)	To provide family and significant others with better understanding of brain injury and issues related to awareness.	Family members and/or significant others may provoke catastrophic reactions in individuals with TBI by attempting to "force awareness" on them.
Supportive therapy for family/significant others	To facilitate coping skills and allow family/significant others to provide more support to individuals with TBI.	Family members and significant others may also be in denial regarding seriousness of deficits.

Note. TBI=traumatic brain injury.

function. For those who acknowledge deficits, it is important to assess whether they accurately attribute those deficits to their TBI. This clarification process informs the treatment process.

A difficult issue is assessing to what extent lack of awareness in any of the preceding dimensions is related to cognitive deficits, psychological denial, or both. Critical to this differentiation is information provided by neuropsychological evaluation. Evidence of significant cognitive impairment makes it more likely that awareness deficits are related to actual brain injury as opposed to the psychological defense mechanism of denial. It should be remembered that individuals can have a combination of injury-induced awareness deficits and psychological responses to those deficits. They then present a mixed picture of neurological and psychological denial.

An important intervention is the establishment of a therapeutic relationship. This is particularly important for individuals who dispute the very premise that they need assistance. The therapist must tread a difficult line between validating the individuals' self and worldview and not fostering unrealistic expectations and hopes. Limited studies have been conducted addressing the therapeutic alliance within brain injury rehabilitation, but a positive relationship between the alliance and outcome is consistently reported (Bieman-Copland and Dywan 2000; Klonoff et al. 1998, 2001; Prigatano et al. 1994; Schonberger et al. 2005). In fact, Schonberger et al. (2006) suggested that brain injury rehabilitation should be seen as a dynamic process that develops between individuals with TBI and their therapists, and they argued for a holistic rehabilitation setting with a phenomenological approach. Even when there is a solid relationship between patient and therapist, however, it can be difficult to overcome some of the awareness deficits. Although some of the more dramatic knowledge deficits such as those seen in Anton's syndrome and the anosognosia associated with hemiplegia resolve over days to weeks, this is not a universal outcome. Many of the deficits associated with TBI, especially those in the areas of social skills and behavior, are permanent. However, these patients often comply with rehabilitation, especially if the rehabilitation is subtle and not called rehabilitation. Some individuals may be open to receiving help in certain areas (e.g., ambulation and speech) but may be resistant to the idea that they need help with interpersonal skills or anger management. When social skills and anger management rehabilitation can be integrated into rehabilitation in domains people are willing to consider, multiple goals can be met. Once an adequate therapeutic foundation is present, interventions should be geared toward gently confronting the individual with the discrepancy between the patient's own view of his or her strengths and abilities and the perceptions of others. Because of the usual associated memory and related cognitive deficits, this must usually be done repetitively and in small doses, taking cues from the individual with regard to his or her tolerance for this process (DeLuca et al. 1996).

To maintain goals made during treatment, therapists should consult patients and set goals that will motivate them. Although individuals are typically poorly motivated

to pursue goals they see as irrelevant, rehabilitation becomes aimless without some appropriate set of goals (Bergquist and Jacket 1993). Creating a realistic set of goals that the patient is motivated to pursue represents a significant but crucial challenge. Making decisions regarding appropriate goals involves obtaining history and input from the patient and other informants and from direct observation. Group therapy may also be effective. Feedback from others who are or have been in similar circumstances can further assist people in recognizing that a problem behavior has occurred. Assistance may be required with generalization of skills as well, because even when an individual is aware of his or her deficits, or at least acknowledges them, he or she can have great difficulty applying that knowledge to real-life situations.

Education and supportive therapy for significant others also play vital roles in the process of improving the patient's awareness (Ergh et al. 2002). They permit the family to gain a better understanding of brain injury and the issues related to awareness and lead to an appreciation of how they apply to their loved one. This facilitates improved coping skills and in turn allows the family to provide more support to the TBI survivor. Modeling the process of gentle teaching about deficits is often necessary to prevent significant others from provoking catastrophic reactions in the brain-injured individual. Further, Sherer et al. (2007) demonstrated that family perceptions and family functioning are important determinants of the therapeutic alliance for patients in postacute brain injury rehabilitation.

Others have proposed that interventions based on motivational interviewing, cognitive and Rogerian therapy, and the Listen-Empathize-Agree-Partner (LEAP) approach to communication improve patients' awareness (Amador 2007). Paillot et al. (2009) found that LEAP improved insight without the use of psychoeducation and argued that by not confronting patients about their awareness deficits and instead focusing on increasing the therapeutic alliance, therapists help patients to gravitate naturally toward becoming more curious about their illness and deficits. LEAP improved insight, motivation to change, and adherence to treatment.

Treatment Advances

We believe that the next steps in the understanding of unawareness may well come from the application of new functional imaging techniques to this critical clinical problem. Specifically, the development of tasks that will allow us to probe the different dimensions of unawareness will facilitate characterization of the circuitry underlying these distinct dimensions. It would not surprise us to learn that the different clinical dimensions (unawareness of deficits, reaction/response to deficits, generalizability/impact of deficits in daily functioning, attribution of deficits) have overlapping but distinct neural circuits that can be clarified with, for example, functional magnetic resonance imaging. We have identified several potential candidate functions that we hypothesize contribute to the neural and cognitive substrates underlying unawareness of illness, including working memory, episodic memory, source/reality monitoring, self-monitoring, and theory of mind. We and others are beginning to explore the utility of these constructs by developing tasks that assess the integrity of these functions and that can be used in functional magnetic resonance imaging paradigms.

KEY CLINICAL POINTS

- Since the 1990s, the research literature on lack of awareness of deficits has burgeoned, primarily in the areas of dementia, other central nervous system (CNS) diseases, and schizophrenia.
- Advances made in understanding lack of awareness in dementia, CNS diseases, and schizophrenia compared with similar deficits found in traumatic train injury (TBI) can illuminate the nature, pathophysiology, and treatment approach needed in individuals with TBI.
- Various dimensions and distinctions can be discerned within the concept of lack of awareness, and there is clinical, research, and theoretical value in making such discriminations.
- Evidence suggests that different aspects or dimensions of lack of awareness have differing neurological underpinnings and treatment implications.
- Increased sensitivity to the multidimensional nature of TBI unawareness-related deficits will not only inform treatment interventions but also shed light on the underlying pathology of lack of awareness in patients with TBI.

- The next steps in the understanding of unawareness may come from the application of new functional imaging techniques. Development of tasks that allow researchers to probe dimensions of unawareness will help to characterize the circuitry underlying these distinct dimensions. The different clinical dimensions (unawareness of deficits, reaction and response to deficits, generalizability and impact of deficits in daily functioning, attribution of deficits) may have overlapping but distinct neural circuits that can be clarified with, for example, functional magnetic resonance imaging.

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CHAPTER 20

Sleep Disturbance and Fatigue

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SLEEP DISTURBANCE AND FATIGUE ARE TWO COMMON disabling symptoms that affect the recovery course and disrupt rehabilitation in patients who survive traumatic brain injury (TBI). Despite the ubiquity of these problems, objective data are scarce on the prevalence, pathophysiology, and treatment of these conditions in the TBI literature. The exact etiology of these disturbances is also unclear. Sleep disturbance and fatigue after TBI can be best conceptualized as primary effects of the trauma itself, which can cause neurohormonal and neurotransmitter dysfunction in the central nervous system or as secondary effects of neuropsychiatric disturbances associated with the TBI. Side effects of medications used to treat TBI and psychological distress associated with trauma may also influence sleep cycle integrity. Sleep disturbance and fatigue, although not well studied after TBI, are common and have important rehabilitation implications for patients (see Figure 20–1).

The complex relationship between sleep and TBI should be considered on a continuum of two points of time following brain injury. The first is the disruption of normal sleep during the period just after injury, which is related to injury severity. The second period is the disruption of sleep that occurs in the chronic phase after brain injury. While related to initial injury, this particular syndrome in the chronic phase after recovery is probably a distinct entity from that which is encountered in the immediate postacute phase. Sleep disturbances after TBI, in both the acute and chronic phase, may be broadly divided into insomnia (difficulty in initiating or maintaining sleep), hypersomnia (excessive daytime sleepiness), and alterations of the sleep-wake schedule (displacement of sleep from its original circadian pattern).

Fatigue is a nonspecific and highly subjective symptom that is often reported as a feeling of exhaustion, tiredness, or weakness. Bigland-Ritchie et al. (1978) defined fatigue physiologically as the inability of a muscle or groups of muscle to sustain the expected or required force of work. This inability could either be due to a central mechanism decrease or inability to sustain the central drive to the spinal motor neurons or to a peripheral mechanism failure of force-generating capacity within the muscle (Comi et al. 2001). Chandhuri and Behan (2000) defined central fatigue as the failure to initiate and/or sustain the attentional tasks and physical activities requiring self-motivation.

In many ways, sleep disturbances after TBI are better defined and understood than fatigue disturbances. Thus, in this chapter we first discuss the prevalence, pathophysiology, evaluation, and treatment of sleep disturbances after TBI. We then focus on fatigue after TBI. Although sleep disturbances and fatigue do clearly overlap, we treat them separately in this chapter for clarity.

Normal Sleep Cycle

Only a brief review of the normal sleep cycle is provided here. For an in-depth understanding, the reader is encouraged to read a standard textbook on sleep disorders (e.g., Kryger et al. 2000). Sleep is an active, complex, and vital process, with multiple regulating factors. Researchers have identified multiple, discrete centers for sleep production and wakefulness. These regions in the central nervous system, including the brain stem, basal forebrain, and hypothalamus, regulate the sleep-wake cycle. Seroto-

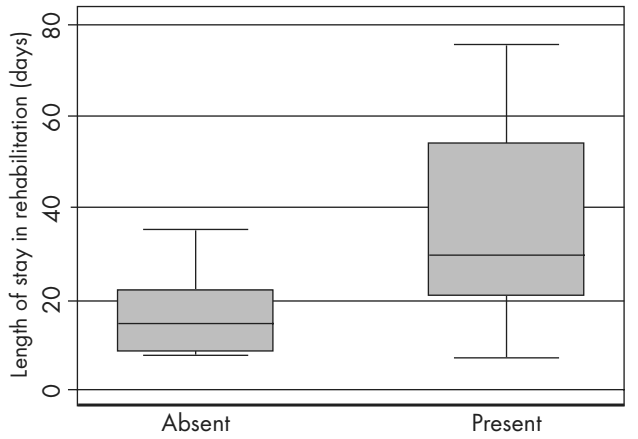


FIGURE 20–1. Length of stay in a rehabilitation unit in those with sleep cycle disturbance present versus those with sleep cycle disturbance absent.

Solid lines within boxes = 50th percentile or median value of data; error bars = 1 SD above and below mean of data.

nin and acetylcholine are two common neurotransmitters involved, although other hormones and endogenous products such as substances C and S, hypocretin, dopamine, and norepinephrine also play important roles. Homeostasis determines the amount of sleep.

Sleep consists of two distinct states, rapid eye movement (REM) and non-REM (NREM) sleep, which affect physiological functions and behavior (Table 20–1). REM periods occur approximately every 90–100 minutes and last about 10–40 minutes. The first REM period occurs approximately 90 minutes after sleep onset (REM latency). REM sleep is characterized by increased brain and physiological activity similar to that of wakefulness. NREM sleep is a more peaceful state. There are four stages of NREM sleep with typical electroencephalographic patterns (Table 20–2).

The sleep-wake cycle is regulated by the interaction of internal biological clocks and environmental influences. The two important internal synchronizers are the suprachiasmatic nucleus of the hypothalamus and the endogenous production of a substance—process S. The external synchronizers, also called *Zeitgebers*, are light-darkness alteration, eating and social schedule, temperature, and relative humidity. Dysfunction or maladjustment of these internal and external time markers due to brain damage, cognitive deficits, and/or sensory deprivation may be responsible for disorders of sleep in TBI patients (Espinar-Sierra 1997). Sleep dysfunction could in turn impair learning and memory and could lead to suboptimal cognitive recovery after TBI (Zafonte et al. 1996). In a study of 14 patients with moderate-severe TBI, Makley et al. (2009) showed that improved sleep efficiency correlated with improvement in posttraumatic amnesia, underscoring the direct relationship between sleep disturbance and memory deficits. Similarly, animal studies have also shown that sleep deprivation induces memory disturbances possibly secondary to multiple factors, including disturbance in neurotransmitter levels and oxidative damage (Kalonia et al. 2008).

TABLE 20–1. Sleep states

State	General characteristics
Rapid eye movement	High level of brain activity
	Physiological activity similar to wakefulness
	Episodic bursts of rapid eye movement
	Dreaming associated with vivid dream recall
	Poikilothermia (inability to regulate body heat)
	Absence of body movement but partial or full penile erection
	Increase in pulse rate, blood pressure, and respiratory rate
	Decreased ventilatory response to increased levels of carbon dioxide
	Cortical electroencephalogram reveals low-voltage mixed-frequency waves
Non–rapid eye movement	Low level of brain activity
	Physiological activity markedly reduced
	No rapid eye movement activity
	Four stages present
	Hypothermia
	Slight decrease in pulse rate, blood pressure, and respiratory rate
	Decrease in blood flow through all tissues
	Intermittent involuntary body movement
	Cortical electroencephalogram reveals increased-voltage slowed-frequency waves
	Four stages present, with arousal threshold lowest in stage 1 and highest in stage 4

TABLE 20–2. Stages of non–rapid eye movement sleep

Stage	General characteristics	Electroencephalographic findings
1	Light stage of sleep Lasts for a brief period Occupies approximately 5% of total sleep	3–7 cycles/second, low-voltage mixed-frequency waves
2	Occupies approximately 50% of total sleep	Spindle-shaped tracings at 12–14 cycles/second K complexes characterized by slow triphasic waves
3	Slow-wave sleep Disorganization during arousal	High-voltage delta waves at 0.5–2.0 cycles/second Occupies 20%–50% of the tracing
4	Slow-wave sleep Disorganization during arousal	High-voltage delta waves Occupies more than 50% of sleep

Prevalence of Sleep Disorders After TBI

Little is known about sleep in the immediate postacute phase following brain injury, although disrupted sleep is commonly seen by the clinician. A study by Makley et al. (2009) of moderate to severe TBI patients admitted to an inpatient rehabilitation unit found nearly 70% of patients had disrupted nighttime sleep. In this study, there was no difference in those with disrupted sleep and those without in the admission Glasgow Coma Scale score, a common index of injury severity. However, affected patients had significantly longer stays in the trauma center and the rehabilitation hospital, suggesting that sleep disturbance may be a marker for more severe injury (Makley et al. 2008).

Sleep disturbances are equally common in the chronic period after TBI, occurring in 36%–70% of patients (Keshavan et al. 1981; McLean et al. 1984). In a prospective study of 50 consecutive postacute TBI patients, Mann et al. (1997) found that 30% reported insomnia. Cohen et al. (1992) suggested that sleep complaints may vary temporally: difficulty in initiating and maintaining sleep occurs soon after injury, and excessive daytime somnolence occurs months to years after injury. In their study of 22 hospitalized patients 3–5 months after injury, 81% had difficulty in initiating and maintaining sleep (early and middle insomnia) and 14% had excessive daytime sleepiness. In a study of 77 outpatients who had sustained TBI 2–3 years previously, 73% complained of excessive daytime sleepiness and only 8% complained of difficulty in initiating and maintaining sleep (Cohen et al. 1992). Rao et al. (2008) evaluated 54 nondelirious patients in the first 3 months after TBI and found abnormal sleep scores in several domains of the Medical Outcome Scale for Sleep, including sleep disturbance, shortness of breath/headache, sleep adequacy, daytime sleepiness, and global sleep scores.

Few studies have used objective measures to assess sleep disturbances after TBI. In a prospective study of 87 TBI patients, Castriotta et al. (2007) found abnormal sleep in 47% of patients using polysomnography (PSG) and excessive daytime sleepiness or abnormal Multiple Sleep Latency Test (MSLT) scores in 25% of patients. It is interesting to note that there was no correlation between subjective scores (Epworth Sleepiness Scale) and MSLT scores. There is little epidemiological literature available specifically on sleep-wake cycle disturbances, although TBI patients commonly report symptoms such as "difficulty in going to sleep until later than usual, but able to have normal amount of sleep."

Relationship Between TBI and Sleep

The cause-and-effect relationship between TBI, sleep disturbance, psychiatric disturbance, and fatigue is not well delineated (Figure 20–2). The understanding of the pathophysiology of these disturbances is based on knowledge of the neuropathology of TBI and the physiology of the sleep-wake schedule. Sleep disturbances may be the primary effect of trauma to the brain or secondary to other neuropsychiatric sequelae of TBI, such as depressive disorders, anxiety disorders, substance abuse, chronic pain, and/or medications.

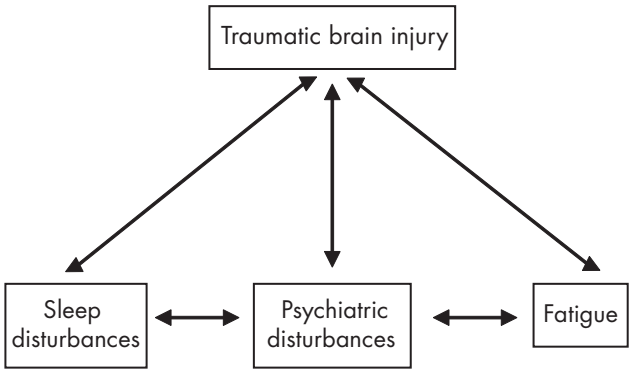


FIGURE 20–2. Algorithm showing possible cause-effect relationship between traumatic brain injury, sleep disturbances, psychiatric symptoms, and fatigue.

Brain injury of any degree of severity is a complex process that affects multiple brain regions (see Chapter 2, Neuropathology). Therefore, it is not surprising that sleep disturbance is a common occurrence after TBI because maintenance of the sleep-wake cycle depends on the proper functioning of multiple levels of the central nervous system: the brain stem, basal forebrain, hypothalamus, and the frontal-subcortical system (Parmeggiani 2000). A study of patients with moderate and severe TBI reported low cerebrospinal fluid levels of hypocretin 1, an excitatory hypothalamic neuropeptide involved in regulation of sleep-wake cycles and known to be reduced or absent in patients with narcolepsy (Baumann et al. 2005). In this study, lower levels of hypocretin were associated with a lower level of arousal. In a study of the correlates of sleep disturbances after closed head injury in the first 3 months after TBI, Rao et al. (2008) found that post-TBI anxiety disorder is the most consistent significant risk factor associated with worsening sleep status. Parcell et al. (2008), in a comparison study of moderate to severe TBI patients with noninjured normal control subjects, had similar results. TBI patients had poorer quality of sleep and higher levels of anxiety and depression compared with control subjects. In addition, TBI patients had an increase in slow-wave sleep, reduced REM sleep, and frequent awakenings at night. No significant correlations were observed between sleep problems and injury severity or duration since injury, indicating that sleep problems after TBI are a general indicator of brain injury and are likely not indicative of severity of injury.

Types of Sleep Disturbances After TBI

Few studies are available reviewing sleep disturbances after TBI. Sleep disturbance may occur as an isolated feature or as a symptom of other psychiatric, medical, or neurological syndromes. A sleep disorder may also be a preexisting

condition; they are found in approximately 30% of the adult population (Rosekind 1992).

The problem of disrupted sleep in the immediate postacute phase after recovery from moderate to severe brain injury, particularly on a rehabilitation unit, is not trivial. Confused patients who are awake at night are often physically restrained by nursing staff to prevent falls and unsafe behavior when fewer staff members are on duty. Restraints in a delirious head-injured patient frequently lead to more agitation, which in turn often requires pharmacological interventions such as benzodiazepines or even antipsychotics. Such medications have been shown, in both animal models and in human subjects, to be detrimental to the recovering nervous system after injury. Patients with excessive daytime somnolence have poor attention and carryover that may make rehabilitation efforts fall short and in some cases lead to transfer of the patient to a lower level of care such as a nursing home.

One of the few clinical studies looking at sleep disturbance during this period used actigraphy to monitor nighttime sleep efficiency in patients with brain injury. An actigraph is a small device worn around the wrist or ankle that quantifies and records movements and thus detects activity during wakefulness and sleep. In a study by Makley et al. (2009), the majority of subjects had markedly impaired sleep efficiency. This study also followed duration of posttraumatic amnesia (PTA) in addition to tracking sleep and found that patients' PTA cleared as their sleep efficiency improved as indicated by O-log score (see Figure 20–3).

Some researchers have suggested that patients with injury of recent onset have problems with initiating and maintaining sleep, whereas patients with chronic injuries experience excessive sleep (Cohen et al. 1992). The pathophysiological changes that occur in the brain during the recovery process and the severity of injury have been postulated to be some of the factors responsible for this temporally related change of sleep complaints (Cohen et al. 1992).

Verma et al. (2007) characterized sleep problems that occur in the chronic TBI period using both subjective and objective measures and found a full spectrum of sleep disturbances. Excessive daytime sleepiness was the presenting complaint in 50% of subjects secondary to sleep apnea, narcolepsy, and periodic leg movements. Insomnia was reported in 25% of subjects. Those who had problems initiating sleep were found to have high anxiety scores as assessed by the Hamilton Anxiety Scale, and those who had problems maintaining sleep had high depression scores as assessed by the Beck Depression Inventory. REM behavior disorder was the most common type of parasomnia, reported by 25% of the sample. Sleep onset REM periods were also found in 32% of subjects who had mean sleep onset latency of less than 5 minutes. Insomnia, hypersomnia, sleep-wake cycle abnormalities, and parasomnia are some of the common sleep disturbances and are described in the following sections.

Insomnia

Insomnia, defined as difficulty in initiating or maintaining sleep associated with daytime fatigue or impaired functioning, is common in patients with acute TBI. The prevalence in this patient group ranges from 36% (McLean et al. 1984) to approximately 70% (Keshavan et al. 1981). Using DSM-IV (American Psychiatric Association 1994) criteria for insomnia, Mann et al. (1997) noted a prevalence of 30% in postacute TBI patients.

Even though clinical evidence reveals that insomnia is a common complaint after TBI in individuals who are also depressed, there are few studies that have documented the relationship between the two. Fichtenberg et al. (2000) evaluated 91 consecutive patients with brain injury admitted to an outpatient rehabilitation center an average of 3 months after injury. They found a significant positive correlation between insomnia, depression as measured by the Beck Depression Inventory, and mild brain injury but no association between insomnia and age, gender, education, and time since the injury.

Frieboes et al. (1999) studied 13 men with severe brain injury (age range, 19–36 years) and 13 age-matched control subjects. They found abnormal sleep electroencephalographic parameters (reduction in stage 2 sleep in the first half of the night and an increase in REM during the second half of the night) and nocturnal hormone secretion (decrease in growth hormone secretion compared with control subjects) similar to that in patients with remitted depression. The significant relationship between depression and insomnia post-TBI is consistent with the increased frequency of insomnia in patients with primary depression (Breslau et al. 1996). Evaluation of patients with insomnia should therefore include careful screening for depression and/or other psychiatric disturbances (Fichtenberg et al. 2000).

There are conflicting results concerning the relationship between severity of brain injury and insomnia. Cohen et al. (1992) found increased prevalence of insomnia in patients with severe brain injury, whereas Clinchot et al. (1998) and Fichtenberg et al. (2000) noted a decreased prevalence in this population. The reason for the decreased prevalence after severe TBI could either be underreporting of sleep problems (Clinchot et al. 1998) or increased awareness of symptoms in the subjects with mild brain injury (Fichtenberg et al. 2000).

There have been inconsistent results when the relationship between pain and insomnia has been examined. Beetar et al. (1996) found a positive correlation between the two, whereas other researchers have not found a significant relationship between insomnia and pain (Fichtenberg et al. 2000). More studies are necessary to establish this association, although clinical evidence reveals that pain is closely associated with insomnia in the general population (Sutton et al. 2001).

Ouellet et al. (2006) examined 452 patients with all severities of TBI for insomnia. The mean duration since TBI was 7.8 years. Fifty percent of the sample reported insomnia symptoms but only 29% met the DSM-IV diagnostic criteria for insomnia syndrome. Mild severity of TBI and increased levels of fatigue, depression, and pain were commonly associated with insomnia.

Early diagnosis and treatment of insomnia are important because they may improve cognitive difficulties, psychosocial distress, and overall quality of life. The Pittsburgh Sleep Quality Index has been found to be a valid and reliable instrument for assessing insomnia among postacute patients after TBI (Fichtenberg et al. 2001). The scale

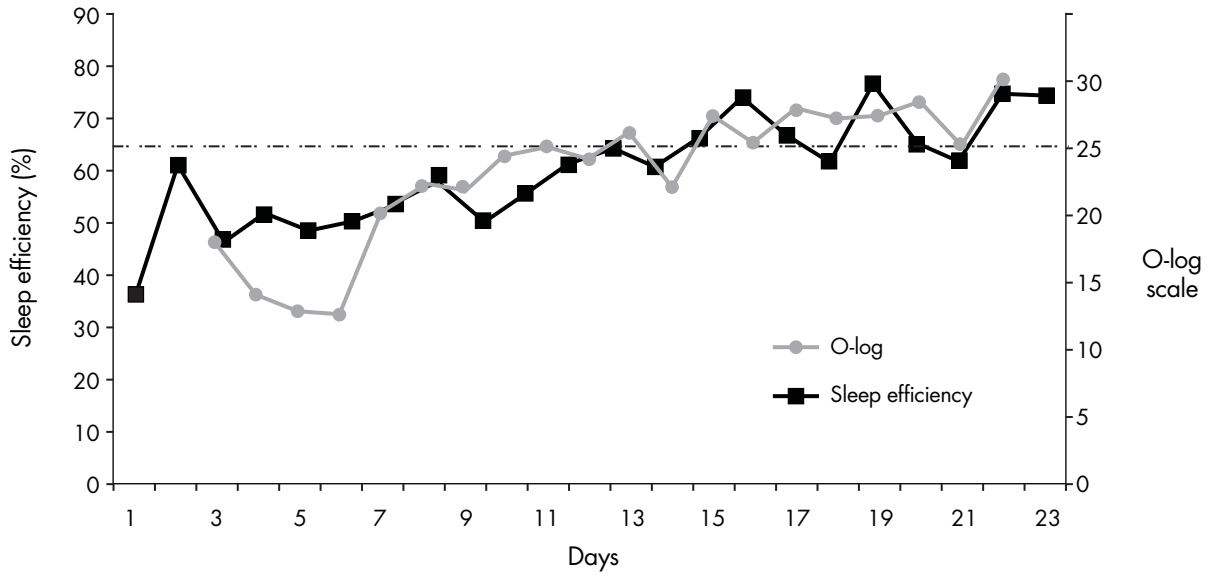


FIGURE 20–3. Sleep efficiency and O-log scores over time in patients with posttraumatic amnesia.

examines a wide range of sleep disturbances; provides information about basic sleep variables such as sleep efficiency, latency, and duration; and is brief and comprehensible, making it uniquely advantageous for brain-injured individuals.

Hypersomnia

Hypersomnia, defined as subjective complaints of excessive daytime sleepiness and objective finding of a score less than 10 on the MSLT, has been reported in individuals after brain injury (Castriotta and Lai 2001; Masel et al. 2001). In a study of 184 patients referred to a sleep clinic approximately 15 months after brain trauma, 98% reported excessive daytime sleepiness (Guilleminault et al. 2000). Approximately 82% of the patients were found to have hypersomnia with an MSLT score of less than 10, and 32% were found to have sleep-disordered breathing problems. Prolonged coma of longer than 24 hours, neurosurgical intervention, pain, and skull fracture were commonly associated with hypersomnia. Eight of these patients were found to be "apathetic" (complained of sleepiness but were found to have normal MSLT scores) and were described as having "pseudohypersomnia" (Guilleminault et al. 2000).

In a study of 71 subjects with brain injury (traumatic and nontraumatic) referred to a rehabilitation facility, hypersomnia (defined as a mean sleep latency score of less than 10) was observed in 47% (Masel et al. 2001). Within this group, 17% had abnormal respiratory indices and periodic leg movements as detected by PSG. No differences were found between the hypersomnolent and the nonhypersomnolent group in Glasgow Coma Scale score, length of coma, time since brain injury, nature of injury, gender, or medications. No significant correlation was noticed between the results of the objective MSLT and self-reported sleep questionnaires such as the Epworth Sleepiness Scale and the Pittsburgh Sleep Quality Index, suggesting the inability of subjects with significant hypersomnia to perceive their hypersomnolence (Masel et al. 2001).

Baumann et al. (2007) noted subjective excessive daytime sleepiness (EDS; defined by the Epworth Sleepiness Scale≥10) in 28% of TBI subjects, objective EDS (defined by mean sleep latency<5 min on the MSLT) in 25% of subjects, and posttraumatic hypersomnia (increased sleep need of ≥2 hours per 24 hours compared with pre-TBI) in 22% of subjects.

Therefore, the individual who has had a TBI and complains of excessive daytime sleepiness should be evaluated for sleep apnea and narcolepsy. Sleep apnea is classified as obstructive (cessation of breathing with continued efforts to breathe caused by collapse of upper airway), central (cessation of breathing with no effort to breathe caused by abnormal respiratory drive), or mixed. Narcolepsy is a disorder of REM sleep with hypersomnia, sleep attacks, early onset REM, and the intrusion of REM sleep into wakefulness. A type of human leukocyte antigen (HLA) called HLA-DR2 is found in 90%–100% of patients with narcolepsy and only in 10%–35% of unaffected individuals. TBI can cause alterations of the respiratory control systems and cause or exacerbate obstructive sleep apnea (Chokroverty 1994). Similarly, other factors associated with TBI, such as injury to the upper airways, cervical cord lesions, sedative drugs (often given to patients for control of aggression), and weight gain (which often occurs in relatively immobile patients), are risk factors for the development of sleep apnea (Mahowald and Mahowald 1996).

Philip et al. (2008) have shown that a simple clinical evaluation known as the Maintenance of Wakefulness Test (MWT) can predict dangerous driving in patients who complain of excessive daytime sleepiness. The MWT evaluation involves video and sleep monitoring during four 40-minute trials. Subjects are instructed to sit still and remain awake for as long as possible. On comparing 38 patients with obstructive sleep apnea (OSA) to 14 healthy

control subjects, the authors found none of the controls slept during the MWT but about 60% of OSA patients were found to be sleepy or very sleepy. Similarly, very sleepy and sleepy patients had increased inappropriate line crossings compared to controls on the driving test. The findings may hold practical implications. This test can be be recommended in addition to PSG for patients complaining of EDS, especially if driving is a concern.

In a study of 10 adult subjects with a history of chronic mild to severe closed head injury and complaints of excessive sleepiness, all were found to have a sleep disorder (Castriotta and Lai 2001). Eight individuals were found to have obstructive sleep apnea. Upper airway resistance syndrome (hypersomnia secondary to sleep disturbance due to increased effort of breathing through a narrow airway without measurable apnea or hypopnea) was found in 1 subject, and narcolepsy was diagnosed in 2 subjects (Castriotta and Lai 2001). Sleep apnea has also been described in the postacute phase. In a prospective study of 28 patients (mean age 34 years) with mild to severe TBI within 3 months of injury, 47% were found to have sleep apnea during overnight sleep studies (Webster et al. 2001). No correlation was found between the occurrence of sleep apnea and TBI severity or other demographic variables. Sleep-related breathing episodes were also found to be primarily more central than obstructive, which is in contrast to those seen in the general population. This also suggests that trauma to the brain may be partly responsible for this phenomenon (Webster et al. 2001).

Narcolepsy has been reported after TBI. Good et al. (1989) reported on a patient with posttraumatic narcolepsy who had both subjective complaints of sleepiness and HLA typing that indicated a genetic predisposition to narcolepsy. Lankford et al. (1994) studied a small group of patients with mild to moderate TBI with persistent sleep complaints and diagnosed posttraumatic narcolepsy using formal sleep studies such as PSG and MSLT. We recommend that clinical diagnosis of narcolepsy should always be accompanied by formal sleep studies and HLA typing. However, even if a patient is confirmed to have the appropriate HLA haplotype, the question always exists whether TBI was the causative factor or a precipitating event.

Sleep-Wake Cycle Disturbances

Sleep-wake cycle disturbance, or circadian rhythm sleep disorder, is defined as inability to go to sleep or stay awake at a desired clock time. Both the duration and pattern of sleep are normal when patients with this disorder do fall asleep (Kryger et al. 2000). There are several varieties of sleep-wake cycle disturbances, including the delayed, advanced, and disorganized types. The pathogenesis remains unclear, although dysfunction of the suprachiasmatic nucleus has been postulated (Okawa et al. 1987). Other factors often associated with this disorder in the general population include shift work and travel through different time zones (Patten and Lauderdale 1992). There is little literature available on the prevalence of this disorder in the TBI population.

Schreiber et al. (1998) described circadian rhythm and sleep-wake cycle abnormalities in 15 patients evaluated after mild TBI using PSG recordings. None had a past history of neurological illness, psychiatric history, or sleep apnea syndrome. More than one-half were diagnosed with delayed-phase type and the rest were diagnosed with disorganized-type sleep-wake cycle disturbance.

Quinto et al. (2000) described the case of a 48-year-old man who presented with sleep-onset insomnia after a severe closed head injury. His complaints included difficulty in initiating sleep, being able to finally fall asleep around 3:00–5:00 a.m., and waking up around noon. His attempts to wake up earlier resulted in poor functioning. Before the injury, he was reportedly high functioning and denied problems with sleep. A diagnosis of delayed sleep phase syndrome was confirmed by sleep logs and actigraphy. Patten and Lauderdale (1992) also reported delayed sleep phase disorder in a 13-year-old boy after mild TBI.

Some studies, however, have not shown a pattern of circadian rhythm dysfunction in TBI patients (Steele et al. 2005). Nevertheless, hypocretin abnormalities have been shown acutely after TBI (Baumann et al. 2005) and in patients with excessive daytime sleepiness at 6 months postinjury (Baumann et al. 2007).

Complaints of sleep disturbance in TBI patients are common, and therefore awareness and diagnosis of this disorder are important. Some patients may respond to simple therapies such as adjusting the time of sleep (described in the later section Chronotherapy) or exposure to bright light (described in the section Phototherapy later in this chapter).

Parasomnias

Parasomnias are undesirable motor or behavioral events that occur during sleep that can result in physical injuries to the patient and mental agony to the caregivers (Mahowald and Mahowald 1996). Sleepwalking, sleep terrors, REM sleep behavior disorders, and nocturnal seizures are some of the varieties of parasomnias. Other than occasional case studies (Drake 1986), there is no literature available on the prevalence and clinical presentation of this condition after TBI.

Evaluation of Sleep Disturbances After TBI

Evaluation of a brain-injured individual with sleep disturbances should be complete and comprehensive (Table 20–3). It is important to determine if these symptoms are occurring in isolation or are secondary to other neuropsychiatric disturbances, such as mood disorder, anxiety disorder, substance abuse, chronic pain, or dizziness. Medical illnesses such as idiopathic sleep disorders, chronic viral illness, malignancies, and medication side effects should always be ruled out. The key elements include obtaining a detailed history from the patient and collateral information from family members with the patient's consent, reviewing old medical records, and performing medical, neurological, and psychiatric examinations.

If the sleep disturbance is not considered to be secondary to another clinical syndrome, sleep studies should be performed. These studies not only help in identifying the type of sleep disturbance but also may be helpful in differ-

TABLE 20–3. Evaluation of sleep disturbances in traumatic brain injury

Detailed history from patient and collateral informants
Key questions:
Level of physical and mental functioning pre- and postinjury
Sleep pattern and duration pre- and postinjury
Type and severity of brain injury
Various treatments received since injury
Alcohol and substance abuse history
Medical history, including chronic pain, dizziness
Current medications and dosages
Past psychiatric history
Duration and description of current problems
Neuropsychiatric evaluation
Physical, neurological, and mental status examination
Neuropsychological tests in subjects with cognitive deficits
Laboratory tests
Blood count, comprehensive metabolic panel, vitamin B_{12} and folate levels, thyroid function test, and erythrocyte sedimentation rate
Brain scans
Computed tomography and/or magnetic resonance imaging
Specific sleep studies
Polysomnography
Multiple Sleep Latency Test

entiating fatigue (normal sleep studies) from sleep disturbances. The most commonly used objective tests include PSG and MSLT (described in the section Multiple Sleep Latency Test, below), as well as actigraphy (described in the section Actigraphy later in this chapter). Detailed information on these tests can be found in comprehensive texts on sleep disorders (Kryger et al. 2000).

Polysomnography

PSG is the standard tool for measurement of sleep disturbances and includes assessment of breathing, respiratory muscle effort, muscle tone, REM sleep, and the four stages of NREM sleep (Castriotta and Lai 2001). Standard electrophysiological recording systems are used in polysomnography. PSG includes at least one channel of electroencephalography, electrocardiography, submental and anterior tibialis electromyography, and continuous monitoring of eye movements. If clinically indicated, multiple respiratory parameters are monitored to evaluate breathing problems during sleep, extensive electroencephalography is monitored for parasomnias, esophageal pH is monitored for gastroesophageal reflux, and penile tumescence is monitored for erectile functions. An all-night polysomnogram will help to accurately quantify sleep and its different stages. In addition, other abnormalities such as disruption of sleep architecture, motor activity, or any other abnormality associated with sleep and cardiopulmonary irregularities can also be determined (Mahowald and Mahowald 1996). PSG aids in the diagnosis of sleep disorders such as obstructive sleep apnea, central sleep apnea, upper airway resistance syndrome, nocturnal seizures, and periodic limb movements.

Multiple Sleep Latency Test

The MSLT is a well-validated measure of physiological sleep and provides objective measurement of daytime sleepiness. It is a useful tool to quantify daytime sleepiness and differentiate pathological sleep abnormalities from subjective complaints of sleepiness and fatigue (Mahowald and Mahowald 1996). It consists of four or five 20-minute naps at 2-hour intervals and quantifies sleepiness by measuring how quickly one falls asleep during the day and also identifies abnormal occurrence of REM during the nap. A mean sleep latency of 5 minutes or less indicates abnormality. The diagnosis of narcolepsy is based on an MSLT score of less than 5 minutes, with REM sleep during at least two of the naps.

Actigraphy

Actigraphs are small, wristwatch-size accelerometers that can be worn on a limb and can record data on patient movement continuously for up to 22 days. They can be purchased from companies specializing in sleep equipment (e.g., Respironics, www.actiwatch.respironics.com; Ambulatory Monitoring, www.ambulatory-monitoring.com; IM Systems, www.actiwatch.respironics.com).

This device differentiates between sleep and waking based on the amount of movement in the limb (Ancoli-Israel et al. 2003). Actigraph technology has been used for over 20 years in sleep research and has been correlated with PSG in patients with a variety of sleep disorders. It has also been successfully used in populations where PSG is difficult to use, such as dementia patients and children. Actigraph technology has also been used to study circadian rhythm disorders in TBI patients with apathy (Muller et al. 2006) and, in the study described earlier, patients in a rehabilitation hospital after moderate to severe TBI. Although PSG is the gold standard for objectively measuring sleep disorders, the elaborate monitoring equipment required makes this impractical in some cases, particularly in the acute phase of recovery from moderate to severe head injury, the hallmark of which is confusion and agitation. In this early stage, actigraphy can provide important information on circadian rhythms of patients and could potentially be used to objectively measure response of treatment interventions. In the chronic phase, actigraphy can be used to monitor sleep efficiency as well as general activity for an extended period of time.

Treatment of Sleep Disturbances After TBI

Establishing a diagnosis is crucial. Recognition and treatment of other coexisting psychiatric and medical disorders are important because they could be contributing to or exacerbating the sleep disturbance. Management includes

pharmacological interventions and an array of nonpharmacological measures, such as sleep hygiene techniques, phototherapy, chronotherapy, and psychotherapy.

Pharmacological Measures

Even though sleep disturbances are commonly seen in TBI patients, there are only a few drug trial studies available in the TBI literature. Medications are mentioned here based on our knowledge of treatment of primary psychiatric disorders and sleep disturbances in the general population (see Table 20–4).

Benzodiazepine Sedative-Hypnotics

It is known that benzodiazepines work by activation of the chloride channel on the γ-aminobutyric acid (GABA) receptor with subjective and objective evidence of improvement in sleep (Chokroverty 2000). However, GABA is the primary inhibitory neurotransmitter in the central nervous system, and administration of benzodiazepines and other GABAergic agents has been shown to impair neural recovery in animal models of brain injury (Simantov 1990). Similarly, studies in humans have shown poorer sensorimotor functioning in stroke patients who received benzodiazepines compared with those who did not (Goldstein and Davies 1990). Therefore, benzodiazepines should be used with caution in individuals with brain injury because they theoretically may impair neuronal recovery. Benzodiazepines commonly used as hypnotics include lorazepam (0.5–2.0 mg at bedtime), temazepam (7.5–30.0 mg at bedtime), and clonazepam (0.25–2.0 mg at bedtime). The main indication is for the treatment of transient insomnia or insomnia of short duration. Benzodiazepines ideally should not be used for more than a few days to a couple of weeks because of the risk of dependence, although that may not often be feasible in clinical practice.

Nonbenzodiazepine Sedative-Hypnotics

Zolpidem (5–10 mg at bedtime) and zaleplon (5–10 mg at bedtime) are two nonbenzodiazepines also used in the treatment of transient insomnia. They are structurally different from the benzodiazepines but act on the benzodiazepine receptor complex with more selectivity to the type 1 receptors that are involved in the mediation of sleep (Damgen and Luddens 1999). Because of nonbenzodiazepines' selectivity, they are less likely to produce cognitive side effects. They also have short half-lives and are less likely to cause daytime drowsiness. Common side effects include anxiety, nausea, and dysphoric reactions; rebound insomnia and anterograde amnesia have also been reported.

In a randomized placebo-controlled double-blind study comparing a 10-mg dose of zolpidem with a 10-mg dose of zaleplon given 5, 4, 3, and 2 hours before awakening in the morning to 36 healthy subjects, zaleplon was found to be free of hypnotic or sedative effects when administered as late as 2 hours before awakening (Danjou et al. 1999). Zaleplon was found to be indistinguishable from placebo in terms of subjective and objective assessment of memory and even adverse reactions. Zolpidem, in contrast, produced results different from that of placebo. Memory problems (immediate and delayed recall) were detected up to 5 hours after nocturnal administration. The differences between the two drugs are more likely to be due to their pharmacokinetic profiles than to their pharmacology (Danjou et al. 1999). Vermeeren et al. (2002), in their study of 30 healthy volunteers, demonstrated that 10–20 mg of zaleplon could be taken at bedtime or even later (up to 5 hours before driving) with no serious risk of impairment. No studies are currently available on the use of zaleplon or zolpidem in TBI subjects.

Modafinil

Modafinil has been found to be both safe and efficacious in the treatment of narcolepsy at a dosage of 200–400 mg/day. However, in patients with liver dysfunction, one-half of the recommended dose should be provided because there is a rare chance it can cause liver toxicity (Elovic 2000). Beusterien et al. (1999) performed a double-blind, placebo-controlled study and looked at quality-of-life issues in patients with narcolepsy. The treatment group reported improvement in energy level and in overall social functioning, increased productivity, and improved psychological well-being. Headache was the only common side effect in clinically therapeutic doses of 200–400 mg/day. However, in a double-blind, placebo-controlled crossover trial with TBI patients, modafinil did not separate from placebo (Jha et al. 2008). Although modafinil appears to be useful in the treatment of hypersomnia, further controlled studies need to be conducted to determine efficacy and side effects after brain injury in individuals with complicated and uncomplicated sleep disorders.

Melatonin

Melatonin is a hormone secreted by the pineal gland. It is a metabolite of serotonin. Darkness augments the production of melatonin, and light suppresses its secretion. It plays an important role in maintaining the body's biological rhythm and synchronizing the sleep-wake cycle with the environment. The suprachiasmatic nucleus, which mediates the circadian rhythm, has several melatonin receptors, suggesting the importance of melatonin in maintaining the body's internal clock (Reppet et al. 1988). Shekleton and colleagues (2010) showed that patients with TBI had significantly lower levels of evening melatonin compared to matched controls. Studies in the general population have shown that exogenous melatonin may be useful in improving duration and quality of sleep and altering the biological rhythm (Lewy et al. 1992).

Information on this drug is limited. Although some people report improvement in sleep while taking a dose of 1.5 mg, the actual therapeutic dose is unknown. Its manufacture is not regulated by government agencies. Because of its vascular constriction property, melatonin should be avoided in patients with atherosclerosis, heart disease, and stroke. Drowsiness is a common side effect of melatonin.

Ramelteon is a melatonin agonist that acts on MT1 and MT2 receptors in the suprachiasmatic nucleus (Neubauer 2008). It has been approved by the U.S. Food and Drug Administration for insomnia characterized by difficulty in sleep onset. As such, it does not directly have sedating effects but rather acts on sleep regulatory mechanisms in the

TABLE 20–4. Management of sleep disturbances

Pharmacological measures
Benzodiazepine sedative-hypnotics
Nonbenzodiazepine sedative-hypnotics
Modafinil
Melatonin
Antidepressants
Antipsychotics
Herbal supplements
Nonpharmacological measures
Balanced diet and lifestyle
Sleep hygiene
Phototherapy
Chronotherapy
Psychotherapy
Always treat underlying medical and psychiatric disorders.

TABLE 20–5. Sleep hygiene

Keep a regular sleep schedule of going to bed and awakening around the same time every day, including holidays and weekends.
Avoid lengthy naps during the day.
If unable to fall asleep within 10 minutes of lying in bed, get up and stay awake.
Avoid coffee, sodas, alcohol, and strenuous exercise late in the day, as they may be too stimulating and delay sleep.
Avoid bright lights and loud noise in the bedroom, especially before bedtime.
Maintain a sleep log, noting duration and quality of sleep.

suprachiasmatic nucleus. Another advantage of this medication is that there is no abuse liability and restrictions in terms of length of use.

Antidepressants

The antidepressant trazodone has been used frequently clinically for insomnia. Although there are no trials specifically for the TBI population, it remains a popular choice. Trazodone has been shown to be helpful for antidepressant-induced insomnia (Nierenberg et al. 1994) and oftentimes is prescribed along with other antidepressants such as selective serotonin reuptake inhibitors. It can be useful for depressed patients with chronic insomnia (Thaxton and Myers 2002). However, there has been some concern about the effects of this medication on neuronal recovery in rodent models (Boyeson and Harmon 1994).

Antipsychotics

Antipsychotics are often used in the context of TBI and sleep disturbance, although there are limited studies. One study did find that risperidone helped with sleep disturbances (as well as psychosis) in a case study of a TBI patient (Schreiber et al. 1998). Quetiapine also has been used for sleep augmentation in various populations and may be helpful, in our experience, with patients with insomnia along with paranoia or agitation after TBI.

Herbal Supplements

Herbs and natural remedies have been widely used to treat numerous ailments, including sleep disturbances (Tariq 2004). A number of these natural remedies have been purported to be effective in the treatment of insomnia. However, there is a paucity of studies in this area (Sateia and Pigeon 2004).

Valerian is one of the traditional herbal sleep remedies that has been studied. Ziegler et al. (2002) conducted a randomized double-blind comparative clinical study in which insomnia patients (ages 18–65 years) took either 600 mg/day valerian extract LI 156 or 10 mg/day oxazepam for 6 weeks. The results found that valerian was as safe and efficacious as oxazepam. However, Glass et al. (2003) conducted a placebo-controlled, double-blind, crossover study comparing single doses of temazepam (15 mg and 30 mg), diphenhydramine (50 mg and 75 mg), and valerian (400 mg and 800 mg) in 14 healthy elderly volunteers (mean age, 71.6 years; range, 65–89 years). Valerian was comparable to placebo in measures of both sedation and psychomotor performance.

Nonpharmacological Measures

Diet and Lifestyle

Diet, rest, exercise, and sleep hygiene programs should be recommended to patients with sleep disturbance. Patients and their families should also be educated about their symptoms and the treatment options available (see Tables 20–4 and 20–5).

Phototherapy

Circadian rhythm disorders may respond to phototherapy. The actual mechanism of action is unknown, but exposure to bright light at strategic times of the sleep-wake cycle produces a shift of the underlying biological rhythm (Mahowald and Mahowald 1996). The timing of light exposure depends on the diagnosis, because morning exposure results in phase advance and evening exposure results in phase delay. Bright light of 10,000 lux is commonly used. The duration of exposure varies from half an hour to 2–3 hours. Common side effects of phototherapy include headache and eye strain. Light therapy should be avoided in photosensitive patients or those who have eye diseases.

Chronotherapy

Chronotherapy involves obtaining a new sleep schedule by advancing or delaying sleep onset by a few hours every day until the desired sleep onset time is obtained. This requires much determination on the part of the patient, not only to obtain the new sleep schedule but also to maintain it thereafter. Similarly, the setting is also important, as hospitalized patients with strict ward rules may not be able to implement chronotherapy effectively (Mahowald and Mahowald 1996). Systematic studies on the indications and effectiveness of chronotherapy are lacking.

Psychotherapy

There are few studies available on the effectiveness of behavioral therapies such as progressive deep muscle relaxation in the treatment of initial and middle insomnia in the general population (Vaughn 2001). In the only available study of cognitive-behavioral therapy (CBT) for the treatment of insomnia associated with TBI, Ouellet and Morin (2007) found it to be efficacious. Eleven patients who developed insomnia after all severities of TBI were administered CBT for 8 weeks. The different types of CBT included stimulus control, sleep restriction, cognitive restructuring, sleep hygiene education, and fatigue management (recognizing and revising dysfunctional beliefs about fatigue and rest). Compared with pretreatment state, there was an average reduction of 54% in the patients' total wake time and improvement in sleep efficiency from 77% to 90% at 3 months. The researchers also noted that improvement in sleep was associated with improvement in fatigue.

Pathophysiology of Fatigue

Much less is known about the pathophysiology of fatigue in TBI than sleep disturbances. Chandhuri and Behan (2000) proposed that central fatigue is due to failure in the integration of the limbic input and the motor functions affecting the striatal-thalamic-frontal cortical system. Studies in patients with multiple sclerosis (MS) suggest that fatigue is often due to "central abnormalities," even though peripheral mechanisms may have some role in the pathogenesis (Comi et al. 2001). A study by Attarian et al. (2004) demonstrated a significant correlation between fatigue in MS patients and sleep disturbances. This study suggested that circadian rhythm abnormalities and sleep disruptions play a role in the pathophysiology of fatigue. Other studies (Tartaglia et al. 2004) have found, using proton magnetic resonance spectroscopy imaging, that widespread cerebral axonal dysfunction is associated with fatigue in MS. Metabolic abnormalities have been found in the frontal cortex and basal ganglia by positron emission tomography in the brains of MS patients with fatigue compared with those patients without fatigue (Roecke et al. 1997). Certain cytokines such as tumor necrosis factor and interleukin-1 have also been implicated in the pathogenesis of fatigue in MS patients (Bertolone et al. 1993). Similar central and immune mechanisms may also be responsible for fatigue in TBI patients because trauma produces injury to multiple levels of the brain and causes secondary inflammatory reactions, with production of tumor necrosis factor and interleukins (Gennarelli and Graham 1998; see also Chapter 2 in this volume, Neuropathology).

Prevalence and Correlates of Fatigue After TBI

The prevalence of fatigue in individuals with TBI ranges from about 40% to 70% (van der Naalt et al. 1999). Kreutzer et al. (2001) studied 722 outpatients with an average of 2.5 years post–brain injury who were referred for comprehensive assessment at a regional Level I trauma center. Of the 42% of patients who met DSM-IV criteria for major depression, 46% complained of fatigue, the most commonly cited symptom of depression. Clinchot et al. (1998), in a study of 145 brain-injured subjects admitted to a rehabilitation facility, noted that 50% of subjects had difficulty sleeping, and 80% of subjects who reported sleep problems also reported fatigue, one of the symptoms included in postconcussion syndrome (see Chapter 15, Mild Brain Injury). Fatigue is the third most common symptom of postconcussive syndrome (Middelboe et al. 1992): 29%–47% of patients complain of fatigue within the first month after TBI (Keshavan et al. 1981), and fatigue continues to be reported frequently (22%–37% of patients) after 3 months (Keshavan et al. 1981; Levin et al. 1987). After 1 year postinjury, approximately 20% of patients still report fatigue (Middelboe et al. 1992). Although there is a trend toward improvement over time, a significant number of TBI survivors still experience fatigue after the first year of injury. In an outcome study of 67 brain-injured subjects interviewed 5 years after TBI, 37% continued to report fatigue (Hillier et al. 1997). Thus, studies indicate that 20%–50% of individuals with TBI complain of fatigue sometime during the recovery period. In a prospective sample of individuals with moderate to severe TBI, Bushnik et al. (2008a) examined the rate of fatigue in the first and second year after TBI and did not find a significant worsening of fatigue with time: 16%–32% reported fatigue at the end of year 1 and 21%–34% reported fatigue at the end of year 2. Poor sleep quality was the most common clinical variable associated with fatigue. Individuals who reported worsening fatigue in the second year were found to perform poorly in several domains, including cognition, motor symptoms, and overall functioning (Bushnik et al. 2008b).

In a study comparing 223 community-dwelling individuals with mild to severe TBI with 85 normal healthy control subjects, Cantor et al. (2008) found that fatigue was more common in TBI individuals and significantly higher in females. However, other studies have not found a relationship between post-TBI fatigue and gender (Borgaro et al. 2005). Even though depression, pain, and sleep were more common in those with fatigue, they accounted for only 23% of the variance in fatigue in the TBI group compared with 53% of the variance in the control group (Cantor et al. 2008). This suggests that post-TBI fatigue cannot be explained by medical or psychiatric comorbidities alone and may probably be related to the brain injury itself.

Evaluation of Fatigue After TBI

Fatigue is one of the common and earliest signs of brain injury, yet there is a paucity of literature on the clinical presentation and evaluation of fatigue in TBI patients. Lezak (1978) suggested that soon after TBI, patients tend to tire more easily and require more concentration and effort for their performance. Years after brain injury, however, fatigue gradually diminishes, and the person learns to cope and adjust to his or her new level of performance.

In our clinical experience, patients rarely complain of

"fatigue." They are more likely to describe their experiences in negativistic terms, such as "I don't feel like working," "I can't concentrate," "I feel drained," or "I have no energy." This may occur either as an isolated symptom or in association with other symptoms such as pain; changes in mood, sleep, appetite, and ability to enjoy activities; or other physical and neurological symptoms.

Because fatigue is a subjective experience, self-report scales are more appropriate for assessing the severity of this symptom, although they have obvious limitations. Both unidimensional and multidimensional fatigue scales are available (Comi et al. 2001). LaChapelle and Finlayson (1998) examined three self-report scales and performed an objective test to assess fatigue in 30 brain-injured subjects and 30 healthy control subjects. The scales were the Fatigue Impact Scale (FIS), which has 64 questions and three sections that assess the incidence and onset of fatigue, factors modulating the fatigue experience, and the impact of fatigue on cognitive, physical, and social functioning; the Visual Analogue Scale for Fatigue (VAS-F); and the Fatigue Severity Scale (FSS), a nine-item scale to assess the impact of fatigue on patients' functioning over the past month. A continuous thumb-pressing task was used as an objective measure of fatigue. Overall, individuals with brain injury were found to experience significant levels of fatigue. Significant group differences were found on the FIS and the FSS but not the VAS-F. The objective motor task found that patients with brain injury fatigued more easily than control subjects and correlated positively with the subjective rating scales.

The VAS-F, although easy to administer, has been criticized for not being able to distinguish between sleepiness and fatigue. The overall score of the FSS was able to differentiate between the group of brain-injured patients and a group of healthy control subjects, but not all of the nine questions were able to do so. Also, the FSS does not address the impact of fatigue on patients' social experiences. In the study by LaChapelle and Finlayson (1998), data from the section regarding the onset of fatigue were not used because brain injury has a sudden onset. There was no significant difference between the patient and control groups on the results from the section of the FIS that included fatigue-modulating factors. There was, however, a significant difference on the section of the FIS that focused on the impact of fatigue on social, cognitive, and physical functioning. This provides a broad indication of what aspects of the patient's life are most impaired by fatigue. The revised version of the FIS is shorter and is designed to evaluate the perceived impact of fatigue, factors that affect patients' perception of fatigue, and how fatigue affects the mental and general health of patients. The scale was first designed to study patients with MS (Fisk et al. 1994) but has also been found to be useful in studies with stroke patients (Ingles et al. 1999).

Other scales to assess fatigue include the Barrow Neurological Institute (BNI) Fatigue Scale (Borgaro et al. 2004) and the Cause of Fatigue (COF) Questionnaire (Ziino and Ponsford 2005). However, they have not been tested extensively and are limited in score to assess the various types of TBI fatigue. Both the BNI Fatigue Scale and the COF Questionnaire have been developed specifically for brain-injured patients. The Barroso Fatigue Scale (BFS) first developed for use in HIV patients has also been used in TBI (Barroso and Lynn 2002). It assesses the impact of fatigue in seven areas, including intensity, activities of daily living, socialization, mental functioning, general impact, relieving factors, and aggravating factors. Dijkers and Bushnik (2008) tested the suitability of the BFS for assessment of fatigue in TBI patients and did not recommend its use in TBI as a multidimensional scale, mainly secondary to its inability to quantify various aspects of fatigue.

Bushnik et al. (2007) examined the relationship between fatigue and endocrine factors in 64 subjects with TBI 1 year after injury. Abnormality in at least one domain of the pituitary axis was found in 90% of subjects, underscoring the importance of conducting endocrine evaluations for people with TBI complaining of fatigue.

The relationship between self-reports of fatigue and objective assessment of fatigue is controversial. While some studies have found a positive relationship between subjective fatigue and poor performance on cognitive tests that require sustained effort, such as tests of attention (Ziino and Ponsford 2006), others have not. Ashman et al. (2008) did not find a positive relationship between subjective fatigue and cognitive performance. Subjective fatigue was associated with reduced speed but not with poor test performance. However, in their study, TBI individuals performed significantly worse than non-TBI individuals on neuropsychological tests and did not improve with practice, suggesting that poor cognitive performance could be secondary to increased mental effort.

We propose using the FIS to assess fatigue in TBI because it is a multidimensional scale that determines the effects of fatigue on the physical, cognitive, and social domains of a patient's life (Figure 20–4).

Treatment of Fatigue After TBI

Treatment of fatigue includes pharmacological and nonpharmacological measures. Knowledge regarding pharmacotherapy in brain-injured patients is derived mainly from our experience in taking care of patients with primary psychiatric disorders and from case reports or small case series. Pharmacological interventions should target the observable symptom and any other coexisting psychiatric disorder, if present. If fatigue, sleep disturbance, or both are secondary to any other psychiatric or medical disorder, the underlying disease should be treated. Because individuals with TBI may be sensitive to medications, it is important to start at the lowest dose and gradually increase, if necessary. See Table 20–6 for a summary of interventions for fatigue.

Pharmacological Measures

There are only a few studies available on the treatment of fatigue specifically after traumatic brain injury. Psychostimulants, amantadine, and dopamine agonists have been used to treat impaired arousal, fatigue, inattention, and hypersomnia after brain injury. However, there are no studies available specifically for the treatment of fatigue in the TBI population.

Name/Study Number: _____ Date: _____

Below is a list of statements that describe how fatigue may cause problems in people's lives. Please read each statement carefully. Circle the number that indicates best how much of a problem fatigue has been for you these **past four (4) weeks**, including today. Please check one box for each statement and do not skip any statements.

Circle one number on each line	No Problem	Small Problem	Moderate Problem	Big Problem	Extreme Problem
1. *Because of my fatigue...* **I feel less alert.**	0	1	2	3	4
2. *Because of my fatigue...* **I feel that I am more isolated from social contact.**	0	1	2	3	4
3. *Because of my fatigue...* **I have to reduce my workload or responsibilities.**	0	1	2	3	4
4. *Because of my fatigue...* **I am more moody.**	0	1	2	3	4
5. *Because of my fatigue...* **I have difficulty paying attention for a long period of time.**	0	1	2	3	4
6. *Because of my fatigue...* **I feel like I cannot think clearly.**	0	1	2	3	4
7. *Because of my fatigue...* **I work less effectively. (this applies to work inside or outside the home).**	0	1	2	3	4
8. *Because of my fatigue...* **I have to rely more on others to help me or do things for me.**	0	1	2	3	4
9. *Because of my fatigue...* **I have difficulty planning activities ahead of time because my fatigue may interfere with them.**	0	1	2	3	4
10. *Because of my fatigue...* **I am more clumsy and uncoordinated.**	0	1	2	3	4
11. *Because of my fatigue...* **I find that I am more forgetful.**	0	1	2	3	4
12. *Because of my fatigue...* **I am more irritable and more easily angered.**	0	1	2	3	4
13. *Because of my fatigue...* **I have to be careful about pacing my physical activities.**	0	1	2	3	4
14. *Because of my fatigue...* **I am less motivated to do anything that requires physical effort.**	0	1	2	3	4
15. *Because of my fatigue...* **I am less motivated to engage in social activities.**	0	1	2	3	4
16. *Because of my fatigue...* **my ability to travel outside my home is limited.**	0	1	2	3	4
17. *Because of my fatigue...***I have trouble maintaining physical effort for long periods.**	0	1	2	3	4
18. *Because of my fatigue...* **I find it difficult to make decisions.**	0	1	2	3	4
19. *Because of my fatigue...* **I have few social contacts outside of my own home.**	0	1	2	3	4
20. *Because of my fatigue...* **Normal day-to-day events are stressful for me.**	0	1	2	3	4

FIGURE 20–4. Fatigue Impact Scale.

Psychostimulants

Psychostimulants exert their effect by augmenting the release of catecholamines into the synapses. Methylphenidate (10–60 mg/day) and dextroamphetamine (5–40 mg/day) are the commonly used stimulants. Psychostimulants are often taken twice a day, with the second dose taken approximately 6–8 hours before sleep to prevent initial insomnia. However, some patients may need to be dosed more frequently, depending on treatment response. Treatment is usually begun at the lowest dose and is gradually increased if necessary. Possible side effects include paranoia, dysphoria, agitation, dyskinesia, anorexia, and irritability. There is a potential for abuse; hence, patients taking these drugs should be closely monitored.

The efficacy of psychostimulants in the treatment of fatigue in patients with cancer, HIV infection, and multiple sclerosis has been studied. In a prospective, open-label pilot study, methylphenidate was used successfully to treat cancer fatigue in seven of nine patients (Sarhill et

Circle one number on each line	No Problem	Small Problem	Moderate Problem	Big Problem	Extreme Problem
21. *Because of my fatigue...* **I am less motivated to do anything that requires thinking.**	0	1	2	3	4
22. *Because of my fatigue...* **I avoid situations that are stressful for me.**	0	1	2	3	4
23. *Because of my fatigue...* **My muscles feel much weaker than they should.**	0	1	2	3	4
24. *Because of my fatigue...* **My physical discomfort is increased.**	0	1	2	3	4
25. *Because of my fatigue...* **I have difficulty dealing with anything new.**	0	1	2	3	4
26. *Because of my fatigue...* **I am less able to finish tasks that require thinking.**	0	1	2	3	4
27. *Because of my fatigue...* **I feel unable to meet the demands that people place on me.**	0	1	2	3	4
28. *Because of my fatigue...* **I feel less able to provide financial support for myself and my family.**	0	1	2	3	4
29. *Because of my fatigue...* **I engage in less sexual activity.**	0	1	2	3	4
30. *Because of my fatigue...* **I find it difficult to organize my thoughts when I am doing things at home or at work.**	0	1	2	3	4
31. *Because of my fatigue...* **I am less able to complete tasks that require physical effort.**	0	1	2	3	4
32. *Because of my fatigue...* **I worry about how I look to other people.**	0	1	2	3	4
33. *Because of my fatigue...* **I am less able to deal with emotional issues.**	0	1	2	3	4
34. *Because of my fatigue...* **I feel slowed down in my thinking.**	0	1	2	3	4
35. *Because of my fatigue...* **I find it hard to concentrate.**	0	1	2	3	4
36. *Because of my fatigue...* **I have difficulty participating fully in family activities.**	0	1	2	3	4
37. *Because of my fatigue...* **I have to limit my physical activities.**	0	1	2	3	4
38. *Because of my fatigue...* **I require more frequent or longer periods of rest.**	0	1	2	3	4
39. *Because of my fatigue...* **I am not able to provide as much emotional support to my family as I should.**	0	1	2	3	4
40. *Because of my fatigue...* **Minor difficulties seem like major difficulties.**	0	1	2	3	4

Total Score: _____

FIGURE 20–4. Fatigue Impact Scale. *(continued)*

Source. Modified from the Fatigue Impact Scale with permission of John D. Fisk. Copyright 1991 J.D. Fisk, P.G. Ritvo, and C.J. Archibald. The scale in any form should not be reused or reproduced without prior permission from Dr. Fisk.

al. 2001). In another randomized, double-blind, placebo-controlled trial of psychostimulants such as methylphenidate and pemoline for treatment of fatigue associated with HIV infection, both of the psychostimulants were found to be equally effective and superior to placebo in decreasing fatigue severity and improving quality of life (Breitbart et al. 2001). Studies of MS patients have not favored pemoline over placebo for the treatment of fatigue (Branas et al. 2000). However, one randomized, placebo-controlled crossover study did indicate that high-dose (1,300 mg) aspirin may help with fatigue in MS patients (Wingerchuk et al. 2005).

Dopaminergic Agonists

Carbidopa/levodopa (10/100 mg to 25/100 mg four times daily) and bromocriptine (2.5–10.0 mg/day) are both dopamine agonists that have been studied in small uncontrolled case studies for the treatment of mood, cognition, and behavior problems in TBI patients. Bruno et al. (1996),

TABLE 20–6. Management of fatigue

Pharmacological measures
Psychostimulants
Dopamine agonists
Amantadine
Modafanil
Nonpharmacological measures
Education
Balanced diet and lifestyle
Sleep hygiene
Regular exercise
Psychotherapy
Always treat underlying medical and psychiatric disorders.

in a study of five post-polio patients with history of moderate to severe fatigue, noted significant improvement in fatigue and cognitive tests of attention and information processing in three patients when treated with bromocriptine up to a maximum of 12.5 mg/day.

Amantadine

Amantadine was first used in the treatment of influenza in the 1960s and was later found to have antiparkinsonian effects. It enhances release of dopamine, inhibits reuptake, and increases dopamine activity at the postsynaptic receptors (Nickels et al. 1994). The usual doses are 100–400 mg/day. Confusion, hallucinations, pedal edema, and hypotension are common side effects. Krupp et al. (1995) conducted a double-blind, randomized parallel trial of amantadine, pemoline, and placebo in 93 patients with MS who complained of fatigue. Amantadine-treated patients improved significantly (both by verbal report and on the MS-specific Fatigue Severity Scale) compared with pemoline and placebo. The benefit was not due to changes in sleep, depression, or physical disability. Studies on the efficacy of amantadine for the treatment of fatigue in TBI patients are warranted.

Modafinil

Modafinil, as mentioned previously in the section on pharmacological treatments of sleep disorders, is in a different category from the stimulants, although there are similarities. Lin and coworkers (1996), in studies of cats given equivalent doses of modafinil, amphetamines, and methylphenidate, noted that although the latter two drugs brought about widespread increase in activation of the cerebral cortex and dopamine-rich areas such as the striatum and mediofrontal cortex, modafinil was associated with activity in the anterior hypothalamus, hippocampus, and amygdala. Modafinil's effect was supposed to be more selective on the pathways that regulate sleep. With regard to the neurotransmitter activity, modafinil has been shown to inhibit γ-aminobutyric acid levels and increase glutamate levels (Ferraro et al. 1999). It has been found to have little activity on the catecholamine system, cortisol, melatonin, and growth hormone (Elovic 2000). The addictive potential of modafinil is much less than that of the classic stimulants.

Teitelman (2001) conducted an open-label study in 10 patients with TBI who complained of excessive daytime sleepiness and in 2 patients with somnolence secondary to sedating psychiatric drugs. Modafinil was well tolerated at a dose of 100–400 mg given once a day. All patients reported improvement in daytime sleepiness. No adverse effects were encountered. However, in another study, modafinil was not found to be efficacious in the treatment of post-TBI fatigue or excessive daytime sleepiness. Jha et al. (2008) conducted a double-blind, placebo-controlled crossover trial of 53 patients with TBI randomly assigned to either modafinil 400 mg or placebo. No significant differences were noted between the modafinil and placebo groups on any of the fatigue outcome measures either during or at the end of the study period. Although modafinil was found to be safe and tolerable, there was a significantly increased rate of insomnia in the modafinil group. Controlled studies of modafinil for fatigue in MS and Parkinson's disease have also been disappointing.

The *R*-enantiomer of modafinil, known as armodafinil, has a longer half-life than modafinil and was approved by the FDA in 2007 for treatment of daytime sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder (Garnock-Jones et al. 2009). Although published studies of its use in TBI are limited at this time, its longer half-life may be a benefit in some patients.

Other Agents

In an experimental pilot study, Sakellaris et al. (2008) determined the neuroprotective effect of creatine in reducing rates of headache, dizziness, and fatigue in children with moderate-severe TBI soon after discharge from the hospital. Children in the creatine group ($n=19$) compared with the placebo group ($n=20$) had significantly lower rates of headache, dizziness, and fatigue in the 6-month follow-up period. However, this is only an experimental study and clearly requires replication with larger numbers and longer duration of follow-up.

Nonpharmacological Measures

Education

Patients and family members should be educated about the frequent occurrence of fatigue in TBI as an isolated problem, as secondary to other psychiatric disturbances, or both. Often, patients' self-esteem is enhanced when they are told that the "feeling of tiredness" is not a sign of laziness but a symptom of the brain injury.

Diet and Lifestyle

Good nutrition and a balance between regular exercise and adequate rest are important measures to combat fatigue. Patients should be encouraged to have three well-balanced meals a day. Regular exercise is important because it prevents deconditioning and promotes normalization of physical efficiency and performance, both physically and mentally. The exercise protocol should be individualized

because too much or too little exercise can be detrimental. Adequate rest is also important, and patients should be encouraged to practice good sleep hygiene measures (see Table 20–5). It is suggested that individuals who have difficulty with fatigue should be encouraged to perform most important activities in the morning or at a time when they feel best.

Psychotherapy

Cognitive-behavioral therapy has been found to be useful in patients with chronic fatigue syndrome (Prins et al. 2001). In a large randomized controlled multicenter trial, cognitive-behavioral therapy was found to be significantly more effective than control conditions for both fatigue improvement and functional performance. Studies of this approach are lacking for the treatment of fatigue after brain injury.

Conclusion

Sleep disturbances and fatigue are common in TBI patients. The etiopathology is unclear. They are probably due to a combination of factors: biological effects of the injury, psychosocial stressors, and environmental factors. In TBI patients, fatigue and sleep disturbance may occur as isolated entities or as symptoms of another medical or psychiatric syndrome. Establishing the correct diagnosis is important because treatment differs. However, diagnosis may not always be possible.

We have treated sleep disturbances and fatigue separately in this chapter for clarity. However, it is clear that the two can be related, although the relationship is both complex and controversial. Sleep disturbances and fatigue may be related to each other or occur independently. Subjective sleep logs, fatigue scales, and objective laboratory sleep tests such as the polysomnogram and the MSLT may help in differentiating the two conditions. Management of these disorders is multidimensional and includes both pharmacological and nonpharmacological interventions.

Despite the wide prevalence of fatigue and sleep disturbances, there is a marked paucity of objective data on the epidemiology, pathophysiology, clinical presentation, diagnosis, and treatment of these conditions. The TBI literature requires more research. Identification and early adequate treatment of these disorders will improve rehabilitation potential and enhance productivity personally, socially, and occupationally for TBI patients.

KEY CLINICAL POINTS

- Disrupted sleep is common after traumatic brain injury (TBI), although the sleep disturbance and its underlying pathophysiology seen in the acute phase of recovery may be entirely different from that seen by the clinician in the chronic phase.
- In the rehabilitation hospital, confused TBI patients with nighttime wakefulness are more likely to be pharmacologically restrained, which may slow their neurological recovery. TBI patients with excessive daytime somnolence may have poor participation in their rehabilitation program, which may necessitate transfer to a nursing home.
- Sleep hygiene should be instituted as the primary mode of treatment in all patients with sleep disturbance, prior to initiation of pharmacological measures.
- In patients who complain of excessive daytime sleepiness, obstructive sleep apnea, endocrine disorders, and narcolepsy should be investigated.
- Evaluation of sleep-wake cycle disturbance in TBI patients should be comprehensive to determine whether symptoms are occurring in isolation or secondary to other neuropsychiatric disturbance such as a mood disorder, an anxiety disorder, substance abuse, or chronic pain.
- Fatigue is a common complaint of patients with TBI. A thorough evaluation of endocrine function should be undertaken.

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CHAPTER 21

Headaches

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POSTTRAUMATIC HEADACHE (PTH) AFFECTS MILLIONS of people annually. It is the most common presenting complaint of the postconcussion syndrome (see Chapter 15, Mild Brain Injury). PTH is defined as a new headache beginning after head or neck (and, presumably, brain) injury. Headache associated with brain injury usually is short-lived but may persist for months to years after the event. Acute PTH generally resolves within weeks. Here the important goals involve diagnosis of any treatable cerebral and/or neck pathology, including cervical spine fracture and intracranial hemorrhage. When PTH persists beyond 3 months, it is termed chronic PTH, and pain management and psychosocial issues become paramount. In this chapter we summarize important features of PTH disorders, including diagnosis, treatment, and prognosis.

Prevalence

Estimates of PTH after injury to the brain or neck vary from 30% to 90% (Gfeller et al. 1994; Rimel et al. 1981). However, definitions are inconsistent, making comparisons of reports problematic. For example, although the International Headache Society (2004) criteria for PTH do not recognize late-onset headaches (headaches beginning more than 7 days after the injury or after regaining consciousness therefrom), such headaches are described. Brain injury may also occur as part of "whiplash" injuries. Just as headache is the most frequent symptom of postconcussion syndrome, 90% of patients evaluated medically after whiplash events complain of headaches (Machado et al. 1988). Precise numbers are elusive because most whiplash events are not reported. Given the common co-occurrence of brain injury and whiplash, an estimate of 4 million cases of PTH annually in the United States is conservative.

PTH seems to occur more frequently in milder brain injuries. Risk factors for developing chronic PTH include female sex, increasing age, and prior headache history. Premorbid psychological illness and mechanical factors at the time of injury are less clear although likely risk factors as well (Young et al. 2008).

Much has been made of the potential confounding effects of litigation and financial compensation on the prevalence of PTH. An often-quoted Lithuanian study (Obelieniene et al. 1998) found an extremely low incidence of PTH, which the authors attributed to the lack of insurance and litigious culture there. A Swedish study concluded the opposite (Berglund et al. 2001). One line of reasoning points out that PTH is relatively rare in athletes who suffer head and neck injuries. However, the velocities and decelerations suffered by athletes on the field are far lower than those sustained by people involved in motor vehicle accidents. Equally controversial are the opinions of experts over the years, but a reasonable position would seem to be that PTH as well as other postconcussional symptoms of varying degrees of persistence may result from even "mild" head and neck injuries.

Definitions

The International Headache Society (2004; IHS) criteria for posttraumatic headache diagnoses are outlined in Table 21–1. The IHS criteria define acute PTH as beginning within 7 days of the trauma and resolving within 3 months. Chronic PTH is defined as beginning within 7 days of the trauma (or after awakening therefrom) and persisting beyond 3 months. In that the majority of PTH resolves within 6 months, it has been proposed that persistence beyond 6 months is a more practical definition of chronic PTH (Packard and Ham 1993). The IHS criteria additionally specify two subtypes of acute PTH. The first subtype is acute PTH attributed to significant head trauma (having at least one of the following: loss of consciousness for more than 30 minutes; posttraumatic amnesia lasting longer than 48 hours; Glasgow Coma Scale score lower than 13) or imaging evidence of a traumatic brain lesion. The second subtype is acute PTH attributed to mild head

TABLE 21–1. International Headache Society criteria for posttraumatic headache

Acute posttraumatic headache

A. Headache, no typical characteristics known, fulfilling criteria C and D
B. Head trauma
C. Headache develops within 7 days after head trauma
D. One or other of the following:
   1. Headache resolves within 3 months after head trauma
   2. Headache persists but 3 months have not yet passed since head trauma

Chronic posttraumatic headache

A. Headache, no typical characteristics known, fulfilling criteria C and D
B. Head trauma
C. Headache develops within 7 days after head trauma or after regaining consciousness following head trauma
D. Headache persists for >3 months after head trauma

Acute postwhiplash headache

A. Headache, no typical characteristics known, fulfilling criteria C and D
B. History of whiplash (sudden and significant acceleration/deceleration movement of the neck) associated at the time with neck pain
C. Headache develops within 7 days after whiplash injury
D. One or other of the following:
   1. Headache resolves within 3 months after whiplash injury
   2. Headache persists but 3 months have not yet passed since whiplash injury

Chronic postwhiplash headache

A. Headache, no typical characteristics known, fulfilling criteria C and D
B. History of whiplash (sudden and significant acceleration/deceleration movement of the neck) associated at the time with neck pain
C. Headache develops within 7 days after whiplash injury
D. Headache persists for >3 months after whiplash injury

Source. Reprinted from International Headache Society, Headache Classification Subcommittee: "The International Classification of Headache Disorders, 2nd Edition." *Cephalalgia* 24 (suppl 1):9–160, 2004.

trauma. Chronic PTH is similarly divided into two subtypes based on severity of head injury. These subdivisions may not be clinically useful.

Whiplash injuries refers to flexion-extension and lateral motions of the neck related to acceleration-deceleration injuries. Because these movements also affect the head and brain, it is not surprising that whiplash injuries can lead to headaches, with both acute and chronic forms defined by the IHS (International Headache Society 2004; see Table 21–1). There is great overlap between postconcussion and postwhiplash headaches, as well as their accompanying symptoms. Apparently, many different types of head and neck trauma can lead to these PTHs, including seemingly benign activities such as roller coaster riding (McBeath and Nanda 2000).

Most cases of PTH clinically resemble tension-type headache (Table 21–2), although many have migrainous features (Table 21–3), such as nausea, unilaterality, pulsatility, and photosensitivity. Radanov et al. (2001) assessed headache characteristics in 112 patients with chronically persistent headache following acceleration-deceleration trauma. Using the International Headache Society (2004) criteria, they found that 37% had tension-type headache and 27% had migraine. (The remainder tended not to fit precisely into any primary headache category.)

Pathophysiological Changes

The mechanisms of PTH are not fully understood. The spinal trigeminal nucleus caudalis is thought to be a point of physiological and anatomical convergence relevant to the genesis of headache. It receives input from the distribution of the trigeminal nerve as well as upper cervical sensory roots. This arrangement explains how neck pain might be referred to the head and vice versa. But what specifically leads to changes in this or other key cranial nociceptive systems that lead to chronic forms of PTH is not clear.

It has been speculated that PTH may be due to "central sensitization." It is suggested that persistent peripheral input through the spinal trigeminal nucleus caudalis results in permanently altered function of second- and third-order neurons along the pain pathway from the spinal trigeminal nucleus through the thalamus (Post and Silberstein 1994). If correct, this concept might explain how persistent musculoskeletal injuries could generate chronic PTH.

During head injury or whiplash, shear forces affect the brain. Asynchronous movements occur between the contents of the posterior fossa (i.e., brain stem and cerebellum) and the cerebral hemispheres. Direct impact is unnecessary (Gennarelli 1993). Acceleration-deceleration

TABLE 21–2. International Headache Society criteria for episodic tension-type headache

A. At least 10 previous episodes occurring <15/month, fulfilling criteria B through D
B. Headache lasting from 30 minutes to 7 days
C. At least two of the following pain characteristics:
   1. Bilateral location
   2. Pressing/tightening (nonpulsating) quality
   3. Mild or moderate intensity
   4. Not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
   1. No nausea and vomiting (anorexia may occur)
   2. No more than one of photophobia or phonophobia

Source. Reprinted from International Headache Society, Headache Classification Subcommittee: "The International Classification of Headache Disorders, 2nd Edition." *Cephalalgia* 24 (suppl 1):9–160, 2004.

TABLE 21–3. International Headache Society criteria for migraine headache

A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache, at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not attributed to another disorder

Source. Reprinted from International Headache Society, Headache Classification Subcommittee: "The International Classification of Headache Disorders, 2nd Edition." *Cephalalgia* 24 (suppl 1):9–160, 2004.

and/or rotational forces can result in stretching, compression, and even anatomical disruption of axons (diffuse axonal injury). These pathological changes most often occur in the internal capsule, corpus callosum, fornices, dorsolateral midbrain, and pons (Blumbergs et al. 1989). Axons traversing the upper brain stem seem to be particularly at risk for axonal injury in this setting. The area encompassing the periaqueductal gray/dorsal raphe nucleus is in this region and has been implicated in headache (migraine) activity. Also in the midbrain/upper pons is the ascending reticular activating system. Damage to the ascending reticular activating system might explain the sleep-wake disturbances and attentional and concentration problems frequently described in postconcussion syndrome.

Severe brain injury may result in ischemic brain damage, but even with lesser degrees of insult posttraumatic vasospasm or abnormal cerebrovascular autoregulation may occur (Junger et al. 1997; Zubkov et al. 1999). Abnormalities demonstrated on cerebral blood flow studies and single-photon emission computed tomography (SPECT) have been reported to persist up to 3 years after the trauma (Taylor and Bell 1996). Similarly, results of positron emission tomography (PET) studies may be abnormal. However, PTH patients generally have not had such studies before their injuries, and SPECT and PET studies are also abnormal during headache.

Packard and Ham (1997) noted similarities in neurochemical changes between experimental brain injury and migraine. These include increased extracellular potassium; increased intracellular sodium, calcium, and chloride; increased release of excitatory amino acids (glutamate); decreased intracellular and total brain magnesium; and possible changes in nitric oxide.

There seems to be an inverse relation between the severity of the brain injury or whiplash and the severity of postconcussion syndrome. Perhaps dysfunction or damage to brain systems allows the genesis of headache, whereas more severe injury (destruction) does not (Packard and Ham 1997).

Assessment

The evaluation of acute PTH usually occurs in the emergency department setting. A thorough history and general physical and neurological examinations need to be performed expeditiously to rule out potentially life-threatening conditions (Table 21–4) (Ward et al. 2001). Cervical spine injury should be considered and evaluated and treated as part of the initial examination. A search for extracranial internal or skeletal injuries is essential, especially after motor vehicle accidents and falls. Patients requiring immediate treatment or in whom a period of observation is deemed prudent are hospitalized. Otherwise, patients may be sent home with supervision and instructions regarding under what circumstances to return for reevaluation. Arrangements for appropriate follow-up appointments should be made.

TABLE 21–4. Secondary ("threatening") causes of acute posttraumatic headache

Condition	Useful tests	Clues to diagnosis
Epidural hematoma	CT scan	Lucid interval followed by drowsiness, coma
Subdural hematoma	CT scan	Elderly age group
Intracerebral hematoma	CT scan	Focal neurological deficits
Cerebral contusions	CT scan	Gradual worsening, focal neurological signs
Cerebral venous sinus thrombosis	Magnetic resonance venography, angiography	Severe headache, papilledema, negative CT
Vascular dissection	Magnetic resonance imaging, angiography	Focal neurological deficits
Cervical spine fracture	X ray, CT scan	Neck spasm, myelopathy

Note. CT=computed tomography.

When patients are evaluated for chronic PTH, the strategy is somewhat different. The possible secondary causes of chronic PTH are different from those in the acute situation (Table 21–5). Trauma can trigger the development of headaches that share many features with primary headaches, but obvious structural etiologies should still be considered. One needs to ensure that nothing was overlooked during the initial evaluation and that a new problem has not declared itself, and to remember that some patients have more than one type of headache.

The patient should be examined, without preconceptions. It is not sufficient simply to rely on prior normal neuroimaging and other evaluations. An adequate assessment includes a neurological examination (with mental status examination) and attention to the head and neck. Any abnormality should prompt consideration of further investigation.

The cranial examination should include inspection for local residua of trauma. Posttraumatic temporomandibular joint syndrome may be a source of discomfort as well as a headache trigger. Typically, there are clicking and popping of the joint, pain with use, and restriction of jaw opening. One may appreciate associated masseter muscle spasm. The head should be inspected and palpated for the possible presence of painful scars and neuromas. The finding of otorrhea or rhinorrhea suggests a cerebrospinal fluid (CSF) leak, which could cause orthostatic headache (CSF hypotension) or predispose the patient to acquiring meningitis. A Tinel's sign over the occipital nerve may suggest occipital neuralgia. However, if there is a persistent side-locked headache with decreased sensation in the ipsilateral C2 or C3 dermatome, the possibility of an upper cervical root entrapment should be considered (Pikus and Phillips 1996).

An abnormality on the examination, or even a worrisome history (e.g., a worsening headache pattern), should prompt further testing. Otherwise, the patient's description of the head pain should allow a diagnosis to be assigned. Although PTH may mimic the primary headaches described by the IHS, posttraumatic neuralgia may also occur. For example, injury or fracture to the styloid process may cause Eagle's syndrome, a symptomatic form of glossopharyngeal neuralgia. Paroxysms of pain occur in the oropharynx or radiate toward the ear. The diagnosis requires a careful description of the head pain(s).

In our experience, the most likely causes of symptomatic (secondary) chronic PTH are chronic subdural hematoma, late-onset hydrocephalus, upper cervical root entrapment, unsuspected vascular dissection, and cerebral vein or venous sinus thrombosis. It is important to remember that increased intracranial pressure may occur (with or without hydrocephalus), and papilledema need not always be present (Mathew et al. 1996). Finally, it has been reported that PTH may be perpetuated by overuse of symptomatic medications, so-called analgesic rebound headache (Warner and Fenichel 1996). In this situation, symptomatic pain medications used daily or nearly daily actually lead to a worsening of the headache pattern. Getting the patient out of this pattern may lead to dramatic improvement.

If the history, the examination, or both suggest the need for further testing, test selection for chronic PTH is somewhat different from that in the emergency department. Although brain computed tomography scanning is often preferred in the acute setting because it is usually more readily available and detects acute hemorrhage well, magnetic resonance imaging, angiography, or venography may be needed to rule out subdural hematoma, vascular dissection, hydrocephalus, or cerebral venous sinus thrombosis. After mass lesion has been ruled out, lumbar puncture may be performed to rule out increased or decreased (by CSF leak) intracranial pressure. In a study of 20 patients with persistent headaches after rear-end collisions, radioisotope cisternography revealed evidence of CSF leakage in 10 of the patients, despite normal magnetic resonance imaging scans, and all responded to epidural blood patching (Takagi et al. 2007). Further tests, such as blood work, are selected in accordance with diagnostic possibilities suggested by the history and examination. If upper cervical root entrapment is suspected on clinical grounds, a deep computed tomography–guided root block may be diagnostic.

Electroencephalography (EEG) is frequently abnormal in patients with PTH; however, the findings are not specific. If seizures are a diagnostic possibility, then EEG is appropriate. Other tests have been reported to reveal abnormalities in PTH, including late evoked potentials, quantitative EEG (brain mapping), SPECT, and PET. Again, the findings are generally not specific for brain injury and are not directly useful for diagnosis or patient management. For example, the American Academy of Neurology (1996) labeled the use of SPECT in the evaluation of PTH "investigational." The P300 late event-related evoked potential has been reported by some authors to be delayed in

TABLE 21–5. Traumatic causes of persistent headaches

Cerebral vein thrombosis
Dysautonomic cephalalgia (following carotid sheath injury)
Hydrocephalus
Intracranial hypotension (cerebrospinal fluid leak)
Intracranial hypertension (pseudotumor cerebri)
Neuralgias (occipital, supraorbital)
Neuroma
Posttraumatic seizures
Styloid process fracture or inflammation (Eagle's syndrome)
Subdural hematoma
Temporomandibular joint injury
Upper cervical root entrapment
Whiplash or cervical spine injury

TABLE 21–6. Symptoms of postconcussion syndrome

Anosmia, changes in taste, change in appetite
Blurred vision, diplopia
Dizziness, vertigo, tinnitus, hearing loss
Dystonia, tremor
Fatigue
Headaches
Photosensitivity and phonosensitivity
Psychiatric symptoms
Anxiety
Depression
Irritability
Mania
Cognitive symptoms
Attentional problems
Difficulty concentrating
Memory dysfunction
Sleep disturbances

patients with mild head injury and could prove to be a useful marker for chronic PTH (Alberti et al. 2001). Although of interest in a research setting, most of these investigations should not be routinely performed.

Many patients with PTH have other symptoms of postconcussion syndrome (Table 21–6). If vertigo is a prominent symptom, ear, nose, and throat referral, including electronystagmography, may document dysfunction of the vestibular apparatus. If psychiatric or cognitive complaints, or both, are found, psychiatric consultation and/or neuropsychological testing may be invaluable. If sleep dysfunction is evident, evaluation by a sleep specialist and possibly polysomnography might be helpful.

Natural History, Prognosis, and Complications

Approximately 80% of patients with PTH improve by the end of the first year. Studies show that 1 year after mild TBI, 8%–35% of patients had persistent headache (Dencker and Lofving 1958; Rutherford et al. 1978). However, after the passage of another 3 years, 20%–24% still had headache. Therefore, Packard (1994) suggested that if reasonable therapeutic maneuvers have been attempted, PTH is likely to be permanent if it lasts longer than 12 months, or longer than 6 months with a lack of further improvement for 3 months. Of note is that chronic PTH seems to be less common in children than in adults, with one study finding an incidence of approximately 7%, most of which resolved within 2 years (Kirk et al. 2008).

Secondary gain is commonly suggested as a significant factor determining the resolution of PTH. However, the weight of evidence seems to suggest that financial settlement does not predict persistence or resolution of symptoms in most cases. Although malingering occasionally occurs, probably fewer than 10% of patients are thought to be manipulating the situation for financial reasons (Gutkelch 1980).

It is difficult to discuss complications of PTH without including symptoms of postconcussion syndrome (Table 21–6). In approximately one-fifth of these patients, the headaches fail to resolve. Beyond the head pain itself, the cognitive and psychiatric problems occurring as part of the clinical picture can lead to significant disability. These symptoms may actually become more prominent clinically as the headaches improve (Packard 1994).

Many of the complications of PTH are related to drug therapy. Overuse of narcotics can lead to dependence, and overuse of other analgesics has led to untold numbers of cases of renal failure, hepatic damage, and gastrointestinal bleeding.

Treatment

The treatment approach for the patient with PTH must be individualized. Although the type(s) of headache must be diagnosed, all of the patient's symptoms must be inventoried to select the appropriate treatments. Many associated symptoms may be quite disabling in their own right, such as vestibular symptoms, cognitive dysfunction, and mood changes, and failure to recognize them may impair compliance and delay recovery.

For headaches due to an obvious underlying etiology, treatment is directed against the underlying condition. This is particularly true for headache in the acute posttraumatic period. Many cases of chronic PTH mimic primary headache (e.g., migraine and tension-type headache), and in these cases treatment is directed at that type of headache. Options include nonpharmacological measures such as physical therapy, cognitive-behavioral therapy, and biofeedback. Pharmacological measures include acute medications for specific episodes and preventive drugs to attempt to lessen the frequency, duration, and severity of the headaches (Ward 2000).

An essential first step in the treatment of PTH is to educate the patient about the diagnosis and integrate his or her participation into the headache plan. The patient's condition should be clearly explained and the natural history

of likely substantial clinical improvement emphasized. Patient preferences regarding therapy should be considered to enhance compliance. Limits on acute medication intake should be set to avoid causing analgesic rebound and inadvertently prolonging the clinical course. The patient's progress should be monitored regularly and any new problems or setbacks dealt with promptly. The use of headache calendars or diaries is important. Patients must understand that optimal treatment is often a team effort, with various consultants involved for the management of specific problems as they are identified.

In general, nonpharmacological measures are nearly always indicated. These may enhance compliance, help identify problems, and reduce the need for medication. Lifestyle adjustments such as sleep regulation, avoidance of trigger activities, discontinuation of nicotine and alcohol, and regular appropriate exercise should be encouraged. Relaxation techniques, including thermal and myographic biofeedback, imagery, and hypnotherapy, have proved helpful for many patients. Cognitive-behavioral programs can also be highly effective but are clearly limited in patients with significant cognitive impairment. Individual (as well as family or group) psychotherapy can address associated posttraumatic mood and behavioral changes but can also provide effective pain-coping strategies. Massage, mobilization techniques, and myofascial release can be effective in management of PTH, particularly in patients in whom cervicogenic headache seems significant. Biofeedback may be very helpful for some patients; 80% of PTH patients in one study found it to be at least moderately helpful (Ham and Packard 1996). Transcutaneous electrical nerve stimulation and acupuncture may be helpful in some patients as well.

Acute symptomatic treatment of PTH pain is best treated with nonaddictive medication. Specific choices, including nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and others, are discussed below. Prophylactic pharmacological therapy for PTH should be considered when acute medications are ineffective, are required frequently, or are not well tolerated. Doses should be low initially and advanced as necessary and as tolerated. Adverse-effect profiles should be tailored to the individual and carefully explained. Multiple symptoms should be targeted with the minimum of medications (e.g., the choice of tricyclic antidepressants for patients with concomitant depression and pain). Daily preventive medications should be challenged for effectiveness and discontinued when possible. The United States Headache Consortium (www.aan.com) has published evidence-based treatment guidelines that address both nonpharmacological and pharmacological options. Although not specifically aimed at PTH, as mentioned earlier, treatment is based on the morphology of the headache, so in patients with typical migraine features, recommended migraine treatment seems reasonable, albeit somewhat speculative.

For tension-type headaches that occur intermittently, NSAIDs can be useful. These may include over-the-counter or prescription drugs. Acetaminophen is also useful. Muscle relaxants may be used if significant neck discomfort is present. Frequent headaches may require prophylaxis, and amitriptyline or other tricyclic antidepressants in relatively small doses given at bedtime may be of great use.

Acute therapy of migraine has been revolutionized by the advent of the triptans. These serotonergic agents have possible therapeutic mechanisms, including vascular constriction and suppression of neurogenic inflammation (Moskowitz 1992). Currently, almotriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, eletriptan, and frovatriptan are available and have similar efficacy. NSAIDs may be useful if given early in the attack and at high enough doses. A gastric motility–enhancing drug such as metoclopramide may improve absorption and increase efficacy. We have found hydroxyzine a useful adjunct for headache pain and associated nausea. Intranasal, subcutaneous, or intramuscular dihydroergotamine remains useful, although less convenient to use than the triptans. Selecting the correct route of drug administration is important. It is also important to consider nonoral routes for medication if there is prominent nausea, vomiting, or both. Injections, nasal sprays, and suppositories may be appropriate (Ward 1998). Troublesome attacks of tension-type headache in patients with migraine may respond to triptan drugs, whereas these headaches in nonmigraineurs usually do not (Lipton et al. 2000).

Numerous medications have been used for migraine prevention. Drug selection is best made with consideration of comorbid and coexistent medical conditions (see Table 21–7). Choices with strong support in the literature include propranolol, sodium valproate, amitriptyline and other tricyclic antidepressants, topiramate, and methysergide. Other beta-blockers, such as atenolol, metoprolol, and nadolol, and calcium channel blockers, such as verapamil and amlodipine, are commonly used. A useful strategy is to start with a low dose of medication, monitor progress with a headache calendar, and adjust the dose upward slowly every few weeks as tolerated and required. Occasionally patients may require more than one preventive medication (Ward 2000). Unfortunately, many prophylactic medications, particularly antidepressants and antiepileptics, may lead to sedation or alterations in cognition, symptoms that patients may already experience as a result of their injury. This must be monitored carefully by both the patient and family members.

Cluster headache is rarely triggered by trauma. The episodic form is characterized by bouts of headaches typically lasting weeks followed by remissions with no headaches for months or years. Individual attacks frequently respond to oxygen, subcutaneous sumatriptan, and transnasal butorphanol. When prevention is used, verapamil is usually the mainstay of therapy. Additional preventive drugs with efficacy include lithium, valproic acid, and methysergide (Ward 2000). An occipital nerve block performed ipsilateral to the pain may control the episodes until a remission occurs (Anthony 1987). Chronic cluster headache is the form that occurs essentially without a significant remission for longer than a year. Occasionally, inpatient therapy with repetitive dihydroergotamine is effective. Truly medically intractable cases may require neurosurgery.

Neuralgic syndromes can frequently co-occur with other headache types in patients with PTH. Local nerve infiltration with lidocaine or bupivacaine can be diagnostic as well as palliative in patients with occipital neuralgia, supraorbital neuralgia, and Eagle's syndrome. In these neuralgias, percussion over the irritated nerve often provokes painful

TABLE 21–7. Therapeutic opportunities and constraints in posttraumatic headache

Comorbid or coexistent conditions	Possibly useful	Relatively contraindicated
Bipolar disorder	Sodium valproate	Tricyclic antidepressants, MAOIs
Depression	Tricyclic antidepressants, MAOIs	Beta-blockers
Epilepsy	Valproate, gabapentin, topiramate	Tricyclic antidepressants
Hypertension	Beta-blockers, calcium channel blockers	
Mitral valve prolapse	Beta-blockers	
Raynaud's phenomenon	Calcium channel blockers	Beta-blockers

Note. MAOIs=monoamine oxidase inhibitors.

paresthesias (Tinel's sign) and/or reproduces the symptomatology. Trigger point injection, particularly in patients with cervicalgia, can also be effective in selected cases.

Refractory daily or frequent severe headaches may require hospitalization. Repetitive intravenous dihydroergotamine as described by Raskin (1986) can be dramatically effective. Other intravenous protocols include chlorpromazine and valproate (Mathew et al. 1999). Appropriate selection and performance of these regimens often require a high level of experience and knowledge. Referral of the patient to a knowledgeable headache expert or headache center may be the most efficient way to manage the patient's headache, especially if more straightforward and simpler measures have failed to provide sufficient benefit. Such referrals are usually appropriate for those patients with unusual conditions, unclear diagnoses, poor response to therapies, or failure to improve over time.

Conclusion

The evaluation and management of patients with posttraumatic headache must be individualized and comprehensive. Attention to the fundamentals of thorough diagnosis and familiarity with all of the various therapeutic modalities available enable the initiation of a treatment plan that should alleviate symptoms and minimize disability. Most patients spontaneously improve within 6 months. The remainder can still be helped by a symptom-based approach that is both competently applied and compassionate. Because PTH is often a component of postconcussion syndrome, it is essential for clinicians to be aware of behavioral, cognitive, sleep-related, and other typical postconcussion symptoms to achieve meaningful improvement for patients.

KEY CLINICAL POINTS

- Posttraumatic headache is the most common presenting symptom of the postconcussion syndrome.
- Pain arising from upper cervical and cranial trauma has a wide referral pattern leading to poor localization of pathology.
- Posttraumatic headaches simulate migraine or tension-type headaches in nearly two-thirds of cases.
- Nonpharmacological techniques and counseling are commonly indicated in posttraumatic headaches.
- Neuralgic pain may coexist with other types of posttraumatic head pain and may respond well to local anesthetic procedures.

Recommended Readings

International Headache Society, Headache Classification Subcommittee: The International Classification of Headache Disorders, 2nd Edition. Cephalalgia 24 (suppl 1):9–160, 2004

Olesen J, Goadsby PJ, Ramadan NM, et al (eds): The Headaches, 3rd Edition. Philadelphia, PA, Lippincott Williams & Wilkins, 2005 (see Chapters 105–107)

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CHAPTER 22

Dizziness, Imbalance, and Vestibular Dysfunction

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Anil K. Lalwani, M.D.

SINCE THE 1940S, DIZZINESS, VERTIGO, AND imbalance have been well documented and commonly reported sequelae of traumatic brain injury (TBI) (Maskell et al. 2006). While long recognized, the complex relationship between dizziness and TBI remains incompletely understood. "Dizziness" in itself is a nonspecific term that may encompass a wide variety of symptoms, including vertigo, imbalance, disequilibrium, light-headedness, altered coordination, and disorientation. Entangled and often inseparable, these symptoms represent a complex continuum of sequelae that cross vestibular, cognitive, and psychosocial domains. This broad spectrum of symptomatology gives some insight into the diversity of pathology present in the TBI patient. It is both the diversity and complexity of injuries that pose unique diagnostic and treatment challenges to the clinician.

After TBI, dizziness may result from a single injury or combination of injuries to the peripheral vestibular system, cranial nerves, brain, somatosensory or proprioceptive spinal tracts, or other extracranial source. Individually or as part of a "postconcussive syndrome," symptoms of dizziness can have a significant impact on the recovery and rehabilitation of patients with TBI (Yang et al. 2007). The multifactorial influence of these symptoms may be seen across a multitude of physical, cognitive, and psychosocial dimensions. Recent literature in a variety of disciplines has begun to elucidate the prevalence, natural history, and pathophysiology of dizziness after TBI, as well as address challenges in both diagnosis and treatment.

Incidence, Prevalence, and Natural History

In both mild and moderate TBI, complaints of dizziness, imbalance, and vertigo abound. Studies performed since 2000 indicate up to 80% of patients complain of dizziness after TBI (Basford et al. 2003; Chamelian and Feinstein 2004; Maskell et al. 2006). These patients also describe headache, fatigue, irritability, and difficulties with memory and concentration, often referred to as postconcussive symptoms (see Chapter 15, Mild Brain Injury) (Alexander 1995; Chamelian and Feinstein 2004; Gurr and Moffat 2001; Hoffer et al. 2004). Symptomatic complaints can be further complicated by physical injury to the somatosensory systems, such as the head, neck, or extremities, or by development or exacerbation of underlying medical disease. Comprehensive understanding and effective evaluation of patients with dizziness after TBI require a basic knowledge of vestibular anatomy and physiology.

Anatomy and Physiology of the Vestibular System

Overview

The vestibular system consists of both peripheral and central components that function to sense and control motion. Head position and movement in space are first detected by the vestibular end-organs in the periphery, where vestibular hair cells transform mechanical stimuli into neuronal signals. These signals are carried along the vestibulocochlear nerve (cranial nerve eight) to the brain stem. This information is then integrated and distributed to complex pathways in the central nervous system (CNS), ultimately resulting in vestibular reflexes that control posture, balance, and eye movements. Specifically, the vestibuloocular reflex (VOR) functions to stabilize eye gaze, and it is readily evaluated clinically through optokinetics and

nystagmus. In addition, peripheral vestibular signals interact with both cervical and lower spinal motor neurons to generate the vestibulocolic and vestibulospinal reflexes. These function to maintain and modulate posture, gait, and head position. The cerebellum also plays a critical role in coordination and the ability to adapt to vestibular injury. Finally, while their exact function remains a subject of ongoing investigation, both cortical and autonomic pathways are believed to play a role in various visceral responses to vertigo, such as nausea, as well as the conscious sense of motion.

The Peripheral Vestibular System

The peripheral vestibular system is composed of three semicircular canals—the horizontal (or lateral), the posterior (or inferior), and the anterior (or superior)—and two otolithic organs—the utricle and saccule (Figure 22–1). Housed within the temporal bone of each ear, these semicircular canals are orthogonal, or mutually perpendicular, and detect angular acceleration in three dimensions. Each canal is paired with the canal in the opposite ear that lies in a parallel plane (i.e., lateral–lateral, right anterior–left posterior, and left anterior–right posterior). Suspended within each fluid-filled bony framework is the membranous labyrinth or the vestibular end-organ. Perilymph, the fluid of bony labyrinth, has an electrolyte composition similar to extracellular fluid with a greater ratio of sodium to potassium. In contrast, the endolymphatic fluid, separate from the perilymph and enclosed within the membranous labyrinth, contains a greater concentration of potassium relative to sodium. Ultimately, the vestibular neuroepithelium, and more specifically the hair cells, use this chemical gradient to drive receptor potentials and convert mechanical stimuli (fluid movement) to electrical neural impulses.

Each semicircular canal contains an eccentric dilated or ampullated end, in which the vestibular sensory receptors, or hair cells, are located. These ampullae are separated from the rest of the canal by a perpendicular septum, the cristae ampularis, containing neuroepithelium, blood vessels, and connective tissue. Vestibular hair cells sit within the crista, and their cilia protrude into the endolymphic space topped by a gelatinous mass called the cupula. Fluid motion, generated by head rotation, generates forces across the cupula that bend the stereocilia of the hair cells. This leads to release of neurotransmitters and depolarization of the afferent nerve fibers that innervate the hair cells. Each hair cell has approximately 70 short stereocilia and one longer kinocilium that project into the gelatinous cupula. It is the laterally located kinocilium that is the primary determinant of the direction of polarization. Importantly, all hair cells in each ampulla have identical configuration, and therefore movement of the cupula causes simultaneous inhibition of excitation of the hair cells.

At rest, there is a high baseline firing rate for the vestibular nerve in each canal. Head movement, leading to deflection of the kinocilium, causes modulation of this basal discharge rate. Deflection of the kinocilium toward the stereocilia causes an increase in neurotransmitter release across the afferent vestibular nerve synapse, whereas movement away leads to the opposite: a decrease or inhibition of resting discharge rate. A variety of neurotransmitters exist throughout the peripheral and central vestibular system with glutamate and related amino acids dominating the afferent vestibular synapses (Highstein and Holstein 2006). In the lateral canals, the kinocilium is located near the utricle, thus utriculo- or ampullopedal flow causes an increase in firing, while flow in the opposite direction (ampullo- or utriculofugal) is inhibitory. Conversely, the opposite is true in the posterior and superior canals. Here the kinocilium is located near the canal side, and deflection of the cupula away from the utricle leads to an excitatory response, whereas deflection toward (utriculo- or ampullopedal) is inhibitory. As most head movement exists in multiple planes, typically all three canals are stimulated simultaneously. Using the bilateral planar-paired canals mentioned previously, complex integration of excitatory and inhibitory impulses lead to detection of angular head motion and position in space.

Unlike rotational movement, linear and gravitational acceleration are detected by the otolithic organs, the utricle and saccule. Located in the bony vestibule and filled with endolymph, they border, but are not continuous with, the semicircular canals. In each, the neuroepithelium is found in a specialized region called the macula, analogous to the cristae of the canals. Overlying the maculae is the otoconial membrane, a gel-like matrix similar to the cupula, into which the kino- and stereocilia of the hair cells protrude. Embedded in the otoconial membrane are deposits of calcium carbonate called otoliths. Gravitational and linear acceleration cause movement of these crystals, leading to deflection of the hair cell stereocilia. Trauma can dislodge these otoconia into the semicircular canals leading to the clinical entity of benign paroxysmal positional vertigo, or BPPV (described in detail later in the chapter). As in the ampullae of the semicircular canals, movement of the kinocilium with respect to the stereocilia allows modulation of neural firing. Orientation of hair cell polarization in the macula is complex and centered around an irregular line called the striola. As in the semicircular canals, the integration of inhibitory and excitatory signals in neural firing allows translation of gravitational or linear movement into mechanical stimuli and, ultimately, electrical impulses.

These compound neural signals then travel from the vestibular end-organs to the CNS via the vestibular portion of cranial nerve eight, the vestibulocochlear nerve. Specifically, impulses from the neuroepithelium of the lateral and anterior canals, as well as the macula of the utricle and part of the saccule, are carried along the superior vestibular nerve, while information from posterior canal and remaining saccular macula are transmitted by the inferior vestibular nerve.

Central Vestibular Projections

Inferior and superior nerve fibers transmit afferent vestibular input from the periphery to four vestibular nuclei in the pontomedullary junction. It is here in the brain stem that the initial integration and distribution sensory afferent input occurs. While a description of the intricate and complex signaling that occurs here is beyond the scope of

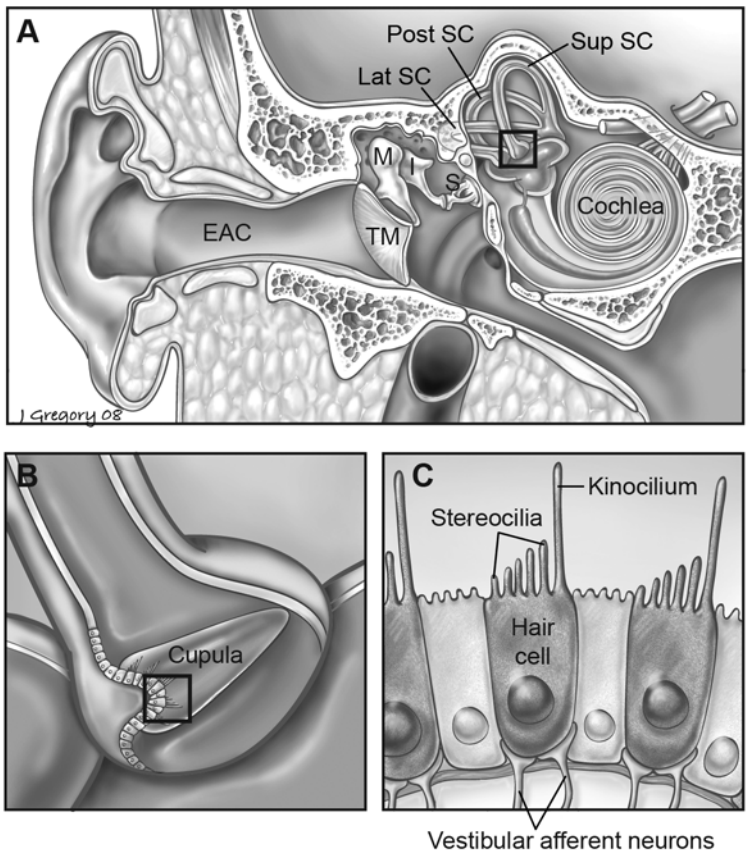


FIGURE 22–1. Anatomy and physiology of the vestibular system.

A. The peripheral auditory and vestibular systems are composed of the external ear, including the auricle and external auditory canal (EAC); the middle ear, including the tympanic membrane (TM) and three ossicles, specifically the malleus (M), incus (I), and stapes (S); and the inner ear, composed of the cochlea and the three semicircular canals (SC) of the vestibular apparatus, specifically the lateral (Lat SC), superior (Sup SC), and posterior (Post SC).

B. Focused view of the dilated, or ampullated, end of a semicircular canal showing the cristae ampullaris, neuroepithelium (including the hair cells), and the cupula. Fluid motion, generated by head rotation, generates forces across the cupula that bend the stereocilia of the hair cells, resulting in release of neurotransmitter into the vestibular synapse.

C. Focused view of vestibular hair cells within the ampulla. Each hair cell has approximately 70 short stereocilia and one longer kinocilium that project into the gelatinous cupula. It is the laterally located kinocilium that is the primary determinant of the direction of polarization. Each hair cell is innervated by vestibular afferent neurons that allow transmission of positional information to the brain.

this chapter, two important pathways are crucial to a general understanding of the central vestibular system. First, knowledge of the VOR is crucial for clinical assessment and can assist with the localization of vestibular pathology. Connections between the vestibular nuclei and oculomotor nuclei allow maintenance of clear vision during head movement (see Figure 22–2). Similarly, in pathological states such as trauma, nystagmus can yield information on the location of the vestibulopathy. In the brain stem, projections from vestibular nuclei synapse on the oculomotor, trochlear, and abducens nuclei (cranial nerves three, four, and six, respectively). As described previously, rotational head movement yields both excitatory and inhibitory peripheral signals depending on the direction of motion. Simply put, these signals ultimately translate to synchronized contraction and relaxation of the extraocular muscles such that head motion and eye movement are coordinated.

A basic example using the horizontal canal illustrates these pathways. To maintain an image on the retina during head rotation to the right, extraocular muscles must compensate and generate conjugate leftward gaze. This is accomplished by activation of left lateral and right medial rectus muscles and inhibition of left medial and right lateral recti. The neural circuitry included in this reflex starts with the vestibular nuclei and ultimately involves both the abducens and the oculomotor nuclei bilaterally. Integration of these signals takes place directly in the medial longitudinal fasciculus and indirectly in the pontine reticular formation. The VOR is also responsible for other eye movements such as smooth pursuit and saccades. Smooth pursuit is responsible for maintaining a moving target on the fovea, while saccadic movements allow quick redirection of gaze from one target to another. Clinically, aberrations in the VOR can be exemplified by nystagmus, difficulty with smooth pursuit or over- or undershooting in

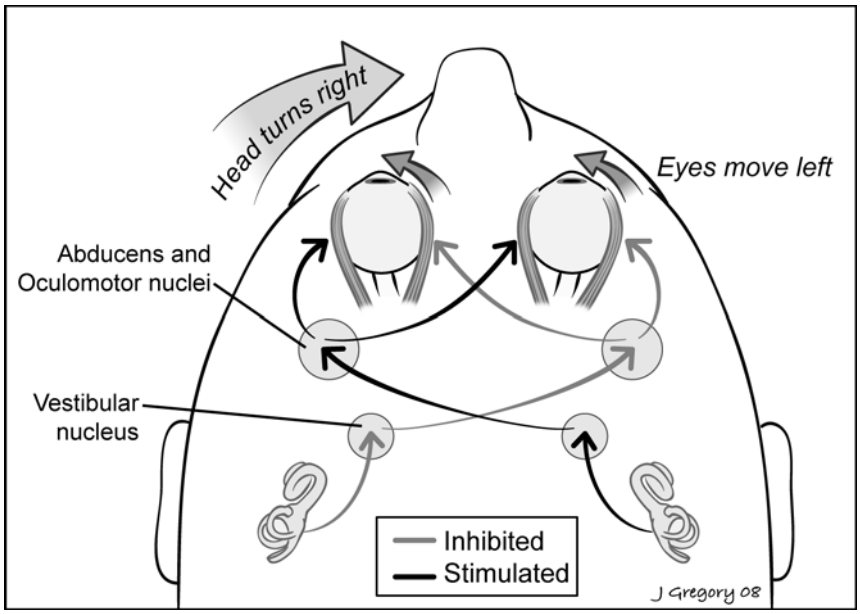


FIGURE 22–2. Vestibular ocular reflex.

Connections among the vestibular, abducens, and oculomotor nuclei allow maintenance of vision during head movement. Rotational head movement yields both excitatory and inhibitory peripheral signals depending on the direction of motion. In this example, maintenance of an image on the retina during head rotation to the right requires conjugate leftward gaze. This is accomplished by stimulation of the right lateral semicircular canal and subsequent activation of the vestibular, abducens, and oculomotor nuclei. Ultimately, this neural circuitry culminates in activation of the left lateral and right medial rectus muscles and inhibition of left medial and right lateral recti. Integration of these signals takes place directly in the medial longitudinal fasciculus and indirectly in the pontine reticular formation (not shown).

saccades. Comprehensive neurologic exam as well as optokinetic testing can assist with localization of pathology or injury. We discuss this further in an upcoming section.

Other notable pathways include the vestibulocolic and vestibulospinal. These reflexes result from multifaceted interactions between peripheral afferent stimuli from the semicircular canals and otolithic organs and the somatic musculature of the neck and spinal cord. These complex pathways allow maintenance of gait, posture, and balance.

Finally, vestibular afferent fibers provide information directly, from the superior vestibular nuclei, and indirectly, to the cerebellum. In addition to posture and balance, the cerebellum is critical to adaptation after vestibular injury.

Comprehensive History and Physical Examination

Vestibular Vocabulary

After vestibular injury, patients with TBI may describe a variety of symptoms, from vertigo to disequilibrium to light-headedness, in an attempt to characterize their experience (Maskell et al. 2006). When interviewing a dizzy patient, the examiner needs to take a detailed, highly specific history because each term may be a clue to the location of the underlying injury.

Vertigo, from the Latin *vertere* meaning "to spin," refers to a hallucination of rotary movement, either of the patient's body or of the environment (Lambert and Canalis 2000). Typically, this points to a peripheral injury or pathology related to the semicircular canals. A sensation of falling forward or linear motion can suggest problems with the otolithic organs. Oscillopsia, or the illusion that stationary objects are moving during head motion, is indicative of a bilateral peripheral vestibular injury (Lambert and Canalis 2000). The meaning of the term *light-headedness* is extremely variable; it can represent vestibular, cerebral, cardiovascular, or metabolic pathology. More specifically, it is often representative of presyncopal sensations and can point to general medical conditions, such as anemia or hypoglycemia, as well as hemodynamic instability, such as orthostatic hypotension or dehydration (Lambert and Canalis 2000; Seemungal and Bronstein 2008). Unsteadiness, imbalance, lack of coordination, and disequilibrium are terms used to describe inability to confidently navigate in one's environment. This vocabulary is, again, nonspecific and can suggest cerebellar, cortical, pyramidal, or spinal tract etiology. In general, it is unusual for a peripheral injury to cause unsteadiness without vertigo. Patients with TBI may experience some or all of these symptoms during the postinjury period.

History

A comprehensive history is crucial to diagnosis of vestibular injury because it may provide the only clues to specific

peripheral or central pathology. Depending on clinical presentation and severity of TBI, history taking may occur immediately after injury or many months later in an outpatient setting. If appropriate, patients should be encouraged to describe the first "spell" or a typical experience in detail. Questions about the time of day, activity at the time of onset, or associated symptoms can spur patients to remember additional critical details they may otherwise not offer. Table 22–1 highlights specific questions to guide vestibular history taking, including a thorough discussion of past medical and surgical histories and a complete list of current medications. As apparent in earlier discussion, details related to general medical conditions, including cardiovascular, orthopedic, ophthalmologic, cerebral, metabolic, or even psychological, can have widespread implications in both the diagnosis and management of patients with TBI.

Physical Examination

As with the history, the mechanism of injury in TBI demands a comprehensive and detailed physical examination of all systems. With respect to the vestibular and neurological exam, the following should be included: opticokinetic exam (including nystagmus, head-shake, head-thrust, saccades, and smooth pursuit), cranial nerve exam, cerebellar testing, gait evaluation, Fukuda and Romberg testing, general motor and sensory evaluation, pneumatic otoscopic and tuning-fork exam, and Dix-Hallpike or positional testing.

The opticokinetic exam, specifically nystagmus, can provide clues to the function of the VOR as described earlier and thus assist in localization of the vestibular injury. To begin, assess visual acuity, gaze, and extraocular motion in all directions, noting both symmetry and presence of nystagmus. As the spectrum of injuries following TBI may include direct damage to eye, surrounding musculature, or visual-cortical anatomy, deficits should be noted prior to the vestibular exam because it may complicate interpretation of results. Opthalmologic referral is warranted if primary ocular abnormalities are suspected.

Nystagmus is an involuntary, repetitive oscillation of the eyes that can be either spontaneous or evoked. Characteristics of peripheral nystagmus include fixed horizontal or rotary direction, diminution or suppression with visual fixation, fatigability, and latency when evoked. In contrast, nystagmus of central origin can occur in any direction and can be direction changing; it has immediate onset when evoked and does not decrease with visual fixation or fatigue.

Complete clinical or bedside opticokinetic exam also includes evaluation of smooth pursuit, saccades, and head-shake and head-thrust tests. Although not required, having the patient wear Frenzel glasses will enhance detection of vestibular pathology by both prohibiting visual fixation and magnifying abnormal eye movements. To test smooth pursuit, the examiner asks patients to maintain ocular fixation on a moving object, such as the examiner's finger, as it moves across their visual field. Rapid gaze change from one object to another will detect integrity of saccadic movements, and abnormalities in ocular symmetry, velocity, and accuracy should be noted. Although best detected and quantified on video- or electronystagmography (described later in this chapter), abnormalities found on bedside or clinical exam can suggest a central cause for the vestibular dysfunction.

TABLE 22–1. Vestibular history taking: questions to assist in diagnosis

Ask the patient to describe the first episode of dizziness in detail: What activity was he/she doing at the time of symptom onset? Did the patient experience vertigo or a sensation of spinning or is it better characterized as light-headedness or imbalance? What time of day did the first event occur? How long did the first episode last? Were there any associated symptoms, such as headache, facial nerve injury, tinnitus, or hearing loss?
What is the temporal relationship between the first episode of dizziness and the traumatic brain injury? Was it immediately after injury or delayed?
Have the symptoms recurred after the first episode? With what frequency? How long does each episode last—seconds, minutes, hours, or days? Are they intermittent or continuous?
Are the symptoms related to head or body position?
Do other symptoms accompany the dizziness, such as headache, visual changes, or nausea? Are there any related otologic symptoms, such as hearing loss, tinnitus, or otalgia?
Are there any precipitating or exacerbating factors?
All interviews should include a thorough past medical and surgical history, complete list of current medications, and detailed review of systems with attention to cardiovascular, orthopedic, ophthalmologic, cerebral, metabolic and psychiatric systems.

In the head-shake test, the examiner gently but rapidly turns the patient's head left to right (approximately 45 degrees in each direction) for 10–20 seconds. After cessation of movement, the eyes are observed for roughly 1 minute for the presence of nystagmus. Greater than five consecutive beats is considered significant and indicative of vestibular pathology.

Unlike the head-shake test, the head-thrust test requires the patient to fixate on a central target. The physician then applies a small amplitude but high acceleration thrust in one direction and observes the patient's eye movements for presence of a corrective saccade. Individuals with normal vestibular function will maintain gaze fixation on the target despite the head thrust; those with abnormal vestibular function, however, will briefly gaze in the direction of head movement and then rapidly return gaze to the target, thus producing a corrective saccade.

Additional components of the bedside vestibular exam include the Fukuda, or stepping test of Unterberger, and the Romberg test. In this test, first described by Unterberger in 1938, patients march in place with their arms outstretched and eyes closed, and directional preponderance or rotation is observed. Standardized by Fukuda (1959) to include 50 steps at a pace of 110 steps/minute, rotation about the central axis of 30 degrees or greater is suggestive of vestibular malfunction.

Lastly, the two-component Romberg test assesses sensorimotor integration and proprioception. After standing with feet together and eyes open, the patient is asked to close his or her eyes for 1 minute. Significant motion with eyes closed, including swaying or near falling, is considered a "positive Romberg." Maintenance of balance in this test requires successful cerebellar integration and intact

function of at least two of the following three complex systems: proprioception, primarily from the dorsal column of the spinal cord; vestibular function; and vision. Those with cerebellar dysfunction are unable to maintain balance even with visual input (eyes open); however, those with vestibular or proprioceptive abnormalities demonstrate imbalance when visual input is eliminated. Thus, a positive Romberg can suggest either a vestibular or a proprioceptive abnormality.

Diagnostic Testing

In the acute or emergent setting, specific vestibular testing often does not play a role in the evaluation of TBI, even when mild. Glasgow Coma Scale scores, duration of loss of consciousness, and posttraumatic amnesia frequently dictate the nature and timing of neurological studies required for diagnosis and immediate management. Typically, radiological imaging, including both computed tomography (CT) and magnetic resonance imaging (MRI), play an important role in the workup and diagnosis of patients with TBI. Abnormalities on imaging can often point to central causes of posttraumatic vertigo, including injuries to the cortex, brain stem, or cerebellum. With respect to the peripheral vestibular system, imaging is characteristically used to evaluate or rule out skull base or temporal bone fractures. These injuries, covered in more detail later, can lead to disruption of bony labyrinth with ensuing vertigo of clear peripheral etiology. Other causes of peripheral vestibular dysfunction are not traditionally discovered on imaging. In fact, outside of posttraumatic vertigo, imaging for symptoms of dizziness is generally not indicated.

Other than radiological imaging, additional testing of the vestibular periphery, such as audiometry, electro- or videonystagmography (ENG or VNG), thermal calorics, rotational chair testing, or dynamic posturography, may be appropriate in the outpatient setting. A list of the diagnostic tests and their application to TBI is presented in Table 22–2.

To start, all patients with a TBI should undergo a complete audiometric analysis both for evaluation and documentation of hearing loss. This should include a bilateral audiometry (including both air and bone conduction and masking, where appropriate), speech testing (including speech reception thresholds and word recognition testing), and acoustic immittance testing (including tympanometry, acoustic reflexes, and acoustic reflex decay). With these components, it is possible to 1) determine the type of hearing loss, such as sensorineural, conductive, or mixed; 2) gain insight into the patient's ability to understand and communicate; and 3) support or suggest an etiology and, possibly, a prognosis for any hearing loss that may be present.

ENG/VNG is a method of testing or investigating the VOR by producing a quantitative, analyzable record of eye movement, either electrically or with video recording. Evaluation includes information on the duration and directional preponderance of nystagmus, number of beats per minute, velocity of the slow phase, as well as optokinetic testing (covered earlier in this chapter) such as smooth pursuit and saccades (Barin and Duyrrant 2000; Ostrowski and Bojrab 2005). Asymmetry in optokinetic tracking supports a central injury. In addition, ENG/VNG may also include positional testing, including the Dix-Hallpike maneuver, which can point to a peripheral injury, specifically BPPV (Motin et al. 2005).

Bithermal calorics involve stimulation of peripheral vestibular system, or more specifically, the lateral semicircular canal, using temperature gradients. By generating endolymphic flow, an intact canal will produce characteristic nystagmus in response to cold and warm temperatures. When abnormal, this test suggests at least a partial peripheral dysfunction (Barin and Duyrrant 2000; Ostrowski and Bojrab 2005). As this test is conducted independently in each ear, it can provide useful information of laterality of a peripheral lesion. In contrast, rotational chair testing is used to investigate and diagnose bilateral vestibulopathy. As with caloric stimulation and ENG, rotary testing provides information on optokinetics as well as the VOR.

Lastly, dynamic posturography is a comprehensive evaluation of balance function and can be helpful in both diagnosis and treatment of vestibular dysfunction after TBI (Andersson et al. 1998; Basford et al. 2003; Geurts et al. 1996). Using six sensory conditions, this evaluation is an attempt to isolate the contributions of the visual, proprioceptive, and somatic motor systems to maintenance of balance (Geurts et al. 1996; Longridge and Mallinson 2005).

Posttraumatic Vestibular Dysfunction: Peripheral

Temporal Bone Fracture

Fracture of the bony labyrinth or vestibule is a well-documented cause of posttraumatic vertigo. Traditionally described as either longitudinal or transverse, these injuries have been more recently reclassified as either involving or sparing the otic capsule (Johnson et al. 2008). While the specific incidence of temporal bone fracture and TBI is not known, approximately 4% of closed head injuries result in temporal bone fracture (Greinwald et al. 2005). Although less common, comprising only approximately 5.6% of fractures, otic-capsule, or transverse, fractures may involve the bony labyrinth. In these patients, the axis of the fracture is characteristically perpendicular to the petrous pyramid and is associated with a higher rate of vertigo, sensorineural hearing loss, and facial nerve paralysis (Johnson et al. 2008). Typical presentation includes sudden and complete vestibular dysfunction with immediate-onset severe vertigo. Physical exam and ENG, including calorics, demonstrate nystagmus and absent vestibular function in the affected ear. Fracture can often be visualized and confirmed with CT imaging. Initial treatment is symptomatic with use of antiemetics and vestibular suppressants. Compensation typically occurs over weeks to months in healthy individuals; however, lasting vestibular dysfunction may be present in the elderly or those with more extensive CNS injury (Greinwald et al. 2005).

TABLE 22–2. Diagnostic testing and application to TBI

Test	Purpose	Application to TBI
Audiologic testing	Includes audiometry, speech testing, and acoustic immittance testing.	For diagnosis of hearing loss, as well as information on etiology and prognosis.
Electro- or videonystagmography (ENG or VNG)	Provides optokinetic evaluation, including smooth pursuit, saccades, and nystagmus. May also include positional testing (Dix-Hallpike).	Asymmetric optokinetics support central injury. Dix-Hallpike suggests peripheral injury, specifically benign positional paroxysmal vertigo.
Bithermal calorics	Tests function of the lateral semicircular canal and the VOR.	Abnormality suggests unilateral peripheral vestibular malfunction.
Rotational chair testing	Tests integrity of VOR.	Useful for bilateral peripheral or central vestibulopathy and documentation or quantification of response to therapy.
Dynamic posturography	Comprehensively tests balance by isolating visual, proprioceptive, and somatic motor systems.	Useful for diagnosis of multifactorial balance problems as well as documentation and quantification of response to therapy.
Computed tomography	Evaluates relevant anatomy, high sensitivity for bony anatomy.	Useful in both acute and chronic settings for evaluation of intracranial trauma, skull base, or temporal bone fractures, bony labyrinthine disruption.
Magnetic resonance imaging	Evaluates relevant anatomy, high sensitivity for soft tissue.	Useful in both acute and chronic settings for intracranial, central, or peripheral nervous system injury or spinal trauma.

Note. TBI=traumatic brain injury; VOR=vestibulo-ocular reflex.

Labyrinthine Concussion

Even without radiological evidence of fracture, head trauma may result in damage to the membranous peripheral vestibular apparatus (Maskell et al. 2006). Initial literature on this entity cited a 24% incidence of labyrinthine concussion in patients with closed head trauma (Griffiths 1979). While not completely understood, proposed mechanisms include disruption of the membranous labyrinth due to shearing forces, hemorrhage, or ischemic injury to the microvasculature (Maskell et al. 2006). As with more obvious labyrinthine fractures, vertigo symptoms are typically self-limited, with complete compensation in healthy patients.

Traumatic Tympanic Membrane Perforation

While tympanic membrane (TM) perforation is more commonly associated with direct trauma or middle ear infection, it can also result from closed head injuries, most notably temporal bone fractures, discussed above, and blast injuries. Because the middle ear is uniquely sensitive to changes in barometric pressure, sudden and dramatic changes in pressure differential may lead to tympanic membrane rupture. Studies on soldiers in combat in recent years have documented a significant correlation between traumatic barometric TM perforation and concussive brain injury (Ritenour et al. 2008; Xydakis et al. 2007). In addition to symptoms of hearing loss, tinnitus, and otalgia, a percentage of these patients also experience vertigo. In the absence of brain injury, vertiginous symptoms related to tympanic membrane perforation are brief and self-limited owing to rapid vestibular compensation.

Posttraumatic Benign Paroxysmal Positional Vertigo

Trauma is the most common cause of secondary BPPV, accounting for approximately 7%–17% of all BPPV cases (Katsarkas 1999). As described previously, TBI may result in shearing forces to the otolithic membrane leading to displacement of the otoconia from the utricle into the endolymph. Although the exact prevalence of posttraumatic BPPV is unknown, studies have diagnosed BPPV in approximately 50% of TBI patients who complain of positional vertigo (Motin et al. 2005). Symptoms of BPPV may not begin until months or years after TBI (Greinwald et al. 2005). While otoconia can become lodged in the lateral or, more rarely, the superior semicircular canal, they typically become displaced in the posterior canal. A characteristic history includes intermittent positional vertigo lasting a few seconds. Diagnosis can be further supported with a Dix-Hallpike test in which placement of the patient in the lateral, head-hanging position elicits torsional nystagmus toward the affected ear. Treatment of BPPV can be accomplished at bedside using a variety of particle repositioning maneuvers, with a recent study citing up to 60% cure after one treatment (Motin et al. 2005).

Posttraumatic Endolymphatic Hydrops

Similar to classic Ménière's disease, posttraumatic endolymphatic hydrops presents with tinnitus, aural fullness, fluctuating sensorineural hearing loss, and episodes of vertigo lasting minutes to hours. As in BPPV, vertiginous symptoms may be delayed in onset for months or even years after the traumatic event. A rare and poorly understood

phenomenon, posttraumatic endolymphatic hydrops is believed to account for approximately 1% of patients with Ménière's disease (Greinwald et al. 2005).

Traumatic Perilymphatic Fistula

Specific prevalence of TBI and traumatic perilymphatic fistula (PLF) has not been investigated to date; however, both are present in cases of significant head injury. Traumatic PLF can result from increased intracranial pressure transmitted through the perilymph of the cochlear aqueduct causing rupture of the round, or less commonly, the oval window. In contrast to this "explosive" mechanism, traumatic force can be transmitted through the tympanic membrane to the membranous labyrinth leading to a PLF through an "implosive" etiology (Greinwald et al. 2005). In both cases, patients may be asymptomatic or they may describe fluctuating sensorineural hearing loss and vertigo (Emmet and Shea 1980). Whereas physical exam findings and diagnostic testing are often normal, the classically described fistula test (vertiginous symptoms or nystagmus with pneumatic otoscopy) may be positive. Treatment options are controversial and range from conservative, expectant management such as bed rest to middle ear exploration and fasical plugging of any labyrinthine fistulae (Emmet and Shea 1980; Greinwald et al. 2005).

Posttraumatic Vestibular Dysfunction: Central

Eighth Nerve Trauma

TBI may be complicated by direct injury to the vestibular or eighth cranial nerve (Maskell et al. 2006; Ostrowski and Bojrab 2005). Shearing forces may lead to transection, hemorrhagic, or ischemic damage to the nerve. This may occur anywhere along its course, either within the internal auditory canal or as it enters the brain stem at the cerebellar pontine angle. Injury to the vestibular nuclei in the brain stem may lead to central findings on both physical exam and diagnostic testing, such as hemorrhage on MRI or unilateral vestibular loss on ENG/VNG. Either with conservative measure or intensive vestibular rehabilitation, improvement in vertigo is usually achieved. Ultimately, however, if the vestibular nuclei on the injured side are nonfunctional, complete compensation may be impossible (Ostrowski and Bojrab 2005).

Diffuse Axonal Injury

Most current literature supports diffuse axonal injury (DAI) as the pathophysiological mechanism for TBI. Characterized by Wallerian degeneration, widespread axonal loss, focal edema, and microvascular ischemia, DAI occurs when significant shearing forces follow sudden deceleration (Hoffer et al. 2004). As discussed previously, DAI affecting any combination of central vestibular pathways in the brain stem, cortical cerebral, or cerebellar tract can lead to symptoms of dizziness.

Research by Suh et al. (2006) suggests that disruption of cerebellar-cortical tracts by DAI may be responsible for both the oculomotor and cognitive impairments (specifically those of attention and executive function) seen in TBI patients. As described previously, smooth pursuit of a moving target requires optimally functioning peripheral and central vestibular systems. In a carefully constructed study, Suh and colleagues (2006) temporarily removed the target, thereby testing "predictive" smooth pursuit eye movements. When the target or object is removed, subjects must rely exclusively on cortical input to predict object trajectory. Overall, Suh et al. found that patients with TBI demonstrated reduced target anticipation, as well as increased oculomotor errors and variability.

Cognitive, Psychosocial, and Emotional Impact of Dizziness and Vertigo After TBI

Regardless of etiology, patients with dizziness or vertigo after TBI experience widespread difficulties across multiple psychosocial, emotional, and cognitive domains (Andersson et al. 1998; Gurr and Moffat 2001; Hellawell et al. 1999; Yang et al. 2007). Patients with TBI commonly have depression and anxiety. Up to 70% report that dizziness has a "moderate" or "extreme" negative impact on their quality of life (Maskell et al. 2006). Multiple outcome measures, inventories, and questionnaires have been developed and validated in the TBI literature in an attempt to further systematize the often highly variable constellation of symptoms experienced by these patients (Maskell et al. 2006). Currently, however, no specific measures are used in a standardized fashion.

Difficulties with short-term memory, cognitive flexibility and reasoning, and selective attention are documented sequelae of TBI. In addition to obvious implications, these impairments also serve to further complicate the evaluation and treatment of dizziness (Maskell et al. 2007; Yang et al. 2007).

Long-Term Sequelae

Although the majority of patients with mild to moderate TBI recover without intervention, approximately 15% of mild and 28% of moderate TBI patients continue to experience postconcussive symptoms for more than 1 year after injury (Alexander 1995; Hellawell et al. 1999). Cited as one of the top five symptoms that fail to resolve spontaneously, dizziness/vertigo can cause significant psychosocial and behavioral distress, as well as lost economic opportunity (Chamelian and Feinstein 2004; Yang et al. 2007). Chamelian and Feinstein (2004) attempted to assess the specific (and difficult to isolate) effect of dizziness on psychosocial outcome after mild-moderate TBI. Dizzy TBI patients demonstrated significantly more anxiety, depression, and psychosocial dysfunction and were less likely to return to work when compared with a group of demographically similar nondizzy TBI patients. In addition, the

presence of dizziness was found to be an independent predictor of return to work at 6 months.

Treatment: Vestibular Rehabilitation

Geared toward enhancement of the innate vestibular compensatory response, vestibular rehabilitation therapy (VRT) has gained acceptance and popularity in recent years as an effective treatment for vestibular dysfunction. A multidisciplinary modality, VRT is administered by a specifically trained physical or occupational therapist and supervised by otologists, neurologists, psychiatrists, and other expert medical consultants. According to Shepard and Telian (1995), traditional VRT involved three components: habituation exercises designed to facilitate CNS compensation by extinguishing pathological responses to head motion, postural control exercises, and general conditioning exercises. Modeled after physical therapy, VRT incorporates both supervised and at-home exercises and typically takes place over a period of weeks to months.

Used to treat a variety of vestibular pathology, VRT specifically in TBI patients has shown promising results (Gurr and Moffat 2001; Shepard and Telian 1995). Shepard and Telian (1995) reported a 30% decrease in vertigo symptoms after 4 months in TBI patients participating in individualized VRT programs. Also, Gurr and Moffat (2001) reported significant improvements in vertigo and anxiety handicap indices, as well as balance testing, after completion of a unique rehabilitation program incorporating a cognitive-behavioral approach into more traditional VRT. In general, this literature supports a multidimensional treatment approach to maximize effectiveness and reduce long-term functional disability in TBI patients.

Conclusion

Although long recognized and acknowledged, the complex relationship between TBI, head trauma, dizziness, and vestibular dysfunction has yet to be fully explored. A multidisciplinary approach plus a detailed history and physical exam can assist with localization of the traumatic pathology. While much remains unknown, recent literature in a variety of disciplines has expanded the current knowledge of TBI and dizziness. As the natural history and pathophysiology of these disease processes become more apparent, so too will answers to the multitude of diagnostic and treatment challenges encountered by patients and clinicians dealing with TBI.

KEY CLINICAL POINTS

- The vestibular system consists of both peripheral and central components that function to sense and control motion. Head position and movement in space are first detected by the vestibular end organs in the periphery (three semicircular canals, the utricle, and saccule) where vestibular hair cells transform mechanical stimuli into neuronal signals. These signals are carried along the vestibulocochlear nerve (cranial nerve eight) to the brain stem. This information is then integrated and distributed to complex pathways in the central nervous system, ultimately resulting in vestibular reflexes that control posture, balance, and eye movements.

- Traumatic brain injury (TBI) may affect the peripheral end organs, central projections, and/or cortical processing, with subsequent vestibular dysfunction and symptoms of vertigo, dizziness, and imbalance.

- A comprehensive history is crucial and should include specific vestibular symptoms (such as sensation of motion or vertigo, light-headedness, and imbalance) as well as a thorough review of systems, notably cardiovascular, orthopedic, metabolic, neurocognitive, and psychiatric.

- As with the history, the mechanism of injury in TBI demands a comprehensive and detailed physical examination of all systems. A complete vestibular exam should include the following: opticokinetic exam (including nystagmus, head-shake, head-thrust, saccades, and smooth pursuit), cranial nerve exam, cerebellar testing, gait evaluation, Fakuda and Romberg testing, general motor and sensory evaluation, pneumatic otoscopic and tuning-fork exam, and Dix-Hallpike or positional testing.

- Radiological imaging, notably magnetic resonance imaging and computed tomography, is crucial to diagnosis of anatomical causes of dizziness or imbalance. Although

typically not appropriate in the urgent or immediate evaluation of TBI, specific vestibular testing such as videonystagmography, platform posturography, and rotational chair can be helpful in both diagnosis and management of vestibular dysfunction.

- Peripheral causes of posttraumatic vestibular dysfunction include temporal bone fracture, labyrinthine concussion, posttraumatic benign paroxysmal positional vertigo, posttraumatic endolymphatic hydrops, and traumatic perilymph fistula. Specific central causes include eighth nerve trauma and damage to the cerebellar-cortical tracts via diffuse axonal injury.

- Patients with dizziness or vertigo after TBI experience widespread difficulties across multiple psychosocial, emotional, and cognitive domains, including problems with short-term memory, cognitive flexibility and reasoning, and selective attention. These impairments manifest as long-term sequelae in many patients.

- Vestibular rehabilitation therapy, geared toward enhancement of the innate vestibular compensatory response, has gained acceptance and popularity in recent years as an effective treatment for vestibular dysfunction in TBI patients.

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CHAPTER 23

Vision Problems

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VISION IS ONE OF THE PRIMARY SENSORY MODALITIES involved in tasks such as stance, gait, reading, and other basic activities of daily living. Furthermore, adequate vision is a requisite for evaluation and treatment performed during most types of rehabilitation, such as optometric, ophthalmological, neuropsychological, physical, vestibular, occupational, and speech and language therapies. Nonetheless, the diagnosis and management of functional vision deficits have been frequently overlooked in textbooks and teaching curricula used by many rehabilitation professionals (Wainapel 1995). The recent increasing interest in functional vision and its integrative effect on rehabilitation in patients with traumatic brain injury (TBI) (Ciuffreda et al. 2007; Kapoor and Ciuffreda 2002; Suter 2004, 2007; Tinette et al. 1995; Wainapel 1995) serve as the impetus for this chapter.

In this chapter, we discuss the prevalence and pathophysiology of vision problems and provide an overview of functional vision anomalies in patients with TBI. Further details are provided elsewhere (Ciuffreda 2002; Kapoor and Ciuffreda 2002; Scheiman and Wick 2002; Suter 2004). A glossary of ophthalmic terms used in the following text is found in the appendix at the end of the chapter.

Prevalence of Vision Problems in TBI

Vision problems have been reported in TBI patients with varying prevalence, depending on the source used and diagnostic criteria adopted (Baker and Epstein 1991; Ciuffreda et al. 2006, 2007; Hellerstein et al. 1995; Lepore 1995; Rutner et al. 2006; Sabates et al. 1991; Schlageter et al. 1993; Suchoff and Gianutsos 2000; Suchoff et al. 1999, 2008; Suter 2004, 2007) (Table 23–1). The most common problems adversely affecting visual function directly are versional and vergence oculomotor anomalies, accommodative dysfunctions, dry eye, cataracts, and visual field defects (Suchoff et al. 1999). Other vision problems affecting function more indirectly include orbital fractures, lid anomalies, blepharitis, blepharoconjunctivitis, pupillary anomalies, optic nerve anomalies, and retinal defects (Rutner et al. 2006; Suchoff et al. 1999).

Pathophysiology

The pathophysiology of all vision deficits in TBI has not been reported in the literature in detail, but it is more evident for some deficits than for others. Oculomotor deficits (Table 23–2) resulting in diplopia, loss of place while reading, nystagmus, and oscillopsia may occur because of sheared or severed cranial nerves (CNs; e.g., CN III, CN IV, CN VI), mechanical restriction of an extraocular muscle, or damage at the level of the neuromuscular junction (Baker and Epstein 1991). Accommodative deficits resulting in blurred vision may occur as a result of damage to the oculomotor nerve (i.e., CN III), more central neurological anomalies, or a side effect of medications (Han et al. 2008).

With respect to ocular pathology, dry eye resulting in intermittent blurred vision and a gritty sensation is quite common in the TBI population. It is typically an ocular side effect of antidepressants, antihypertensives, and oral contraceptives (Bartlett and Jaanus 2008; Han et al. 2008). Blepharitis and blepharoconjunctivitis are also frequently found and typically occur because of poor lid hygiene (Rutner et al. 2006). Pupillary anomalies may result from damage along the pupillary pathway in association with a CN III palsy, asymmetrical optic nerve disease or anomaly, the presence of a space-occupying lesion, or disrupted autonomic innervation. Visual field defects such as noncongruous hemianopias and quadrantanopias may occur with TBI depending on the nature and severity of the injury, but they are more typically associated with stroke. Clinical experience and recent research have demonstrated that the majority, as much as 58% (Suchoff et al. 2008), of TBI patients present with scattered visual field defects without

TABLE 23–1. Percentage of visual and ocular conditions in an acquired brain-injured (ABI) sample with comparative values for a random adult population

Ocular/visual condition	Occurrence in an ABI sample (%)	Occurrence in a random adult population (%)	Occurrence in an ABI/random adult occurrence
Exophoric deviations	41.9	2.1	19.9
Esophoric deviations	1.6	1.3	1.3
Vertical deviations	9.7	1.6	6.1
Oculomotor dysfunctions	39.7	NA	NA
Accommodative dysfunctions	9.6	NA	NA
External eye pathologies: dry eye/blepharitis/keratitis/ pterygium/corneal degeneration	22.6	11.2	2.0
Lid defects: ptosis/dermatochalasis/blepharochalasis	4.8	2.1	2.3
Aphakia/pseudophakia/cataracts	24.1	12.3	2.0
Optic nerve cupping/optic atrophy/glaucoma suspect/ glaucoma	19.4	8	2.4
Color vision defect	0	8.3 (male) 0.5 (female)	0
Contrast sensitivity defect	0	NA	NA
Posterior pole anomalies: retinopathies (including diabetic retinopathy, hypertensive retinopathy, and maculopathy)	9.7	1.5	6.5
Retinal defects/detachments	1.6	0.1	20.0
Peripheral retinal degenerations/vitreoretinal degenerations	9.7	2.6	3.7
Blindness/enucleation	6.5	1.6	4.1
Pupillary anomaly	1.6	1	1.6
Visual field defects	32.5	NA	NA

Note. NA=normative data for a random adult population not available.

Source. Adapted from Suchoff IB, Kapoor N, Waxman R, et al: "The Occurrence of Ocular and Visual Dysfunctions in an Acquired Brain-Injured Patient Sample." *Journal of the American Optometric Association* 70:301–309, 1999. Used with permission.

hemifield lateralization, as described in the section Visual Field Defects. The etiology of this scattered visual field defect remains poorly understood.

There are other ocular sequelae that may occur with blunt trauma to the periorbital region, but these are not common in TBI. These sequelae are orbital fracture, lid anomaly, corneal abrasion, lens dislocation, angle recession, traumatic glaucoma, traumatic cataract, traumatic uveitis, and retinal or vitreal detachment (Rutner et al. 2006). The pathophysiology of these conditions is not addressed further because it is beyond the scope and aim of this chapter.

Some of these conditions, however, do occur with increased frequency in the TBI population when compared with the non-brain-injured population (Rutner et al. 2006; Suchoff et al. 1999), and this may result in reduced visual acuity, reduced contrast sensitivity, and/or visual field defects. Orbital fractures and lid anomalies secondary to blunt and severe head trauma require immediate medical intervention because of the concern of additional inflammation or infection (e.g., orbital cellulitis). Inflammation, infection, shearing, or compression may occur at any point along the optic radiations in the primary visual pathway between the occipital cortex and retina as a result of trauma. Retinal defects and tears occur often with severe blunt trauma. Retinal vascular insufficiencies, which are often associated with hypertension and diabetes, are also possible sequelae. Such vascular compromise may occur at the level of the ophthalmic artery or at the level of the carotid arterial supply from which the ophthalmic artery arises. Additionally, there is an increased frequency of cataracts and glaucoma, but the pathophysiology remains unclear.

Vision Care Professionals

As with any health condition, appropriate diagnosis is required for the effective treatment and management of vision deficits. Diagnosis of vision problems in the TBI population is made appropriately through two professions involved in vision care: optometry and ophthalmology.

Optometry is a profession specializing in nonsurgical, noninvasive, and often rehabilitative vision care including the application of lenses, prisms, tints, and vision rehabilitation therapy. Additionally, optometry's scope of practice has expanded significantly over the past 30 years to include the use of diagnostic and therapeutic pharmaceutical agents. However, optometry's incorporation of

TABLE 23–2. Oculomotor deficits following traumatic brain injury

Deficit	Possible underlying mechanism	Clinical manifestation
Blurred vision	Ocular injury to cornea, lens, and/or retina	Constant or intermittent blurred vision in one or both eyes
	Damage to the optic nerve or anywhere along the primary visual pathway	Fatigue or eyestrain with sustained visual tasks
	CN III damage	
	Midbrain injury	
	Refractive error	
	Amblyopia	
Binocular vision anomalies	Diminished oculomotor control (i.e., paresis or palsy of CN III, CN IV, or CN VI)	Constant or intermittent diplopia in some or all positions of gaze
	Midbrain injury affecting medial longitudinal fasciculus and/or the oculomotor nuclei	Reduced accuracy of depth perception
		Difficulty localizing objects in space
		Confusion with sustained visual activities
Nystagmus	Brainstem damage	Abnormal ocular oscillations resulting in oscillopsia, nausea, blurred vision, and visual confusion
	Cerebellar damage	
Deficits of pursuit	Lesion in either hemisphere with or without brainstem damage	Difficulty tracking in any plane
Deficits of saccades	Lesion in frontal eye field (area 8) or parietal area	Difficulty in rapid localization of objects in space
		Difficulty with reading

Note. CN=cranial nerve.

Source. Reprinted from Hellerstein LF: "Visual Problems Associated With Brain Injury," in *Understanding and Managing Vision Deficits: A Guide for Occupational Therapists.* Edited by Scheiman M. Thorofare, NJ, Slack, 1997, pp 233–247. Used with permission.

primary eye care, vision therapy, low vision, refraction, and visual perception provides the foundation of a subspecialty referred to as *neuro-optometric rehabilitation.* Optometrists practicing neuro-optometric rehabilitation manage patients with acquired brain injury, including TBI, and can be located by searching the websites for either of the following organizations: College of Optometrists in Vision Development (www.covd.org) and Neuro-Optometric Rehabilitation Association (www.nora.cc). Because of the progressive increase in awareness and expertise of neuro-optometrists, this subspecialty is gradually becoming a contributing member of the TBI interdisciplinary rehabilitation team, with the responsibility of managing functional vision problems from a rehabilitative aspect.

In contrast, *ophthalmology* is a medical specialty with several relevant subspecialties that relate to the treatment of individuals with TBI, such as neuro-ophthalmology, oculoplastics, reconstructive, retina, strabismus, and low vision, to name a few. If vision anomalies are evident during the acute stage of TBI, the neuro-ophthalmologist is recruited for the patient's management. Retinal and oculoplastics ophthalmologists may be consulted on occasion, depending on the nature and severity of any structural vision problems such as physical insults to the globe and associated periorbital region. Ophthalmologists and neuro-ophthalmologists may continue to manage patients with TBI over the long term regarding vision and ocular care. However, relative to rehabilitative optometrists or neuro-optometrists, they may not be as involved in the rehabilitative aspects of vision function following TBI.

Ocular Anatomy and the Visual Pathways

The globe of the human eye, from anterior to posterior, consists of the following major structural anatomical components: cornea, conjunctiva, sclera, iris, aqueous humor, anterior and posterior chamber, crystalline lens, vitreous humor, retina, choroid, and sclera (Figure 23–1).

Primary Visual Pathway

The primary visual pathway commences at the level of the retina, where axons of the two types of ganglion cells (i.e., the *magnocellular* or *transient cells,* and the *parvocellular* or *sustained cells*) exit the retina as the *optic nerve* via the optic nerve head (Miller et al. 2004). The axons of the optic nerve proceed to the *optic chiasm,* where there is a *partial decussation* of the nerve fibers from each eye. This partial decussation ensures that visual information from the right and left sides of the visual field is separated and subsequently corresponds to the left and right sides of this pathway, respectively.

From the optic chiasm, the fibers proceed via the *optic tract* to the *lateral geniculate body,* where the visual input is combined with nonvisual neural inputs (Miller et al. 2004). Some of these fibers then proceed to the following areas: 1) the primary visual cortex, or the *occipital cortex,* via the *optic radiations,* to perform the early stages of

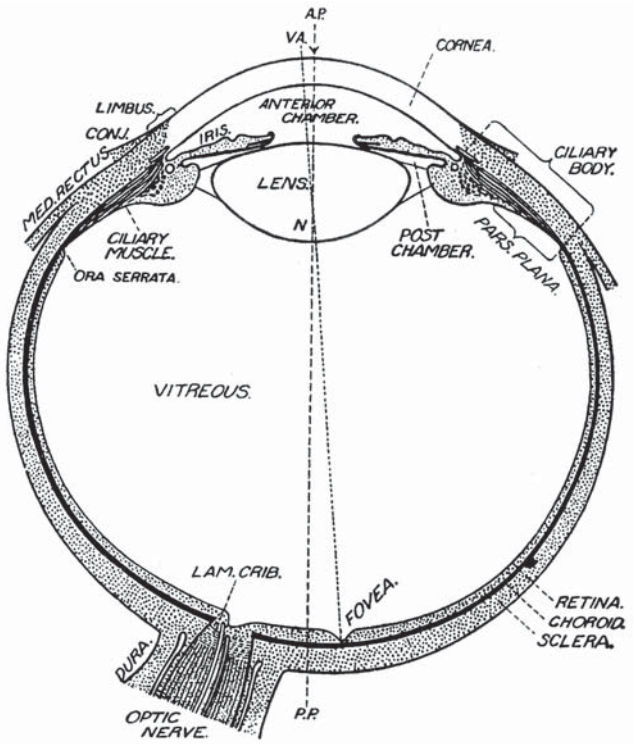


FIGURE 23–1. Horizontal section of the human eye.

AP=anterior pole; CONJ=conjunctiva; LAM CRIB=lamina cribrosa; MED=medial; N=nodal point; PP=posterior pole; VA=visual axis.

Source. Reprinted from Last RJ: *Wolff's Anatomy of the Eye and Orbit.* Philadelphia, PA, WB Saunders, 1968, pp 39–181. Used with permission.

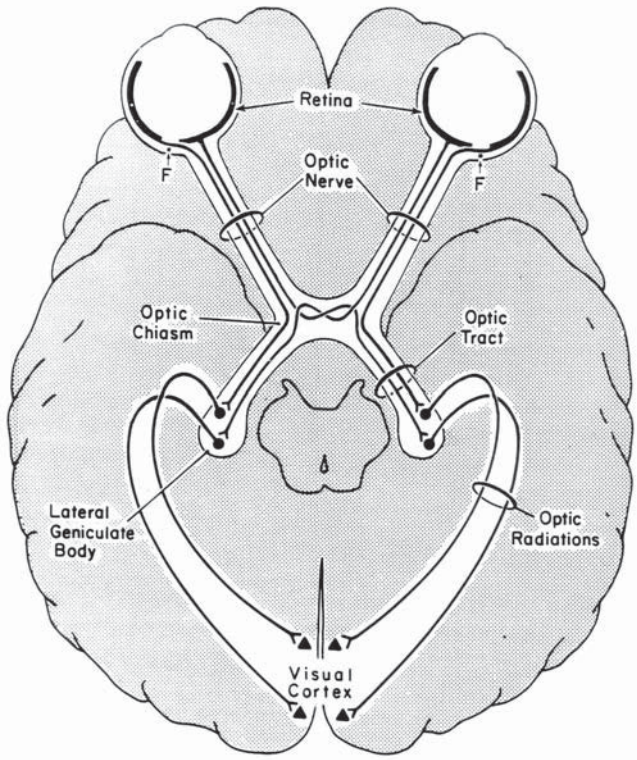


FIGURE 23–2. Schematic representation of primary neural visual pathways.

F=fovea.

Source. Reprinted from Trobe JD, Glaser JS: *The Visual Fields Manual: A Practical Guide to the Testing and Interpretation.* Gainesville, FL, Triad Publishing, 1983, pp 29–62. Used with permission of the publisher.

visual information processing (this is referred to as the primary visual pathway [Miller et al. 2004]; see Figure 23–2); 2) the *tectum,* to participate in pupillary function; or 3) the *superior colliculus,* to participate in eye movement and related multisensory integrative behaviors.

Secondary Visual Pathway

A second level of visual information processing begins at the *extrastriate portion of the visual cortex* and is referred to as the *secondary visual pathway* (Girkin and Miller 2001; Milner and Goodale 1995). From the extrastriate visual cortex, the ventral visual pathway is primarily composed of parvocellular cells communicating with the *inferior temporal* area, which is associated with visual identification and recognition of objects, or the "what" aspect of visual perception. However, the dorsal visual pathway is primarily comprised of magnocellular cells proceeding via the middle temporal area to the parietal cortex, which is associated with motion and spatial vision, or the "where" aspect of visual perception (Girkin and Miller 2001; Milner and Goodale 1995; Robertson and Halligan 1999; Stein 1989).

Some cortical areas that are common to many of these oculomotor subsystems are the cerebellum, midbrain, frontal eye fields, superior colliculus, parietal cortex, and visual cortex. Therefore, damage to one or more of these areas could affect a range of ocular motility functions (Baker and Epstein 1991; Leigh and Zee 2006; Sabates et al. 1991) (Table 23–3).

Standard Protocol for the Vision Examination

The initial stage of the vision examination of the TBI patient involves an extensive case history. Subsequent to the case history, the vision examination includes an assessment of the following major areas: refractive, sensorimotor, and ocular health status, including special testing as appropriate. Below is an overview of the testing involved for each of the four elements of the vision examination (Eskridge et al. 1991):

1. *Case history,* including specific queries regarding reading ability, eyestrain or fatigue, blurred vision, diplopia, visual field loss, light sensitivity, dizziness, loss of balance, vertigo, and motion sensitivity.
2. *Refractive assessment,* including visual acuity, keratometry, retinoscopy, and subjective refraction to determine the appropriate refractive correction at far and at near (i.e., emmetropia, myopia, hyperopia, astigmatism, and presbyopia).

TABLE 23–3. Structural impairments following traumatic brain injury

General category	Specific areas of vision difficulty
Soft tissue injuries	Extraocular muscle avulsion
	Hemorrhage and edema
Orbital fractures	Floor
	Medial wall
	Lateral wall
	Roof
Cranial neuropathies	Oculomotor nerve
	Trochlear nerve
	Abducens nerve
	Sphenocavernous syndrome
	Orbital apex syndrome
Intra-axial brainstem damage	Internuclear ophthalmoplegia
	Horizontal gaze paresis
	Vertical gaze paresis
	Parinaud's syndrome
	Skew deviation
	Abnormalities of accommodation, convergence, and fusion
	Cerebellar lesions
	Vestibular system dysfunctions
Cerebral lesions	Saccade
	Pursuit

Source. Adapted from Baker RS, Epstein AD: "Ocular Motor Abnormalities from Head Trauma." *Survey of Ophthalmology* 35:245–267, 1991. Used with permission.

3. *Sensorimotor assessment,* including versional ocular motility, vergence ocular motility, stereopsis, and accommodation.
4. *Ocular health assessment and special testing,* including confrontation visual field, color vision, pupils, anterior segment evaluation, applanation tonometry, posterior segment evaluation, and automated perimetry. Special testing includes visual evoked potentials, contrast sensitivity testing, application of tinted lenses, and application of yoked prisms.

Functional Vision Anomalies After TBI

Functional vision anomalies may negatively affect the ability of the TBI patient to perform basic activities of daily living such as reading, writing, walking, shopping, driving, and navigating through crowded environments, to name a few (Hellerstein 1997; Suchoff and Gianutsos 2000; Suter 2004). Even simpler tasks such as sorting and reading mail, washing dishes, doing laundry, and dusting can be troublesome to the TBI patient with impaired functional vision. Several common functional vision anomalies, as well as their associated signs and symptoms, are described in the following sections. Table 23–4 outlines the most common categories of vision deficits and their associated principal vision symptoms.

Accommodative Dysfunctions

Accommodative dysfunctions in the prepresbyopic TBI population may impair a patient's ability to sustain near vision for prolonged time periods without ocular fatigue, thereby decreasing overall visual efficiency and reading ability (Fox 2005; Leslie 2001; Scheiman and Gallaway 2001). The most common accommodative dysfunction in the TBI population is accommodative insufficiency, for which the primary diagnostic criterion is reduced amplitude of accommodation (Ciuffreda et al. 2007, 2008). Symptoms of general accommodative dysfunctions include intermittent blurred vision, inability to sustain prolonged near vision, tearing, and occasionally headaches (Baker and Epstein 1991; Ciuffreda et al. 2008; Hellerstein 1997; Hellerstein et al. 1995). Prescribing separate reading spectacles with or without concurrent oculomotor rehabilitation may benefit the patient by enhancing the amplitude, facility, and sustainability of accommodation while the spectacles are worn (Benjamin 2006; Griffin and Grisham 2002; Scheiman and Wick 2002).

Refractive Changes

Refractive changes may sometimes be the cause of constant blurred vision in the TBI population. Reduced best-corrected visual acuity may arise because of damage along the primary visual pathway anywhere from the optic nerve head to the occipital cortex via the optic radiations (Sabates et al. 1991). Because there is a visual basis for many of the evaluative and treatment strategies involving TBI rehabilitation, optimizing and stabilizing visual acuity by initially assessing the refractive status are of utmost importance.

For example, there are cases in the TBI population in which prepresbyopic patients may require a near-vision correction. Relatively small amounts of hyperopia in younger individuals without TBI can typically be easily overcome by their accommodative focusing mechanism. However, if a 20-year-old hyperopic patient who did not previously wear a near-vision correction experiences damage to CN III as a result of a brain injury, this patient might experience blurred near vision and require a reading correction because of the newly developed accommodative dysfunction secondary to the brain injury.

Prescribing spectacles for TBI is important in terms of functional vision for prepresbyopic, nonemmetropic patients with accommodative deficits, as well as for presbyopic patients, because they require different spectacle corrections for distance and near vision. Despite optical and cosmetic advances, the progressive, or "invisible-line" bifocal, lens is not appropriate for the TBI population because of its residual optical distortions as well as the requirement for precise and coordinated eye, head, and neck movement on the part of the patient (Han et al. 2003a, 2003b). These peripheral optical distortions produce dizziness, nausea, and illusory motion in many TBI patients

TABLE 23–4. Vision deficits following traumatic brain injury and their associated principal vision symptoms

Vision deficit	Associated principal vision symptom
Deficit of accommodation	Constant or intermittent blur
Refractive changes	Constant blur at a particular viewing distance
Deficit of versional ocular motility	Reading-related difficulty, with slower reading speed and loss of place when reading
	Difficulty shifting gaze or tracking objects during ambulation
Deficit of vergence ocular motility	Constant or intermittent diplopia, eliminated with monocular occlusion
Visual-vestibular disturbances	Disequilibrium/dizziness with increased sensitivity to visual motion in multiply visually stimulating environments (e.g., supermarkets, malls), accompanied by nausea and/or headache
Photosensitivity	Elevated sensitivity to light (all types of lighting or selective to fluorescent lighting)
Visual field impairment	Missing a portion of one's visual field, with or without inattention
	Having relative defects scattered throughout field of vision

during ambulation and therefore adversely affect daily function. Often the range of head and neck movement is limited in TBI patients because of the injuries incurred at the time of their initial trauma. For these reasons, *all* multifocal lenses are contraindicated for ambulation in the TBI population, especially in those with vestibular deficits and sensitivity to visual motion. To optimize vision function by allowing minimal head and neck movement and, hence, minimal adverse effects, one should prescribe separate distance and near single-vision spectacles.

Deficits of Versional Ocular Motility

Versional oculomotor deficits, including those of pursuit, saccades, vestibulo-ocular reflex (VOR), and fixation, affect the ability to track objects smoothly, track objects as they move rapidly from point A to point B, and maintain steady visual fixation on a target, respectively (Ciuffreda and Tannen 1995), with or without concurrent head movement. Saccadic deficits are the most common versional dysfunction in visually symptomatic individuals with TBI (Ciuffreda et al. 2007). Individuals with versional oculomotor deficits primarily report reading difficulties: reading slowly, loss of place while reading, misreading or rereading words and paragraphs, text that appears to "swim" and "shimmer," and, occasionally, apparent visual motion perhaps related to vergence misalignment and/or frank oscillopsia. Further, studies (Suh et al. 2006a, 2006b) on pursuit in mild TBI revealed a correlation between cognitive function (specifically attention and executive control) and impaired predictive smooth pursuit. Some of these symptoms may also be related to vestibular deficits (see the section Visual-Vestibular Disturbances later in this chapter, as well as Chapter 22, Dizziness, Imbalance, and Vestibular Dysfunction). Oculomotor rehabilitation is also beneficial for versional deficits (Ciuffreda et al. 1996, 2006, 2008; Kapoor and Ciuffreda 2002; Scheiman and Wick 2002).

Deficits of Vergence Ocular Motility

Convergence Insufficiency

Convergence insufficiency (CI) is a binocular vision vergence anomaly in which the eyes cannot rotate inward and maintain single vision at close distances (Benjamin 2006; Griffin and Grisham 2002; Scheiman and Wick 2002). This condition is the most common nonstrabismic vergence dysfunction in TBI patients, varying in occurrence from approximately 41% to 65% (Ciuffreda et al. 2007; Hellerstein et al. 1995; Suchoff and Gianutsos 2000; Suchoff et al. 1999; Suter 2004). Vision-related symptoms associated with near-work include eyestrain (ocular "fatigue"), intermittent closing of one eye, diplopia, abnormal sensitivity to visual motion, and the perception that printed text is "floating above the page" or "shimmering." Patients with CI may also position themselves relatively far from or not be able to maintain eye contact with people during conversation to avoid diplopia. If the magnitude of the CI is sufficient to produce frequent diplopia at near distances, fusional prisms may be prescribed. CI is amenable to oculomotor rehabilitation (i.e., optometric vision therapy; Ciuffreda 2002) designed to increase the extent, stability, and sustainability of the vergence response (Ciuffreda et al. 2008; Han et al. 2004; Kapoor and Ciuffreda 2002).

Vertical Oculomotor Deviations

Vertical oculomotor deviations, including heterophorias and heterotropias, are more complex to manage because of the variability in magnitude of the deviation as a function of gaze position and time of day. In addition to the symptoms outlined in the section above for CI, patients with vertical deviations may also report impaired binocular depth perception and headaches (Ciuffreda et al. 2007, 2008). The aim of oculomotor rehabilitation is to train sensory and motor fusion (i.e., single binocular vision) initially in primary gaze and then increase the field of fusion (Benjamin 2006; Griffin and Grisham 2002; Scheiman and Wick 2002). Surgical intervention is also an option, depending on the status of the patient's overall health. If oculomotor rehabilitation is unsuccessful, and surgery is not an option, then occlusion of one eye as needed to eliminate diplopia may be recommended. Although neurological or mechanical restriction of the extraocular muscles does limit the benefit of oculomotor rehabilitation for increasing the range of horizontal and vertical fusion, it still should be attempted to improve vision function and overall visual efficiency (Han et al. 2004; Kapoor and Ciuffreda 2002; Suter 2004).

Visual-Vestibular Disturbances

Visual-vestibular disturbances (see also Chapter 22, Dizziness, Imbalance, and Vestibular Dysfunction) result in symptoms of dizziness, loss of balance, vertigo, nausea, motion sensitivity, oscillopsia, and, frequently, photosensitivity. Patients with visual-vestibular disturbances report difficulty shopping in department stores with high shelving because of the sensation of visual motion in their periphery (Bronstein 2004), being in visually crowded environments such as busy restaurants, watching movies or television because of the rapid movement from scene to scene, reading because of the sensation of "shimmering" and "floating," and using the computer monitor because of screen flickering.

Patients with vestibularly based symptoms are referred typically to neurology, neurotology, and, finally, vestibular rehabilitation, an area in which vision becomes especially important (Bronstein 2004; Bucci et al. 2004; Malamut 2001). One particular subset of vestibular exercises directly incorporates the VOR, which is a reflex stabilizing the visual world while one's head is in motion (Baloh and Honrubia 2001; Leigh and Zee 2006). This reflex is used in vestibular rehabilitation through a series of exercises referred to as *gaze stabilization training,* or *VOR training* (Baloh and Honrubia 2001; Leigh and Zee 2006). The VOR training may be performed horizontally and vertically. Because the horizontal VOR is affected often, understanding that the horizontal VOR involves cranial nerves III and VI communicating via the medial longitudinal fasciculus with cranial nerve VIII (Baloh and Honrubia 2001; Bucci et al. 2004; Leigh and Zee 2006) reveals that appropriate versional and vergence ocular motility is required, especially under dynamic conditions. The VOR must rapidly adapt with changes in target distance involving complex vestibular-vergence interactions (Bucci et al. 2004; Leigh and Zee 2006). Despite the fact that the patient and target are stationary during standard clinical binocular vision testing, unstable fusion in association with symptoms of nausea and dizziness during the actual binocular vision clinical testing is often evident in patients with vestibular dysfunction.

Oculomotor rehabilitation, with the incorporation of fusional prisms for diplopia and tinted lenses for photosensitivity, is designed to improve and stabilize fusional vergence under static and dynamic viewing conditions at all distances and directions (Ciuffreda 2002). Additionally, as stated in the section Refractive Changes, it is important to prescribe single-vision spectacles for patients requiring different corrections for far and near viewing for presbyopia and accommodative deficits. Oculomotor rehabilitation and spectacle correction have been shown to markedly enhance one's ability to perform gaze stabilizing techniques and other aspects of vestibular rehabilitation and to function in terms of basic activities of daily living (Malamut 2001).

Photosensitivity

Photosensitivity, even in the absence of ocular inflammation and pain, produces significant discomfort. In the literature, this increased light sensitivity is often referred to as *photophobia,* which really refers to elevated light sensitivity in conjunction with frank ocular pain because of contraction and relaxation of inflamed ocular tissue (Stedman's Medical Dictionary 2005). It is our opinion that, because TBI patients experience varying degrees of increased light sensitivity in the absence of any such ocular pain, this phenomenon should be referred to as *photosensitivity* rather than *photophobia* (Kapoor and Ciuffreda 2002).

Recent research suggests that there are two major categories of photosensitivity: 1) increased sensitivity to all types of lighting, and 2) increased sensitivity predominantly toward fluorescent lighting. Current studies on TBI correlate anomalous dark adaptation thresholds with general photosensitivity (Du et al. 2005) and possible anomalous critical flicker fusion frequency thresholds with selective photosensitivity to fluorescent lighting (Chang et al. 2007). Although the neurological correlates for generalized or fluorescent photosensitivity have not yet been elucidated, the discomfort associated with both categories of photosensitivity may be alleviated considerably by wearing brimmed caps and using tinted lenses, with a lighter tint used for indoors and a darker tint used outdoors (Jackowski 2001; Kapoor and Ciuffreda 2002). More recently, Bengtzen et al. (2008) proposed that wearing sunglasses may indicate nonorganic visual loss. However, because their study did not specify whether scotopic thresholds or critical flicker fusion frequency were assessed when ruling out causes of photosensitivity, the results may not apply to those with TBI.

Visual Field Defects

Although visual field defects, such as homonymous hemianopias with or without visual inattention, are more common among the stroke population, they may occur in the TBI population as well (Hellerstein 1997; Hellerstein et al. 1995; Kapoor et al. 2001; Suchoff and Ciuffreda 2004; Suchoff and Gianutsos 2000; Suchoff et al. 1999, 2008; Suter 2007). Patients with hemianopia report either of the following: 1) "being told" that part of their visual field is missing, if they have visual inattention; or 2) being aware that part of their visual field is missing, if they do not have visual inattention. They may have difficulty reading (e.g., finding the beginning of the next line of print because of a left hemianopia) or manifest slow and laborious reading as they saccade cautiously in small steps from left to right into their blind field (because of a right hemianopia). Hemianopic patients may also report that they bump into objects on one side, miss food on one side of the plate, have trouble dressing one side of their body, and have problems navigating streets and buildings (Hellerstein 1997; Hellerstein et al. 1995; Robertson and Halligan 1999; Suchoff and Ciuffreda 2004; Suchoff and Gianutsos 2000; Suchoff et al. 2008; Suter 2007). Hemianopia significantly and irreversibly alters numerous basic functional aspects of patients' lives. It often limits their independence through the restriction or even prevention of common tasks, such as driving and unaccompanied ambulation.

In some hemianopic patients, laterally displacing (i.e., yoked) prism spectacles, half-Fresnel prisms, and mirrors can be useful (Suchoff and Ciuffreda 2004; Suchoff and

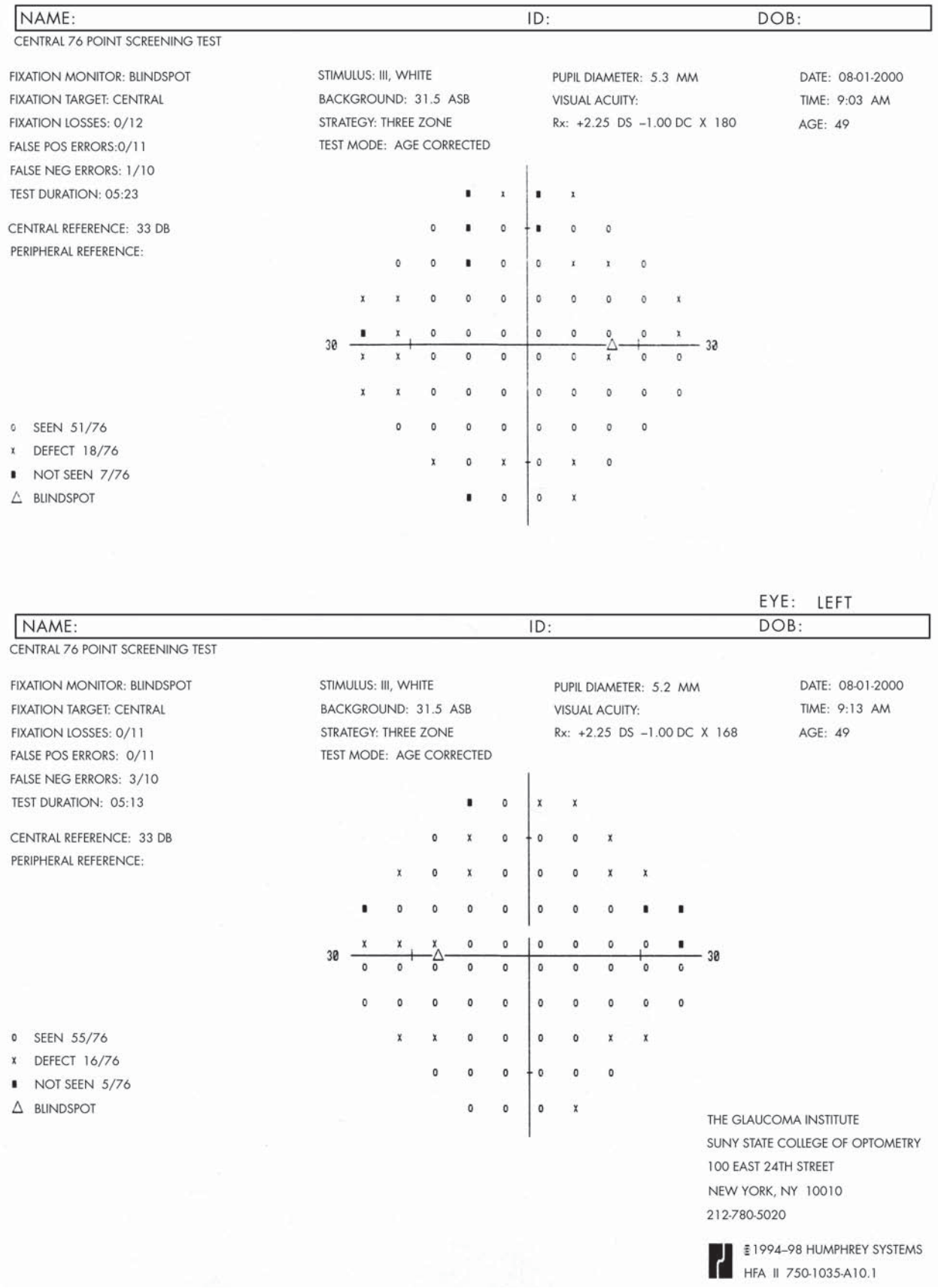


FIGURE 23–3. Typical scattered visual field defect pattern after traumatic brain injury.

Gianutsos 2000; Suter 2007). These optical devices are designed to increase the patient's awareness of the affected field. Scanning techniques, either alone or in conjunction with a field-enhancing optical device (Suter 2007), may also benefit the patient (Kapoor et al. 2001).

Another type of visual field defect that we typically find in the TBI population is a scattered visual field pattern (Figure 23–3). Patients presenting with this type of field loss typically do not report functional vision limitations. Such field defects should be monitored twice yearly for any variation over time. Optical devices typically are not helpful in these cases.

Conclusion

The primary sensory input for most aspects of rehabilitation in the TBI patient is vision. Therefore, increased awareness of the visual system's anatomy, physiology, neurology, clinical evaluative procedures, and key related anomalies is important for the physician who treats individuals with TBI. Heightened awareness and recognition of these vision anomalies on the part of the physician lead to improvement in the patient's ability to function in terms of overall rehabilitation, as well as in basic activities of daily living.

KEY CLINICAL POINTS

- The clinician treating a patient with traumatic brain injury should be alert to the more common functional vision deficits and associated principal symptoms.
- Symptoms associated with functional vision deficits may include blurred vision, difficulty in reading, difficulty in tracking objects, dizziness, and light sensitivity, among others.
- Appropriate referrals to a vision care professional should be provided to the patient to address presenting vision symptoms and optimize the impact on affected activities of daily living.

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Appendix 23–1

Glossary of Ophthalmic Terms

accommodation: the crystalline lens-based mechanism used to obtain and maintain a clear retinal image of an object of interest.

accommodative amplitude: the closest point of clear vision.

accommodative facility: ability to change focus rapidly.

ametropia: uncorrected blurred distance vision.

astigmatism: uncorrected blurred distance vision in selected meridians.

diopter: the unit of lens power.

esophoria: the inward turning of one eye when binocular vision is prevented.

exophoria: the outward turning of one eye when binocular vision is prevented.

fusion: single vision under binocular viewing conditions.

heterophoria: the turning of one eye relative to the other when binocular vision is prevented.

hyperopia: farsightedness.

myopia: nearsightedness.

near point of convergence: the closest point of binocular, single vision.

orthophoria: the absence of the turning of one eye when binocular vision is prevented.

oscillopsia: the apparent sensation of movement of stationary targets.

prism diopter: the unit of prism power.

relative accommodative range: a lens-mediated change in focus without a concurrent change in vergence.

relative fusional range: a prism-mediated change in vergence without a concurrent change in focus.

strabismus (heterotropia): the turning of one eye relative to the other under binocular viewing conditions.

vergence: the coordinated inward/outward or upward/downward movement of the eyes when tracking objects moving in depth.

version: the coordinated movement of the eyes (laterally, vertically, or obliquely) when tracking objects at a fixed distance.

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CHAPTER 24

Chronic Pain

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A Brief Overview of Pain

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey and Bogduk 1994, pp. 209–214). Acute pain, usually occurring in response to identifiable tissue damage or a noxious event, has a time-limited course during which treatment is aimed at correcting the underlying pathological process (if any such intervention is deemed necessary). Chronic pain, generally considered as pain persisting for longer than 6 months, may or may not be associated with any obvious tissue damage or pathological process. In the case of chronic pain, presentation may be characterized by maladaptive protective responses or pain behaviors, protracted courses of medication use and minimally effective medical services, and marked behavioral or emotional changes, including restrictions in daily activities. Pain-related avoidance behaviors and reduced activity are likely to result in a cyclic disability-enhancing pattern. The longer pain persists, the more recalcitrant it becomes and the more treatment goals focus on improved coping with pain and its concomitants (Kulich and Baker 1999; Martelli et al. 1999a). Finally, there is increasing evidence and growing acceptance that persistent pain may be associated with peripheral sensitization or central sensitization effects in which hyperresponsiveness or spontaneous discharge of components of the pain system develops (Lidbeck 2002; Nicholson 2000b; Nicholson and Martelli 2004). In this regard, it has been noted that there is an association between posttraumatic stress reactions and the development of chronic pain (Bryant et al. 1999; Miller 2000; Sharp and Harvey 2001), with uncontrollable pain after physical injury potentially representing the core trauma, resulting in posttraumatic symptomatology (Schreiber and Galai-Gat 1993).

It is widely held that pain should be considered a multidimensional, subjective experience mediated by emotion, attitudes, and other perceptual influences. Variability in pain responses is the rule rather than the exception and appears to reflect complex biopsychosocial interactions of genetic, developmental, cultural, environmental, and psychological factors (Gatchel et al. 2007; Hinnant 1994; Turk and Holzman 1986). Important distinctions between pain and suffering (Fordyce 1988) reflect the variability in response to pain problems. Although some pain patients appear to present with unusual and possibly exaggerated suffering or disability, others present with "la belle indifference," in which extremely high reported pain severity may produce no apparent affective distress, pain behavior, or interference in many life activities. In some cases, the onset, maintenance, severity, or exacerbation of pain is primarily associated with psychological factors and may warrant a DSM-IV-TR (American Psychiatric Association 2000) diagnosis of pain disorder associated with psychological factors. However, one should avoid the pitfalls of mind-body dualism and always consider both psychological and organic factors in the presentation of any chronic pain patient (Martelli et al. 2007b; Nicholson et al. 2002).

The issue of comorbid acute and chronic pain as clinical phenomena in persons with traumatic brain injury (TBI) has not received significant attention until recently, nor has there been a significant empirical literature base established with regard to the incidence, prevalence, etiology, assessment, and treatment of these important comorbid conditions in this special population of patients (Martelli et al. 2007b; Nampiaparampil 2008; Zasler 1999; Zasler et al. 2004, 2007). A systematic review found that pain complaints were more than twice as frequent after mild than more severe TBI and that there was a prevalence of approximately 50% for chronic pain, independent of comorbid factors like posttraumatic stress disorder (PTSD), with chronic headache being the most common subtype (Nampiaparampil 2008). Central pain following TBI is rare

but has been studied and should be recognized by clinicians when patients present with high levels of allodynia and hyperpathia, among other clinical features (Ofek and Defrin 2007). Recent review of this pain state indicates that individuals with somatosensory impairments are more at risk for development of this pain disorder (Finnerup et al. 2010).

Finally, it should be recognized that complexities in pain presentation in persons with TBI may warrant referral to pain management specialists, specialty interdisciplinary pain programs, or both. Referral is particularly warranted in cases of intractable pain and/or functionally disabling pain even in situations in which the pain condition does not qualify by temporal criteria as chronic (i.e., lasting greater than 6 months).

Neuroanatomy of Pain

The neuroanatomical pathways associated with pain perception are complex and not completely understood. Readers are referred to more in-depth sources for further detail (Bromm and Desmedt 1995; Vogt et al. 1993; Willis and Westlund 1997; Zasler et al. 2007). Primary afferents are composed of A delta fibers and C fibers. A delta fibers are small, thin, myelinated neurons 1–5 μm in diameter with conduction velocities in the range of 5–30 m/sec. Pain mediated by A delta fibers tends to be fast, sharp, localized, and well defined. These fibers have small receptive fields and tend to be modality specific. They are divided into thermoresponsive and mechanoresponsive subgroups. C fibers are small, unmyelinated afferent fibers with diameters of 0.25–1.5 μm and conduction velocities from 0.5 to 2.0 m/sec. Pain mediated by C fibers tends to be slow, diffuse, poorly localized, and of a burning, throbbing, or gnawing nature. These polymodal fibers subserve noxious nociceptive input from thermal, mechanical, and chemical stimuli, as well as nonnoxious, low-intensity stimulation. Input to the primary afferents is provided through nociceptors that are the first step in the sensory pathway of transduction of a painful stimuli to a relevant neural signal. Nociceptors occur in cutaneous, muscular, and visceral structures.

Pain centers involve widely distributed neural networks. The distinction between the lateral and medial pain systems (Vogt et al. 1993) is considered to be of paramount importance. The former may mediate primarily the sensory-discriminative components of pain, whereas the latter may mediate primarily emotional-motivational components. However, these systems are heavily interconnected, reflecting the unitary experience of pain. There has also been the suggestion that the lateral and medial pain systems are mainly responsible for processing acute and chronic pain, respectively (Albe-Fessard et al. 1985). The lateral pain system involves inputs to the thalamus and somatosensory cortex from the lateral spinothalamic tract. The medial pain system involves projections of the medial thalamic nuclei to area 24 of the anterior cingulate cortex and other forebrain areas. The anterior cingulate cortex is an extensive area of the limbic cortex overlying the corpus callosum and is involved in the integration of cognition, affect, and response selection. The descending connections of the anterior cingulate cortex to the medial thalamic nuclei and to the periaqueductal gray in the brain stem suggest that this system may also be involved in the modulation of reflex responses to noxious stimuli.

Pain may be triggered by sensory inputs, especially when acute, but may also be generated independently, especially when chronic. Sensitization effects represent hyperresponsiveness in either the peripheral or central components of the nervous system. Supraspinal sensitization effects associated with the medial pain system (Vogt et al. 1993) and related limbic structures (Chapman 1996; Gabriel 1995) seem to mediate the pain response. Thus, pain could be produced by the output of a widely distributed neural network in the brain, rather than directly by peripheral nociceptive stimuli. Importantly, the central pain control processes seem to encompass the cognitive-evaluative, motivational-affective, and sensory-discriminative systems (Melzack 2001) that characterize the pain response. The pain system is intimately related to other systems in the brain (e.g., motor, mnemonic, and social systems). Chronic pain has many elements of acute and subacute pain but is generally promulgated by additional factors, including psychological ones. Current evidence strongly supports mechanisms of central sensitization in chronic pain phenomena that are not present in the acute and subacute periods. Central sensitization is a phenomenon that has been demonstrated in both animal and human studies. Specifically, nociceptive input to the central nervous system (CNS) may be increased because of activation or sensitization of peripheral sensory afferents. This barrage of nociceptive impulses may result in sensitization of second- and third-order neurons in the CNS. In this way, sensitization may play a role in initiation and maintenance of chronic pain (Bendtsen 2002; Bolay and Moskowitz 2002; Lidbeck 2002; Melzack 1999).

Considering the high prevalence of posttraumatic headache, it is also worthwhile to mention the expanding literature on the functional connectivity between trigeminal and cervical sensory afferents that must be considered when evaluating patients with TBI-related headache. Given the frequency of comorbid cervical injury with TBI, knowledge regarding the functional neuroanatomy of neck pain as well as referred cervicogenic headache mechanisms is crucial for clinicians treating this group of patients (Fernández-de-Las-Peñas et al. 2007; Simons 2008). Animal models have shown convergence of cutaneous, musculoskeletal, dural, and visceral afferents onto nociceptive neurons in the cervical dorsal horn for the craniofacial area (Morch et al. 2007). Research has also shown convergence of cervical and trigeminal sensory afferents that clinically results in dual activation of trigeminal and cervical territory symptoms when trigeminal activation occurs as well as when cervical activation occurs (Piovesan et al. 2003). The trigeminal nerve has been found to receive afferent nociceptive input from the anterior portions of the head, the occipital nerves, and the posterior upper cervical roots. The anatomical and functional convergence of trigeminal and cervical afferent pathways may hold a key to management of a variety of primary as well as posttraumatic headache disorders (Busch et al. 2006; Goadsby and Bartsch 2008).

Traumatic Brain Injury, Chronic Pain, and Cognitive Dysfunction

Cranial trauma and TBI are associated with a high comorbidity of chronic pain problems (Lahz and Bryant 1996). As previously noted, a systematic review (Nampiaparampil 2008) found a prevalence rate of 50% for chronic pain following TBI. Headache is the primary complaint in virtually all surveys of postconcussion syndrome (e.g., Nampiaparampil 2008; Nicholson 2000c). The frequency of posttraumatic headache has been found to range from as high as 90% immediately postaccident period to as high as 44% at 6 months (Martelli et al. 1999a). Controlled prospective study data (Faux and Sheedy 2008) indicated a prevalence of 15% following mild head injury at 3 months (compared with 2% for minor deceleration injury controls), while systematic review found a notably higher rate for chronic pain, independent of PTSD and psychological factors. In addition to headache, the many other pain problems that follow trauma include back pain, complex regional pain syndrome (CRPS), and fibromyalgia, among others.

The role that pain may play in symptom presentation following TBI is gaining increasing attention, especially with regard to cognitive complaints. Several reviews of literature (e.g., Hart et al. 2000) objectively assessing these complaints were reviewed by Martelli et al. (2007b). The available evidence strongly supports the conclusion that chronic pain, especially head pain and neck pain and pain-related symptomatology, independent of TBI or neurological disorder, can and often does produce impairment of cognitive functioning. Multiple lines of evidence, including studies of acute and chronic pain, animal and human studies, experimental and clinical studies, and neurophysiological studies, support this conclusion regarding cognitive impairment. Other reviews report similar conclusions (e.g., Kreitler and Niv 2007). A summary of the converging evidence that supports this conclusion is presented in Table 24–1. Notably, attentional capacity, processing speed, memory, and executive functions, as assessed on neuropsychological tests, are the cognitive domains most likely to be affected.

It is clear that chronic pain and associated problems can complicate the symptom picture in TBI (McCracken and Iverson 2001; Miller 1990). Especially in cases of persistent sequelae following mild TBI, increasing evidence suggests that chronic head and other pain and associated problems can present a differential diagnostic challenge and contribute to or maintain symptoms. This evidence provides strong support for the argument that resolution of the postconcussive syndrome and successful adaptation to residual sequelae may rely on successful coping with posttraumatic pain and/or other pain and associated symptomatology. In addition, careful consideration of pain in the differential diagnosis of brain injury is required. Some simple basic recommendations to minimize the confounding effects of chronic pain during neurocognitive examinations are presented in Table 24–2.

These reviews indicate that the concomitants of chronic pain may be as important or more important than pain itself in producing cognitive impairment. Specifically, cognitive impairment in patients with chronic pain has been associated with mood change/emotional distress, somatic preoccupation, pain "catastrophization," sleep disturbance, fatigue, and perceived interference with daily activities that are potential sources of chronic stress, in addition to pain medications (for a review, see Martelli et al. 2007a). These associated factors have consistently been found to be more strongly associated with both cognitive complaints and impairments than is pain severity, and emerging review evidence associates these individual factors with decrements in cognitive functioning, independent of chronic pain.

For example, major depression is frequently found following mild TBI and is associated with higher postconcussion symptom endorsement, poor functional outcome, high distress levels, disability, and cognitive impairment that typically remit after effective treatment for depression (Mooney et al. 2005). Several meta-analytic studies and reviews (Banks and Dinges 2007; Kundermann et al. 2004; Verstraeten 2007; Zhang and Liu 2008) report that partial sleep deprivation impairs cognitive and motor performance, produces hyperalgesic changes, and can counteract analgesic medication effects and that slowed information processing from sleep deprivation versus hypoxemia likely explains cognitive impairments found in patients with sleep apnea.

Pain Assessment

Because pain is a complex perceptual process composed of behavioral, affective, cognitive, and sensory components, evaluation of any patient post-TBI should be conducted in a holistic fashion, including not only the patient's medical findings but also physiological, psychosocial, behavioral, and cognitive-affective aspects of functioning such as vulnerabilities and strengths. A comprehensive, biopsychosocial assessment becomes even more critical when pain is chronic and should address beliefs about a patient's condition, coping strategies, psychological adjustment, activity level, and quality of life (Gatchel and Turk 1999). Psychological assessment is a required element of pain treatment programs accredited by the Commission on Accreditation of Rehabilitation Facilities (Gonzales et al. 2000) as well as several managed care companies. Interested readers are referred to other resources for more detailed discussions of psychological aspects of pain assessment in TBI (Martelli and Zasler 2002; Martelli et al. 2007a, 2007b; Zasler et al. 2007). Table 24–3 presents a survey of general classes and useful pain assessment instruments.

Pain is a subjective experience, and the patient's self-report of pain is the cornerstone of the pain assessment. There are several important aspects of the experience of pain that should be assessed. Inquire about pain character, onset, location, duration, and factors that exacerbate or relieve pain. The clinician should also query about pain frequency and intensity, as well as interference with everyday activities. The lowest, highest, and average pain severity levels for all pain problems should be determined. Two useful methods of assessing pain intensity in adults

TABLE 24–1. Evidence of negative effects of pain on cognition in animals and humans

1. Experimental animal and human information processing/attentional capacity literature indicating that distractors that are less aversive than pain disrupt attention, as does pain.
2. Experimental rodent and other mammalian studies showing pain-related disrupted maze and other learning for both appetitive (e.g., food reward) and avoidant (e.g., shock) stimuli.
3. Experimental rodent studies showing improved performance with cessation of pain.
4. Experimental rodent and other mammalian studies showing improved performance after administration of pain-relieving medications known to disrupt cognition.
5. Experimental human studies showing improved cognitive performance after discontinuation of pain stimulus and/or administration of psychoactive opioid pain relievers.
6. Animal studies showing that stress (including chronic pain) is associated with damage to the hippocampus, inhibition of neurogenesis, and deficits in hippocampal-based memory function.
7. PTSD findings of deficits in hippocampal-based declarative verbal memory associated with smaller hippocampal volume.
8. Recent preclinical evidence showing that selective serotonin reuptake inhibitor antidepressants promote neurogenesis, reverse the effects of stress on hippocampal atrophy, and improve cognitive deficits observed in obsessive-compulsive disorder, depression, etc.
9. A majority of studies indicating pain cognitive interference effects, at least attention dysregulation, in chronic and acute pain patients. Study designs including experimental pain, neuropathic pain, neurophysiological measures, combination neuropsychological and neurophysiological measures, and reward designs helped to bolster conclusions about interference effects despite failure of most studies to use explicit response bias detection measures for pain and cognition.
10. Consistent neurophysiological studies showing specific neurophysiological (e.g., anterior cingulate cortex) effects associated with chronic pain and attentional disruption, often coexisting with other patterns, consistent with other disorders also having reasonable evidence of cognitive impairments and neurophysiological expressions (e.g., hypofrontality and depression).
11. Neural plasticity/cerebral reorganization associated with chronic pain showing functional cerebral changes (e.g., studies showing expansion of sensory cortex).
12. Neuroendocrine and hypothalamic-pituitary-adrenal [HPA] perturbation in chronic pain and evidence that pain and chronic stress (and depression) are linked via chronic stress-induced HPA dysfunction (along with evidence of combined muscle energy depletion) and serotonin deficiency (peripherally, but also centrally), along with depressed levels of somatomedin C, caused by deficit of stage 4 sleep–dependent release of growth hormone, and elevated norepinephrine response levels in fibromyalgia.
13. Neurophysiological evidence of central sensitization and disrupted pain inhibitory mechanisms associated with dysfunctional anterior cingulate cortex functioning of both anterior/ventral and posterior/dorsal quadrants (associated with cognitive and affective regulation, respectively), plus evidence that less severe and less disruptive chronic pain is associated with a greater habituation response to painful stimuli (vs. sensitization) and not associated with cognitive disruption. The newest integration of these findings links a biopsychosocial model in which genetics, learning history, and psychological variables interact, with a clear role being played by anxiety and avoidance conditioning, to produce a pattern of pain arousal that mimics obsessive-compulsive disorder, chronic or severe depression, PTSD, or high trait anxiety, with hypoaroused inhibition (anterior cingulate cortex hypofunction) of pain, obsessional thoughts, anxiety, somatic concerns, intrusive associations/memories, and disrupted allocation of attentional resources.
14. Evidence that the concomitants of chronic pain alone may account for cognitive disruption; sleep disturbance/deprivation (e.g., meta-analytic studies showing impaired attention and psychomotor function, including greater impairment compared to alcohol intoxication; studies indicating significant traitlike interindividual variability in sleep deprivation effects that are stable within individuals); pain medications; depression and anxiety; and suggestion that combinations are additive.
15. Consistent findings showing both normalization of neuropathophysiology and cognitive function (for performance and self-reported improvements in cognition) after effective pain reduction interventions.
16. Indications that chronic pain, as well as depression, is associated with structural cerebral changes. For example, chronic pain has been associated with decreased prefrontal and thalamic gray matter density and metabolic hypoactivity compared with matched controls, suggesting that the pathophysiology of chronic pain includes thalamocortical processes.

Note. PTSD=posttraumatic stress disorder.
Source. Adapted from Martelli et al. 2007b.

are the Visual Analogue Scale and the Numerical Analogue Scale. The visual scale is typically a 100-cm line often with the anchors of "no pain" at one end of the scale and "the worst pain imaginable" at the other, whereas the numerical scale solicits a rating of pain from 0 to 10, often with the same anchors. These two scales are sensitive to treatment changes and are widely used in clinical settings (Jensen and Karoly 2001; Martelli et al. 2007b). The Numerical Analogue Scale is easily administered and is recommended.

Assessment of pain problems and related complaints during the clinical interview, physical examination, or other clinical settings is typically of primary importance for the treating physician but is also relevant to other potential

TABLE 24–2. Recommendations for assessing and minimizing the confounding effects of pain during neurocognitive examination

Always assess pain when present, when posttraumatic adaptation seems compromised by pain and related symptomatology, or when limitations in daily functioning and decrements in test performance seem atypical. Clarify the frequency, intensity, and character of pain during the examination and, more generally, the characteristics of the chronic pain experience and related problems.
Assess problems that are commonly associated with chronic pain (e.g., sleep disturbance, fatigue, somatic preoccupation, anxiety, depression, pain medication effects) as these can adversely affect cognitive functioning.
Assess effort, motivation, and response bias during examination, especially with regard to symptom complaints.
Consider postponing cognitive assessment in cases in which pain and related symptomatology have not been appropriately or aggressively treated.
Use accommodating procedures during examinations when possible—for example, optimizing comfort, providing frequent breaks, allowing frequent position changes and use of personal orthotics (cushions, heating or ice pads, etc.), and modifying lighting and sound.

treatment team members. It is critical in the context of assessment to take a thorough pain history to provide an adequate foundation for identifying the responsible pain generators. An adequate history should include the individual's preinjury pain state as relevant, pain vulnerabilities, family history as germane to genetic loading risk factors for posttraumatic pain issues (e.g., history of migraine, depression, obsessive-compulsive disorder), and injury-related pain history. The following are important issues to include in the clinical interview:

- Character of pain
- Onset of pain (sudden, insidious, or always present?)
- Location of pain
- Duration of pain
- Exacerbating factors
- Relieving factors
- Time of onset of pain postinjury
- Functional impact of pain
- Frequency of pain
- Severity of pain
- Prior pharmacological agents used for the posttraumatic pain condition, dosages, and pain modulation response, if any

Ideally, corroboratory interviews should also be requested as relevant to understanding the patient's pain through "other eyes," its functional ramifications, and presentation consistency across different settings and persons.

The physical examination should take into consideration the historical record and interview data (both direct patient and corroboratory) to determine how the physical exam should be focused. The evaluating clinician should possess adequate knowledge regarding both neurological and musculoskeletal assessment if a physical exam is going to yield "usable data" that will have a positive impact on coming to an accurate diagnosis regarding the etiology of the pain and ultimately guide appropriate pain management interventions. An in-depth knowledge of appropriate examination techniques for neuropathic/neurogenic (both peripheral and central), as well as musculoskeletal sources of pain including appropriate use of inspection and palpation (superficial and deeper layers) skills, among others, is required to adequately assess this group of patients. Understanding the potential myriad sources of pain in posttrauma patients with TBI is a primary underpinning of doing a thorough pain exam, as is adequately assessing for pain response biases and psychoemotional state, both of which can significantly affect patient presentation and pain adaptation/coping.

Detailed criteria that the physician may use for the discrimination of the DSM-IV-TR diagnoses of pain disorder associated with a general medical condition, pain disorder associated with both psychological factors and a general medical condition, or pain disorder associated with psychological factors have recently been proposed (Mailis-Gagnon et al. 2008). The DSM-IV-TR pain disorder diagnoses are considered especially useful in directing treatment options (i.e., biomedical, psychosocial, or both). Particular attention should be paid to whether there may be a response bias to report pain or a hypersensitivity to pain. In clinical settings, this is usually associated with high pain severity ratings. There may be dramatic nonverbal pain behavior associated with such pain severity ratings or there may be a seeming lack of pain behavior, the patient being in good spirits and with very little or very circumspect pain behavior. There may be marked differences in pain behavior depending on whether the patient is attending to his or her pain or not. Pain typically is exacerbated by psychosocial stressors. It is important to notice if there is undue guarding or pain avoidance behavior as this may indicate adverse psychological and behavioral patterns and adaptation that perpetuate the pain condition.

Clinicians are cautioned against assumptions that commonly reported pain symptoms are due to the brain injury itself (e.g., posttraumatic headache) because pain and other symptoms are commonly produced by extracerebral injury (Martelli et al. 2004; Zasler 1999; Zasler et al. 2007). Evaluating clinicians should be familiar with both the broad array of pain symptoms that may be reported by posttrauma patients and assessment methodologies for the various types of pain seen in this population. Clinicians are referred to various other sources for a more detailed description of patient assessment methodologies for persons with TBI and pain, or pain in more general terms (e.g., Turk and Melzack 1992; Zasler 1999; Zasler and Martelli 2002; Zasler et al. 2007).

During the acute care phase, the primary pain generators in trauma patients are fractures, intra-abdominal injuries, peripheral nerve injuries, soft tissue injuries, and pain associated with invasive procedures. Pain treatment should be tailored to the degree of pain assessed and reported via metric (e.g., numeric scale) or qualitative (e.g., mild, moderate, severe, excruciating) descriptors. In the subacute setting, many of the same issues present in the acute care setting continue

TABLE 24–3. A brief sample of general classes and common instruments for assessing psychological variables relevant to adjustment and coping with chronic pain

General and specific measures of behavioral, cognitive/attitudinal, and emotional coping

Vanderbilt Pain Management Inventory (Brown and Nicassio 1987) measures chronic pain coping strategies (e.g., active, passive) and provides useful information for treatment planning and recommendations.

Cognitive Coping Strategies Inventory (Butler et al. 1989) assesses the degree to which patients engage in adaptive and maladaptive cognitive coping strategies.

Coping Strategies Questionnaire (Rosensteil and Keefe 1983) rates the frequency of engagement in 48 different behavioral and cognitive coping strategies in response to pain or physical symptom experience.

Measures of general health functioning and behavior

Millon Behavioral Health Inventory (Millon 1999), one of the most frequently used health inventories in the United States, provides information across four broad categories: basic coping styles, psychogenic attitudes, specific disease syndromes, and prognostic indices. It has good psychometric properties, a large normative database of representative medical patients, with specific disease scales developed for specific patient groups. It has recently been upgraded to the Millon Behavioral Medicine Diagnostic test (Millon et al. 2000). It assists with identification of significant psychiatric problems, making specific recommendations, pinpointing personal and social assets to facilitate adjustment, identifying medical regimen compliance problems, and structuring posttreatment plans and self-care responsibilities in the patient's social network.

Sickness Impact Profile (Bergner et al. 1981) is a behaviorally based measure of health status designed to assess both psychosocial and physical dysfunction. It has sound psychometric properties, is used widely with chronic pain patients, and can provide relevant information regarding degree of functional limitation in daily activity.

Illness Behavior Questionnaire (Pilowsky and Spence 1975, 1976), although not a pure behavioral measure, does provide useful information about attitudes, perceived reactions of others, and psychosocial variables. It delineates seven factors that include general hypochondriasis, disease conviction, psychological vs. somatic focusing, affective disturbance, affective inhibition, denial, and irritability. In addition, it has value in identifying patients who rely on illness behavior as a coping style for need procurement.

Specific pain domain inventories

Multidimensional Pain Inventory (Rudy and Turk 1989) uses a biopsychosocial conceptualization to assess relevant psychosocial, cognitive, and behavioral aspects of responses to pain and includes specific norms for different statistically derived chronic pain subtypes: interpersonally distressed with inadequate social support, globally dysfunctional coping, and adaptive coping. It includes specific norms, its classification system has been replicated with another measure (Jamison et al. 1994), and an inexpensive software scoring program is available (Rosensteil and Keefe 1983). This multiaxial classification system appears to be a psychometrically sound and objective method of integrating useful psychological information with data from multiple sources and offers benefit for matching patients to types of pain management interventions. The recent addition of a measure of defensiveness seems to increase the inventory's validity (Hopwood et al. 2008).

Profile of Chronic Pain: Extended Assessment Battery (Ruehlman et al. 2005) is an 86-item instrument with 1) 33 items assessing pain location and severity, pain characteristics (e.g., worst daily pain), medication use, health care status, the identity of the most important person in the patient's life, and functional limitations in 10 areas of daily living; and 2) 13 multi-item subscales addressing aspects of coping (e.g., guarding, ignoring, task persistence, and positive self-talk), catastrophizing, pain attitudes and beliefs (including disability beliefs, belief in a medical cure for pain, belief in pain control, and pain-induced fear), and positive (tangible and emotional) and negative (insensitivity and impatience) social responses. National stratified samples across three age groups, two survey studies providing strong evidence for the hypothesized factor structure, internal consistency, independence from response bias, validity, and the presence of normative data suggest good diagnostic and prescriptive utility.

Hendler Chronic Pain Screening Test (Green and Shellenberger 1991) assesses contribution of physical vs. psychological variables to pain behavior expressions. It represents a composite predictor approach for which ratings are derived. Higher scores reflect less objective and strong psychologically influenced or motivated pain behavior and suggest recommendations for conservative treatments with multimodality treatment programs. Very high scores typically require psychiatric referral and intervention.

Tampa Kinesiophobia Scale (Houben et al. 2005; Todd 1998) is a quick screening measure of unreasonable or irrational fear of pain and painful reinjury upon physical movement. It assesses pain phobias or avoidance-conditioned pain-related disability (i.e., unhealthy pain-maintaining habits that are a major contributor to pain-related disability) and correlates highly with similar measures. High scores, once malingering factors are ruled out, signal the need for combination therapies with emphasis on providing reeducation, countering maladaptive phobic responses, and promoting adaptive attitudes and treatment participation/cooperation (e.g., graduated exposure, cognitive reinterpretation, and systematic desensitization).

Headache Disability Rating procedure of Packard and Ham (Montgomery 1995) is a scale that estimates impairment from headache rated on frequency, severity, and duration of attacks and how activities affect functional skills and activities of daily living. It includes a modifier variable for rating motivation (i.e., treatment motivation, exaggeration/overconcern, and legal interest) that is used to adjust the total impairment rating.

Pain Disability Index (Tait et al. 1987) is a brief instrument that assesses pain-related disability. It shows good internal consistency in assessing both discretionary activities and activities more basic to daily living and survival.

Fear-Avoidance Beliefs Questionnaire (Waddell et al. 1993) is a reliable measure of fear-avoidance beliefs about physical activity and work activity that predicts disability in activities of daily living and at work, especially given high level of distress. This is another measure that helps identify persons likely to benefit from psychosocial interventions.

TABLE 24–3. A brief sample of general classes and common instruments for assessing psychological variables relevant to adjustment and coping with chronic pain *(continued)*

Pain Catastrophizing Scale (Sullivan et al. 1995) is a brief, well-researched measure of the negative mental set in the presence or anticipation of pain marked by magnification, rumination, and helplessness. Higher catastrophizing is predictive of higher pain intensity ratings, lower tolerance, higher analgesic use, poorer physical functioning and greater disability, more reports of pain interference, reduced ability to work and less general activity, and higher psychological distress and psychosocial dysfunction. Pain catastrophizing is a robust predictor of analgesic use, distress, psychosocial dysfunction, and disability and is superior in comparisons to disease severity, pain levels, age, sex, depression, or anxiety. It also demonstrates benefit as a therapeutic measure of cognitive restructuring (Tan et al. 2002).

Chronic Pain Acceptance Questionnaire (Wicksell et al. 2009) is a brief and psychometrically sound measure of the components of pain severity, interference, and emotional burden. Its two scales, activities engagement and pain willingness, as well as the total scale, were found to be strongly associated with pain intensity, disability, depression, and life satisfaction measures and explained more variance in one study than a measure of kinesiophobia (Vowles et al. 2008).

General psychological measures: mood, anger, and anxiety

Zung Self-Rating Depression Scale (Zeigler and Paolo 1995) appears well suited for medical settings and has advantages over other measures: it is shorter and simpler to administer and score, is at a lower reading level, fits well with medical and injury situations, and can be easily administered in an interview format. Items are self-ratings ranging from 1 to 4 ("Not at all" to "Most/all of time") and scored in the direction of increased depressive symptomatology (>40 raw score suggests mild depression).

Beck Depression Inventory-2 (Beck et al. 1961) is a common self-report measure that assesses depressive symptomatology. It has been reported to differentiate chronic pain patients with and without major depression (Fordyce 1979) (optimal cutoff score of 21) and has well-documented predictive validity.

State-Trait Anger Expression Inventory-2 (Skevington 1990), as well as its recent update, is a reliable, well-normed instrument for assessing the experience, expression, and control of both current state and trait anger, an underappreciated concomitant of chronic pain. Anger Expression and Anger Control scales assess four relatively independent anger-related traits: 1) expressing anger outwardly, 2) holding anger in, 3) controlling outward expression, and 4) controlling internal angry feelings. It provides information regarding how experience, expression, and control of anger may contribute to psychophysiological arousal and symptoms and increase risk for developing somatic symptoms and medical problems. Indirectly, it offers suggestions for the direction of appropriate interventions.

Beck Anxiety Inventory (Spielberger 1999) is a screening measure of severity of patient anxiety. Specifically designed to reduce overlap with symptoms of depression, it assesses both physiological and cognitive components of anxiety in 21 items describing subjective, somatic, or panic-related symptoms. It reliably differentiates anxious and nonanxious groups in a variety of clinical settings.

Perceived Stress Scale (Cocchiarella and Andersson 2001) is a widely used instrument for measuring the degree to which situations in one's life are appraised as stressful. Items measure how unpredictable, uncontrollable, and overloaded respondents find their lives and directly query current levels of experienced stress. Higher scores have been associated with greater vulnerability to physical and psychological symptoms after stressful life events.

Comprehensive personality assessment

Minnesota Multiphasic Personality Inventory-2 (MMPI-2) (Butcher et al. 1989; Dahlstrom et al. 1975) is the most widely used psychological assessment instrument in the United States. The MMPI is a 567-item (true/false) objective measure of personality function and emotional status with 10 clinical and 7 validity scales that were derived through empirical discrimination. Its predictive abilities are based on more than 50 years of actuarial data collection and analysis. It is a sensitive measure of psychological states, traits, and styles (e.g., excessive anxiety, tension, depression, hostility and problematic anger, somatization tendencies, sociopathy, substance abuse, deviant thinking and experience, social withdrawal). Through configural interpretation of the relative scale elevations, tentative hypotheses regarding personality and coping style and relative degree of particular types of psychological disturbance can be gleaned. Importantly, although the MMPI can and is frequently misused and misinterpreted (e.g., application of psychiatric norms to medical patients tends to beg psychiatric interpretations), it represents one of the most useful adjuncts to personality assessment and treatment planning. Although efforts to distinguish organic vs. psychological causes for chronic pain and use of cookbook interpretations on the basis of psychiatric patient normative data (Schreiber and Galai-Gat 1993; Vendrig 2000) represent failed applications, other significant information regarding emotional distress and coping styles can be derived.

Pain assessment measures with built-in response bias indicators

Millon Behavioral Health Inventory (Millon 1999; Millon et al. 2000) includes three built-in validity scales.

Minnesota Multiphasic Personality Inventory-2 (MMPI-2) (Butcher et al. 1989) includes seven validity scales, along with research and content scales that are potentially useful in evaluation of response bias. Arbisi and Butcher (2004) provided a rationale for the use of the MMPI in the comprehensive assessment of chronic pain, including detection of response bias or malingering. Meyers et al. (2002) provided evidence for an MMPI-derived validity index specific to chronic pain patients.

Hendler Chronic Pain Screening Test (Green and Shellenberger 1991): is a measure on which scores of 21–31 suggest exaggeration of pain symptoms, while higher scores suggest primary psychological influence of pain behavior.

to serve as pain generators. Changes in patient status in the subacute setting may reflect underlying neural changes that are adaptive or maladaptive. Maladaptive changes can result in additional pain generators (e.g., progression or increase of tonal abnormalities, or both, resulting in hypertonicity and rigidity), as well as central pain phenomena.

Pain often affects functional assessment in persons with TBI, including those with disorders of consciousness. In these patients, pain must be adequately assessed (and, of course, treated) when clinically appropriate. In persons with disorders of consciousness, pain may be associated with spasticity/posturing, fractures, pressure sores, peripheral nerve damage due to trauma or compression, soft-tissue ischemia, CRPS, contractures, and postsurgical incisional pain, among other causes. Issues of pain assessment and management in persons with disorders of consciousness remain controversial on several levels; however, there are sufficient data and experience now available to generally guide assessment as well as treatment. Current evidence indicates that persons in vegetative states cannot process pain at a secondary somatosensory cortical level, which implies that they are likely therefore unaware of the pain and additionally do not suffer. It is clear that distinctions must be made when discussing pain experience of the differences between perceiving pain and suffering (Schnakers and Zasler 2007). Persons in a minimally conscious state, however, seem to have the ability to integrate pain information in a manner that may allow them to both be aware of pain and suffer (Schnakers and Zasler 2007). The degree of the pain experience and/or suffering remains unquantifiable based on current knowledge. Specific measures for pain assessment in persons with disorders of consciousness have recently been developed, including the Nociception Coma Scale, which may facilitate both assessment and tracking of pain responses over time (Schnakers et al. 2010).

Although it may not be readily available in many clinical settings, the use of sodium amobarbital, or related agents, can be useful in distinguishing between pain associated with peripheral versus central structural pathology and pain associated with functional disorders versus central sensitization effects (Mailis and Nicholson 2002). This technique is rarely taught outside the domain of psychiatry and a few select neurology training programs and is seemingly rarely used in clinical practice even though its morbidity has been shown to be very low.

Lastly, clinicians would be wise to avoid dogmatic conclusions that any particular pain patient is malingering their pain, as there are few, if any, unambiguous indicators to state this conclusively (Nicholson and Martelli 2007). The literature regarding assessment of nonorganic pain presentations remains highly debated, including the methods for differential diagnosis of malingered pain, conscious symptom amplification of pain (whether or not for financial gain), factitious pain complaints, pain amplification due to poor coping, and somatoform and other psychogenic pain disorders.

Pain Management

The goal of pain management is to modulate and, ideally, negate the associated physical and psychological symptoms of pain, prevent chronicity, and reduce functional disability. Realistic endpoints of pain relief consistent with the clinical situation should be established. Pain management methods include nonpharmacological or pharmacological methods, or both. Clinicians should strive to identify pain generators and treat them as directly as possible versus simply treating the symptoms of pain. The simplest and least invasive pain management approach should be used whenever possible. When pharmacological agents are used, analgesia should be delivered with minimal adverse effects and inconvenience to the patient, both of which will optimize compliance.

Medical Management Issues

In the acute care setting, already compromised neurological status may limit the array of pharmacotherapeutic agents that might be appropriate to use in a patient in whom the neurosurgical and neurological status is either stabilized or static. Medications that potentially alter any aspect of the neurological assessment should be used with caution if there is a more significant brain injury, neurological instability, or both. Additionally, consideration should be given to medications with reversible effects (e.g., narcotic reversal with naloxone) whenever there is a question of medication effect versus ongoing deterioration of neurological status.

For neurologically compromised patients with response limitations, prophylactic pain management should be practiced on the basis of injuries sustained and clinical presentation. Pharmacological pain prophylaxis should also be considered in patients with disorders of consciousness (e.g., vegetative or minimally conscious states) given 1) difficulty in assessment of pain and controversies regarding pain appreciation and suffering in this patient group and 2) the negative effect of pain (even in a vegetative state) related to subcortical physiological responses to nociceptive stimuli, including increased tone and posturing, tachycardia, tachypnea, and diaphoresis, in addition to other adverse effects (Schnakers and Zasler 2007).

It is likely that the effects of medication may be partly due to a reduction in sensitization. The patient experiencing chronic pain should be treated just as aggressively as a patient with acute or subacute pain but, because peripheral pain triggers are frequently less obvious, with different modalities. With chronic pain, biopsychosocial models for assessment and management are indicated, and inclusion and integration of behavioral and psychological interventions usually optimize treatment outcome. Certainly, all clinicians should consider potential placebo as well as nocebo effects of any particular pain treatment intervention.

As patients are weaned from pain medication, pain experience can increase and acute pain generators can evolve into subacute pain generators. Ongoing attention to pain management must be continued as patients are moved to neurosurgical step-down units, inpatient rehabilitation units, or both.

Pharmacological Management

Mild pain medicines that should be considered typically include aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs). For moderate pain, the fol-

lowing may be considered: high-dose aspirin or acetaminophen, high-dose standard NSAIDs (or topical NSAIDs), newer generation NSAIDs such as cyclooxygenase-2 inhibitors, alternate NSAIDs, injectable NSAIDs, mixed narcotic analgesics with aspirin or acetaminophen (with or without caffeine), compounded topical, and tramadol. For severe pain, medications to consider would include parenteral narcotics (morphine sulfate is standard), mixed agonist antagonists (e.g., pentazocine, nalbuphine), partial agonist narcotics (e.g., buprenorphine), ketamine (intravenously or subcutaneously), antidepressants, anticonvulsants, continuous peripheral nerve blocks using local anesthetic, and/or atypical agents including, among others, cannabinoids. Although some have advocated use of certain stimulants such as methylphenidate to counter opioid-induced sedation and cognitive impairment, others have expressed concern about the potential for encouraging "speedballing." Recent reviews of pain pharmacotherapy can provide interested readers with more in-depth discussion on this important topic (Guindon et al. 2007). Some common medications used in pain management are included in Table 24–4.

Many posttrauma patients present with a number of different pain problems or pain processes, including 1) nociceptive pain associated with the normal operation of the pain system in response to a noxious peripheral stimulus or pathological process (e.g., mechanical pressure or inflammation) and 2) neuropathic or neurogenic pain resulting from the abnormal operation of the pain system associated with a primary lesion or dysfunction of the nervous system. Care should be taken to determine whether pain is idiopathic, given that such pain is often unresponsive to opioids or other pharmacological interventions.

Medications that have been used for opioid-insensitive pain include NSAIDs; tricyclic antidepressants (TCAs); newer-generation antidepressants such as venlafaxine; anticonvulsants, including carbamazepine-based derivatives, gabapentin, levetiracetam, pregabalin, and lamotrigine; and less commonly used agents such as mexiletine, among other drugs.

Adjuvant analgesics are drugs that are analgesic in specific circumstances but have primary indications other than for pain management. Adjuvant analgesics are usually combined with analgesics. Corticosteroids and anti-inflammatory medications, such as prednisone, are commonly used as short-term therapy to decrease pain and nausea and improve mood, appetite, and general sense of well-being. Adverse effects of short-term corticosteroid use include edema, dyspepsia, and neuropsychiatric changes. Patients with diabetes should be counseled about careful blood glucose monitoring while taking corticosteroids because of their hyperglycemic effect.

Antidepressants and anticonvulsants are used to manage a variety of neuropathic pain states that have not been responsive to opioid analgesics (Table 24–5). TCAs, particularly amitriptyline, have shown efficacy in the management of diabetic neuropathy and are used for other neuropathic states (Fishbain 2000a, 2000b, 2002; Lynch 2001; Mattia et al. 2002). TCAs can also manage underlying depression in pain states. Other TCAs such as nortriptyline, imipramine, and desipramine are also used. Agents with mixed noradrenergic and serotonergic properties, such as venlafaxine, have also been found effective in certain pain conditions (Fishbain 2000a, 2000b, 2002; Lynch 2001; Mattia et al. 2002). TCA adverse effects include anticholinergic effects (dry mouth, sedation), weight gain, orthostatic hypotension, and cardiac arrhythmias. Secondary amines such as nortriptyline and desipramine have fewer adverse effects and should be used in patients, such as the elderly, when there is concern for anticholinergic effects, sedation, and orthostatic hypotension. Antidepressants generally should be initiated at a low dosage and titrated up slowly on the basis of pain relief and patient tolerance.

Anticonvulsants, such as carbamazepine, gabapentin, and pregabalin, can be effective for management of neuropathic pain, particularly lancinating or paroxysmal pain. Because carbamazepine can decrease platelets, neutrophils, and red blood cells, patients who are taking carbamazepine should have complete blood cell counts performed routinely. Gabapentin has shown efficacy in diabetic neuropathy and postherpetic neuralgia and generally has a

TABLE 24–4. Medications for pain

Drug	Typical dose
Antidepressants (bedtime dose [hs] may help sleep and pain)	
Amitriptyline	75 mg qhs
Desipramine	75 mg qhs
Nortriptyline	75 mg qhs
Fluoxetine	20 mg qd
Paroxetine	20–40 mg qd
Duloxetine	60 mg qd
Analgesics	
Acetaminophen	650 mg q4–6h
Tramadol	100 mg q4–12h
Steroids	
Prednisone	20–80 mg qd
Dexamethasone	4–16 mg qd
Anticonvulsants (especially for lancinating pain)	
Carbamazepine	200 mg q8h
Valproic acid	250 mg q8h
Phenytoin	100 mg q8h
Clonazepam	0.5 mg q8h
Gabapentin	600 mg q8h
Levetiracetam	250–500 mg q12h
Lamotrigine	50–100 mg q12h
Oxcarbazepine	300–600 mg q12h
Pregabalin	300–450 mg/day
Local anesthetics	
Lidocaine	1.5 mg/kg iv
Mexiletine	225 mg q8h
Flecainide	150 mg q12h
Topical anesthetics	
Capsaicin	Topical qid
"Speed gel"	Topical tid–qid

TABLE 24–5. Opioids

Short-acting			Long-acting[a]			Mixed short- and long-acting	
	Equivalent doses			*Equivalent doses*			
Drug	Oral	Parenteral	Drug	Oral	Parenteral	Drug	Oral
Morphine	30 mg q3–4h	10 mg q3–4h	MS-Contin	90–120 mg q12h	—	Avinza (morphine sulfate)	30–120 mg/day as a single dose
Hydromorphone	7.5 mg q3–4h	1.5 mg q3–4h	Levorphanol	4 mg q6–8h	2 mg q6–8h		
Codeine	200 mg q3–4h	—	Methadone	20 mg q6–8h	10 mg q3–6h		
Hydrocodone	30 mg q3–4h	—	Oramorph SR	90–120 mg q12h	—		
Oxycodone	30 mg q3–4h	—	Oxymorphone	—	1 mg q3–4h		
Meperidine	300 mg q2–3h	100 mg q3h					
Fentanyl	im or iv		Fentanyl	Transdermal patch: 25 µg/h 45–135 mg morphine po over 24 hours			

[a]Opioid-naive adults and children of ≥ 50 kg body weight.

milder adverse effect profile, consisting of sedation and ataxia, and does not require routine laboratory work. Recent data have also demonstrated gabapentin efficacy in traumatic neuropathic pain due to nerve injury (Gordh et al. 2008). Several studies have also shown efficacy of pregabalin treatment for neuropathic pain of various etiologies (aside from its actions as an anticonvulsant and anxiolytic) (Stacey and Swift 2006; Tassone et al. 2007). As with the antidepressants, these medications should be instituted at a low dosage and titrated upward slowly on the basis of clinical response and potential side effects. Valproate, oxcarbazepine, lamotrigine, topiramate, phenytoin, and clonazepam are other anticonvulsants that also have been used for neuropathic pain.

Other agents that have more recently been recognized as adjuvants in the pharmacological management of pain include tizanidine and sodium amobarbital (see earlier discussion, p. 382). Tizanidine, an α_2-adrenergic agonist, has antinociceptive properties without producing pronounced hemodynamic changes. On the basis of experimental evidence, this drug depresses dorsal horn convergent neuronal activity, probably in part by a postsynaptic inhibitory action. Owing to the role of convergent neurons in pain processes, this could explain, at least partially, the analgesic action of this compound. It is thought to have several mechanisms of action resulting in a decrease in polysynaptic spinal cord reflex activity, including inhibition of the release of excitatory neurotransmitters from presynaptic sites and of substance P from nociceptive sensory afferents (Gray et al. 1999; Nance et al. 1994). Tizanidine has been shown to be effective in a variety of pain conditions, including fibromyalgia and myofascial pain as well as tension-type headache (Malanga et al. 2008).

Capsaicin can be used topically to help decrease pain associated with peripheral neuropathies. Capsaicin depletes peptides such as substance P that mediate nociceptive transmission. Application of capsaicin is usually associated with a burning sensation, which may be severe enough to require premedication with either an oral analgesic or a topical lidocaine cream or ointment. Patients should be counseled not to touch mucous membranes after applying capsaicin. Compounded agents, typically formulated through "compounding pharmacies," may also play a role in pain management of the post-TBI patient. Such standard formulas as "speed gel" (containing amitriptyline, lidocaine, guaifenesin, and ketoprofen) can work quite well for neuropathic or neuralgic scalp pain. Similar compounded topicals with varying ingredients such as gabapentin, ketamine, and clonidine, among other agents, may be helpful as adjuvants for various pain conditions, including neuropathic pain states such as scalp dysesthesias and CRPS, as well as musculoskeletal pain disorders. Newer-generation time-released topicals, including lidocaine patches and NSAID patches, can also be considered for certain types of posttraumatic pain, including musculoskeletal pain disorders.

Surgery produces pain by releasing pain and inflammatory mediators via damaged tissue. This pain is acute pain and improves as the wound heals and the patient convalesces. The goal of postoperative pain management is to provide continuous and effective analgesia with minimal adverse effects. NSAIDs such as parenteral ketorolac are used both intraoperatively and postoperatively to decrease the production of inflammatory prostaglandins released at the site of injury. The ketorolac dose depends on route, patient age, and weight and should only be continued at the appropriate dosage for 5 days because of the development of renal dysfunction and gastrointestinal toxicity.

Opioid analgesics are the most commonly used medications for postoperative pain, usually administered intramuscularly or intravenously on an as-needed basis. This approach can lead to delays in the patient receiving adequate analgesia because of medication administration delays and intramuscular route absorption. Patients should

be switched over to oral opioid analgesics without diet restrictions when oral administration is tolerated. Patient-controlled analgesia (PCA) is a process in which the patient is allowed to self-administer low doses of intravenous opioid analgesics to maintain analgesia (Rudolph et al. 1999). To use PCA, a patient should be sufficiently cognizant to understand the goals of PCA and understand the use of the equipment. Patients who are confused or cognitively impaired are not good candidates for PCA. The number of injections and attempted injections can be monitored for efficacy and adverse effects in addition to the patient's report of pain. Opioid analgesics can also be administered into the epidural or intrathecal space combined with local anesthetics such as bupivacaine or ropivacaine for postoperative pain management. Patient-controlled epidural analgesia may be considered in specific circumstances. The current consensus among pain specialists is that concerns regarding addiction are not generally a contraindication to opioid treatment for otherwise intractable pain. We highly recommend that patients with prior drug abuse histories or addiction-prone personalities be carefully screened if being considered for chronic narcotic treatment for pain. Lastly, we always recommend the use of a "narcotics agreement" when using such agents for pain management (Fishman and Kreis 2001; see Appendix).

Newer data indicate that pharmacotherapy for pain will likely become more sophisticated as the interactions among pharmacogenomics, ontogeny, coadministration of medication, and comorbidities such as renal dysfunction are factored into making clinical decisions about what the most appropriate pain medication might be for a particular patient (Allegaert and van den Anker 2008). The physician should aim for drug prescriptions that optimize compliance and minimize potential side effects. Particularly in cognitively impaired patients, physicians should aim for once- to twice-a-day drug dosing. Patients should be counseled on the goals of treatment and what to expect regarding adverse effects, especially constipation with opioid analgesics or gastrointestinal side effects with NSAIDs. Fears regarding dependence should be openly discussed, as should any sexual function side effects. Ideally, the clinician should aim for decreasing polypharmacy; however, when appropriate, combination drug regimens should be considered. It is critical to ascertain whether patients are taking their medicine correctly (e.g., taking scheduled medicine on an as-needed basis) and/or supplanting their prescribed medications with over-the-counter products.

Nonpharmacological Management

A wide variety of psychological, behavioral, physical (e.g., physiotherapy, exercise, chiropractic, and massage), or other medical interventions may be beneficial in the treatment of chronic pain. In this chapter, we focus on what we think are the most promising behavioral and medical treatments. For fuller review, readers may consult more comprehensive summaries (McQuay and Moore 1998), a review of evidence-based recommendations for management of chronic nonmalignant pain (American Society of Anesthesiologists Task Force 2010; College of Physicians and Surgeons of Ontario 2000; Fishbain 2000a, 2000b, 2002; Martelli et al. 2004, 2007a, 2007b; Recla 2010; Zasler et al. 2007), or the many systematic reviews prepared for the Cochrane Collaboration (2002).

Depending on the etiology of the pain generator in question, numerous nonpharmacological approaches may be considered in the management of pain conditions, including use of physical agents and modalities, injection therapies, exercise, biofeedback, adaptive equipment, and/or psychological interventions. These treatment modalities should all be given adequate consideration in conjunction with possible pharmacological alternatives if physicians are to develop adequate functionally oriented treatment regimens for addressing chronic pain issues in persons with TBI.

It should be emphasized that pain is a highly aversive condition. Mitigation of especially resistant and severe chronic pain can be extremely challenging and often unsatisfactory. Hence, search for pain relief can lead to both desperation on the part of persons with pain and premature claims of efficacy by practitioners and proponents of particular treatment modalities. Importantly, reviews of efficacy and evidence-based reviews, as well as clinical knowledge and common sense, should be relied on to guide the specific use of these interventions for specific diagnostic syndromes and conditions.

Physical modalities. Physical agents used to modulate pain may include superficial heat and cold. The most common modalities used are hot/cold packs, heat lamps (incandescent or infrared), paraffin baths, laser therapy, and cryotherapy. Hydrotherapy interventions for pain management may involve prescription of whirlpool or contrast baths. Various diathermy techniques may also be used to facilitate pain control, including ultrasound, phonophoresis, and short-wave and microwave diathermy (Weber and Allen 2000). There are also a number of electrical stimulation techniques used in pain management such as transcutaneous electrical nerve stimulation and iontophoresis that are commonly used as adjuvants for pain control (Mysiw and Jackson 2000).

Cranial electrotherapy stimulation (CES) is a treatment for pain reduction that, unlike transcutaneous electrical nerve stimulation, targets CNS function. It involves attachment of electrodes carrying microcurrent across the scalp and induces an approximate 15-Hz cortical rhythm. A large number of studies, many well controlled, have examined CES since the 1970s. Findings from these studies indicate that this relatively unknown and underutilized intervention is a safe and surprisingly useful treatment for pain, especially chronic pain and its associated symptomatology of anxiety, depression, and insomnia (Kirsch 1999; Kirsch and Smith 2000; Rosen et al. 2009).

Physical modalities tend to play a more predominant role in the treatment of pain complaints of musculoskeletal origin and may include traction, manual medicine techniques (e.g., joint manipulation, myofascial release techniques, and strain counterstrain), and massage (Atchison et al. 2000). Injection techniques, including intra-articular, periarticular, peritendinous, ligamentous/fibrous tissue (i.e., prolotherapy), and trigger point, can all be used in various types of musculoskeletal pain disorders. Newer techniques, such as injection of platelet-rich plasma, seem promising for musculotendinous injury-related pain (Mishra et al.

2008). Occipital neuralgia is a common contributor to posttraumatic headache and can often be effectively remediated via anesthetic injection (Young et al. 2008). Axial injections such as epidurals and zygapophyseal joint and sympathetic blocks may all be relevant considerations for pain treatment in this population, depending on the presumptive pain generators (Lennard 1994).

Exercise is an underappreciated and underprescribed treatment intervention (e.g., DeLateur 2000; Gordon et al. 1998; Philadelphia Panel Evidence-Based Clinical Practice Guidelines 2001), especially in persons post-TBI with pain complaints. Exercise can play a significant role in controlling pain, both on a central and a peripheral basis, and in commensurately improving weight control, affect, and general state of health and well-being. Adaptive equipment such as reachers, sock aides, long-handled scrubbers, and/or brushes as well as ergonomically modified work environments are a few of the many different interventions that may also facilitate greater pain modulation and improved function (Trombly 1995). Newer and seemingly surprising techniques such as vestibular stimulation have also been used to treat neurogenic central pain (McGeoch et al. 2008).

Fear of pain and related pain- and anxiety-based avoidant behaviors often represent significant impediments to recovery through decreased activity that can prevent the normal restoration of function and perpetuate painful experience. Graduated activity programs that combine reeducation; anxiety-reduction procedures such as graduated exposure, cognitive reinterpretation, and promotion of adaptive attitudes; and treatment participation and cooperation are especially helpful (Martelli et al. 1999b).

Behavioral-psychological management. Behavioral treatment interventions in persons with TBI and concomitant chronic pain typically begin with an assessment of relevant treatment issues (e.g., personality variables, social support) and facilitation of the patient-therapist relationship. A detailed clinical interview; personality, emotional status, and coping measures; and specific pain assessment instruments may be supplemented by psychophysiological assessment (e.g., examination of muscle tension or electromyography for different muscle groups). These results are integrated into a specifically tailored treatment plan that provides a framework for treatment, defines goals and patient and therapist expectations and sequences, and provides psychoeducational information about the particular type of chronic pain and rationale for treatment (Gonzales et al. 2000; Martelli et al. 1999a).

Although there is an abundance of available treatment outcome studies (e.g., van Tulder et al. 2001), relatively few specifically examine the behavioral treatment of pain after TBI. However, the available literature suggests that, with the exception of some reports of greater treatment resistance, there are mostly similarities in clinical presentations, pathophysiologies, and treatment responses for persons with chronic pain who do and do not have an associated TBI (Andrasik 1990, 2010). Especially in cases of posttraumatic pain, the severity and frequency of pain attacks and chronic pain-related sequelae such as coping abilities, depression, and anxiety may be significantly improved by combined psychological treatment protocols (Eccleston et al. 2003; Jenson et al. 1987; Lazarus and Folkman 1984; Martelli 1997; Rosensteil and Keefe 1983; van Tulder et al. 2001). Supportive counseling that begins early after trauma and is continuous results in better patient response (e.g., Rosensteil and Keefe 1983), and combination treatments appear to increase likelihood of benefit (e.g., Grayson 1997).

McQuay and Moore (1998) and Martelli et al. (2007b) reviewed various behaviorally based chronic pain treatment interventions for which efficacy data are available. Some authors have more systematically reviewed the evidence supporting the utility of these behavioral interventions (e.g., Eccleston et al. 2003; Kreitler and Kreitler, 2007; van Tulder et al. 2001). Table 24–6 includes a summary of frequently used strategies for which there is empirical support.

Conclusion

For uncomplicated cases in which the patient has well-defined and manageable pain triggers and no significant psychological interaction, pain can often be managed medically. However, for most cases of chronic pain, approaches to chronic assessment and management ideally will make use of a biopsychosocial perspective (Gatchel and Turk 1999; Gatchel et al. 2007; Martelli et al. 2007b). Biopsychosocial models conceptualize health and illness as occurring in a dynamic and interactive system of interdependent biological, psychological, and social subsystems. In this conceptualization, each subsystem reflects individual differences and variabilities, and pain experience can have multiple expressions and causal pathways. From this perspective, the most suitable interventions are ones that are offered holistically, addressing function in somatic, psychological, and psychosocial domains.

A wide variety of pharmacological and other medical or physical interventions exists; many of the more useful and promising ones have been reviewed in this chapter. Currently, multicomponent treatment packages are the treatment choice for chronic pain (Martelli et al. 2007b; Miller 1993, 1998, 2000). The most promising current interventions are combination treatments that are holistic in nature (targeting not only the pain but also the patient's reaction to it within daily life).

Increasing evidence supports an interactive biological and psychological conceptualization of chronic pain that represents a convergence of findings across multiple specialties (Nicholson 2000a). Most forms of chronic pain are now considered to include a hyperresponsiveness of the pain system, involving "windup" or sensitization in the CNS or brain (e.g., Jay et al. 2001; Nicholson 2000a, 2000b, 2000c; Nicholson et al. 2002), along with dysregulation in pain inhibitory mechanisms. Conceptually, the thrust of current efforts in chronic pain management seem to be toward "desensitization" of the CNS through combination treatments. Table 24–7 offers a preliminary classification model that has been found useful in our treatment planning, especially for more challenging chronic pain situations. It offers an intuitively appealing classification system for conceptually organizing the wide variety of available treatment interventions and in planning combination treatments.

The emotional disturbances associated with pain are also frequently comorbid with TBI, highlighting the

TABLE 24–6. Summary of useful behavioral treatments for chronic pain

Patient education: The most modifiable pain-contributing factor is the stress reaction component. The best treatment packages generally contain elements targeting numerous factors. Posture may be addressed by awareness training. Stress management can assist with reducing sympathetic arousal/discharge that exacerbates pain. Accurate information and expectancies help with this and also assist with coping with pain more adaptively. Education about expected symptoms and course after mild traumatic brain injury has been shown to reduce the anxiety and selective attention and misattribution that can unnecessarily prolong symptoms (Mittenberg et al. 1998).

Biofeedback: Extensive research supports the utility of EMG or thermal biofeedback for headache pain and chronic musculoskeletal pain disorders more generally. The forehead, trapezia, frontal-posterior neck, and neck areas are frequent EMG feedback sites. Patterns of pathophysiological neuromuscular activity that underlie pain complaint and functional limitations, which can be remediated through feeding back physiological information to allow self-correction, include the following: 1) stress-related hyperarousal in musculoskeletal or other physiological systems; 2) postural dysfunction; 3) hyper- or hypotonicity induced by reflex systems activated by inflammation, active trigger points, and cumulative strain or recurrent trauma; 4) learned guarding or bracing to mitigate anticipated pain or injury; 5) learned inhibition or avoidance of muscle activation/activity; 6) chronic compensation for joint hypermobility/hypomobility (e.g., muscles taking over the role of damaged joint tissue); and 7) faulty motor schema and muscle imbalance reflecting development of one or more of the preceding syndromes and resulting in the lack of coordination and stability between typically coordinated muscle groups. Recent data indicate that EEG biofeedback and associated EEG-driven stimulation offer efficacy in treatment of some persistent pain and persistent postconcussive symptoms (DeVore 2002; Nestoriuc et al. 2008; Othmer and Othmer 2005). Finally, evidence has been reported that individuals can gain specific voluntary control over rostral anterior cingulate activation to directly control pain perception in severe, chronic clinical pain (Decharms et al. 2005). Newer techniques, including virtual reality biofeedback in chronic pain have also shown efficacy (Steffin 2008).

Relaxation training: Progressive muscle relaxation is the most studied relaxation procedure (Blanchard 1994). It involves the systematic tensing and relaxing of various muscle groups to elicit a deepening relaxation response, usually with combination of muscle groups and addition of diaphragmatic breathing to shorten the protocol. Meta-analytic reviews generally conclude that relaxation training and biofeedback training are equally effective. Relaxation training presumably serves to 1) reduce proprioceptive input to the hypothalamus, thereby decreasing sympathetic nervous system activity and 2) directly reduce muscle tension or preheadache vasoconstriction (e.g., Auerbach and Gramling 1998; Ham and Packard 1996; De Tommaso et al. 2008).

Operant treatment: Treatment based on the operant model (e.g., Fordyce 1974, 1976) requires altering environmental contingencies to eliminate pain behaviors (e.g., verbal complaints, inactivity, and avoidance) and reward well behaviors (e.g., incrementally increased exercise and activity level).

Cognitive-behavioral treatments: Cognitive approaches incorporate the physical, psychological, and behavioral aspects of the pain experience in promoting patient self-management of pain (Kreitler and Kreitler 2007). They typically emphasize learning self-regulation and self-control skills and taking greater personal responsibility for lifestyle habit change, especially with regard to identifying and replacing maladaptive beliefs about pain. Specific training is provided in cognitive strategies and skills to replace such inappropriate negative expectations and beliefs as catastrophization and associated magnification, rumination, and helplessness that maintain physiological arousal and maladaptive avoidance and illness behaviors that complicate symptom resolution (e.g., Holroyd and Andrasik 1978; Keefe 1996; Turk 2004). A comprehensive multimodal approach should include education, skills acquisition, cognitive and behavioral rehearsal, homework, and generalization and maintenance (Brown and DeCarvalho 2006). Interestingly, Smith and Haythornthwaite (2004) in a review of clinical trials suggested that aggressive management of sleep disturbance reaches beyond improvement in sleep. A growing literature supports efficacy of cognitive-behavioral therapies for pain and sleep management in patients with chronic pain, and this relationship is reciprocal such that treatment of either holds promise in improving both.

Social and assertiveness skills training: Skills training may help some patients with more effective communication of needs. Increased need fulfillment decreases distressful emotions, reducing the physiological arousal that contributes to pain experience (Miller 1993).

Imagery and hypnosis: By using a combination of autohypnosis, suggestions of relaxation, and visual imagery, patients are generally instructed to visualize the pain (i.e., give it form) and focus on altering the image to reduce the pain. Imagery-based treatment is most effective after establishment of a good therapeutic alliance to facilitate compliance (Forsa et al. 2002; Martin 1993; Olness et al. 1999).

Habit reversal: These treatment packages teach pain patients to detect, interrupt, and reverse maladaptive habits (e.g., maladaptive head/jaw posture, jaw tension, and negative cognitions). Specific skills are taught to reverse poor functional habits and stressful thoughts as well as feelings that precipitate or perpetuate them (Gramling et al. 1996).

Note. EEG=electroencephalography; EMG=electromyography.

importance of a biopsychosocial perspective. Such a perspective allows for a holistic conceptualization of the patient, incorporating multimethod, multimodal assessments that facilitate individualized treatment planning. Treatment goals include not only reduction of or relief from pain but also increased self-control, increased adaptation to life changes secondary to pain and brain injury, and improved functioning and quality of life. There is a pressing need for more research on topic and skills training for all professionals as relevant to their roles in the care of persons with TBI and pain disorders. Tyrer and Lievesley (2003), among others, recommended development of specific pain management facilities designed for persons with brain injuries. In the meantime, this chapter can promote familiarity with and understanding of biopsychological approaches to the assessment and management of pain in persons with TBI. We hope this will assist with making appropriate referrals and promoting effective carryover and integration of pain management principles into care of persons with concomitant TBI.

TABLE 24–7. A desensitization model for chronic pain treatment interventions

Desensitizing peripheral nervous system procedures Electromyography biofeedback; various relaxation and imagery procedures; transcutaneous electrical nerve stimulation
Desensitizing central nervous system medications Antiepileptic drugs, tizanidine hydrochloride, sodium amobarbital (Amytal), neuroimmunomodulators, selective serotonin reuptake inhibitors, etc.
Desensitizing behavioral activity procedures Operant behavioral activity programs; graduated exposure and graduated activity programs
Desensitizing psychotherapeutic procedures Emotional desensitization of catastrophic reaction to injury and pain and other fears and trauma; splinting of emotional reactions and calming of catastrophic reactions and hypervigilance to pain; specific formal pain and fear desensitization procedure
Desensitizing neurophysiological procedures Cranioelectrotherapy stimulation: consider electroencephalography biofeedback or adjunctive procedures such as sound and light (audiovisual stimulation), transcranial magnetic stimulation, and brain electrical stimulation

KEY CLINICAL POINTS

- Pain is a multidimensional, subjective experience mediated by emotion, attitudes, and other perceptual influences. It reflects complex biopsychosocial interactions of genetic, developmental, cultural, environmental, and psychological factors. Variability in pain responses is the rule.
- The neuroanatomical pathways associated with central nervous system pain perception are complex and not completely understood but include a matrix involving cortical and subcortical structures as well as spinal mechanisms.
- Chronic pain may not be associated with obvious tissue pathology and may be characterized by maladaptive protective responses or pain behaviors, protracted courses of medication use and minimally effective medical services, and marked behavioral or emotional changes.
- Chronic pain may be associated with peripheral or central sensitization effects in which hyperresponsiveness of the pain system develops.
- Emotional disturbances associated with pain often are comorbid with traumatic brain injury (TBI), highlighting the importance of a biopsychosocial perspective. Both reactive psychological and organic factors must always be considered, and the pitfalls of mind-body dualism should be avoided.
- An adequate history will include determination of preinjury pain state, injury-related pain history, pain vulnerabilities, and family history as germane to genetic loading risk factors for posttraumatic pain issues (e.g., history of migraine, depression, obsessive-compulsive disorder).
- Head pain and other symptoms post-TBI are commonly produced by extracerebral injury.
- Chronic pain, especially head and neck pain and associated symptoms, can produce cognitive impairment independent of TBI or neurological disorder. Attentional capacity, processing speed, memory, and executive functions are most likely to be affected.
- The concomitants of chronic pain may be at least as important as the pain itself. Sleep disturbance, mood change and emotional distress, somatic preoccupation and pain catastrophization, fatigue, and perceived interference with daily activities are especially important as potential sources of chronic stress.

- Persons with disorders of consciousness may experience pain as a result of spasticity/posturing, fractures, pressure sores, peripheral nerve damage due to trauma or compression, soft-tissue ischemia, complex regional pain syndrome, contractures, post-surgical incisional pain, or other causes.
- The goals of pain management should be to modulate and, ideally, negate the associated physical and psychological symptoms of pain, prevent chronicity, and reduce functional disability.
- A holistic conceptualization of pain incorporates multimodal assessments; efforts to first identify any pain generators and treat them as directly as possible; and individualized treatment planning with consideration of combined pharmacological and non-pharmacological treatment modalities. Goals of treatment include reduction of or relief from pain, increased self-control, increased adaptation to life changes secondary to pain and brain injury, and improved functioning and quality of life.
- There are no currently available unambiguous indicators of malingering. The literature regarding assessment and differential diagnosis of malingered pain remains highly debated. Therefore, it is advisable to avoid dogmatic conclusions about pain malingering in individual patients.
- Pending the development of specific TBI pain management facilities, it is hoped that promotion of wider understanding of biopsychological approaches to pain assessment and management will assist clinicians in making appropriate referrals and will enhance the effective carryover and integration of pain management principles in TBI treatment.

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Appendix 24–1

PATIENT AGREEMENT FOR CONTROLLED SUBSTANCE PRESCRIPTION

Controlled substance medications (i.e., opiates, tranquilizers and barbiturates) are very useful but have a high potential for misuse and are, therefore, closely controlled by local, state and federal governments. They are intended to relieve pain, thus improving function and/or ability to work. The purpose of this agreement is to protect your access to controlled substances, as well as, protect our ability to prescribe them to you. Because these drugs have the potential for abuse or diversion, strict accountability is necessary. In order for Dr. Zasler to consider prescribing controlled substances or continue to prescribe controlled substances to you, there must be agreement to the following terms:

I, therefore, agree to the following:

1. I am responsible for the controlled substance medications prescribed to me. If my prescription is lost, misplaced, or stolen, or if I "run out early," I understand that it will not be replaced. I will take my medication as prescribed and not take additional doses without first having it approved by Dr. Zasler. I understand that misuse could result in serious medical complications including my death.

2. Refills of controlled substance medications:

   Will be made only during regular office hours Monday through Friday, 9am - 4pm in person, once a month, during a scheduled office visit. Refills will not be made at night, on weekends, or during holidays. No phone refills on opiates are legally permissible.

   Will not be made if I "run out early," or "lose a prescription," or "spill or misplace my medication." I am responsible for taking the medication in the dose prescribed and for keeping track of the amount remaining.

   Will not be made as an "emergency," such as on Friday afternoon because I suddenly realize I will "run out tomorrow." I will call at least twenty-four (24) hours ahead if I need a refill.

   Will only be made by Dr. Zasler's office unless so directed by Dr. Zasler or one of his staff.

3. I will establish an ongoing relationship with one pharmacy and get my controlled medicine refills only at that pharmacy. I understand that in the context of monitoring my medications, I agree to waive any applicable privilege or right of privacy and give permission for my provider and pharmacy to cooperate fully with any city, state or federal law enforcement authorities.

4. It may be deemed necessary by my doctor that I see a medication-use specialist at any time while I am receiving controlled substance medications. I understand that if I do not attend such an appointment, my medications may be discontinued or may not be refilled beyond a tapering dose to completion. I understand that if the specialist feels that I am at risk for psychological dependence (addiction), my medications will no longer be refilled.

5. I agree to comply with random urine, blood, saliva and/or breath testing, documenting the proper use of my medications as well as confirming compliance and absence of use of alcohol and other drugs including illicit substances (e.g. marijuana, cocaine, etc.). I agree that I am ultimately responsible for the costs associated with such testing if my insurance does not cover such testing.

6. I understand that driving a motor vehicle may not be allowed while taking controlled substances/ medications (i.e. if you become in any way impaired as related to your driving skills) and that it is my responsibility to comply with the laws of the state in which I am in while taking the prescribed medications.

7. I agree not to share, sell or trade my prescribed medication for money, goods and/or services. I will also safeguard my medication from theft, loss or potential misuse (do not leave your medicine where others can access it…particularly children).

8. I understand that if I violate any of the above conditions, my prescription for controlled substance medications may be terminated immediately. If the violation involves obtaining controlled substance medications from another individual, or the concomitant use of non-prescribed illicit (illegal) drugs, it may also be reported to my physicians, medical facilities and appropriate authorities.

9. I understand that the main treatment goal is to reduce pain and improve my ability to function and/or work. In consideration of this goal, and the fact that I am being given a potent medication to help me reach my goal, I agree to help myself by the following better heath habits: exercises, weight control, and avoidance of the use of tobacco and alcohol. I must also comply with the treatment plan as prescribed by my physician. I understand that a successful outcome to my treatment will only be achieved by following a healthy lifestyle.

10. I understand that the long-term advantage and disadvantages of chronic opioid use have yet to be scientifically determined and my treatment may change at any time. I understand, accept, and agree that there may be unknown risks associated with the long-term use of controlled substances and that my physician will advise me of any advances in this field and will make treatment changes as needed.
11. I have been fully informed by Dr. Zasler and his staff regarding psychological dependence (addiction) of controlled substance medications, which I understand is rare. I know that some individuals may develop a tolerance to the medications, necessitating a dose increase to achieve the desired effect and that there is a risk of becoming physically dependent on the medication. This will occur if I am on the medication for several weeks. Therefore, when I need to stop taking the medication, I must do so slowly and under medical supervision or I may have withdrawal symptoms.
12. I agree to be treated with alternative methods, either drug or non-drug in nature, as they become available, and at the recommendation of Dr. Zasler, even if my pain condition is modulated by the use of opioid medication of any type.

I have read this document and I fully understand its content and the consequences of violating the terms of this agreement which include potential discontinuation of prescription of controlled substances by Dr. Zasler to the patient in question and possible termination of the physician patient relationship.

Patient Name (printed): _____

Patient Signature: _____ Date: _____

The above terms and conditions have been discussed with, and understood by, the aforementioned patient:

_____ Date: _____
Nathan D. Zasler, MD
Medical Director, CCCV and TOLS

Note: **This is a sample opiate agreement and does not constitute medical or legal advice per se.**

CHAPTER 25

Sexual Dysfunction

Nathan D. Zasler, M.D.
Michael F. Martelli, Ph.D.

TRAUMATIC BRAIN INJURY (TBI) MAY ADVERSELY affect the expression of sexuality and/or sexual functions because of a variety of different factors. A TBI may affect myriad aspects of functioning germane to sexual expression, including cognitive, emotional, behavioral, physical, and psychosocial functioning. The complexity of these factors, not only singly but also integrated into their influence on human behavior, presents clinical assessment and treatment challenges as well as methodological challenges for research (Sandel et al. 2007). Brain injury may produce sexual dysfunction at the genital level as well as adversely affect expression of sexuality at the nongenital level. Ultimately, the mediating factors in these functional alterations include disruption of neuroanatomical pathways or aberrations in neurophysiological function, or both, as a result of the TBI. To better comprehend the effect of brain injury on sexuality, one must first understand the basic neuroanatomical pathways and neurophysiological mechanisms that are involved in the mediation of sexual function.

Appropriate neuromedical, psychiatric, and rehabilitative interventions should be available to the TBI patient population to allow for the maximal reintegration into preinjury sexual lifestyles at the personal, family, and community levels. Professionals must address the area of sexuality as they do other functional areas of human "performance," including mobility, activities of daily living, and bowel and bladder function, to provide a comprehensive approach to the problem and minimize any resultant functional impairment. Abnormal and/or inappropriate sexual behavior typically affects not only the patient but also potentially his or her spouse, family, and/or caretakers. Attitudes regarding sex and sexuality often serve as obstacles to dealing with these important issues in a structured, educated, and timely fashion (Johnson et al. 2006). By providing appropriate early intervention after trauma and appropriate follow-up, the professional allows for better adjustment to and treatment of postinjury sexuality issues.

Sexual Response Models

Several models that have been posited to outline the normal sexual response cycle deserve mention within the context of a general discussion of sexuality and TBI. Masters and Johnson (1966) proposed a four-stage model of sexual response, which they described as the human sexual response cycle. They defined the four stages of this cycle as excitement/full arousal, plateau, orgasm, and resolution. Their research showed no difference between Freud's purported "vaginal orgasm" and "clitoral orgasm"; the physiological response was identical, even if the stimulation was in a different place. Masters and Johnson's findings revealed that men undergo a refractory period following orgasm during which they are not able to ejaculate again, whereas there is no refractory period in women. This makes women capable of multiple orgasm. They also were the first to describe the phenomenon of the rhythmic contractions of orgasm in both sexes occurring initially in 0.8 second intervals and then gradually slowing in both speed and intensity.

In 1979, Kaplan added the concept of desire to the model and condensed the response into three phases: desire, arousal, and orgasm. Kaplan's framework has been called into question for women for a number of reasons. First, it assumes that men and women have similar sexual responses, and hence it could lead to erroneous conclusions about normal sexual behavior in women. Second, many women do not move progressively and sequentially through the phases as described. Last, as a largely biological model, the Masters and Johnson and Kaplan frameworks have been criticized because they do not take into account nonbiological experiences such as pleasure and satisfaction, nor do they place sexuality in the context of the relationship.

The aforementioned models have been termed *linear models* of sexual response. In 1997, Whipple and Brash-McGreer proposed a *circular sexual response* pattern for

women. This concept is built on the Reed model, which comprises four stages: seduction (encompassing desire), sensations (excitement and plateau), surrender (orgasm), and reflection (resolution) (Sandel et al. 2007). By making Reed's model circular, Whipple and Brash-McGreer demonstrate that pleasant and satisfying sexual experiences may have a reinforcing effect on a woman, leading to the seduction phase of the next sexual experience. If the reflection phase is inadequately pleasing/arousing, then the woman may not have a desire to repeat the experience (Whipple and Brash-McGreer 1997).

Nonlinear models for sexual response have also been proposed; in particular, Basson's (2001) model encompassed factors including emotional intimacy, sexual stimuli, and relationship satisfaction. This model proposes that the female response cycle is much more complex and circuitous than the male sexual response cycle, with the former being significantly affected by psychosocial factors such as relationship status, prior sexual experiences, and self-image.

Sexual Neuroanatomy and Neurophysiology

To understand how sexual function and sexuality may be adversely affected by TBI, an appreciation of neuroanatomical, neurophysiological, and neurochemical correlates of sexual function is critical. By gaining a sense of the numerous interactions required for "normal" sexual function, diagnosis and treatment can be improved when functional difficulties occur following TBI.

Sexual Neuroanatomy

Studies involving mapping of neuronal pathways in animal models have allowed scientists to develop a better understanding of the neuronal organization of central nervous system pathways involved in controlling various aspects of sexual functioning. Retrograde and anterograde tracing techniques have allowed the identification of many such pathways. Agents such as neurotropic viruses have been used as neuronal tracers to map entire networks of neurons in various animal models. More recently, functional imaging using positron emission tomography and functional magnetic resonance imaging has corroborated that multiple areas of the brain are activated during the sexual response (Rees et al. 2007).

The multiple neural networks involved are believed to include structures in the peripheral nervous system (both autonomic and somatic), brain stem, subcortex, and cortex. (Table 25–1 lists the primary structures and their theorized behavioral correlates as related to the sexual response cycle.) Other areas, including the left inferior parietal lobule, thalamus, nucleus accumbens, caudate, and cerebellum, also play roles in the response cycle (Rees et al. 2007). Given the propensity for frontotemporal focal cortical contusion and diffuse axonal injury, it is not surprising that sexual dysfunction commonly occurs after any significant brain insult (Horn and Zasler 1990).

TABLE 25–1. Sexual neuroanatomy: substructures and theoretical behavioral correlates

Neuroanatomical structure	Neuroanatomical substructure	Theorized behavioral correlate
Cortical	Piriform cortex Frontal lobes Temporal lobes	Modulation of drive, initiation, and sexual activation
Cortical	Piriform cortex Frontal lobes Temporal and parietal lobes	Modulation of drive, initiation, and sexual activation
Subcortical	Hippocampus Amygdala Septal complex Hypothalamus	Modulation of sexual behaviors and genital responses
Brainstem	Reticular activating system Afferent input Efferent output	Maintenance of arousal and alertness and conduit for information
Peripheral nervous system	Autonomic Sympathetic Parasympathetic Somatic	Genital sexual function

Cortical structures, including the frontal, temporal, parietal, and paralimbic cortex, are involved in the mediation of sexual function. Stimulation of cortical structures has produced genital hallucinations and erections (MacLean 1975). Certain cortical structures, such as the piriform cortex, are in intimate connection with more primitive "sexual" systems, including the olfactory system. Animal studies have shown that lesions in these areas may produce hypersexuality (Mesulam 1985). The frontal lobes are intimately involved with limbic and paralimbic structures through numerous neural connections. Frontal injury may result in various behavioral abnormalities. Inferomedial frontal injury may produce disinhibited and sexually inappropriate behavior, whereas dorsolateral frontal injury typically results in impaired sexual initiation (Walker 1976). Clinical experience has revealed that certain patients with frontal injury demonstrate a compromised ability to fantasize that may impede masturbation. Observations derived from patients who have had strokes suggest that right brain injury results in a greater degree of sexual impairment (Coslett and Heilman 1986). However, frontal involvement rather than laterality may be the more significant factor (Horn and Zasler 1990).

Research has demonstrated that lesions in the nondominant hemisphere may lead to an array of deficits that compromise expression of sexuality, including dysprosody, visuoperceptual problems, and anosognosia (i.e., lack of awareness of deficit secondary to neurological injury or disease) (Zasler 1991). Additionally, the nondominant temporal lobe has been theorized to be the sexual activa-

tion center for the brain (Cohen et al. 1976). Lesions in the dominant hemisphere may produce aphasias and apraxias, thereby compromising both communication and motor performance (Zasler 1991).

The midbrain central gray or periaqueductal gray has been shown to be involved with control of both male and female sexual function. Stimulation of this area can result in elicitation of sexual responses. These neurons have extensive connections with brainstem sites and also have significant projections to other subcortical structures (McKenna 2001).

Subcortical structures, including the hippocampus, amygdala, septal complex, and hypothalamic nuclei, play important roles in mediation of sexual function. MacLean (1975) hypothesized that penile tumescence is modulated by the hippocampus (Steers 2000). The septal complex has been theorized to be involved in erection as well as pleasurable sexual sensations similar to orgasm (Heath 1964; Penfield and Rasmussen 1950; Steers 2000). The amygdala has been studied quite extensively through ablation and stimulation studies. Among the classic studies were those involving removal of the anterior temporal lobes, resulting in so-called Klüver-Bucy syndrome, with hypersexuality as a behavioral hallmark; discrete lesions of the amygdala, however, do not seem to induce hypersexual behavior. The hypersexuality induced by large lesions of the temporal lobes is likely caused by loss of inhibitory control secondary to destruction of the pyriform cortex.

The anterior hypothalamus is involved in endocrine activity and associated copulatory behaviors. The posterior hypothalamus has been linked functionally to copulatory behaviors and precocious puberty (Bauer 1959; Boller and Frank 1982). The paraventricular nucleus of the hypothalamus contains multiple projections to the autonomic outflow as well as direct projections to pelvic autonomic and somatic efferents. The paraventricular nucleus receives extensive input from the medial preoptic area and may mediate genital as well as nongenital autonomic components of sexual arousal. Thalamic relays from sensory afferents in the ventrolateral and intralaminar nuclei have also been postulated to play important roles in normal sexual functioning (Horn and Zasler 1990). Stimulation of ascending thalamic sensory inputs has been shown to produce erection (MacLean 1975; Walker 1976). Hypersexuality has also been reported as a sequelae of thalamic lesion (Miller et al. 1986). Basal ganglia stimulation may produce complex forms of species-specific ritualistic sexual behaviors (MacLean 1975).

Brainstem structures such as the catecholaminergically "driven" pontine and mesencephalic reticular activating systems are responsible for maintaining arousal and alertness. These systems innervate limbic and frontal structures responsible for many sexually oriented behaviors. The brain stem also serves as the conduit for sexual information carried by afferent and efferent fibers (Horn and Zasler 1990). Injury to brainstem pathways can result in decreased ability to prepare the organism for processing incoming information. This fact takes on additional importance given the evidence supporting the need for activation within certain limbic and cortical structures for normal libido and potency (Coslett and Heilman 1986; Miller et al. 1986). There is a discrete population of neurons in the rostral medulla that tonically inhibit spinal sexual reflexes through serotonergic mediation. Studies have demonstrated a role of the nucleus paragigantocellularis in the medulla in modulating normal sexual functioning (McKenna 2001).

The peripheral autonomic and somatic nervous systems comprise the remaining structures involved with sexual function. Penile and clitoral erection are influenced by sensory innervation through the pudendal nerve, proerectile parasympathetic innervation, antierectile sympathetic innervation, and somatic innervation that contributes to penile rigidity. Autonomic activity is mediated through the sympathetic and parasympathetic nervous systems. Sympathetic fibers emanate from the T10 to L2 level and from the inferior mesenteric ganglion and merge to form the hypogastric plexus and provide innervation to the testes, prostate, seminal vesicles, and vas deferens. Parasympathetic innervation occurs via the nervi erigentes formed by the preganglionic fibers that originate in the intermediolateral nuclei of the sacral spinal cord between S2 and S4. These fibers innervate the penis, prostate, seminal vesicles, and vas deferens. An afferent parasympathetic system also exists via the posterior roots at the S2 to S4 level. The pudendal nerve, which arises from S2 to S4, carries somatic innervation in both sexes and provides motor innervation to pelvic floor musculature with the sensory dermatomes being supplied by S2 to S5. The pudendal nerve becomes the dorsal nerve distally in both the female and the male (Goutier-Smith 1986). In females, the sympathetic nerve supply is mixed; however, the parasympathetic nerve supply is through the pelvic nerves via the uterine and hypogastric plexi. The uterus and ovaries receive only sympathetic innervation, whereas other genital structures receive mixed autonomic innervation (Horn and Zasler 1990; Rees et al. 2007; Zasler 1991).

Sexual Neurophysiology

The major pituitary hormones involved in the regulation of sexual function include follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin. These glycoproteins regulate levels of gonadal hormones, specifically testosterone in males and estrogen in females. Testosterone secretion is stimulated by the effect of LH on the cells of Leydig in the testes. FSH acts on the seminiferous tubules complementing the effects of LH relative to spermatozoa maturation. FSH and LH in females are mainly involved with the control of the menstrual cycle. Prolactin levels are suppressed in the presence of hypothalamic portal system dopamine. Prolactin secretion is increased secondary to stress, in association with certain types of seizure disorders, and as a consequence of certain medications (mainly antidopaminergic drugs such as neuroleptics). Normally, increases in prolactin exert an inhibitory effect on the hypothalamic-pituitary-gonadal axis (Horn and Zasler 1990).

Cells in the arcuate nucleus of the hypothalamus secrete gonadotropin-releasing hormone into the portal circulation and subsequently stimulate the release of both LH and FSH from the anterior pituitary. Gonadotropin-releasing hormone release is regulated by feedback from gonadal hormone levels, prolactin levels, and other extra-

hypothalamic structures in the brain stem and limbic system. Oxytocin levels are greatly increased by sexual arousal. It seems likely that oxytocin may activate penile erection at both hypothalamic and spinal sites.

Gonadal hormones play an integral role in normal sexual maturation and function. The principal male gonadal hormone is testosterone. Androgens, including testosterone, are secreted mainly by the cells of Leydig in the testes but also in smaller amounts by the ovary and adrenal glands. Testosterone is responsible for the development of the male sexual organs, secondary sexual characteristics, and behavioral patterns. Ovarian hormones consist principally of estrogens, progesterones, and small amounts of androgens, and are required for normal female sexual maturation, including sex organ development, secondary sexual characteristics, menstruation, and libido. (Please refer to Table 25–2 for a summary the origins and effects of sexual hormones.)

Neuroendocrine dysfunction has received increased attention in the last decade as a relevant clinical phenomenon following TBI, particularly in relation to the incidence, evaluation, and treatment of hypopituitarism. The literature now suggests that at least 25% of persons with TBI develop one or more pituitary hormone deficiencies (Behan and Agha 2007). Variances in prevalence data likely are influenced by differences in patient selection, normative data used, assessment methodology used, and timing of testing (Kokshoorn et al. 2010). Some researchers have theorized that trauma-induced hypopituitarism has a neuroinflammatory underpinning, linked to genetic and autoimmune factors (Tanriverdi et al. 2010). Untreated hypopituitarism is associated with significant morbidity risk and can also aggravate TBI-related impairments in other areas. Immediate hormone replacement is recommended in the clinical scenario of panhypopituitarism, hypothyroidism, adrenal insufficiency, and/or diabetes insipidus.

Anterior pituitary dysfunction may lead to compromised production of thyroid, prolactin, glucocorticoid, and growth hormones as well as sex hormones. Anterior pituitary dysfunction is often seen in association with posterior pituitary dysfunction. Hypothyroidism may manifest clinically with weight gain, bradycardia, fatigue, and cold intolerance. A decrement in production of sex hormones or hypogonadism may result in infertility, end organ atrophy, diminished libido, erectile dysfunction, and menstrual irregularities. Growth hormone deficiency is an area of neuroendocrine impairment that has attracted increased attention (Casanueva et al. 2009). This deficiency may cause cognitive impairment, loss of muscle mass, fatigue, and truncal obesity. Adrenocorticotropic hormone and cortisol production irregularities are associated with fatigue, weight loss, postural hypotension, and sleep irregularities (Acerini and Tasker 2008).

Central precocious puberty, although rare, has been reported in pediatric cases and is theorized to be a result of disinhibition of neuronal pathways to the hypothalamus with early activation of gonadotropin-releasing hormone (Acerini and Tasker 2007). Hyperprolactinemia can impede libido, sexual arousal, and orgasm and can occur as a consequence of treatment with certain medications, in particular antidepressants and antipsychotics. Adrenal axis suppression also can be secondary to stress from psychological and/or physical causes.

TABLE 25–2. Sexual neurophysiology: hormone source and effect

Hormone	Site of release	Physiological effect
Gonadotropin-releasing hormone	Hypothalamus	Stimulate release of LH/FSH
FSH	Pituitary	Promote sperm maturation
LH	Pituitary	Increase testosterone secretion
Prolactin	Pituitary	Inhibit hypothalamic-pituitary-gonadal axis
Testosterone	Testes	Promote primary and secondary male sexual characteristics and libido
Estrogen and progesterone	Ovaries	Promote primary and secondary female sexual characteristics and libido

Note. FSH=follicle-stimulating hormone; LH=luteinizing hormone.

Posterior pituitary dysfunction is more commonly observed than anterior dysfunction following TBI. Abnormalities in production of vasopression or antidiuretic hormone can result in disrupted homeostasis, and particularly in serum sodium abnormalities. Hyponatremia, predominantly secondary to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), has been reported in 2.3%–36.6% of survivors of TBI. This wide range reflects different patient selection criteria, different definitions of SIADH, and varying durations of plasma sodium monitoring following TBI. Most cases of SIADH manifest in the first 2 days after TBI, but hyponatremia can occur up to 18 days after injury. SIADH is almost always transient and is unrelated to the severity of TBI. Diabetes insipidus is well recognized to occur after TBI, with a reported frequency of 3%–26% in the acute period. Use of the gold standard water deprivation test is recommended for diagnosis of both partial and complete diabetes insipidus. Neither transient nor permanent diabetes insipidus seems to be related to anterior hypopituitarism. Diabetes insipidus may persist in a small percentage of patients, although the majority will recover normal vasopressin secretion (Acerini and Tasker 2008; Agha et al. 2004; Behan and Agha 2007).

In addition to neuroendocrine dysfunction, there are multiple neuroactive substances that may affect sexual behavior. The relationship of neurotransmitters and neuromodulators to sexual function is important also because certain pharmacotherapeutic agents may adversely affect sexual function, whereas others may be therapeutically beneficial. One peptidergic agent, orexin A (hypocretin-1), has been associated with regulation of the sleep-wake cycle and may be diminished after more severe TBI, resulting in hypersomnolence that can interfere with general functional capacities, including sexual activity (Horn and

Zasler 1990; Rees et al. 2007; Zasler 1991; Zasler and Horn 1990) (see Table 25–3).

Neuroendocrine dysfunction has long been associated with epilepsy and consequent reproductive and sexual dysfunction. Epilepsy itself may influence endocrine control centers in the brain, altering production of sex hormones. Antiepileptic drugs may also alter hormone release from the hypothalamic-pituitary-gonadal axis and directly inhibit reproductive functions through changes in steroid sex hormone metabolism and protein binding. Both sexes may experience fertility and sexual function–related issues. Some of the more frequently reported problems in females include decreased libido, polycystic ovarian syndrome, menstrual irregularities, hyperandrogenism, weight gain, and ovulatory failure. Males may have decreased libido, sperm and testicular abnormalities, and delayed sexual development (Hamed 2008; Luef 2008).

Review of Research Literature

There is a growing literature on sexual dysfunction in persons after TBI. Bond (1976), for example, examined issues of psychosocial changes arising from severe brain injury using interview assessments. He found that the level of sexual activity was not related to posttraumatic amnesia, level of physical disability, or level of cognitive impairment. Specific sexual function patterns were not examined. Rosenbaum and Najenson (1976) interviewed wives of wartime patients with either brain or spinal cord injuries (SCIs). Reduced sexual function and emotional distress were present more often in the brain injury group relative to a group of uninjured individuals. The greatest level of mood disturbance was found for the wives of men with brain injury when compared with the wives of the spinal cord–injured group and the control group. There was no significant relationship between the locus of injury and the specific area of sexual dysfunction. Oddy et al. (1978) studied 50 adults with TBI who were at least 6 months postinjury and had a minimum of 24 hours of posttraumatic amnesia. One-half of the 12 married patients reported an increase in sexual intercourse, and one-half reported a decrease. In a subsequent study, Oddy and Humphrey (1980) investigated alterations in sexual behavior 1 year after injury. Slightly less than 50% of spouses reported that they were significantly less affectionate toward their injured partners.

Lezak (1978) reported that many patients demonstrated completely absent libido, whereas others reported increases in sexual drive. Generally, altered sexual interest as well as other commonly seen posttraumatic cognitive-behavioral problems contributed to family and marital difficulties. Social adjustment 2 years after severe TBI was assessed by Weddell et al. (1980). They interviewed relatives of a group of patients after they completed a rehabilitation program. Although no direct inquiries were made regarding sexuality issues, personality changes were examined. Irritability was the most frequent behavioral alteration, followed by altered expression of affection. This study reinforced perceptions regarding the deleterious effects of poor interpersonal skills on community reentry and psychosocial reintegration commonly seen in survivors of significant TBI.

TABLE 25–3. Sexual pharmacology: drug class and clinical effect

Drug class	Clinical effect
Anabolic steroid Methandrostenolone	(–) Decreased libido
Anorexiant Amphetamines	(–) Decreased libido, impotence, ejaculatory dysfunction, anorgasmia
Anticholinergic Oxybutynin Scopolamine	(–) Inhibited erection and ejaculation, decreased libido
Anticonvulsant Carbamazepine Phenytoin	(–) Impotence and decreased libido
Antidepressant Doxepin Nortriptyline	(–) Decreased libido, delayed orgasm in women, ejaculatory and erectile dysfunction
Antihypertensive β-Blockers Clonidine Methyldopa	(–) Impotence, decreased libido, and ejaculatory dysfunction
Antiparkinsonian Bromocriptine Levodopa	(+) Generally increased libido; may also improve erectile function
Antipsychotic Haloperidol Olanzapine Quetiapine Risperidone	(–) Impotence, decreased libido, ejaculatory dysfunction, hyperprolactinemia, and priapism
Antispasticity Baclofen	(–) Impotence, ejaculatory dysfunction, and menstrual irregularities
Diuretic Thiazides	(–) Decreased libido and impotence
Estrogens	(–) Decreased libido in both sexes
H_2 antihistamine Ranitidine	(–) Decreased libido, erectile dysfunction
Nonsteroidal anti-inflammatory Naproxen	(–) Erectile problems and anejaculation
Noradrenergic agonist Yohimbine	(+) Increased libido in both sexes
Phenoxybenzamine	(–) Ejaculatory dysfunction
Progestin Medroxyprogesterone	(–) Decreased libido, impotence
Serotonergic agonists and atypical/mixed antidepressants Mirtazapine Trazodone Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors	(–)/(+) In general, decreased libido (though reports of increased libido have occurred); abnormal ejaculation/orgasm, anorgasmia, dyspareunia, impotence, painful erection, priapism

Note. +=positive; –=negative.

One of the earliest studies on alterations in sexual function after brain injury was done by Kosteljanetz et al. (1981) of a group of 19 male patients who had experienced concussions. They found that a majority of patients (53%) reported reduced libido and that a lesser but still significant percentage (42%) reported erectile dysfunction (ED). A positive correlation was noted in this study between reports of sexual dysfunction and intellectual impairment. A survey of 40 wives and mothers of male patients with brain injury (not necessarily after trauma) by Mauss-Clum and Ryan (1981) found that a large proportion (47%) of the respondents reported that the survivor was either disinterested in sex or preoccupied with it. Forty-two percent of wives also reported that they had no sexual outlet. Miller et al. (1986) suggested that sexual behavior changes were related to injury neuropathology; specifically, medial basal-frontal or diencephalic injury was more highly correlated with hypersexuality, whereas limbic injury was more likely to result in altered sexual preference. Kreutzer and Zasler (1989) developed the Psychosexual Assessment Questionnaire and administered it to 21 sexually active male patients after TBI. This 11-item questionnaire assesses changes in sexual behavior, affect, self-esteem, and heterosexual relationships. The majority of these patients reported negative changes in sexual behavior, including decreased libido, ED, and decreased frequency of intercourse. There was no relationship between the level of mood change and altered sexual behavior. Despite negative changes, there was evidence that the quality of the marital relationships was preserved.

Garden et al. (1990) studied 11 men and 4 women who had sustained TBI at least 2 months before the evaluation. Both the spouses and the patients completed a sexual history and function questionnaire. A variety of factors were assessed. Only a few significant positive correlations were found. Intercourse frequency decreased for 75% of female patients, whereas 55% of the male patients reported a decline. Although male genital sexual dysfunction rarely was reported, female spouses reported a significant decline in their ability to achieve orgasm after their partner was injured. O'Carroll et al. (1991) examined the psychosexual and psychosocial sequelae of TBI in a series of 36 patients followed for up to 4 years after injury. Using several previously validated scales, they assessed both patients and partners. Approximately one-half of all male patients scored within the dysfunctional range on the psychosexual profiles. The major psychosexual complaint was decreased frequency of sexual intimacy, including intercourse. There was a clear relationship noted between advancing patient age and psychosexual dysfunction. Neurological injury severity did not correlate highly with psychosexual complaint rate. Time since injury was positively correlated with the degree of sexual dissatisfaction among male survivors of TBI in this study.

A study by Sandel et al. (1996) demonstrated that, in a group of 52 outpatients with a history of TBI, persons with frontal lobe lesions reported an overall higher level of sexual satisfaction and functioning than those individuals without such lesions. Overall, persons with TBI in this study reported lower orgasm and sexual drive than noninjured individuals on the Derogatis Interview of Sexual Function. Sexual arousal dropped off with time postinjury. Perhaps counterintuitively, persons with right hemispheric lesions reported higher sexual arousal and sexual experiences. Elliott and Biever (1996) reviewed the literature dealing with TBI and sexuality and mainly focused on the behavioral consequences of the injury. In particular, they discussed problems with impulsivity, sexual inappropriateness, libidinal alterations, and sexual dysfunction.

A number of studies dealing with sexuality and TBI have been published by the Israeli researcher Aloni and her group at Beit Loewenstein Hospital (Aloni and Katz 1998, 1999; Aloni et al. 1999). These authors have recognized the complex underpinnings of sexual dysfunction in persons with TBI relative to the contributions of primary versus secondary sexual problems. In their 1999 study, Aloni et al. concluded that in the early postinjury phase, most individuals after severe TBI had relatively high self-ratings of self-confidence, sex appeal, and mood levels. Only 7.7% reported sexual function difficulties. The authors concluded that, on the basis of their findings and the literature on the high incidence of sexual complaints in the more chronic phases post-TBI, sexual dysfunction seen in the later stages of recovery was most probably because of "reactive behavioral changes" and not underlying organic brain damage. They also went on to argue in their second article published that year in *Brain Injury* (Aloni et al. 1999) that it was difficult to accurately differentiate between primary and secondary sexual problems after TBI and the manner in which each problem might affect sexual function.

In a study examining partner relations and functioning after SCI as well as TBI, Kreuter et al. (1998b) found that the majority (55%) of relationships in persons with TBI were established after injury. Both SCI and TBI were associated with significantly more depressive feelings compared with a noninjured control group. Overall quality of life ratings were lowest in persons with SCI. Single persons rated themselves significantly lower on global quality of life measures than those with partners. Another study by the same first author (Kreuter et al. 1998a) looked at sexual adjustment after TBI and its predictors. Ninety-two persons were studied (65 men and 27 women). Median time postinjury was 9 years. Of note is that more than one-half of the participants had a stable partner relationship at the time of the investigation. A high degree of physical independence and maintained sexual ability were the most important predictors for sexual adjustment. Common complaints included decreased erectile ability, diminished orgasmic capability, and decreased frequency of sexual intercourse.

A long-term outcome study of a small male population of TBI survivors ($n=14$) with complaints of sexual dysfunction authored by Crowe and Ponsford (1999) found that those with TBI scored lower than non-brain-injured control subjects ($n=14$) on the Sexual Imagery subscale of the Imaginary Processes Inventory. It should be noted that the researchers corrected for the level of depression via analysis of covariance. Of note was the fact that persons with TBI had lower levels of performance on the Sexual Imagery subscale of the Imaginary Processes Inventory than matched control subjects after correction for mood. The researchers concluded that sexual arousal distur-

bances might therefore exist above and beyond the disturbances to affect associated with the psychosocial effects of the TBI. That is, factors other than mood were likely mediating reported alterations in sexual function.

A long-term retrospective outcome study examining sexual dysfunction after TBI was authored by Hibbard et al. in 2000 that examined a large group of TBI survivors (n=322), both men and women, as well as a control group of nondisabled individuals (n=264). They found that age was the only variable that related to reports of sexual difficulties in individuals with TBI and men without disability. Age at onset and severity of injury were negatively correlated to reports of sexual difficulties in persons with TBI. In men with TBI and without disability, the most sensitive predictor of sexual dysfunction was level of depression. For women without disability, an endocrine disorder was the most sensitive predictor of sexual dysfunction. For women with TBI, age at injury and milder injuries predicted greater difficulties, yet depression and an endocrine disorder combined were the most sensitive predictor of sexual dysfunction. The authors concluded by emphasizing the need for broader based assessment of sexual functioning in persons post-TBI in conjunction with implementation of treatment studies to enhance sexual functioning in persons after these types of injuries.

In an article by Bell and Pepping (2001), the authors pointed out the lack of a more adequate research data on women and TBI. They noted that although most of the effects of TBI are gender neutral, there are a plethora of issues unique to women relative to endocrine, reproduction, and sexual functioning. Additionally, they endorsed the view that TBI in women would affect family dynamics differently than in men because of female roles of wife, mother, and daughter.

Simpson et al. (2001) studied 25 males post-TBI with sexually aberrant behavior and noted that this group had a significantly higher rate of psychosocial disturbance in areas of nonsexual crime and failure to return to work than a matched TBI group, with significant differences in numerous other pre- and postinjury biopsychosocial variables, including neuropsychological testing results. The authors cautioned against a simplistic explanation of sexually aberrant behavior as the product of damage to the frontal systems or premorbid psychosocial disturbance, suggesting instead that more wide-ranging assessments were needed in such patients. Other research has shown that prepubertal history of TBI is a risk factor for development of pedophilic behavior (Blanchard et al. 2003).

There is a great deal of literature on temporal lobe epilepsy (TLE); however, the patient populations that formed the bases of these studies were typically quite heterogeneous and not necessarily posttraumatic. However, given the frequency of post-TBI TLE (more than 20% of all posttraumatic epilepsy), it is important to mention the effect of TLE on sexual behavior. Herzog (1984) found that 40%–58% of males with TLE were impotent or hyposexual and that up to 40% of women had menstrual irregularities. Blumer (1970a) reported that 70% of patients with TLE reported sexual problems. The most chronic alteration in sexual behavior was hyposexuality, indicative of a loss of libido. Anecdotal observations suggest that mesial temporal involvement may be correlated with libidinal alterations in TLE; however, no well-controlled studies have confirmed this finding (Blumer 1970b; Blumer and Walker 1967). Less commonly, hypersexuality (which may be associated with surgical intervention, anterior bitemporal contusions or medication), homosexual behavior, and ictal or postictal sexual arousal have been reported.

Klüver-Bucy syndrome has been noted to occur following various forms of brain injury, including trauma; it is marked by hypersexuality and hyperorality, among other behaviors, and is often seen in association with a seizure disorder (Jha and Patel 2004). Blanchard et al. (2003) noted that pedophilic men had a statistically increased likelihood of reporting a TBI prior to the age of 13 years than did nonpedophilic men. Interestingly, they also found an association between a history of TBI in pedophilic men and both left-handedness and attentional problems.

In summary, the literature in the area of sexuality and sexual dysfunction in patients with TBI is developing slowly, and there has been little apparent interest in pursuing further research in this field in recent years. Few studies have focused specifically on sexual behavior, and many of these have disparate results. Many of the studies are anecdotal reports and do not provide empirical evidence to guide clinical decision making or relate information to patients and families. It is not surprising that alterations in sexuality as well as sexual function occur in patients with TBI, but so far, research has yielded only a sense of the magnitude of this area of functional deficit. This is unfortunate given the importance of sexuality to most people, whether or not they are involved in a sexual relationship.

Clinical Evaluation

Problems occurring after TBI can result from a number of factors, including nongenital and genital dysfunction. Genital dysfunction can include ED, ejaculatory problems, orgasmic dysfunction, vaginal lubrication problems, and vaginismus. Nongenital problems that may adversely affect sexual intimacy include sensorimotor deficits, communication deficits, perceptual deficits, limited joint range of motion, neurogenic bowel and bladder dysfunction, dysphagia with or without problems controlling secretions, motor dyspraxias, posttraumatic behavioral deficits, as well as alterations in self-image and self-esteem (Zasler and Horn 1990).

A decreased serum testosterone level, in an otherwise healthy male, often first manifests as a decrease in libido and later as impotence and infertility. There may also be loss of secondary sexual characteristics. Females with acquired hormonal dysregulation may present with oligomenorrhea or amenorrhea, infertility, and signs of relative androgen access such as acne and hirsutism (Horn and Zasler 1990). It is critical that professionals treating patients after TBI recognize clinical presentations suggestive of neuroendocrine dysfunction. Trauma-induced problems such as pelvic floor myofascial dysfunction and/or pelvic floor muscle hypertonicity/spasticity may also result in complaints of sexual dysfunction and should be considered in the overall clinical evaluation of patients with complaints referable to genital function (Voorham-

TABLE 25–4. General Rehabilitation Assessment Sexuality Profile

Sexual history
Interview both patient and partner if possible
Obtain information about preinjury medical and sexual status and performance
Delineate sexuality concerns
Provide a private room, and take your time
Use appropriate vocabulary
Clarify sexual preference
Sexual physical examination
Assess general mobility and activities of daily living
Assess general hygiene
Inspect and palpate genitalia
Do neurourological assessment: rectal examination, sensory testing, lumbosacral reflex arc testing
Clinical sexual diagnostic testing
Urodynamics
Male: penile biothesiometry, dorsal nerve somatosensory-evoked potential, nocturnal penile tumescence, response to intracavernosal pharmacotherapy, and International Index of Erectile Function
Female: photoplethysmography, thermal clearance, heat electrode, biofeedback registration using a vaginal or anal probe, Female Sexual Function Index, and vaginal pulse amplitude
Neuroendocrine evaluation: follicle-stimulating hormone, luteinizing hormone, prolactin with testosterone (male) and estradiol and dehydroepiandrosterone (female)

Source. Adapted from Zasler and Horn 1990.

van der Zalm et al. 2008). Clinical evaluation techniques such as measurement of vaginal pulse amplitude (Laan et al. 1995), use of the International Index of Erectile Function (Rosen et al. 1997), and use of the Female Sexual Function Index (Rosen et al. 2000) may all be relevant in the assessment of the patient with sexual function complaints post-TBI.

Clinicians working with this patient population must have an appreciation for the appropriate assessment and management of this class of functional deficits. One protocol that has been proposed is the General Rehabilitation Assessment Sexuality Profile, which divides assessment into the sexual history, sexual physical examination, and clinical diagnostic testing (Zasler and Horn 1990) (Table 25–4).

Sexual History

A thorough sexual history defines needs, expectations, and behavior. Additionally, it identifies problems, misconceptions, and areas for education, counseling, and reassurance in relation to sexuality issues. When possible, interviews should be conducted with both the patient and the sexual partner. The assessment should include demographic and personal information as well as past medical history to identify medical disorders that potentially affect sexual function. Questions pertaining to premorbid sexual functioning, practices, and relationships should be asked. Both partners should be questioned about genital function as well as sexuality concerns, including birth control, fertility, genital dysfunction, libidinal alterations, and others. Sexuality issues may not be important for all patients. This fact must be recognized by treating professionals. Key points when interviewing include provision of a private atmosphere, not rushing the interview, being frank yet empathic, and using nonconfrontational techniques and appropriate vocabulary relative to the patient's educational and cultural background (e.g., "Do you suffer from premature ejaculation?" versus "Do you come too quickly?"). The clinician should avoid as much as possible putting the patient in conflict with religious or moral beliefs with regard to their sexual behavior.

The status of an individual's sexual preference should be clarified and discussed. Ultimately, the interview can serve as a foundation for demonstrating to the patient that he or she has a right to be sexual and that sexual expression resulting in intimacy, not necessarily vaginal intercourse, is the goal of the process (Zasler 1991). Sexual prejudices serve no constructive purpose in dealing with issues germane to alternative sexual lifestyles and choices (Sandel et al. 2007).

It is important for examining clinicians to keep in mind issues of sexual identity and the need to explore prior sexual experiences as related to degree of psychosexual and psychosocial maturity. Additionally, issues relating to heterosexual, homosexual, as well as bisexual, transgender, and intersex orientation should also be explored as relevant to the individual with TBI. There are no good evidence-based resources reporting the incidence of alternate sexual orientations after TBI and/or if TBI itself is a risk factor for an organically based alteration in sexual orientation, although the latter phenomenon has been reported but not causally proven. Gender attitudes and stereotypical perspectives should also be considered, as should the effects of TBI on such attitudes. Recent research has shown that there may be a dissociable effect of prefrontal and anterior temporal cortical lesions on stereotypical gender attitudes, with persons demonstrating ventrolateral prefrontal lesions showing decreased stereotypical attitudes (Gozzi et al. 2009).

Questionnaires have been developed that can provide important information to the evaluating clinician regarding sexuality issues in persons with TBI as well as other conditions. The Overt Behavior Scale was designed as a comprehensive measure of common challenging behaviors observed after brain injury in community settings. It includes both inappropriate sexual behavior and social behavior among the other areas assessed in this 34-item tool, which appears to be both valid and reliable (Kelly et al. 2006). The St. Andrew's Sexual Behavior Assessment was developed as a measure of inappropriate sexual behavior as a result of neurological impairment and is divided into four categories with four levels of severity. It has been shown to have strong construct and content validity as well as good interrater and test-retest reliability (Knight et al. 2008). Numerous other questionnaires exist, including the Psychosexual Assessment Questionnaire, Golombok-Rust Inventory of Sexual Satisfaction, the Sexual Interest and Satisfaction Scale, the Female Sexual Function Index, the Female Sexual Distress Scale, and the Sexual Function

Questionnaire, and all may be used to address different issues depending upon the sex of the patient and the sexuality issues that are being addressed (Sandel et al. 2007).

Evaluating clinicians should also make sure that accurate information is obtained regarding the patient's current medication regimen, including drug dosing, because medications can often be proven to be the culprit in a number of sexual function complaints, particularly ED. In most cases, such adverse side effects are limited to the duration of continued use of the offending agent and cease on discontinuation of the drug. Common drugs prescribed to persons with TBI that have been associated with sexual side effects include antidepressants, antihypertensives, antipsychotics, anxiolytics, anticholinergics, and hormonal agents (Clayton and Shen 1998). In practice, probably one of the most common classes of drugs to produce sexual side effects in this population are selective serotonin reuptake inhibitors (SSRIs), which can produce decreased libido, delayed ejaculation, and difficulty reaching orgasm, if not anorgasmia. Other drugs, including histamine-2 receptor blockers, may produce adverse consequences through their antiandrogenic effect and increased central prolactin. Anticonvulsant medication such as phenytoin may decrease circulating levels of sex hormone via induction of hepatic enzyme systems, resulting in a relative secondary hypogonadism. Assessment of medications and appropriate substitutions to optimize sexual functioning is critical in the physician's role in the management of sexuality issues in this population (Finger et al. 1997).

Sexual Physical Examination

The sexual physical examination begins when the clinician first sees the patient. Mobility deficits may provide clues as to physical limitations that may adversely affect sexuality and sexual function. Of particular importance are the flexibility of the hips and degree of adductor spasticity. The clinician should note the patient's general hygiene status and use of adaptive equipment. Obviously, ruling out other preexisting neurological or medical conditions that might contribute to sexual dysfunction is critical as well as assessing for posttraumatic neuromedical sequelae, including epilepsy, neuroendocrine dysfunction, and affective disorders.

The genitals should be examined from both a neurological and nonneurological standpoint by a physician comfortable in these examination procedures. In the female, direct visualization of the genitalia followed by a bimanual examination is critical. The vaginal walls must be evaluated for tone and mucosal alterations. In the male, the clinician must palpate the penis to assess for plaques as found in Peyronie's disease. Testicular presence in the scrotal sacs and size and consistency should all be evaluated. In both males and females, assessment of hair distribution in the genital region and in locations of secondary sexual hair growth is paramount to rule out possible endocrinopathies that could be either primary or secondary in nature. The neurological assessment of the genitalia includes a rectal examination, sensory testing, and assessment of lumbosacral reflex integrity. The skilled clinician can use the information from bedside testing to guide recommendations as well as prognosticate genital sexual function relative to the neurological insult in question (Zasler 1991; Zasler and Horn 1990).

Clinical Sexual Diagnostic Testing

Urodynamics can help obtain a better understanding of the integrity of genital innervation. Afferent neurological assessment can be performed with penile biothesiometry or dorsal nerve somatosensory-evoked potentials, or both. Penile biothesiometry, which measures the vibration perception threshold of the skin of the penis, is performed using a portable handheld electromagnetic vibration device with a fixed frequency and variable amplitude. A dorsal nerve somatosensory-evoked potential provides an objective physiological assessment of the entire pudendal nerve afferent pathway. Efferent neurological assessment, whether motor or autonomic, can be performed in a gross manner via nocturnal penile tumescence or response to intracavernosal pharmacotherapy, or both (Padma-Nathan 1988).

Female sexual clinical assessment is less sophisticated and has been conducted with various techniques. Photoplethysmography, thermal clearance, and heat electrode techniques have been used to assess vaginal hemodynamics via indirect evaluation of vaginal wall blood flow parameters (Levin 1980). These techniques can be used to treat orgasmic and arousal deficits via biofeedback training (Levin 1980; Zasler 1991; Zasler and Horn 1990).

It is crucial to ascertain whether a patient is taking any prescribed drugs excessively or using illicit drugs in a way that may adversely affect sexual functioning. Alcohol, although often not seen as an agent of abuse or illicit substance, is the most widely used aphrodisiac in the United States. Acute and/or chronic substance misuse or abuse may affect sexual functioning in a variety of ways and therefore must be clarified as part of the relevant history. Other illicit drugs that must be inquired about include marijuana, cocaine, opiates, and amphetamines, among numerous others.

Initial laboratory evaluation should include assessment of FSH, LH, prolactin, and free testosterone in males. Given the pulsatile cycle of the release of these hormones, it has been suggested that three samples be obtained approximately 20 minutes apart and then be combined for a single measurement. In females, the same hormones should be assessed in addition to estradiol and dehydroepiandrosterone. Because of normal menstrual variations, the best time for this assessment is during the early follicular phase. Provocative testing of pituitary function with such agents as thyrotropin-releasing hormone and gonadotropin-releasing hormone may be useful to assess for more subtle aspects of neuroendocrine dysfunction (Grossman and Sanfield 1994).

An awareness of appropriate neuroendocrine tests relative to specific clinical presentations is paramount for any practitioner working with patients with TBI (Table 25–5). Clinicians should keep in mind that other factors, such as medications or physiological stress in patients with acute TBI, may contribute to neuroendocrine abnormalities.

TABLE 25–5. Posttraumatic neuroendocrine dysfunction: clinical presentation and appropriate laboratory evaluation

Clinical syndrome	Clinical presentation (possible symptoms)	Neuroendocrine evaluation
Male postpubertal sexual dysfunction	Decreased libido	FSH, LH, PRL, free testosterone
	Impotence	R/O associated medical condition
	Ejaculatory dysfunction	
	Infertility	
Female postpubertal sexual dysfunction	Oligomenorrhea	FSH, LH, PRL, estradiol, dehydroepiandrosterone
	Amenorrhea	
	Virilization	R/O associated medical condition
	Galactorrhea	
	Decreased libido	
	Recurrent spontaneous abortions	
Male prepubertal sexual dysfunction	Delay in development of secondary sexual characteristics	FSH, LH, PRL, free testosterone
	Precocious puberty	
Female prepubertal sexual dysfunction	Delay in development of secondary sexual characteristics	FSH, LH, PRL, estradiol, dehydroepiandrosterone
	Precocious puberty	
Sexual dysfunction associated with temporolimbic epilepsy	Male: impotence, decreased libido, and endocrine disturbances	Same as above
	Female: menstrual irregularities, endocrine disturbances, and polycystic ovarian syndrome	Same as above
		R/O drug side effect

Note. FSH=follicle-stimulating hormone; LH=luteinizing hormone; PRL=prolactin; R/O=rule out.

Clinical Management

The management of sexual dysfunction must take into consideration the many issues that may directly or indirectly contribute to alterations in sexual function after TBI, including neuroendocrine, nongenital, and genital dysfunction. Clinicians should be aware of how subjective complaints may provide clues to guiding treatment. Additionally, adequate knowledge of the potential benefits and side effects of pharmacological agents in this patient population is critical in optimizing outcome (see Table 25–3). Multiple issues related to sexuality after TBI require management through counseling interventions, including matters of birth control, sex education, competency to engage in sexual activity, sexual abuse, and sexual "release."

Neuroendocrine Dysfunction

Neuroendocrine dysfunction may occur after TBI; however, the general clinical experience has been that this phenomenon is not commonly responsible for significant sexual function complaints in the TBI population. In postpubertal females, cyclic administration of oral estrogen–progesterone preparations restores the menstrual cycle, maintains secondary sexual characteristics, and reduces the risk for osteoporosis. In the postpubertal male, hypogonadism may be treated with intramuscular testosterone (200–400 mg) replacement, typically given every 2–4 weeks. In cases of delayed puberty, treatment should begin during adolescence; males are typically treated with human chorionic gonadotropin (500–1,000 U.S. Pharmacopeia (USP) units three times per week for the first 3 weeks, followed by 500 USP units two times per week for 1–2 years) and subsequently followed by maintenance testosterone therapy. In females, cyclic estrogen and progesterone therapy should be instituted to establish menses and secondary sexual characteristics (Zasler and Horn 1990). Clinicians should be familiar with the myriad symptoms that may be indicators of underlying neuroendocrine dysfunction and the appropriate laboratory evaluation of those conditions (see Table 25–5).

Nongenital Dysfunction

Other areas of nongenital neurological impairment must also be assessed relative to treatment options, whether pharmacological, surgical, or compensatory. Sensorimotor deficits, cognitive and behavioral deficits, language-based alterations, changes in libido, as well as neurogenic bowel and bladder dysfunction can all be addressed by the clinician because they affect sexual expression (Zasler and Horn 1990). Libidinal changes can be treated behaviorally and pharmacologically. Hormonal treatment or serotonergic agents, or both, can be used for hypersexuality. Medroxyprogesterone acetate has been used in varying doses to suppress both aggressive behavior and sexual arousal (100–200 mg/week typically preceded by a loading dose of 400 mg/week over the first 2–3 weeks). The use of "chemical castration" for hypersexuality after TBI has been the subject of many case reports; however, we are aware of no controlled, prospective studies (Britton 1998).

The use of agents such as medroxyprogesterone has been debated with regard to the ethical, medicolegal, and patient rights issues that must be adequately discussed and considered by the treating clinician. We have had some success with serotonergic agents such as trazodone for suppression of libido in doses typically ranging from 3.0 to 5.0 mg/kg body weight. The use of SSRIs in the treatment of sexual dysfunction has been the topic of some recent literature, but none that we are aware of is specific to post-TBI impairments. Clearly, the literature on the adverse sexual side effects of this drug class is much more abundant than that on the therapeutic use of such agents for treatment of sexual dysfunction (Montejo et al. 2001). SSRIs, however, tend to have a dose-dependent adverse effect on sexual functioning, including suppression of libido; however, other mechanisms, including reuptake mechanisms, anticholinergic side effects, inhibition of nitric oxide synthetase, and propensity for accumulation over time, must be considered (Rosen et al. 1999). LH-releasing hormone agonists have also been used for reducing sexual desire (Bradford 2001).

Noradrenergic agonists or hormonal supplementation, or both, have been used for hyposexuality, particularly in males (Blumer and Migeon 1975; Lehne 1986; McConaghy et al. 1988; Zasler and Horn 1990).

Clinicians should recall that patients with temporolimbic epilepsy may present with alterations in neuroendocrine status and sexual function. The presence of characteristic "temporal lobe personality" traits such as circumstantiality, viscosity, and obsessionalism in combination with altered sexuality, even in the absence of "clinical" seizures and/or electrographic seizures, suggests consideration for treatment with a psychoactive anticonvulsant such as carbamazepine or valproate (Gualtieri 1991). Patients with Klüver-Bucy syndrome have also shown hypersexual behaviors as part of this symptom complex that respond in a favorable fashion to treatment with psychotropic anticonvulsants such as carbamazepine (Stewart 1985).

Genital Dysfunction

Genital sexual dysfunction after TBI may take a number of potential forms. Males may present with erectile, ejaculatory, and/or orgasmic dysfunction. The present state of the art in neurological management of ED focuses on one of five main treatment categories: oral therapies such as phosphodiesterase type 5 inhibitors (e.g., sildenafil, tadalafil, vardenafil) as well as the dopaminergic agonist apomorphine (Dinsmoor 2004), penile prostheses, intracavernosal pharmacotherapy, MUSE (medicated urethral system for erection), and external management (Meinhardt et al. 1999). Given the relative ease of use and good side-effect profile, agents such as sildenafil (Jarrow et al. 1999) may become the mainstay of treatment for neurogenic ED after TBI; however, there are no studies that have looked specifically at this drug's application to ED in this population. Some authors have found that tachyphylaxis effects may limit the long-term use of sildenafil (El-Galley et al. 2001). Enteral agents have been used, including noradrenergic agonists such as yohimbine (5.4–6.0 mg orally 3 times per day) (Morales et al. 1982) as well as other drug classes such as dopamine agonists. Work is ongoing relative to the efficacy of enteral agents in patients with ED, including, but not limited to, sublingual apomorphine, oral phentolamine, and vardenafil (a phosphodiesterase type-5 inhibitor) (Rosen 2000). Problems with premature ejaculation should be first addressed behaviorally to assess how much of the problem is functionally based. Methods such as the "squeeze" technique, which involves application of pressure to the penile shaft just proximal to the glans penis when the male feels that he is about to ejaculate, can be taught to prolong the time until ejaculation. On occasion, medication could be considered for the male patient who complains of premature ejaculation; this could include topical anesthetics to the penile shaft (5%–10% lidocaine) or anticholinergic (imipramine 100–200 mg/day) and sympatholytic medication (phenoxybenzamine, 10 mg 2–3 times per day) administered orally. Literature and experience have also shown a role for SSRIs in the treatment of premature ejaculation (McMahon and Touma 1999). Orgasmic dysfunction is generally approached from a behavioral standpoint in both men and women. Females may complain of alterations in vaginal lubrication or orgasmic dysfunction, or both. Inadequate vaginal lubrication can generally be treated with artificial lubrication using water-soluble products. Behavioral therapy, including imagery and body exploration and sensitization training, may benefit some females who have arousal or orgasmic dysfunction (Halvorsen and Metz 1992; Sarwer and Durlak 1997; Zasler 1991).

A number of "natural" remedies have been advocated for improving various aspects of sexual function. Zestra for Women is a botanical feminine massage oil formulated to enhance female sexual pleasure; to increase warmth, sensitivity, sensation; and to facilitate arousal when applied to the clitoris, labia, and vaginal opening. Zestra for Women is not a drug but has been developed under the U.S. Cosmetics Act. The ingredients are a proprietary blend of borage seed oil, evening primrose oil, Angelica root extract, *Coleus forskohlii* extract, ascorbyl palmitate, DL-alpha-tocopherol, and natural fragrances. The borage and evening primrose oils contain high amounts of gamma-linolinic acid, which is metabolized in the skin to prostaglandin E1. This process is generally recognized to cause increased blood flow and nerve conduction. Angelica root extract contains osthole, which increases cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP), nonspecifically. *Coleus forskohlii* extract contains forskolin, coleonol, and related diterpenes, which are adenylate cyclase stimulants (Ferguson et al. 2003). Other agents, either used individually or potentially conjointly to enhance sexual response include citrulline, pyrano-isoflavones, bererine, dehydroepiandrosterone, Korean red ginseng, and yohimbine (the latter can also be enhanced with L-arginine glutamate, a nitric oxide precursor) (Sandel et al. 2007).

Counseling Issues

There are numerous controversial issues pertaining to sexuality in patients with TBI that affect medical, ethical, and legal fronts, thereby obliging clinicians to address them. Among these issues are matters pertaining to sex education, including birth control, sexually transmitted disease,

sexual abuse, sexual release, and masturbation. Other issues that may arise include decisions regarding sterilization as well as more germane and "socially acceptable" issues such as dating, marriage, sexual preference issues, child-rearing matters, and psychosocial behavior.

Clinical experience and some literature (Simpson and Long 2004) demonstrate that appropriate educational programs tend to have beneficial effects on both patients and caretakers. Quite frequently, patients with TBI assume that they will be unable to find a compatible sexual companion because they have had a brain injury. Various recommendations can be provided to maximize community reintegration, including attending church or synagogue functions, brain injury survivor meetings, local organization social gatherings, or participating in dating services for people with disabilities such as Handicapped Introductions and DateAble (Garden 1988). Professionals also can assist clients by teaching or "reteaching" the psychosocial graces that may many times be adversely affected by significant TBI before attempting more aggressive community reentry efforts. Responsible decisions regarding sexual relations are critical for both single and married people with brain injury, and ongoing follow-up is essential to ensure that there is compliance with the recommendations as well as sex life satisfaction.

Generally, patients who have been evaluated as competent and who have the capacity to understand and remember the ramifications of their actions are probably capable of being sexually active in a responsible fashion. Sexually active patients, whether male or female, should be instructed in the appropriate use of condoms given the ever-present fear of acquired immunodeficiency syndrome. For patients demonstrating especially poor "sexual judgment" and/or uncontrollable sexual behaviors that are resistant to other treatments (e.g., indiscriminate masturbation or hypersexuality), the professional may need to consider either chemical or surgical sterilization. Some authors have proposed specific assessment and treatment models for sexually intrusive behavior following brain injury that encourages multidisciplinarity (Bezeau et al. 2004). Given the variability in state laws regarding competency/capacity issues and decisions regarding sterilization, it is recommended that professionals consult legal counsel regarding each case in question.

Sex therapy, although a field that often conjures up many misconceptions, should be considered in appropriate circumstances for patients with or without established sexual relationships. Ideally, the sex therapist and treating physician should coordinate care and focus treatment on a specific area of dysfunction. Numerous behavioral techniques are used in sex therapy, including relaxation, desensitization, nondemand pleasuring, directed masturbation, the quiet vagina exercise, Kegel exercises, visualization, start-stop techniques, and the squeeze method. Certainly, a therapist with TBI experience would generally be more effective because they could modify techniques based on the patient's cognitive, behavioral, and physical impairments. Families and patients should be counseled regarding alternatives for sexual release, particularly for patients without active sexual partners. Masturbation should be discussed as one potential option as long as it is done in an appropriate social context. For those clients requiring external stimulation to aid in successful masturbation, sexual stimuli (e.g., erotic reading materials, pictures, videotapes, and telephone sex services) can be provided. Obviously, many of the aforementioned suggestions may not be acceptable to certain people because of their moral or religious beliefs, or both, but they should be discussed with all patients and families as appropriate.

Some health care professionals and family members have advocated, as well as condoned, the use of sexual surrogates and prostitutes in addressing the sexual frustrations of people after TBI who might otherwise never find sexual partners. Although there are differences between surrogates and prostitutes, many state laws do not make a legal distinction. In an era of high awareness regarding sexually transmitted diseases and legal liability, most professionals seem to be shying away from making use of this class of "community resources." Professionals should counsel patient and family alike regarding dealing with alterations in sexual preference, which are more commonly a result of lack of heterosexual partners (for heterosexual patients) than a result of organically based alterations in sexual orientation because of the TBI itself (Miller et al. 1986). Appropriate counseling for heterosexuals and homosexuals alike should be available. Counseling clinicians should always inquire about the patient's sexual orientation. All patients, regardless of sexual preference, should be counseled on high-risk sexual practices.

Sexual abuse of persons with TBI and/or by persons with TBI may be encountered on occasion. Although poorly documented because of a general trend toward not studying things that make people feel uncomfortable, clinicians must recognize abuse when they see it. Health care professionals are legally and morally obligated to ensure that the proper authorities are notified if a person with TBI, a family member, an attendant, or an acquaintance is engaged in sexual misconduct or abuse, or both. If sexual abuse is suspected, proper measures should be taken to either remove the patient from the environment in question or remove the suspected perpetrator from the patient's immediate milieu.

Family Issues

Sexuality is a classic example of an integrative function, requiring cognitive, physical, and psychobehavioral components. A double sensitivity often exists regarding sexuality and disability (Chigier 1980), which often prevents the person with a brain injury from being seen as a sexual being. All people, whether patient, family, or treating professionals, must learn to accept the fact that sexuality issues exist for most survivors, regardless of injury severity, and must be dealt with relative to sexual function issues, sexual rights, rehabilitation interventions, and family or attendant counseling. Family issues may arise in a variety of situations, including single individuals living with parents, married people living with spouses, and parents living with children with brain injuries (Zasler and Kreutzer 1991). There are a number of issues, some highly controversial, regarding reproductive issues for women with TBI. Some of the important issues in this subgroup of TBI patients including competency/capacity to carry to term and act responsibly with regards to sexual activity and actions

during pregnancy; seizure risk and management during pregnancy, including potential teratogenic effects of antiepileptic drugs; controversies of management of women who are pregnant at the time of their TBI and risks to both mother and child; contraception techniques given cognitive, behavioral, and physical challenges; and assessment of fertility and management of infertility when secondary to neuroendocrine dysfunction (Sandel et al. 2007).

Sexual problems after TBI can occur in at least three different scenarios. First, people with brain injury (classically, adolescents or young adults) may be living with their parents. They commonly may be unable to maintain sexual relationships established before their injury or to establish new relationships after the injury, or both. Sexual problems for these individuals include finding a suitable partner as well as diminished physical capabilities. Second, some TBI survivors are unable to maintain previously established relationships. These people may be married, living with a significant other, or single and dating. Diminished frequency of intercourse and physical dysfunction may stem from emotional or physical problems. Third, sexual problems may arise between married relatives of the injured person and may be attributable to the negative consequences of brain injury in other family members (e.g., children, siblings, or parents). The stressors associated with alteration of preinjury roles related to caring for the injured person may cause a variety of psychological reactions, including burnout, feelings of guilt, and displacement, to name only a few, resulting in spousal alienation, sexual disinterest, and, potentially, sexual dysfunction.

Supporting Organizational Structures

In order to provide adequate services to address the sexual concerns and needs of persons with TBI, it appears necessary to have a number of organizational structures in place, including, but not limited to, the following: development of agency sexuality policies, understanding of sexuality-related government legislation, staff training, resource and knowledge development, and creation of interservice networks. Many believe that sexuality has been an ignored aspect of mental health and neuromedical care in general and certainly for select populations of patients such as those with TBI. Oftentimes the limiting factor in addressing sexuality concerns are the staff's own perceptions of their discomfort with the topic and/or their knowledge of same. Through appropriate education and use of protocols such as the Permission, Limited Information, Specific Suggestion, and Intensive Therapy (PLISSIT) model, treatment teams should be able to improve the level of sexuality care that they are providing to their patients (Simpson and Long 2004).

Conclusion

Health care professionals are only beginning to examine the neurological and functional ramifications of TBI on sexual function. At present, information on which clinicians can base prognostication, assessment, or treatment is relatively scarce; however, the knowledge base is expanding slowly but surely. Better acknowledgment of the importance of sexuality and sexual function to quality of life may stimulate researchers and clinicians alike to allocate more resources to answering many of the questions that remain. The treating physician must be able to address sexuality issues effectively by relying on an approach that holistically defines problematic areas, determines what changes can realistically be made, and works toward effecting those changes and accepting what cannot be changed. In the interim, clinicians and researchers alike should remain cognizant of the importance of sexual expression relative to other areas of human function after TBI. Awareness, in and of itself, will provide an impetus for further critical examination of this important area of psychophysiological function.

KEY CLINICAL POINTS

- Sexuality is a complex behavioral construct that melds myriad biopsychosocial elements to produce the given behavior. Clearly, individual life experiences, genetic loading variables, cultural and religious norms, social mores, cognitive and physical abilities, and other factors all affect how a person manifests and expresses his or her own sexuality.

- The male and female sexual response cycles are very distinct, with variable factors influencing reinforcement of the sexual response and females being more significantly driven by psychosocial factors.

- The neural matrix associated with sexual function is not fully understood, but it comprises diffuse central nervous system elements involving cortical, subcortical, and spinal mechanisms; the peripheral nervous system; and the autonomic nervous system relative to both parasympathetic and sympathetic divisions. Traumatic brain injury (TBI) can disrupt the neural matrix and thereby adversely affect sexual functioning and sexuality expression.

- Neuroendocrine dysfunction remains a highly controversial area of post-TBI care, with particular debate about the incidence of clinically significant hypopituitarism and the preferred methodologies for assessment.

- Clinical evaluation of sexual dysfunction following TBI should consider both genital and nongenital problems that may adversely affect sexual expression.

- An adequate sexual history should be taken to serve as a foundation for understanding factors that may be contributing to the patient's sexual difficulties. A biopsychosocial and holistic approach should be taken to the interview, which ideally should be done with the patient and his or her sexual partner, if any. Consideration should be given to the use of structured questionnaires.

- Clinicians should be aware of how to conduct a sexual physical examination including both general aspects and genital ones, the latter including both neurological and non-neurological elements.

- Numerous clinical diagnostic tests are now available that may be used to objectify subjective sexual function complaints. Clinicians should be aware of these tests and know how to access them for their patients.

- Using a holistic approach to clinical management, clinicians should consider what interventions can be offered to modulate, if not ameliorate, the impairments that are serving as obstacles to sexual expression. Interventions may include use of compensatory strategies, prescription of medications, and various counseling interventions, including behavioral therapies, among other strategies.

- Family issues and sexuality can be a very challenging area for clinical management involving persons with TBI. One of the biggest challenges is the propensity for family members to see the person with TBI as a "nonsexual" being.

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Part IV

SPECIAL POPULATIONS AND ISSUES

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CHAPTER 26

Traumatic Brain Injury in the Context of War

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TRAUMATIC BRAIN INJURY (TBI) IS A COMMON INJURY in wartime. The notion that combat is a risk factor for TBI was recognized long ago, as indicated by the fact that soldiers throughout the world have been using helmets since ancient times. TBI is common in war because, as Carey (1987) wrote, "the head is preferentially exposed in combat as the soldier constantly monitors his environment by means of exteroceptive neurosensory structures (eyes, ears, and nose) in order to enhance his own survival" (p. 6). Ballistics researchers estimate that the head and neck together constitute 12% of the total body area that is exposed during combat, and yet 15% to 25% of the wounds incurred during combat in World War II, Korea, and Vietnam were to the head-neck region (Carey 1987). The only body region with a higher proportion of wounds in these wars was the extremities, which accounted for 53% to 55% of injuries (Carey 1987).

There are several reasons why the military population is unique when it comes to TBI. One, obviously, is the increased TBI risk associated with combat. Another is the mechanism of injury. Although TBI in military personnel are often caused by the same mechanisms that cause TBI in civilians (e.g., motor vehicle crashes), military personnel in combat environments also face the risk of injury from explosions, which are rare in nonwar environments. Military personnel in combat environments are also at risk for a variety of comorbidities, especially injuries to other body regions and psychiatric disorders, which can delay the detection of TBI, complicate management and rehabilitation, and possibly slow recovery. The military population is unique in that it is intrinsically easier to study. Procedures such as the mandatory Post-Deployment Health Assessment (PDHA) that all U.S. service members undergo after returning to their home base make it possible to screen large numbers of returning service members. This assessment captures those with concussion who may have postponed evaluation or treatment during deployment and therefore were not identified by reviewing medical databases. This has enabled researchers to gather data about a common type of TBI—concussion—that is difficult to identify in the general civilian population.

In this chapter, we discuss TBI in the U.S. military populations with an emphasis on service members who participated in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF). We present data about the prevalence of TBI in this population, mechanisms of injury, methods used to identify those with TBI, levels of care, management techniques, and rehabilitation strategies. We also provide data about the future direction of TBI research. The goal of this chapter is to summarize some of the knowledge and insights about TBI that have been gained by treating and studying service members injured in war. It is our hope that this knowledge will help improve understanding of traumatic brain injury in any of the contexts in which it occurs and lead to better outcomes for those who sustain TBI.

Operational Definitions of TBI

In 2006, a working group of the Defense and Veterans Brain Injury Center (DVBIC) developed the following operational definition of TBI in military operations:

> an injury to the brain resulting from an external force and/or acceleration/deceleration mechanism from an event such as a blast, fall, direct impact, or motor vehicle accident which causes an alteration in mental status typically resulting in the temporally related onset of symptoms such as: headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping, sleep disturbances, drowsiness, sensitivity to light/noise, blurred vision, difficulty remembering, and or difficulty concentrating. (DVBIC 2006, p. 2)

This definition is consistent with those put forth by the Centers for Disease Control and Prevention, the American Academy of Neurology, and other groups with TBI interest in that it specifies an injury event with subsequent alteration in consciousness.

Epidemiology

The total incidence and prevalence of war-related TBI among members of the U.S. armed forces serving in OIF and OEF are not known. However, data from recently published survey-based studies of service members and veterans who served in OIF/OEF suggest that war-related TBI is common in this population (Hoge et al. 2008; Schell and Marshall 2008; Schneiderman et al. 2008; Schwab et al. 2007; Terrio et al. 2009). The most recent in-theater Mental Health Assessment Team (MHAT) found that 11.5% of soldiers surveyed in the middle of their tour endorsed having had at least one concussion at the time of the survey. Supplemental TBI postdeployment surveys of combat-exposed units demonstrate a range of 10%–20% for probable mild TBI or concussion during deployment. The MHAT studies used the Soldier-Marine Well-Being Survey, which is a lengthy questionnaire focusing predominantly on psychological health concerns, as opposed to a validated TBI screening tool. The highest reported frequency of TBI from any of these studies is 22.8%, which was obtained from an active duty army brigade combat team that was screened for TBI during the mandatory PDHA (Figure 26–1) after spending 1 year in Iraq (Terrio et al. 2009). A telephone study of a sample of OIF/OEF veterans from all branches of the armed forces found that 19.5% screened positive for a war-related TBI (Schell and Marshall 2008). Two other studies of Army personnel found that 15.2%–15.8% screened positive for TBI (Schell and Marshall 2008; Schwab et al. 2007). The lowest frequency of TBI was 12%, which was obtained from a sample of veterans from all service branches who were mailed TBI screening questionnaires (Hoge et al. 2008). Each of these studies used the Brief Traumatic Brain Injury Screen (BTBIS) (Schwab et al. 2007) to screen for concussion. Two of the studies also used validated screening tools for posttraumatic stress disorder (PTSD) and depression, factoring these results as potential causes of symptoms. The slight variance in results across the three studies may be a reflection of method of screening (paper, telephone, face-to-face interview) and time since injury.

The TBI reported in these studies are almost exclusively mild traumatic brain injury (mTBI). In early evaluations of combat-related TBI, a loss of consciousness (LOC) up to 60 minutes was considered mTBI. In October 2007, a Department of Defense–wide severity of injury was published that decreased the allowable time for LOC in mTBI to 30 minutes or less (Assistant Secretary of Defense 2007). The definitions for moderate and severe remained consistent, and although time parameters for LOC and alteration in consciousness (AOC) are provided, those with more evident injury are often classified by Glasgow Coma Scale scores.

Schwab et al. (2007) found that only 2.1% of those who screened positive for war-related TBI had an injury that was greater than mild, and Hoge et al. (2008) found that only 1% of those who screened positive for TBI had an injury that was greater than mild. However, to best understand these screening results, it is important to realize that the majority of moderate and severe TBI are identified immediately and enter the trauma system of care; most are medically evacuated from the theater and are therefore not intended to be identified on routine screening measures. Furthermore, most of those with mild TBI on screening had the mildest form of mTBI. Schwab et al. (2007) found that 70% those with TBI had reported only AOC, such as being dazed or confused, "seeing stars," or having their "bell rung." Hoge et al. (2008) found that 68% of those who screened positive for TBI reported AOC, and Terrio et al. (2009) found that 63% of those with TBI reported only AOC.

Few data about those who were hospitalized for TBI from the current conflicts have been published. An analysis of data from 433 service members evacuated to the Walter Reed Army Medical Center (WRAMC) found that 88.5% had closed TBI (Warden et al. 2005). Fifty-six percent of these injuries were moderate to severe (including penetrating), and 44% were mild (Warden et al. 2005). Twenty-eight percent of those evacuated to WRAMC with combat injuries had TBI (Warden 2006). It should be noted, when interpreting the data, that WRAMC is one of only three military treatment facilities that provide care for combat-related severe and penetrating TBI. In addition, isolated mTBI patients were not included in this study because they did not require hospitalization.

Blast is a common mechanism of injury in the setting of OIF/OEF. A study of a Marine Corps mechanized battalion stationed in Iraq found that 97% of combat injuries were caused by explosive weapons such as improvised explosive devices (IEDs) and mines and just 3% were caused by direct fire, such as being shot at (Gondusky and Reiter 2005). Sixty-eight percent of those evacuated to WRAMC with a TBI were injured by a blast (Warden 2006). Among returning service members who were screened for TBI during the PDHA, 88% of those who reported being injured reported blast as a mechanism (Terrio et al. 2009). However, the screening surveys do not specify exactly which mechanism caused the TBI. Attributing combat-related TBI to a specific mechanism is often difficult because in the context of these current wars, many injuries

9.a. During this deployment, did you experience any of the following events? *(Mark all that apply)*

(1) Blast or explosion *(IED, RPG, land mine, grenade, etc.)*	○ No	○ Yes
(2) Vehicular accident/crash *(any vehicle, including aircraft)*	○ No	○ Yes
(3) Fragment wound or bullet wound above your shoulders	○ No	○ Yes
(4) Fall	○ No	○ Yes
(5) Other event *(for example, a sports injury to your head)*. Describe:	○ No	○ Yes

9.b. Did any of the following happen to you, or were you told happened to you, IMMEDIATELY after any of the event(s) you just noted in question 9.a.? *(Mark all that apply)*

(1) Lost consciousness or got "knocked out"	○ No	○ Yes
(2) Felt dazed, confused, or "saw stars"	○ No	○ Yes
(3) Didn't remember the event	○ No	○ Yes
(4) Had a concussion	○ No	○ Yes
(5) Had a head injury	○ No	○ Yes

9.c. Did any of the following problems begin or get worse after the event(s) you noted in question 9.a.? *(Mark all that apply)*

(1) Memory problems or lapses	○ No	○ Yes
(2) Balance problems or dizziness	○ No	○ Yes
(3) Ringing in the ears	○ No	○ Yes
(4) Sensitivity to bright light	○ No	○ Yes
(5) Irritability	○ No	○ Yes
(6) Headaches	○ No	○ Yes
(7) Sleep problems	○ No	○ Yes

9.d. In the past week, have you had any of the symptoms you indicated in 9.c.? *(Mark all that apply)*

(1) Memory problems or lapses	○ No	○ Yes
(2) Balance problems or dizziness	○ No	○ Yes
(3) Ringing in the ears	○ No	○ Yes
(4) Sensitivity to bright light	○ No	○ Yes
(5) Irritability	○ No	○ Yes
(6) Headaches	○ No	○ Yes
(7) Sleep problems	○ No	○ Yes

FIGURE 26–1. Post-Deployment Health Assessment (PDHA) Screening.

Source. U.S. Department of Defense, DD Form 2796, January 2008.

are produced by "blast-plus," that is, injuries by blast/explosion in conjunction with motor vehicle crashes, falls, and fragmentation. Therefore, it is difficult to discern the true mechanical force by which the TBI occurred.

Acute postconcussive symptoms are common in service members with war-related TBI. Ninety-one percent of those with TBI treated at WRAMC had postconcussive symptoms (Warden et al. 2005). Among those who screened positive for TBI during the PDHA at Fort Carson, Colorado, 92% reported having had postconcussive symptoms at the time of injury (Terrio et al. 2009). However, the proportion of service members who reported symptoms persisting until time of returning home was much smaller: 33% reported postconcussive symptoms during the PDHA (Terrio et al. 2009). In the Fort Carson sample, 39% of those who screened positive for TBI reported postconcussive symptoms at the time of screening after returning from theater, but only 11% of those injured without TBI reported symptoms (Terrio et al. 2009). Also of note from the Fort Carson study, the average time from date of injury to PDHA was 6.1 months. In the sample in Fort Bragg, North Carolina, 64% of those who screened positive for TBI reported three or more problematic postconcussive symptoms versus 41% of those who screened negative for TBI (Schwab et al. 2007).

Service members with war-related TBI are also at risk for psychiatric conditions. Returning service members who screened positive for TBI were more likely to have psychiatric disorders than those who were injured but did not have an associated TBI (Hoge et al. 2008). Furthermore, those who reported LOC were more likely to report a psychiatric disorder than those with AOC only (Hoge et al. 2008). In the WRAMC inpatient sample, 43% of those with TBI had a psychiatric disorder noted in their records, with depression being the most common disorder (Warden et al. 2005). Among those who were not hospitalized for their TBI and who returned with their units, PTSD was the most common psychiatric disorder (Hoge et al. 2008). PTSD is a frequent cause of postconcussive-type complaints in patients screening negative for TBI (Hoge et al. 2008; Schneiderman et al. 2008) (see also Chapter 12, Posttraumatic Stress Disorder, in this volume).

Mechanisms of Injury

In the conflicts of OIF/OEF there have been an array of weapon mechanisms that lead to varying levels of TBI severity. Despite many developments in body armor and helmet technology, TBI among wounded soldiers has been estimated to be as high as 22% (Okie 2005). Of service members medically evacuated with battle-related injuries from the deployed setting to WRAMC, 31% had a TBI (DVBIC 2008). The top three primary injury agents include 55% blast (IED, rocket-propelled grenades, mortars, mines, bombs, grenades), 27% multiple mechanisms of injury, and 7% vehicular injury (DVBIC 2008). According to a report by Galarneau et al. (2008), IEDs were responsible for far more TBI diagnoses among those wounded or killed in action than any other mechanism of injury, including bullet wounds.

There is increasing awareness of another class of injury, referred to as a "blast TBI" (Ling 2008). This injury

results from proximity to explosion or blast. In the current conflicts, blast injuries resulting from IEDs are extremely prevalent, but their influence on traditional biomechanical dynamics of brain injury is yet unclear (Taber et al. 2006). There is some discussion that this may be the same injury that was described as "shell shock" during World Wars I and II. Studies estimate that the rate blasts result in brain injuries is approximately 60% (Galarneau et al. 2008). Multiple mechanisms can contribute to blast brain injury. Primary blast injury to the brain is hypothesized to result from direct exposure to overpressure or negative pressure waves that follow an explosion (Mayorga 1997). Initially, primary blast injury was thought to be a rare cause of TBI, although it is a well-known cause of injuries to air-filled organs such as the lungs, gut, and ears. However, there is mounting evidence that primary blast injury affects organs with fluid interfaces that allow transfer of kinetic energy. It is hypothesized that this likely results in diffuse axonal injury in the brain and spinal cord. Preliminary results from diffusion tensor imaging studies indicate significant differences in fractional anisotropy in service members with blast TBI versus blunt TBI (C. MacDonald, "Diffusion Tensor Imaging in TBI." Unpublished data, 2010). Secondary blast injury results when the explosive force energizes surrounding objects, setting them in motion. As these objects strike a person, injury occurs. This injury pattern is typically seen in the neck and extremities because these areas are not completely covered by body armor. Tertiary injury results when kinetic injury from the explosion causes a person to be thrown into a stationary object. Burns and inhalation of gases or other toxic substances produce the fourth category of blast injury, quaternary injury.

Traditional acceleration/deceleration injuries also occur in combat settings. Typically resulting from motor vehicle collisions or falls, these injuries are similar to those seen in the civilian setting.

Penetrating brain injury can occur as a result of traditional gunfire or from secondary blast effects. This may result in minor to severe cerebral dysfunction. Data from Armonda et al. (2006) demonstrate that patients with penetrating injury are at increased risk for cerebral vasospasm and pseudoaneurysm compared with patients with blunt TBI.

In many patients who sustain combat-related brain injury, multiple mechanisms of injury are present. For example, the detonation of explosive devices commonly affects moving vehicles. As the explosion takes place, blast-related phenomena occur. In rapid succession, the vehicle may strike another stationary object, leading to the development of acceleration/deceleration-type injuries.

Settings of Care

Combat-related TBI management is provided at different levels of care (Albertson et al. 2004). Initial TBI management in the deployed setting begins on the battlefield (Level I) in the form of buddy aid. First and foremost, this involves cover-fire and evacuation to safety and stabilization of serious injury. Special Forces (SEALS, Rangers) units are often trained in more advanced life support measures. As soon as the mission allows, the injured are evacuated from the battlefield to higher levels of care. The Battalion Aid Station (BAS), also considered Level I care, provides triage, minor treatment, and evacuation capabilities. The BAS is generally staffed by medics, physician assistants, and occasionally physicians. At this level, TBI care is limited to observation, rest, and management of noncritical symptoms (e.g., headache). In the event that more intensive evaluation or treatment is necessary, evacuation to higher echelons occurs. This evacuation does not always occur in a linear fashion but rather to the facility that allows safe and rapid transport.

Level II facilities offer basic medical care, basic diagnostic capabilities, and in some cases life-saving surgery. There is limited inpatient bed space, and therefore, holding times are limited to 72 hours. These facilities are highly mobile and may relocate on the basis of operational needs.

Level III facilities represent the highest level of medical care available in deployed settings. Commonly referred to as the Combat Support Hospital, the Level III site has full surgical and intensive care capabilities. Important to TBI care, computed tomography (CT) scans and neurosurgical intervention can be performed here. Imaging techniques allow for reconstructions that can aid in forensic evaluation and ballistic trajectories, helping to ensure that no injuries are missed. Once stabilized, patients with severe or penetrating TBI are transferred out of the combat zone. Patients with less severe injury may be sent if prolonged recuperation is expected. This guarantees bed availability for the constant influx of casualties.

Definitive medical and surgical care outside the combat zone occurs at Level IV facilities. For OEF and OIF, these services are provided at Landstuhl Regional Medical Center in Germany. If indicated, aggressive management of intracranial pressure (ICP), including ICP monitoring, decompressive craniectomy, and vasopressor support, is fully implemented in accordance with the Guidelines for the Management of Severe Traumatic Brain Injury (Brain Trauma Foundation 2007). Those patients requiring ongoing care are subsequently transferred stateside to a Level V facility. These facilities are comparable with the American College of Surgeons' designated Level I trauma centers.

Transportation of critically ill TBI patients is done by critical care air transport teams on U.S. Air Force fixed wing aircraft. Moderate and severe TBI are routed to the National Naval Medical Center in Bethesda, Maryland, or WRAMC in Washington, D.C. Those with comorbid burns are treated in San Antonio, Texas. The National Naval Medical Center in Bethesda is the designated center for all penetrating injuries. While en route to the United States, complex critical care is provided by skilled critical care nurses and physicians. Altitude-approved monitors, ventilators, and other necessary medical devices are routinely used. Depending on injury patterns (e.g., pneumocephalus), flight patterns may be altered to prevent complications associated with altitude travel. In addition, those with severe brain injury and sensitive ICP may require position changes while in flight (head first, feet first) and prior to takeoff and landing to minimize effects on ICP. Those with mTBI are transported to other designated military TBI centers throughout the United States.

Military Acute Concussion Evaluation (MACE)

Defense and Veterans Brain Injury Center

Patient Name: _____

SS#: _____-_____-_____**Unit:** _____

Date of Injury: _____/_____/_____ **Time of Injury:** _____

Examiner: _____

Date of Evaluation: _____/_____/_____ **Time of Evaluation:** _____

History: (I – VIII)

I. **Description of Incident**
Ask:
a) What happened?
b) Tell me what you remember.
c) Were you dazed, confused, "saw stars"? ❒ Yes ❒ No
d) Did you hit your head? ❒ Yes ❒ No

II. **Cause of Injury** (Circle all that apply):
1) Explosion/Blast 4) Fragment
2) Blunt object 5) Fall
3) Motor Vehicle Crash 6) Gunshot wound
7) Other _____

III. **Was a helmet worn?** ❒ Yes ❒ No Type _____

IV. **Amnesia Before: Are there any events just BEFORE the injury that are not remembered? (Assess for continuous memory prior to injury)**
❒ Yes ❒ No If yes, how long _____

V. **Amnesia After: Are there any events just AFTER the injuries that are not remembered? (Assess time until continuous memory after the injury)**
❒ Yes ❒ No If yes, how long _____

VI. **Does the individual report loss of consciousness or "blacking out"?** ❒ Yes ❒ No If yes, how long _____

VII. **Did anyone observe a period of loss of consciousness or unresponsiveness?** ❒ Yes ❒ No If yes, how long _____

VIII. **Symptoms** (circle all that apply)
1) Headache 2) Dizziness
3) Memory Problems 4) Balance problems
5) Nausea/Vomiting 6) Difficulty Concentrating
7) Irritability 8) Visual Disturbances
9) Ringing in the ears 10) Other _____

Examination: (IX – XIII)

Evaluate each domain. Total possible score is 30.

IX. **Orientation:** (1 point each)

Month:	0	1
Date:	0	1
Day of Week:	0	1
Year:	0	1
Time:	0	1

Orientation Total Score _____/5

07/2007 DVBIC.org 800-870-9244
This form may be copied for clinical use.

FIGURE 26–2. Military Acute Concussion Evaluation (MACE).

Source. Defense and Veterans Brain Injury Center, July 2007.

Screening

TBI screening is performed at many locations and at all levels of care within the military. Screening is performed in-theater as soon as possible after an injury-causing event by field medics/corpsmen as well as at higher-echelon medical facilities such as combat support hospitals. Screening is also performed in those medically evacuated from theater for injury (battle or nonbattle) or disease, at Landstuhl Regional Medical Center, to identify comorbid TBI that may not have been identified prior to medical evacuation from theater for other injuries. In addition, service members are screened within 30 days of returning to their home bases during the mandated PDHA (Figure 26–1), followed by a general symptom inventory during the Post Deployment Health Reassessment (PDHRA) 3–6 months later. Finally, all OIF and OEF veterans who present to Veterans Affairs (VA) medical centers for any reason are screened for symptomatic TBI as well.

The Military Acute Concussion Evaluation (MACE) (Figure 26–2) is used to screen for acute TBI. The MACE was designed specifically for the purposes of assessing and documenting the mechanism of injury, acute characteristics, and cognitive deficits in military personnel with suspected mTBI in an austere environment (G. Grant, W. Isler, M. Baker, D. Erlanger, and T. Kaushik, "Preliminary Validation of the MACE." Unpublished data, 2008). It can be administered by any trained medical personnel including field medics/corpsmen to service members who are involved in the following events that are often associated with TBI: blasts, falls, motor vehicle crashes, direct impacts to their body, or other circumstances when TBI is suspected. The MACE includes sections for describing the injury event, guidelines for a gross neurological examination, and a brief cognitive evaluation. The neurological and cognitive assessments included in the MACE are those from the Standardized Assessment of Concussion that was introduced in the late 1990s (McCrea et al. 1997).

The screening tools used at other locations are variants of the Brief Traumatic Brain Injury Screen (BTBIS) (Figure 26–3). The BTBIS questions are designed to ascertain whether a service member had an injury that at least met the criteria for mTBI that were established by the American

3 Question DVBIC TBI Screening Tool

1. Did you have any injury(ies) during your deployment from any of the following? (check all that apply):

A. Fragment
B. Bullet
C. Vehicular (any type of vehicle, including airplane)
D. Fall
E. Blast (Improvised Explosive Device, RPG, Land mine, Grenade, etc.)
F. Other specify: _____

2. Did any injury received while you were deployed result in any of the following? (check all that apply):

A. Being dazed, confused or "seeing stars"
B. Not remembering the injury
C. Losing consciousness (knocked out) for less than a minute
D. Losing consciousness for 1-20 minutes
E. Losing consciousness for longer than 20 minutes

NOTE: Endorsement of A-E meets criteria for positive TBI Screen

F. Having any symptoms of concussion afterward (such as headache, dizziness, irritability, etc.)
G. Head Injury

NOTE: Confirm F and G through clinical interview

H. None of the above

3. Are you currently experiencing any of the following problems that you think might be related to a possible head injury or concussion? (check all that apply):

A. Headaches
B. Dizziness
C. Memory problems
D. Balance problems
E. Ringing in the ears
F. Irritability
G. Sleep problems
H. Other specify:_____

FIGURE 26–3. Brief Traumatic Brain Injury Screen (BTBIS).

Source. Reprinted from Schwab KA, Ivins B, Cramer G, et al.: "Screening for Traumatic Brain Injury in Troops Returning From Deployment in Afghanistan and Iraq: Initial Investigation of the Usefulness of a Short Screening Tool for Traumatic Brain Injury." *Journal of Head Trauma Rehabilitation* 22(6): 377–389, 2007.

Congress of Rehabilitative Medicine (Kay et al. 1993). Service members who report having an injury event that results in one or more of the above characteristics are considered to have screened positive for a possible TBI and are referred for further evaluation. The BTBIS also asks those who had a possible TBI about problematic postconcussive symptoms they are currently experiencing. Slight variants of these questions form the basis of screening tools used at the Landstuhl Regional Medical Center, during the PDHA and PDHRA, and at the VA. The questionnaires used during the PDHA and PDHRA and at the VA ask about the presence of symptoms at the time of injury and at the present. To screen positive on the VA questionnaire (Table 26–1), a veteran must have had an injury that met mTBI criteria and resulted in postconcussive symptoms at the time of injury and must have current postcon-

cussive symptoms as well. This captures those patients in need of TBI services but does not improve mTBI surveillance because asymptomatic patients are not recorded.

Studies have begun to provide preliminary evidence of the validity of the MACE and the BTBIS. In a recent study of service members with blast-related mTBI who were assessed within 24 hours of injury, the scores from the MACE's cognitive evaluation were significantly correlated with duration of LOC and the Repeatable Battery for the Assessment of Neuropsychological Status immediate memory factor (Grant et al., unpublished, 2008). Previous studies have demonstrated the validity of the Standardized Assessment of Concussion for mTBI (McCrea et al. 1997, 1998; Naunheim et al. 2008). A study of the BTBIS found that 83% of a sample of Army soldiers who screened positive for war-related TBI had their TBI confirmed by a clinical interview (Hoge et al. 2008). Clinical interview is the standard for diagnosing mTBI. The study also found that a significantly higher proportion of those who screened positive for war-related TBI (64%) had three or more problematic postconcussive symptoms after returning than those who screened negative for TBI (41%) (Hoge et al. 2008). Another study found that TBI, resulting in LOC as identified by the BTBIS, was an independent predictor of having three or more current postconcussive symptoms when controlling for the presence of PTSD and demographic variables (Schneiderman et al. 2008). Further validation studies of the MACE, BTBIS, and the VA TBI screening tool are currently under way.

TBI Management in the Military

As previously stated, medical management of severe and moderate TBI begins on the battlefield and in rapid triage and evacuation. Neurosurgical and critical care management varies little from that of similar civilian injuries with one exception. Decompressive craniectomies are widely used for patients with potential ICP problems. This minimizes ICP elevations that may occur during times when other intervention may be limited (i.e., during transport). Once stabilized, these patients are considered for either autologous or synthetic bone flap replacement. This typically occurs after the patient's physical condition improves following inpatient rehabilitation at one of four designated Department of Veterans Affairs polytrauma rehabilitation centers (Table 26–2). These facilities are staffed with highly experienced personnel skilled in treating this unique population.

The greatest numbers of service members sustain concussion. Those who present for medical attention are screened and assessed for the presence of concussion-related symptoms (Figure 26–4). During the exam, if red flags are noted, patients are transferred to medical facilities that have CT capability for further evaluation. In the absence of red flags, efforts are made to manage these patients locally for up to 14 days. Service members are placed on duty restrictions for at least 24 hours, longer if symptoms persist. Once asymptomatic, exertional testing is performed. This procedure uses principles from the cardiac literature, in which patients exercise to their target heart rate. Following the exercise, a brief cognitive exam (Standardized Assessment of Concussion or similar) is given, and the patient is assessed for the recurrence of any symptoms. The presence of exercise-induced cognitive difficulties or symptom recurrence triggers ongoing duty restrictions. Absence of problems after exertional testing leads to the removal of duty restrictions. Service members with a diagnosis of concussion are given an information sheet and education in a context of expectation of recovery. Those with ongoing symptoms are screened for comorbid psychological health issues, including depression and PTSD. Those patients not showing improvement within the specified time frame are then transferred to a Level III facility where further evaluation occurs. Neuropsychological testing may be done, and the previously established treatment plan may be modified. Ongoing symptoms at this time lead to evacuation out of the theater of operations.

TABLE 26–1. Veterans Affairs clinical reminder traumatic brain injury screen

Screen has four sequential sections

Events

1. During any of your OEF/OIF deployment(s) did you experience any of the following events?
    a. Blast or explosion
    b. Vehicular accident/crash (including aircraft)
    c. Fragment wound or bullet wound above shoulder
    d. Fall

Immediate symptoms following the event

2. Did you have any of these symptoms IMMEDIATELY afterwards?
    a. Losing consciousness/"knocked out"
    b. Being dazed, confused or "seeing stars"
    c. Not remembering the event
    d. Concussion
    e. Head injury

New or worsening symptoms following the event

3. Did any of the following problems begin or get worse afterwards?
    a. Memory problems or lapses
    b. Balance problems or dizziness
    c. Sensitivity to bright light
    d. Irritability
    e. Headaches
    f. Sleep problems

Current symptoms

4. In the past week, have you had any of the symptoms from Section 3?
    a. Memory problems or lapses
    b. Balance problems or dizziness
    c. Sensitivity to bright light
    d. Irritability
    e. Headaches
    f. Sleep problems

Note. For all four responses, an answer of "yes" requires further evaluation. Screen does not diagnose traumatic brain injury but generates referral for further evaluation.

OEF=Operation Enduring Freedom; OIF=Operation Iraqi Freedom.

Source. Veterans Health Administration Directive 2007-013.

TABLE 26–2. Department of Veterans Affairs (VA) polytrauma rehabilitation centers

Center	Location
Minneapolis VA Medical Center	Minneapolis, Minnesota
H.H. McGuire VA Medical Center	Richmond, Virginia
James A. Haley VA Medical Center	Tampa, Florida
VA Palo Alto Health Care System	Palo Alto, California

Management at the Level IV facility often involves magnetic resonance imaging (MRI), including gradient recall echo and diffusion-weighted imaging sequences, which are more sensitive to brain injury than conventional T1- and T2-weighted sequences. In addition, the patient is evaluated by a neurologist. This prompts the decision to either return to the combat setting or, more likely, return stateside for ongoing medical care. Clinical algorithms, based on available literature and expert consensus, are used to guide the management of all patients with combat-related TBI.

Warfighters are unique individuals who may put the mission and comrades ahead of themselves. For this reason, those with concussion do not always seek immediate medical care. It is through routine PDHAs that previous concussion may be identified or ongoing symptoms are reported. In delayed presentation such as this, efforts are made at normalizing the service members' sleep patterns. Following this, other potentially debilitating symptoms such as headaches and dizziness are addressed. Often requiring pharmacotherapy, headaches may also respond to alternative techniques such as physical therapy, occipital nerve blocks, or botulinum toxin injections (see Chapters 21 and 35, this volume). Dizziness and balance complaints (Hoffer et al. 2004), often seen without vertigo following TBI, are evaluated using isobalance testing. If indicated, canalith repositioning is performed, or for noncandidates, habituation exercises are initiated. Data from the Naval Medical Center San Diego indicate that those with blast exposure are more likely to suffer constant vestibular symptoms, whereas those with blunt trauma experience intermittent problems (Hoffer et al. 2010). A primary care model is used for early concussion management. Patients failing primary care management may be referred to one of 15 TBI specialty centers across the United States for further assessment and management.

Service members with concussion who are stationed at remote bases where TBI assets are limited may be treated via primary telemedicine initiatives. Consults can be arranged via the Virtual TBI Clinic. Through video conferencing, patients at remote locations are seen by a TBI provider from an established TBI clinic. Recommendations are then made to the local clinician. Video follow-up can be scheduled as needed. A second mechanism utilizes e-mail for providers in areas that have less sophisticated conferencing capabilities. After seeing a patient with known or suspected TBI, the provider may send the de-identified history and physical to an e-mail account that is staffed by a variety of TBI experts. Recommendations are then forwarded to the provider, usually within 4 hours. This mechanism has been used successfully by providers both stateside and in the combat setting. Follow-up communication with the referring clinician is usually established within 30 days of the consult, serving as a quality assurance mechanism. With either of these mechanisms, patients exhibiting findings that raise concern can be scheduled for transfer to a more sophisticated medical facility.

The DVBIC has recently established the TBI Regional Care Coordination (RCC) program. Currently, all TBI patients evacuated from the combat setting are identified to the RCC staff. The patient is contacted immediately to confirm demographics and care needs. Patients are provided contact information for the RCC program. Additional contact with each patient is attempted at 3 months, 6 months, 1 year, and 2 years. During these telephone interviews, patients may discuss any ongoing issues and request additional guidance. Each RCC maintains a database of known TBI resources within its service region. Although referrals cannot be made directly from the RCC, the program is able to provide the patient with necessary information to facilitate care. This program interfaces with the Veterans Health Administration's Federal Care Coordination program, which focuses on polytrauma patients. Service members may opt out of this program at any time. Maintaining contact with this patient population remains challenging given the highly mobile status of the military. Efforts to expand this program to all service members identified with TBI are likely as the program evolves.

Return-to-Duty Criteria

A service member's return to duty—both restricted and unrestricted—occurs after clinical assessment, treatment, and reevaluation of progress. Cases are individually reviewed and processed according to best practices. Though patients may have the same diagnosis, symptoms and treatment response are highly variable, thereby requiring careful consideration before duty restrictions are removed. It is important to evaluate cognition before return to duty. Efforts are under way to evaluate a practical cognitive assessment for such determinations. Computer-based cognitive testing should not be done until at least 24 hours postinjury. There are a variety of tools to test cognition. The Automated Neuropsychological Assessment Metrics (ANAM) has empirical data as well as some military normative values, making this a useful tool (Vincent et al. 2008). As recommended by multiple professional societies and commissions, the Department of Defense recently mandated the use of the ANAM for baseline predeployment neurocognitive testing while other instruments are evaluated in a head-to-head study to evaluate their sensitivity and specificity for TBI. Computer-based cognitive testing can also be used following TBI to assess neurocognitive changes as part of a return-to-duty evaluation.

For settings in which computer-based cognitive testing is not available, the current military strategy for return to duty includes the MACE, which contains a validated screening tool, the Standardized Assessment of Concussion (McCrea et al. 1997), that is used to evaluate athletes for return to play. The MACE is most sensitive for use immediately postinjury but has also been used days later to

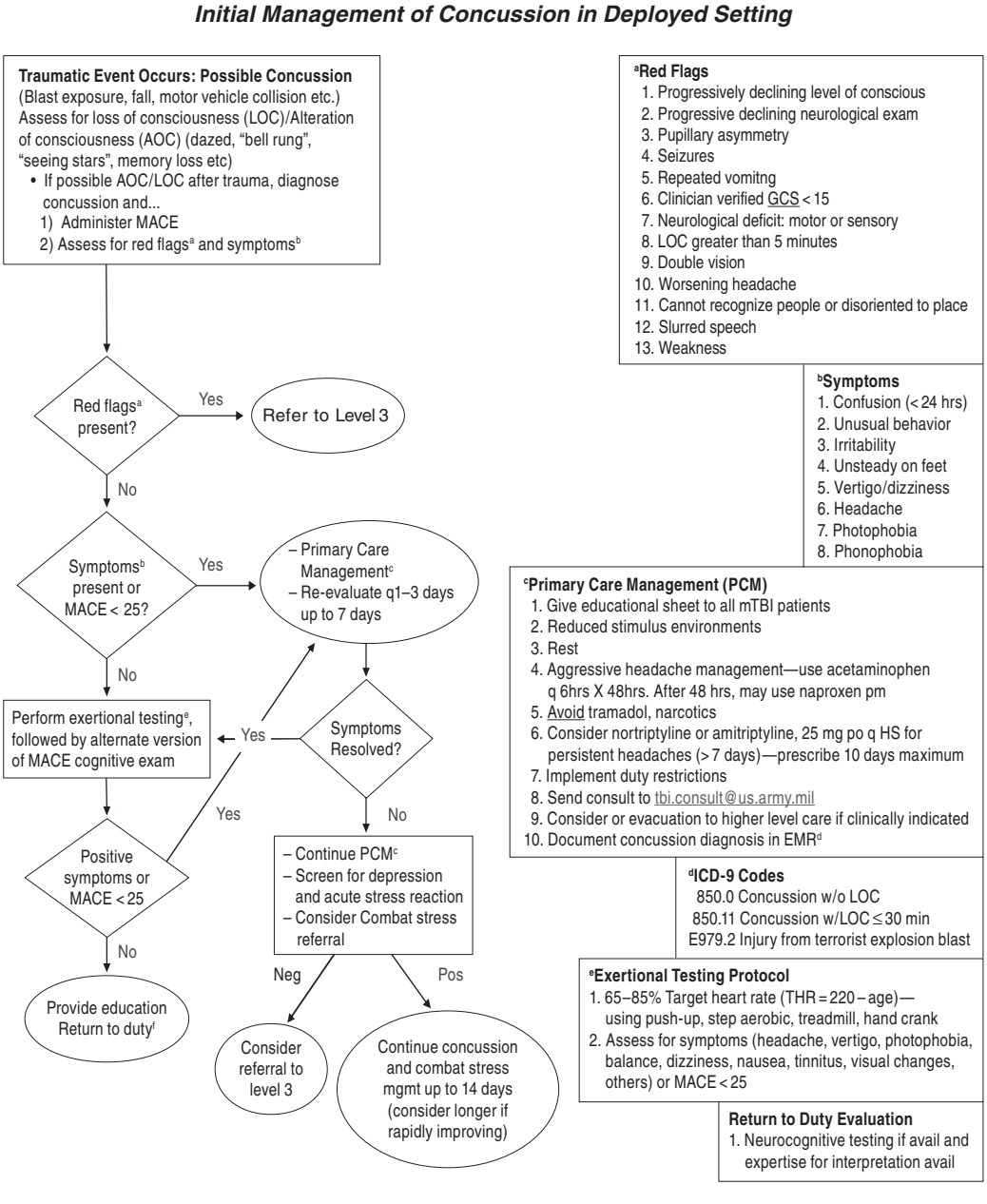


FIGURE 26–4. Deployed Setting Provider Algorithm.

Source. Defense and Veterans Brain Injury Center.

screen for improvement or decline in condition. This tool has been widely distributed for use.

Vestibular testing and exertional testing are highly valued examinations that should occur prior to consideration for return to duty. Much research is currently under way looking at the mechanism of injury and vestibular complications (dizziness, balance issues), length of symptoms, and the ability to return to work (Gotshall et al. 2007). Vestibular trauma is of concern because of its ramifications of service member's stability in activity, awareness of surroundings, and overall safety of oneself and colleagues. Dizziness is often the mTBI patient's primary disability (Hoffer et al. 2004).

Exertional testing is another vital component in the assessment steps for return to duty. Research in this specialty has mostly been done in the sports medicine arena or animal models (Griesbach et al. 2008). Experts in sports-related TBI conclude that before one returns to play, he or she must be free of all postconcussion symptoms at rest and exertion (Cantu 2001) (see Chapter 27, Sports Injuries,

this volume). Military exertional testing considerations include exercise to achieve 65%–85% of the target heart rate. Upon reaching the target heart rate, the patient is assessed for symptoms and cognition with an alternative version of the MACE. If the patient is asymptomatic and without cognitive dysfunction following exertion, return to duty can be considered.

Rehabilitation and Community Reentry

Once medically stable, the small percentage of service members with severe or penetrating TBI undergo state-of-the-art rehabilitation at a VA polytrauma rehabilitation center or comparable civilian partner. These programs offer extensive multidisciplinary care for the improvement and progression of health and activities of daily living. Many return to functional status, but for those requiring ongoing care, options may include federally supported assisted-living or coma emergence programs. These programs are offered at select VA medical centers or DVBIC civilian partners.

Families often provide in-home care for these wounded warriors. The National Defense Authorization Act of 2007, Section 744, mandated the development of a family caregiver curriculum to "train family members in the provision of care and assistance to members and former members of the Armed Forces with traumatic brain injuries." This curriculum is currently being developed by a presidentially-appointed committee of subject matter experts.

Two civilian community reentry programs within the DVBIC network providing symptom management, cognitive therapy, and social skills have been instrumental in returning those patients with significant cognitive and behavioral issues to a home setting. In addition to therapy, these settings provide work trials that may increase the rate of gainful employment postdischarge.

Finally, technology is being levered to increase the independence in those service members with cognitive deficits. Pilot projects utilizing cell phones and personal assistive devices are under way. Using calendar and alarm functions, these devices are being tested as memory aids. Automated medication delivery systems that dispense only the appropriate dose and alarm at set dosing intervals are being evaluated in some care settings in an effort to increase medication safety and compliance.

Future Directions and Clinical Research Opportunities

In the fall of 2008, the Uniformed Services University of the Health Sciences (USUHS) opened the Center for Neuroscience and Regenerative Medicine with the goal of studying the effects and treatments of TBI and PTSD. Specifically, USUHS is establishing a consortium between Walter Reed National Military Medical Center, the National Institutes of Health, the Defense Center for Traumatic Brain Injury and Psychological Health, the Army Medical Research Command labs, and Navy labs. This network will work with USUHS as the coordinating center to accelerate regenerative medicine programs across these institutions so that fundamental studies are moved to translational laboratories and, in turn, this science will migrate quickly so as to advance development in a clinical setting.

The recently established DVBIC Armed Forces Institute of Pathology TBI Research Center focuses on translational applications of biophysics and neuropathology. The lab offers advanced imaging, including 7-tesla and 9.4-tesla MRI machines with the ability to perform cutting-edge magnetic resonance microscopy. The lab has obtained a CARS microscope that will allow for in vivo studies of the effects of blast on the brain.

Numerous studies are planned or in progress to further elucidate the nature of blast-related TBI, effects of treatment, and long-term outcome. The following is a partial list of TBI research initiatives:

- Elucidation of the cellular and molecular mechanisms underlying the pathophysiological events following TBI
- Development and validation of computerized and animal model systems to explore the synergistic effects of TBI (including blast and impact) on the dynamic strains within brain tissue in combat injuries
- Drug interventions: neuroprotective/anti-inflammatory, regenerative
- Neuroimaging studies to assess or map injury as predictor of outcome
- Stem cell implantation to enhance neural regeneration
- Biomarker studies to identify and characterize TBI
- Epidemiological studies to determine incidence of mTBI and sequelae of TBI, including vestibular dysfunction and pituitary/endocrine dysfunction
- Fifteen-year longitudinal study of TBI
- Assessment of current and development of novel cognitive rehabilitation therapies
- Clinical trials to evaluate the efficacy of therapeutics to improve outcome following mild, moderate, and severe TBI
- Development of helmet-mounted sensors to quantify blast exposure
- Validation study of the use of the MACE in an austere environment; study recently funded by Congressionally Directed Medical Research Programs
- Longitudinal study of mTBI to evaluate the validity of the TBI screening tool used at large military bases, within the PDHA, and by the Department of Veterans Affairs
- Driving simulation study to evaluate driving safety in patients with TBI

In the summer of 2008, the VA's Office of Research and Development announced a request for applications for TBI-related projects, developed in part with recommendations from the State of the Art TBI conference held in May 2008 (www.research.va.gov/funding/solicitations/docs/TBI.pdf). The wide spectrum of TBI-related issues calls for an integrated research endeavor. Important efforts have begun in the VA, Department of Defense, National Institutes

of Health, and DVBIC. The military and VA health care systems are committed to fully provide comprehensive programs required for optimal treatment of patients with TBI. More recently, collaborations with civilian partners (Massachusetts Institute of Technology, University of Florida, and others) has led to the development and improvement of technology that can further elucidate patterns associated with blast-induced TBI.

KEY CLINICAL POINTS

- Traumatic brain injury (TBI) is a common war-related injury.
- Explosions are a prevalent mechanism of combat-related injury, although primary blast brain injury appears to be a rare phenomenon.
- TBI screening occurs at multiple time points during active duty and in veteran medical care.
- Treatment algorithms that consider resource availability and tactical limitations drive TBI care in the combat setting.
- Current research efforts are focused on identifying and mitigating blast-related brain injury.

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CHAPTER 27

Sports Injuries

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THE MAJORITY OF SPORT-RELATED HEAD INJURIES are mild traumatic brain injury (mTBI) events, traditionally referred to as concussions. Per consensus definition, "concussion is…a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces" (Aubry et al. 2002, p. 57). Five specific common features are noted: 1) causation by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head; 2) a typically rapid onset of short-lived impairment of neurological function that resolves spontaneously; 3) acute clinical symptoms primarily reflecting functional disturbance versus structural injury; 4) a resulting graded set of clinical syndromes that may or may not involve loss of consciousness (LOC), with resolution of clinical and cognitive symptoms generally following a sequential course; and 5) typical association with grossly normal structural neuroimaging studies. Five domains of specific signs and symptoms of acute concussion are noted in Table 27–1; problems in one or more of these domains raise the index of suspicion for diagnosis of concussion.

The consensus definition of concussion and its related features was maintained after recent review, although it was noted that "in a persistent small percentage of cases, post-concussive symptoms may be prolonged" (McCrory et al. 2009, p. 186). The National Athletic Trainers' Association (NATA) and American College of Sports Medicine have also published comprehensive documents on sport-related concussion, all with varying degrees of agreement and distinctiveness (Cantu 2007a). Overall, efforts in the area of researching and defining sport-related mTBI are considered to be works in progress, with the expectation of continued updates as time progresses (Cantu 2006).

Epidemiology

The reported incidence of sport-related concussion has grown dramatically. Estimates from the Centers for Disease Control and Prevention are that 1.6–3.8 million sport- and recreation-related concussions occur each year in the United States (Langlois et al. 2006). A major review by Toth (2008) broke down epidemiology by specific sport or activity. Boxing, U.S. football, soccer, and ice hockey seem to have the highest concussion rates, generally measured in terms of athlete exposures, defined as one player taking part in one game or practice in which the player is exposed to the possibility of being injured.

TABLE 27–1. International Conference on Concussion in Sport: five clinical domains of symptoms and signs of acute concussion

1. Symptoms: somatic (e.g., headache), cognitive (e.g., "fogginess"), emotional (e.g., emotional lability)
2. Physical signs (e.g., loss of consciousness, amnesia)
3. Behavioral change (e.g., irritability)
4. Cognitive impairment (e.g., slowed reaction, unawareness of period/opposition/score)
5. Sleep disturbance (e.g., drowsiness)

Source. Adapted from McCrory P, Meeuwisse W, Johnston K, et al.: "Consensus Statement on Concussion in Sport—3rd International Conference on Concussion in Sport Held in Zurich, November 2008." *Clinical Journal of Sport Medicine* 19:185–200, 2009. Used with permission.

Epidemiological information must also be considered in the context of patient underreporting in sport-related traumatic brain injury (TBI) (Consensus Conference 1999), the continued evolution of mTBI diagnostic criteria, and the variation in organizational definition statements. mTBI often goes unrecognized or undiagnosed when patients do not report LOC, which is significant given that over 90% of cerebral concussions do not involve LOC (Cantu 1998). Even with LOC well established, some research indicates little correlation with patient outcome (Lovell et al. 1999). The length of posttraumatic amnesia (PTA) and other symptoms following a head injury may be a better predictor of outcome; however, PTA duration is difficult to assess reliably (Forrester et al. 1994).

Sport-related TBI bears the additional consideration of increased frequency among children and young adults (i.e., ages 5–24 years), which may result in interference with attainment of full educational and occupational potential, and lengthy periods of disability in more severe cases (Consensus Conference 1999). There is also a gathering body of evidence that multiple concussions, or even subconcussive events, increase the risk for poor outcome and cumulative effects (Collins et al. 1999, 2002; Iverson et al. 2004; Jordan et al. 1997; Killam et al. 2005; Matser et al. 1999; Roberts et al. 1990), although evidence to the contrary (Guskiewicz et al. 2002; Macciocchi et al. 2001) is also found. From a clinical perspective, the presence of some studies indicating increased risk for poorer outcome with multiple concussions is of concern.

Neurophysiology in Sports-Related mTBI

The general neurophysiology of mTBI and genetic factors are addressed at length elsewhere in this volume (see especially Chapter 2, Neuropathology, and Chapter 3, Genetic Factors). With reference to sports injuries, it is clear that physical forces applied to the player increase as mass and velocity increase. Studies have not yet demonstrated the amount of g-force required to induce clinically significant structural and/or functional changes in the brain, although several have measured acceleration in on-field impacts associated with concussion (Brolinson et al. 2006; Pellman et al. 2003; Zhang et al. 2004), and Naunheim et al. (2000) suggested 200 g as a threshold for permanent damage from a single head injury. Efforts to establish such empirical cutoff levels are useful; however, the wide range of factors involved in any specific injury (e.g., multiple directions of acceleration leading to rotational/angled versus linear impacts, the player's degree of preparedness for acceleration, use/lack of protective equipment, prior history of concussions) complicates matters considerably. Further, there is a paucity of research examining cognitive and functional changes as a function of measured forces applied to the brain, making it difficult to clearly define "how much is too much."

Functional magnetic resonance imaging (fMRI) studies involving sport-related brain injury are few to date. Lovell (2008) implemented a long-term prospective study incorporating postconcussion fMRI paradigms and baseline neuropsychological testing with the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), allowing correlation between these data sources. In a preliminary sample of 200 athletes evaluated within 1 week postinjury, the researchers found a greater latency to clinical recovery (i.e., symptom-free with normal neuropsychological test performance) among the participants with the greatest degree of fMRI abnormalities (Lovell et al. 2007).

Genetic Factors

The role of the apolipoprotein E (apoE) genotype has been examined in boxers by Jordan et al. (1997), who found that a greater risk for dementia was associated with possession of the *APOE*E4* allele among those with higher boxing exposure as defined by number of bouts. Cognitive risk factors have also been investigated in other sports, such as a study of younger versus older U.S. football players (Kutner et al. 2000) that found lower-than-expected performance on neurocognitive tests in players with versus without the *APOE*E4* variant. Polymorphic alleles in the apoE promoter region may also play a role in concussion risk. For example, Terrell et al. (2008) found that in a sample of college athletes, T homozygotes at the *G-219T* allele in the promoter region had a significantly increased report of concussion history, in particular more severe (i.e., Cantu grade 2 and higher) concussion events. Overall, although genotyping may be of benefit in addressing TBI, primarily in relation to *APOE*E4* status, the significance of such genetic factors in sports concussion risk or injury outcome is not yet clear, and the consensus is that "routine genetic screening cannot be recommended at the present time" (McCrory et al. 2005, p. 201).

Second-Impact Syndrome

Saunders and Harbaugh (1984) described the classic example of second-impact syndrome (SIS), that is, an athlete returning to play while still symptomatic from a brain injury, then experiencing a second injury resulting in edema and consequently fatal cerebral hemorrhage. Notably, there is a strong association of SIS with younger groups of athletes, typically under the age of 21 (Buzzini and Guskiewicz 2006; Solomos 2002). In terms of SIS mechanisms, one theory is that a loss of cerebral vascular autoregulation, different from that following a singular TBI (as described by Hovda et al. 1999), after the first impact sets up a vulnerability to vascular engorgement and rapidly increasing intracranial pressure leading to uncal, subtentorial, or cerebellar tonsillar herniation from the later, second impact. According to this view, the second injury may be relatively mild, without LOC, or even missed by the player and close observers (Cantu and Voy 1995; Kelly et al. 1991). Within a short period of time, however, the athlete experiences confusion, collapse, loss of function, and, potentially, death.

Some researchers have called SIS into question based on a review of published cases (McCrory 2001; McCrory and Berkovic 1998). Of the 17 cases found in the literature by the authors, none met all their criteria for definite SIS,

and only 5 cases met criteria for probable SIS. There was also evidence of a possible cultural bias because, despite similarity in sport-related concussion rates worldwide, virtually all the SIS reports occurred in the United States. On the basis of these findings, McCrory (2001) argued against the acknowledgment of SIS as a clinical entity per se. Instead, he proposed a rare complication of head injury called "diffuse cerebral swelling," unrelated to the occurrence of a second impact, as the culprit.

Brain Injury in Organized Sports

Boxing

Boxing is the best-known organized sport in which the infliction of injury is the main goal, with the inducement of LOC via blows to the head a prime objective. An epidemiological study of sports injury (Toth et al. 2008) found that boxing enormously exceeded all other sports, including U.S. football, in terms of mTBI incidence. The continued practice of activities encouraging such goals is of concern to the medical community, and organizations such as the American Medical Association (1999), Australian Medical Association (2007), and World Medical Association (2005) have issued positions advocating the elimination of boxing. Although there has not been a major controlled scientific study of boxing and long-term neurological sequelae, and the existing literature is mixed in terms of findings, there is sufficient evidence in this ongoing area of research to inform participants of the potential risks, at least from a conservative standpoint.

Brain injury in boxing tends to be severe in contrast to other sports-related head injury. Accounts of boxing-associated neurological changes, termed "*punch drunk" syndrome,* date back as early as 1928 (Martland 1928). Later on, "dementia pugilistica" (Lampert and Hardman 1984) became more widely used term. The term *chronic traumatic encephalopathy* (CTE) appears to be most popular at present. Early accounts of boxing neurological sequelae describe an initial confusion and loss of coordination, followed by increasing latency of speech and slowed motor functions with associated upper-body tremor. Martland (1928) observed that this symptom pattern was similar to that of Parkinson's disease, and dementia pugilistica is often associated with parkinsonism in the literature. In terms of prevalence, estimates are that 9%–25% of professional boxers ultimately develop CTE (Ryan 1987).

The greater degree of neurological impairment observed in boxing as opposed to other sports may be related to the multiple injury mechanisms in the sport. Damage may result from direct blows to the head as well as from rotational torque, leading to both focal and diffuse injuries. Direct blows are associated with linear acceleration, resulting in compressive and tensile stress on axons, deceleration on impact, and carotid injuries, whereas rotational forces cause shearing injury (Cantu 1996; Lampert and Hardman 1984). A study of biomechanical forces in boxing found rotational forces to be the most important factor in boxing concussion (Walilko et al. 2005) and also noted a strong correlation between weight class and injury risk. Injury to the carotid arteries in boxing may also create reflexive hypotension, with resulting light-headedness that increases the risk of further injury. Zetterberg et al. (2006) found increased levels of cerebrospinal fluid biomarkers for neuronal and axonal injury following bouts of amateur boxing, most pronounced for boxers who received many hits or high-impact head blows.

In addition to acute injury, boxers are subject to successive head trauma through concussive and subconcussive blows, with the potential for a range of other neurological problems, including increased vulnerability for subsequent neurodegenerative conditions (Jordan 1987, 1993). Neuropathological changes observed in boxers include cerebral atrophy, cerebellar degeneration, and cortical and subcortical neurofibrillary tangles (Corsellis et al. 1973). Behavioral research on the neurocognitive effects of boxing head injury has mixed findings. Mendez (1995) found that amateur versus professional status of the participant accounted for the largest amount of variance in cognitive functioning, with greater negative impact on professionals, particularly when professionals had neuroimaging evidence of neurological injury (e.g., subdural hematomas and perivascular hemorrhage). Amateur boxers, in contrast, demonstrated neuropsychological functioning similar to that of other amateur athletes. A review article examining amateur boxers (Butler 1994) also indicated no consistent evidence of neuropsychological deficiency apart from decreased, though not impaired, nondominant-hand fine motor coordination, which may reflect mild peripheral nerve damage rather than central nervous system injury.

McLatchie et al. (1987) found significantly greater neuropsychological impairment in boxers compared with control subjects with orthopedic injuries, as well as irregular electroencephalogram (EEG), clinical, and computed tomography (CT) findings among some of the boxers. The authors noted that only a few of the boxers demonstrated severe neuropsychological impairment. Other researchers investigated the relationship between neuropsychological testing and functional neuroimaging in amateur boxers (Kemp et al. 1995). In Kemp et al.'s study, the number of bouts correlated positively with poor neuropsychological test performance. Notably, these researchers found neuropsychological assessment to be the most sensitive indicator of cerebral dysfunction in boxing studies as compared with other methods such as EEG, neurological examination, and single photon emission CT scans, primarily due to the ability of neuropsychological assessment to detect more subtle deficits.

Potential selection bias and the lack of appropriate comparison control groups are issues in boxing research. As recently as the mid-1980s, it was commonly believed that neurological and neurocognitive deficits in boxers were artifacts of prior substance abuse, poor education, and poor training (American Medical Association Council on Scientific Affairs 1983). In response, Casson et al. (1984), using EEG, CT, and neuropsychological testing, studied a sample of current and former professional boxers with "responsible jobs [and] secondary or college education" (p. 2663) and no history of neurological illness or substance abuse. The authors found abnormalities on at least two of the assessments for the majority of boxers. The

remaining subjects showed deficiency on at least some neuropsychological measures (e.g., immediate and delayed verbal memory). Findings were not related to the number of concussions or amnestic episodes.

U.S. Football

U.S. football involves direct player-to-player contact as a fundamental aspect of the sport and has a high incidence of significant concussions relative to many other sports. In comparison with more serious injuries, it is only relatively recently that mTBI in football has received significant scientific attention. Multiple studies have indicated that the rate of concussion in football is as high as 5% of all acquired injuries (DeLee and Farney 1992; Karpakka 1993), and it is often the case that football players receive "dings" or "see stars" only to have the symptoms ignored or minimized to facilitate return to play (Magnes 1990).

A landmark multisite study conducted by Barth and colleagues (1989) at the University of Virginia examined mTBI in football among 2,300 collegiate players using preseason baseline testing and postinjury serial assessment (24 hours, 5 days, and 10 days postinjury). Almost all concussed players were observed to have some alteration of consciousness or postinjury confusion, with very few experiencing LOC. Their data were matched with those of nonconcussed football players. Results showed that concussed players had mild neurocognitive deficits or failed to show expected practice effects on cognitive testing compared with control subjects, primarily on measures of sustained attention and visuomotor speed. Symptom resolution generally occurred by 5–10 days postinjury, and accompanying subjective complaints of dizziness, headache, and memory dysfunction largely resolved by the tenth day.

Findings from the University of Virginia study were supported by Lovell and Collins (1998), who examined mTBI in 63 Division I college football players. Preseason neuropsychological assessment and subsequent postinjury evaluation of participants, including 4 players with documented concussions, revealed sub-baseline performance on measures of information processing speed and verbal fluency, as well as a lack of expected improvement from practice effects. These studies, among others, have led to the use of preseason baseline neurocognitive screening as described by the Sports as a Laboratory Assessment Model (SLAM) developed by Barth et al. (2001, 2002), which is becoming the gold standard for concussion assessment and management.

There is debate regarding whether participation in U.S. football can lead to long-term neurocognitive deficits, such as in boxing. In their review, Casson et al. (2008) maintained that the strong evidence for CTE in boxers stood in contrast to the paucity of support in American professional football players, which they indicated was primarily found in "isolated case reports and survey type studies of retired players" (p. 238). Further, the authors cited prior research that found no higher frequency of cognitive or memory impairment among players reporting three or more concussions as compared with players who had two or fewer (Pellman et al. 2004).

Cantu (2007b) responded to the abovementioned findings, noting that the study sample included data only from active players in their 20s and 30s collected during a relatively brief span of 6 years. Additional limitations were noted, including lack of prior concussion history, no inclusion of LOC data, no uniform method of evaluation for concussion, and lack of applicability to nonprofessional players. In support of this position, a large-scale study of collegiate football players found that a history of previous concussions was associated with slower recovery of neurological function (Guskiewicz et al. 2003). Notably, this study also found a threefold greater risk of future concussions for players with a past history of three concussions versus those with no concussion history, which may be indicative of increased vulnerability following recurrent injuries.

In terms of the association between concussion history and risk of developing long-term neurocognitive impairment, a study of retired professional football players found that those with three or more reported concussions had a fivefold prevalence of having a diagnosis of mild cognitive impairment and threefold prevalence of self-reported significant memory problems as compared with retirees reporting no significant concussion history (Guskiewicz et al. 2003).

Soccer

Soccer players risk potential injury from collision with the ground, ball, goalposts, and other players, with head injury estimated to account for 4%–20% of all soccer injuries (Roass and Nilsson 1979). Studies of brain injury risk in soccer have been complicated by questions of head injury from heading the ball, and findings have been mixed in this area (Putukian et al. 2000; Rutherford et al. 2005; Tysvaer and Storli 1981; Witol and Webbe 2003). Current consensus is that there are insufficient published data to support recommendations against the allowance of heading the ball or mandating the use of protective headgear for soccer players (Guskiewicz et al. 2004; Rutherford et al. 2003).

Head injuries in soccer are most frequently the result of head-to-head, head-to-ground, and elbow-to-head contact (Andersen et al. 2004; Boden et al. 1998). Early comprehensive studies with both active and retired soccer players showed mild EEG abnormalities as well as considerable subjective complaints of postconcussive symptoms in comparison with matched control subjects (Tysvaer et al. 1989). Another study using neuroimaging found cerebral atrophy in one-third of a sample of retired soccer players, and approximately 80% demonstrated deficient performance on measures of attention, concentration, memory, and judgment in comparison with age-matched control subjects (Sortland and Tysvaer 1989).

These early findings were not consistently replicated in subsequent research (Haglund and Eriksson 1993). More recent investigations found no evidence of impaired neurocognitive functioning among collegiate soccer players as compared with nonsoccer athletes and student nonathletes (Guskiewicz et al. 2002), professional football players (Straume-Naesheim et al. 2005), or a sample of 13- to 16-year-old student soccer players (Stephens et al. 2005). In contrast, Matser et al. (1999) found that soccer players demonstrated deficits in planning and memory and an

inverse relationship between number of concussions and performance on measures of simple auditory attention span, facial recognition, immediate recall of complex figures, rapid figural encoding, and verbal memory. These findings retained significance after correcting for education, concussions unrelated to soccer, number of treatments with general anesthesia, and alcohol use. Notably, the last was statistically higher among the soccer players.

Potential factors that might account for the variability of findings are differences in inclusion criteria from study to study, a reduction over time in the composition and make of soccer balls (in relation to ball-to-head injury) reducing potential mass on impact (Jordan et al. 1996), and lack of consistent use of control subjects across studies for other factors known to influence cognition such as alcohol use and malnutrition (Victor et al. 1989). Failures to account for preexisting learning disorders and non-soccer-related concussion are other potential sources of confound. Differences between early and more recent research may also be related to gradual improvement in measuring concussion history.

Sports-Related mTBI and Clinical Practice

Concussion Classification

Attempts have been made to classify concussion severity in the interest of assessment and tailoring management/intervention. Maroon et al. (1980) proposed a graded system of concussion classification on the basis of LOC. Under this system, "mild concussion" referred to injuries with no LOC, "moderate concussion" included injuries with brief LOC and retrograde amnesia, and "severe concussion" encompassed injuries with LOC of 5 minutes or more. Cantu (1998) included length of PTA, defined as any memory problems associated with brain trauma such as retrograde and anterograde amnesia, in addition to LOC, to create guidelines for rating concussion severity (Table 27–2).

Other systems, such as the practice parameters established by the American Academy of Neurology (1997), have placed a greater emphasis on LOC and confusion with amnesia. Unlike the Cantu scale, American Academy of Neurology practice parameters (Table 27–3) consider any LOC a grade 3 severe concussion, and the concept of confusion is viewed as a hallmark of concussion.

TABLE 27–2. Cantu grading: severity of concussion

Grade	Loss of consciousness		Duration of posttraumatic amnesia
1 (mild)	None		<30 minutes
2 (moderate)	<5 minutes	or	≥30 minutes but <24 hours
3 (severe)	≥5 minutes	or	≥24 hours

Source. Reprinted from Cantu RC: "Return to Play Guidelines After a Head Injury," *Clinics in Sports Medicine* 17:52, 1998. Copyright 1998, WB Saunders Company. Used with permission.

Although well over 20 other systems exist for grading concussion severity, the Cantu and American Academy of Neurology practice parameters severity scales have been among the most widely used. Cantu (2001) suggested evidence-based modifications to his grading system based on prospective studies of the connection between duration of postconcussion symptoms (PCS), PTA, and results from neuropsychological assessment. This system introduces consideration of PCS signs and symptoms assessed on the sidelines by the use of measures such as the Standardized Assessment of Concussion (SAC) (McCrea et al. 1997) or other brief mental status or cognitive examinations. This revision of Cantu's concussion severity rating system defined grade 1 concussion as no LOC with PTA or PCS symptoms of less than 30 minutes; grade 2 as LOC less than 1 minute and PTA or PCS symptoms greater than 30 minutes and less than 24 hours; and grade 3 as LOC greater than 1 minute or PTA greater than 24 hours, plus PCS symptoms longer than 7 days (Cantu 2001). The cumulative aspects of multiple concussions have also been considered in classification and management. For example, Echemendia and Cantu (2004) suggested that significant increases in the length of PCS symptoms (i.e., from days to weeks to months) with each successive concussion may indicate reduced resiliency.

Overall, despite the fact that some systems are encountered more frequently than others in practice, there does not seem to be a single overall concussion classification system used in the management of sport-related head injury.

TABLE 27–3. American Academy of Neurology practice parameters for concussion severity

Grade	Symptoms	Loss of consciousness
1 (mild)	Transient confusion; symptoms or mental status abnormalities on examination resolve in <15 minutes	None
2 (moderate)	Transient confusion; symptoms or mental status abnormalities on examination last >15 minutes	None
3 (severe)	—	Any loss of consciousness, either brief (seconds) or prolonged (minutes)

Source. Adapted from Kelly JP, Rosenberg JH: "The Diagnosis and Management of Concussion in Sports." *Neurology* 48:575–580, 1997. Copyright 1997, American Academy of Neurology. Used with permission.

TABLE 27–4. Cantu guidelines for return to play after concussion

Grade	First concussion	Second concussion	Third concussion
1 (mild)	Return to play if asymptomatic for 1 week	Return to play in 2 weeks if asymptomatic at that time for 1 week	Terminate season; may return to play next season if asymptomatic
2 (moderate)	Return to play after asymptomatic for 1 week	Minimum 1 month out; may return to play if asymptomatic for 1 week; consider terminating season	Terminate season; may return to play next season if asymptomatic
3 (severe)	Minimum 1 month out; may return to play if asymptomatic for 1 week	Terminate season; may return to play next season if asymptomatic	

Note. *Asymptomatic* means no headache, dizziness, or impaired orientation, concentration, or memory during rest or exertion.

Source. Reprinted from Cantu RC: "Return to Play Guidelines After a Head Injury," *Clinics in Sports Medicine* 17:56, 1998. Copyright 1998, WB Saunders Company. Used with permission.

Sideline Assessment

In addition to the player, personnel such as team physicians, teammates, athletic trainers, and coaches play a role in observing and identifying when a possible concussive event has occurred. Once identified, the player should receive a sideline assessment involving both gross neurological assessment and brief neurocognitive screening. Verification of a concussion using sideline assessment should lead to removal of the athlete from competition and instigation of return-to-play criteria, which may involve additional brief or more comprehensive neuropsychological assessment.

It should be noted that traditional orientation questions (e.g., to person, time, and place) have been found unreliable in comparison to memory assessment for sideline evaluation (Maddocks et al. 1995; McCrea et al. 1997; McCrory et al. 2009). A popular and well-studied measure used for sideline assessment is the Standardized Assessment of Concussion (SAC; McCrea et al. 2000). The SAC is a brief evaluation of attention/concentration, memory, and rapid novel problem-solving that can be administered by an athletic trainer, and it is recognized as being sensitive to mild cognitive and mental status impairment. Coupled with a brief neurological examination, the SAC provides the minimum data necessary for making immediate removal and return-to-play decisions. The SAC is most effective when preseason baseline scores are obtained for comparison with postconcussion performance; even one additional error suggests cognitive compromise. The SAC is also available in a computer-administered version, allowing simple and accurate tracking over time. The 2008 Zurich statement also includes a copy of the updated Sport Concussion Assessment Tool, which combines key elements of multiple concussion measures (Maddocks et al. 1995) into a single instrument.

Return-to-Play Criteria

The expectation for outcome following a first uncomplicated sport concussion is that most athletes will experience complete resolution within 5–10 days (Barth et al. 1989). Multiple concussive or subconcussive events may result in PCS and complaints that persist for weeks or months (Barth et al. 1989; Collins et al. 1999; Gronwall and Wrightson 1974; Guskiewicz et al. 2003; Iverson et al. 2004; Killam et al. 2005). Individual differences or vulnerabilities are likely an important moderating factor in such cases, including a history of learning disabilities, attention deficit disorders, or previous head injuries.

The first formal return-to-play criteria primarily conformed to Quigley's rule (Schneider 1973), which recommended termination of participation in contact sports after three concussions, regardless of severity. Later, Cantu (1998) and the American Academy of Neurology (1997) extended and expanded Quigley's rule, recommending that an athlete be held from competition for 1 week after sustaining an initial grade 1 concussion, with termination of play for the season after the third grade 1 concussion. An athlete sustaining a first grade 3 concussion would be held from play for a minimum of 1 month, with return to play considered only after 1 week without any PCS during rest or exertion (Table 27–4). No athlete should be returned to play under any circumstances if he or she reports current neurological or postconcussive symptoms.

Echemendia and Cantu (2004) further advanced return-to-play criteria with their proposal of a dynamic and case-individualized model of decision making, noting that most published criteria were based solely on aspects of concussion, such as LOC or PTA. The authors argued for consideration of multiple factors in determining return to play, including patient medical history (e.g., normal neurological exam and lack of structural lesions on neuroimaging exam), neuropsychological performance at or above baseline levels, player factors (e.g., presence of patient symptom minimization, level of concussion risk for the players' position), team factors (amateur vs. professional competition), and even situational factors such as the type of playing surface and field conditions.

Most recently, the 2008 Zurich statement provided guidelines for management of concussive injury, including a return-to-play protocol (Table 27–5). The statement also emphasized that the basis of concussion management is "physical and cognitive rest until symptoms resolve" (p. 188) followed by gradual and monitored reengagement in exertion pending medical approval of return to play. Some potential complicating factors are also addressed in the Zurich statement, including that athletes should not be taking medications that affect or modify concussion symptoms, in addition to being symptom free. Guidelines for the management of modifying factors of concussion include an expectation of more prolonged rehabilitation,

with management by doctors who have specialized expertise in sport-related head injury.

Reflecting recent updates regarding concussion management, the National Collegiate Athletic Association (NCAA) issued a policy statement memorandum (Debra Runkle, memorandum, April 29, 2010) to all NCAA head athletic trainers that included a list of recommended best practices for concussion management in a variety of collegiate sports, including football and soccer. Regarding return to play, it was indicated that "an athlete exhibiting an injury that involves significant symptoms, long duration of symptoms or difficulty with memory function should not be allowed to return to play during the same day of competition." The same restriction was recommended for non-athletic activity. Another key recommendation was the completion by student athletes of a baseline assessment (e.g., neurocognitive testing) preceding the start of practice, with postinjury follow-up as indicated. A similar policy has been adopted by the National Football League (NFL).

Overall, while the Zurich statement guidelines provide a reasonable and more standardized basis for making return-to-play decisions, the position of Echemendia and Cantu (2004) that individual factors play a significant role is sound and conforms to the general move in clinical care toward greater consideration of individual patient factors. This would also include athlete personality factors, particularly because neuropsychiatric symptoms such as irritability, restlessness, depression, and fatigue may emerge as a consequence of concussion. Athletes also may be reluctant to acknowledge symptoms, particularly psychiatric sequelae, thus making careful observation and assessment essential, as well as obtaining corroborating data from secondary sources. In short, the emotional sequelae of mTBI should resolve just as neurocognitive and other postconcussion symptoms before returning to play, and some of these factors are addressed in the Zurich statement as well.

TABLE 27–5. International Symposium on Concussion in Sport acute concussion evaluation and graduated return-to-play protocol

Acute concussion evaluation and management

1. Player is medically evaluated onsite using standard emergency management principles
2. Treating healthcare provider determines player disposition in a timely manner

2a. If no provider, player is removed from play/practice with urgent referral to physician

3. First aid completion followed by concussion assessment (e.g., using SCAT-2 [2009])
4. Player is accompanied/monitored for deterioration over the few initial hours
5. No same-day return to play if concussion is diagnosed (exceptions in Zurich statement)

Graduated return-to-play protocol

1. Complete physical/cognitive rest until symptom recovery, followed by:
2. Permission to perform light aerobic exercise/increase heart rate, no resistance training;
3. Return to sport-specific exercise to add movement, no head impact activities;
4. Participation in noncontact drills, may add progressive resistance training;
5. Medical clearance followed by full-contact training; and finally
6. Return to normal game play

Source. Adapted from McCrory P, Meeuwisse W, Johnston K, et al.: "Consensus Statement on Concussion in Sport—3rd International Conference on Concussion in Sport Held in Zurich, November 2008." *Clinical Journal of Sport Medicine* 19:185–200, 2009. Used with permission.

Neuropsychological Testing

Neuropsychological assessment is frequently used in the evaluation of sport-related head injury to gauge patients' neurocognitive and functional status, particularly in more complex cases of concussion. To completely evaluate severity of concussions and assist in return-to-play decisions, the SLAM methodology developed by Barth et al. (2002) remains the gold standard, using preseason and postconcussion neurocognitive assessment. Preseason testing allows for control of any premorbid cognitive dysfunction, which has the potential to affect test results and mimic the neurocognitive effects of concussive injury (Collins et al. 1999; Matser et al. 1999).

In terms of methods, neuropsychological baseline testing of athletes generally takes 20–30 minutes and focuses on measures sensitive to concussion sequelae, including processing speed, attention/concentration, memory, and reaction time (Lovell and Collins 1998). A variety of measures may be used, including paper-and-pencil tests, computerized assessments, and Web-based evaluation. Examples of computerized tests used for neuropsychological assessment include the Automated Neuropsychological Assessment Metric (ANAM; Bleiberg et al. 2000; Reeves et al. 1995) and the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) instrument (Lovell et al. 2000). The advent of Web-based testing has also introduced measures such as the Concussion Resolution Index (CRI) developed by HeadMinder, Inc. (Erlanger et al. 1999), a set of neurocognitive tests targeting attention, reaction time, memory, and problem solving. This approach allows appropriate assessment personnel and the athletes to log into the system at any time to access the 20- to 30-minute assessment battery, and it permits current neurocognitive assessment results to be instantly compared with previous findings (i.e., baseline data), controlling for practice effects by internal statistical analysis, to determine the probable absence or presence of decline or improvement. In addition, a summary is offered indicating potential risks and suggestions for consideration by the appropriate medical personnel in making return-to-play decisions.

Following mild concussion, players should receive a brief repeat baseline neurocognitive assessment within 24 hours to detect any performance changes. Such an approach may offer increased sensitivity in identifying cognitive impairment associated with mild concussion in which symptoms are mild or subtle (Broshek and Barth 2001). Further, repeat administration of the baseline neurocognitive tests can then be used to track progression of

change in neurocognitive functioning over time. In the case of computer-aided assessments, authorized medical and athletic personnel can access results and use them to assist in making return-to-play decisions.

The 2008 Zurich document affirmed that neuropsychological testing "has been shown to be of clinical value and continues to contribute significant information in concussion evaluation" (p. 187) with regard to both assessment and management of the individual athlete (McCrory et al. 2009), particularly given that neurocognitive recovery may follow the resolution of other clinical symptoms (Bleiberg et al. 2004). In terms of specifics, the statement emphasizes that neuropsychological testing should not be performed while the player remains symptomatic, being of little benefit in return-to-play decisions during the acute phase, as well as introducing threat to validity for later testing via potential practice effects. It was also put forth that neurocognitive assessment should not be the sole basis for management decisions (e.g., extended timeout or return to play) and that the final return-to-play judgment should be a medical one that incorporates a multidisciplinary approach. Finally, it was noted that in the absence of neuropsychological testing, "a more conservative return to play approach may be appropriate" (p. 187) and that neuropsychologists are the most suitable care providers for interpretation of such testing.

Prevention

The 2008 Zurich statement (McCrory et al. 2009) maintains that "there is no good clinical evidence that currently available protective equipment will prevent concussion" (p. 1909). Somewhat in contradiction to this view, NATA (Guskiewicz et al. 2004) noted that helmet use should be enforced for "reducing the severity of cerebral concussions" (p. 283). In terms of more severe head injuries, the consensus is that protective equipment may be helpful and is an important issue for certain sports, such as ice hockey or baseball in which there is published evidence that use of appropriate helmets reduces head injuries (Aubry et al. 2002). Overall, it should be recognized that improved data collection is needed to obtain additional information on sport-specific and global injury factors to better identify risk factors that can be addressed to prevent future injury (Thurman et al. 1998).

The Centers for Disease Control and Prevention includes three recommendations for prevention in its current concussion and sports information sheet: the consistent and correct use of properly fitted and maintained protective equipment appropriate to the activity, observance of sport-specific safety rules, and the practice of good sportsmanship. In terms of protective equipment, the NATA position statement indicates that certified athletic trainers should enforce the standard use of helmets for protection and ensure all equipment needs are met according to standards set by either the National Operating Committee on Standards for Athletic Equipment or the American Society for Testing and Materials (Guskiewicz et al. 2004). The NATA statement also advocates standard use of mouth guards, although it notes there is no scientific evidence supporting their use for reducing concussive injury. Regarding soccer, NATA maintains that athletic trainers should neither endorse nor discourage use of headgear for concussion prevention at this stage.

An additional concern in the area of protective equipment noted in the 2008 Zurich statement is the possibility of so-called risk compensation (McCrory et al. 2009), which refers to behavioral change on the part of athletes resulting in riskier playing techniques and a paradoxical increase in injury rates due to the "false security" from using protective gear. In general, consensus statements from the International Conferences on Concussion in Sport indicate that rule changes and rule enforcement in reducing and preventing concussions may be appropriate, especially when a clear-cut injury mechanism has been implicated, such as banning head checking in ice hockey or making initial contact with the head while blocking and tackling in U.S. football.

In terms of prevention education basics, athletes should be instructed in the proper use and maintenance of protective headgear and the importance of inspecting their helmet daily, and frivolous concerns should be addressed, such as not wearing helmets because they look "silly" (Powell and Barber-Foss 1999). In addition, athletes should undergo conditioning and strengthening of the neck muscles as a means of reducing the transmission of impact forces to the brain (Johnston et al. 2001). The playing arena surface should be inspected at each game to ensure that there are no hazards that might increase the risk of injury (Powell and Barber-Foss 1999), and the playing surface should be made of shock-absorbing material where possible. Appropriate padding on goalposts and the corners of scorers' tables may minimize injury, likewise the removal of potential obstructions on the sidelines. Ready availability of basic concussion information may also be helpful, such as fact sheets or wallet cards for athletes and wallet cards for coaches with signs and symptoms and referral information, available through the Centers for Disease Control and Prevention.

Pediatric Considerations

Estimates are that around 10% of all pediatric head injuries are related to sports (Chorley 1998). Much as with adults, the majority of sport-related head injuries in young athletes are concussions. Brain injury in the pediatric population is complicated, however, by ongoing development in physical, psychosocial, and neurocognitive domains. In terms of physical changes, risk for head injury rises in general with the progression from early to later grades (ages) due to an increase in participants' weight and speed, leading to greater momentum and force of impact in sport injury incidents (Proctor and Cantu 2000).

In terms of neurocognitive functioning, the physiological maturation of the central nervous system is a key consideration in assessing brain-injured youth. Unlike adults, who have achieved relative stability from which a decline can be demarcated, TBI-related changes during childhood and adolescence occur in the context of rapid and significant knowledge and skill acquisition (Patel et al. 2005). Thus, there is a need to consider delay or failure in attaining age-appropriate developmental capacities in addition

to the detection of decline from previous functioning. This issue is of particular concern for neuropsychological assessment related to intraindividual comparison and comparison with normative data, and NATA recommends that younger athletes receive more frequent updates of their baseline measures (Guskiewicz et al. 2004). Limitations also exist due to the lack of well-established child and adolescent norms for many common neuropsychological tests, as well as the wider degree of variability in test performance among this age group.

The 2008 Zurich statement also addressed the specialized nature of pediatric concussion, including the important recognition that "the recovery time frame may be longer in children and adolescents" (p. 186). In addition, regarding the use of neuropsychological testing, the Zurich statement emphasizes the use of neuropsychologists in interpretation of testing results with child and adolescent athletes, particularly when modifying factors such as attention-deficit/hyperactivity and learning disorders may be involved.

Gender and Sports-Related Concussion

Although female participation remains relatively low in the sports most commonly associated with head injury overall, namely boxing and U.S. football, a study conducted by the National Center for Catastrophic Sports Injury Research concluded that female athletes are at significant risk of sustaining sports concussions or more significant brain injuries. Some researchers found a larger number of persisting symptoms 1 year post-mTBI among females (Rutherford et al. 1979), as well as a greater incidence of depression (Fenton et al. 1993). Findings also include an increased risk for postconcussion syndrome at 1-month follow-up (Bazarian et al. 1999). A review of the literature further found past research related to issues of interest to male athletes, such as studies finding that males may experience greater motivation to minimize symptoms of mild head injury (Kelly 1995) and may be more easily pressured to play while injured (Granite and Carroll 2002).

Studies specifically related to female athlete concerns were less evident. A prospective study of high school and college athletes by Broshek et al. (2005) was one of the first efforts in this area. These researchers found that female athletes experienced more significant declines in simple and complex reaction time as compared with male athletes relative to baseline scores collected during the preseason and that female athletes reported more postconcussion symptoms. The role that helmets might have played in these findings was addressed, because few female sports require headgear and a preponderance of male concussions were in football, and female athletes had greater objective simple and complex reaction time deficits and more self-reported concussion symptoms even after adjusting for the effects of helmets. The authors hypothesized that factors including gender differences in aggressivity, hormonal systems, cerebral organization, and neck musculature might partially explain their findings.

Covassin et al. (2007) found gender differences following sport-related concussion in one of five cognitive domains assessed; specifically female athletes had significantly lower scores on a visual memory measure. Further, in contrast to the Broshek et al. (2005) study, this study found that male athletes actually reported more frequent and intense postconcussion vomiting and sad mood compared with their female counterparts. Covassin and colleagues pointed out methodological differences between their study and that of Broshek et al., specifically greater balance between sex representation in their comparison groups and that this population only included college athletes, suggesting that gender differences may manifest differently depending on age.

Overall, consideration of the sports concussion literature as a whole regarding gender issues primarily reveals a paucity of research, although current findings appear sufficiently compelling to warrant further investigation, especially as more women become involved in collegiate and professional sports.

KEY CLINICAL POINTS

- The most common type of sports head injury is a mild traumatic brain injury (mTBI), or concussion. Many definitions of sports concussion exist. In general, it can be thought of as a complex pathophysiological process affecting the brain that is induced by traumatic biomechanical forces.

- The reported incidence of sports concussion has increased significantly in recent years. Boxing, U.S. football, ice hockey, and soccer are among the sports with the highest concussion rates.

- Biomechanical forces in sports concussion commonly include an initial change in velocity (acceleration/deceleration) caused by a blow to the head or, indirectly, to the body. The initial impact is followed by a migration of physical forces through the brain, and these may include rotational vectors, leading to shearing injury in the subcortical white matter.

- Physical effects of mTBI are generally not visible on neuroimaging, apart from cases involving contusions.
- Regions of the brain most commonly affected in sports concussion include the basal forebrain, medial temporal lobes, and some midbrain structures, as well as subcortical white matter. These regions are associated with neurocognitive functions including attention/concentration, initiation and behavioral regulation, and short-term memory, which may be impaired following sports concussion.
- Research has estimated that the normal recovery curve for an uncomplicated sports concussion is 5–10 days.
- Many concussion classification systems exist, all generally recognizing mild, moderate, and severe forms of injury.
- Sideline assessment and computerized neurocognitive screening (including preseason baseline performance) are commonly used in the evaluation of all sports concussions. Formal neuropsychological assessment may be needed in more complex or severe cases.
- Although some formal guidelines exist for making return-to-play decisions, the complexity of sports concussion often requires a more dynamic model that takes into account individual athlete factors, including potential psychological issues.
- Primary care physicians and medically supervised athletic trainers may make return-to-play decisions in cases of simple concussion. More complex cases should involve specialists such as neurologists, neurosurgeons, and sports medicine doctors specializing in sports concussion.
- The final return-to-play judgment should be a medical one that incorporates a multidisciplinary approach.

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CHAPTER 28

Children and Adolescents

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THIS CHAPTER FOCUSES ON THE RELATIVELY understudied area of neuropsychiatric aspects of pediatric traumatic brain injury (TBI). The chapter includes briefer sections that review neurological, neurocognitive, language, and educational aspects of pediatric TBI with specific relevance to child neuropsychiatry. Citations for review articles are provided on these topics for readers who desire more in-depth reviews of each of these areas.

Epidemiology

TBI in children and adolescents is a major public health problem, with an annual incidence of 400 per 100,000 constituting a major cause of death and disability in the United States (Langlois et al. 2005). The male-to-female incidence rate ratio is approximately 1.8:1 and increases to 2.2:1 when children ages 5–14 are considered. The incidence in males and females is similar at ages 1–5 years (160 per 100,000 population) but then increases at a higher rate in males. In late childhood and adolescence, brain injury rates increase for males but decrease for females. Higher incidence rates have been found to be related to median family income even when age and/or race and ethnicity were controlled (Kraus et al. 1990). The proportion of brain injury caused by motor vehicle or motor vehicle–related accidents increases with age from 20% in children ages 0–4 years up to 66% in adolescents (Levin et al. 1992). Pedestrian- or bicycle-related injuries more likely affect younger children, whereas adolescents are more often injured in motor vehicle accidents. The mechanisms of injury in almost 50% of cases of infant, toddler, and young child brain injury are related to assaults or child abuse and falls. The distribution of brain injury, by severity, ranges from 80% to 90% for mild, 7% to 8% for moderate, and 5% to 8% for severe brain injury.

Etiology and Pathophysiology

Focal injuries including subdural, epidural, and intracerebral hematomas occur with a higher incidence in adults (30%–42%) than in children (15%–20%). There is an antero-caudal gradient in the frequency of focal lesions. There is a higher frequency of children with lesions in the dorsolateral frontal region (middle and superior frontal gyri), orbitofrontal region (orbital, rectal, and inferior frontal gyri), and frontal lobe white matter; a few areas of abnormal signal in the anterior temporal lobe; and isolated areas in more posterior areas (Levin et al. 1993). Skull fractures occur in approximately 5%–25% of children and are less commonly associated with epidural hematomas (40%) than in adults (61%). Children more frequently present with diffuse injury and cerebral swelling (44%) resulting in intracranial hypertension than adults. Diffuse axonal injury and vascular injury are the principal histopathological findings of a diffuse injury in children. Reviews of advances and challenges in the understanding of the pathophysiology of pediatric brain injury as well as initial assessment, management, and treatment of pediatric brain injury are available (Kochanek 2006).

Posttraumatic seizures are of particular interest and relevance to psychiatrists who treat children with TBI. The incidence of early seizures (within the first week of TBI) is approximately 5% among all individuals with TBI and is higher in young children, among whom the incidence is approximately 10% (Yablon 1993). Immediate seizures (within the first 24 hours of TBI) constitute 50%–80% of early seizures and are particularly frequent among children with severe TBI. Late seizures (beyond the first week after TBI) occur in approximately 4%–7% of adults with TBI and occur less frequently in children. A population study has shown an increased relative risk for seizures 10 years after mild TBI, severe TBI, and skull fractures (Christensen et al. 2009). Elevated rates of psychiatric disorder are consistently found in cohorts of epilepsy individuals who have not incurred a TBI (Plioplys et al. 2007). Antiepileptic drugs may positively influence behavioral or psychiatric presentation in children by helping to achieve seizure control or may compound psychiatric problems through side effects.

School Sequelae

Academic functioning within the school environment is the childhood equivalent of occupational functioning for

adults. Adults are not guaranteed reentry into the occupational arena after severe TBI, but educators are mandated to provide services to children under the Individuals With Disabilities Education Act. The need for special education services is high for children with more serious TBI (Ewing-Cobbs et al. 2006). The special education services required for these TBI survivors have to be tailored toward their particular needs, which are often different from those of children with developmental learning disabilities. Special education services are necessary for various problems including poor academic function related to 1) skill deficits in major domains such as arithmetic, spelling, and reading; 2) behavioral and emotional disorders; or 3) a combination of the above with or without underlying complications of preinjury developmental learning disabilities in some children. For more in-depth review of educational and neuropsychological aspects of pediatric TBI, see Armstrong et al. 2001; Catroppa et al. 2007; Ewing-Cobbs et al. 2004, 2006; Max 2005; Max et al. (in press); and Ylvisaker et al. 2007.

Psychiatric Disorders

Psychiatric disorders that occur after child and adolescent TBI pose major challenges to community reentry and to quality of life.

Methodological Concerns

Study design is critical to the determination of the quality and generalizability of data generated. Many of the controversial issues in the child and adolescent TBI clinical outcome field have their basis in the overinterpretation of data from studies with major design flaws. This is especially true in the debate concerning outcome after mild TBI in children (Satz et al. 1997). Most studies with rare exceptions (Ewing-Cobbs et al. 2006) exclude children with a history of physical abuse. Therefore, unless otherwise indicated, this review refers only to accidental injury.

In general, psychiatric aspects of child and adolescent TBI have received scant attention from researchers. In fact, there have only been two prospective studies of consecutive hospital admissions of children and adolescents with TBI in which standardized psychiatric interviews were used to assess psychopathology (Brown et al. 1981; Max et al. 1997a), and only one of these studies had injured control children (Brown et al. 1981). There is also a large literature that addresses postinjury behavioral changes reported by parents and teachers, typically by questionnaires, which tend not to be specific for generating a psychiatric diagnosis or a psychiatric treatment plan (Fletcher et al. 1990; Rivara et al. 1994; Yeates et al. 2009).

Preinjury Psychiatric Status

Preinjury behavioral status in children who have a TBI is an area of some debate. The only prospective psychiatric studies that have used standardized psychiatric interviews found that between one-third and one-half of children had a preinjury lifetime psychiatric disorder (Brown et al. 1981; Max et al. 1997c). The investigation of preinjury psychopathology using behavioral checklists soon after the child's TBI has produced conflicting data (Donders 1992; Light et al. 1998; Pelco et al. 1992). Absence of evidence for preinjury psychopathology in childhood TBI children, as assessed primarily by behavioral checklists or developmental screens, may be related to insensitivity of the instruments (Bloom et al. 2001). A large epidemiological study involved a birth cohort studied at age 5 and then again at age 10 (Bijur et al. 1988). The study found that children who went on to sustain injuries (e.g., mild brain injury, burns, and lacerations) in the follow-up period were rated as having more behavioral problems, particularly aggression, before their injuries when compared with children who did not have injuries.

Postinjury Psychiatric Status

The first stage in the evolution of research in child and adolescent psychiatric outcome after TBI has focused on the emergence of new or "novel" psychiatric disorders. The term *novel* psychiatric disorders has been coined to describe two possible scenarios. First, this could occur in a child with TBI free of preinjury lifetime psychiatric disorders who then manifests a psychiatric disorder. Second, this could occur in the case of a child with a lifetime psychiatric disorder who manifests a psychiatric disorder that was not present before the TBI. These disorders are varied, thus demonstrating that behavioral outcome after brain injury is not a unitary construct. This categorical classification system of new/novel disorders has value because it reflects functional outcome in children and informs us about risk factors for psychiatric disorder in this population. The second stage in this evolution is the examination of characteristics including risk factors and phenomenology of specific clusters of psychiatric symptoms or specific psychiatric disorders that emerge after TBI. Research on specific new psychiatric disorders is necessary because it is likely that different disorders will have different psychosocial and biological (including lesion) characteristics. The findings from this research may have relevance to the understanding of phenotypically similar disorders in children who have not experienced brain injury.

New Psychiatric Disorders

New psychiatric disorders recorded approximately 2 years following severe TBI have been noted in 54%–63% of children, following mild/moderate TBI in 10%–21% (or up to 100% in referred samples) of children, and following orthopedic injury in 4%–14% of children (Brown et al. 1981; Max et al. 1997a, 1998f). As shown in Table 28–1, predictors of novel psychiatric disorders include severity of injury, preinjury psychiatric disorders, preinjury family function, family psychiatric history, socioeconomic status, preinjury intellectual function, and preinjury adaptive function (Brown et al. 1981; Max et al. 1997a). The most consistent predictor of novel psychiatric disorders in one study was preinjury family function (Max et al. 1997a). Because preinjury psychiatric disorders are predictors of novel psychiatric disorders, the importance of retrospectively assessing

TABLE 28–1. Predictive variables of "novel" psychiatric disorders in the 2 years following child traumatic brain injury

Severity of injury
Lifetime preinjury psychiatric disorder
Preinjury teacher-rated behavior
Preinjury parent-rated adaptive function
Family psychiatric history
Preinjury family function
Socioeconomic status
Preinjury intellectual function

whether these disorders were present before the injury cannot be overstated.

An important lacuna in the psychiatric literature concerns psychiatric outcome after mild TBI in children. The rate of psychiatric disorder in children with mild TBI varies widely, from 10% to 100% depending on study design (Brown et al. 1981; Massagli et al. 2004; Max and Dunisch 1997; Max et al. 1997a, 1998f; Rune 1970). The range reported in the subset of studies of consecutively treated children with mild TBI is narrower (10%–40%), with larger studies generally finding higher rates. The rate at which children with mild TBI versus injured control children developed new-onset psychiatric disorder was similar in one study (Brown et al. 1981) and higher, although not significantly so, in other small underpowered studies (Luis and Mittenberg 2002; Max et al. 1998f). However, children with mild TBI had nonsignificantly higher (Lehmkuhl and Thoma 1990), marginally higher (Rune 1970), or significantly higher (Massagli et al. 2004; McKinlay et al. 2002) rates of new-onset psychiatric disorder compared with uninjured control groups of children in four studies. Unlike for cohorts of mild to severe TBI in which robust psychosocial and injury risk factors for new-onset psychiatric disorder have been identified (Max et al. 1997a), there are minimal data in cohorts of children limited to mild TBI. My colleagues and I reported that children with mild/moderate TBI were at significantly higher risk for developing new-onset psychiatric disorder in the first 3 months after injury if they had a history of psychiatric disorder before the injury (Max et al. 1997c). Similar results were obtained in a study of postconcussion symptoms in which children with mild TBI who experienced an increase in symptoms had poorer preinjury behavioral adjustment than those who did not (Yeates et al. 1999).

Findings from a more recent prospective behavioral study of mild TBI with injured controls may presage findings from future psychiatric studies of mild TBI. Children with mild TBI are more likely than injured control children to demonstrate transient or persistent increases in postconcussive symptoms in the first year after injury, especially if the injury was more serious (Yeates et al. 2009). Postconcussive symptoms were not related to the apolipoprotein epsilon 4 allele (Moran et al. 2009). The families of mild TBI children experienced more burden and distress than the families of injured control children, and this was more closely linked with postconcussive symptoms than type of injury itself (Ganesalingam et al. 2008).

Family Function and Psychiatric Disorder in Children With TBI

When children and adolescents have a TBI, the family is affected. Only one study has investigated the relationship of postinjury family function and psychiatric complications of TBI (Max et al. 1998e). This showed that the strongest influences on family functioning following childhood TBI are preinjury family functioning and the development of a novel psychiatric disorder. Preinjury family life events or stressors and immediate postinjury coping style emerge as significant variables later in the follow-up. The importance of novel psychiatric disorders for family functioning is evident at 6, 12, and 24 months postinjury. The direction of these effects is as expected (worse outcome with poorer family function, presence of novel psychiatric disorder, more stressors, and use of fewer sources of support).

Other studies also show that family function (pre- and postinjury) and child behavior (pre- and postinjury) are closely related. Thus pre- and postinjury family function predicted behavioral problems after TBI (Taylor et al. 1999; Yeates et al. 1997), and behavior problems developing shortly after TBI were associated with family burden, family distress, or poorer family function at follow-up (Ganesalingam et al. 2008; Josie et al. 2008; Rivara et al. 1993). Furthermore, investigators have demonstrated tentative support for bidirectional influences of child behavior and family function after TBI (Taylor et al. 2001).

Specific Psychiatric Disorders/Symptom Clusters

Table 28–2 provides a summary of current lesion-behavior correlates for specific psychiatric disorders and symptom clusters after pediatric TBI.

Personality Change Due to Traumatic Brain Injury

The most common "novel" disorder after severe TBI is personality change due to traumatic brain injury (PC) (Max et al. 2000, 2001) or its approximations in other diagnostic nomenclatures. The diagnosis of PC is made in patients who, as a consequence of the injury, display clinically significant symptoms of affective instability, aggression, disinhibited behavior, apathy, or paranoia. The Neuropsychiatric Rating Schedule (Max et al. 1998c) can be used to establish a diagnosis of PC. Approximately 40% of consecutively hospitalized severe TBI children had ongoing persistent PC an average of 2 years postinjury (Max et al. 2000). An additional approximately 20% had a history of a remitted and more transient PC. PC occurred in 5% of mild or moderate TBI but was always transient. Other studies of consecutive TBI admissions found that 5 of 31 (16%) (Brown et al. 1981) to 17 of 45 (38%) (Lehmkuhl et al. 1990) children with severe TBI developed a syndrome that resembled PC. The labile, aggressive, and disinhibited subtypes are common, whereas the apathetic and paranoid subtypes are uncommon (Max et al. 2000, 2001). Table 28–3 shows the items rated on the Neuropsychiatric Rating

TABLE 28–2. Summary of lesion findings in psychiatric disturbances after pediatric traumatic brain injury

Disorder	Lesion correlate (timing of outcome)	Source
Attention-deficit/hyperactivity disorder	Right putamen, thalamus (12 months)	Gerring et al. 1998; Herskovits et al. 1999
	Orbital frontal gyrus (6 months)	Max et al. 2005b
Personality change due to traumatic brain injury	Superior frontal gyrus (6 and 12 months)	Max et al. 2005a, 2006
	Frontal white matter (24 months)	Max et al. 2006
Posttraumatic stress disorder (reexperiencing criterion)	Right limbic area (including cingulum) lower lesion fraction (12 months)	Herskovits et al. 2002
Posttraumatic stress disorder (hyperarousal symptoms)	Left temporal lesions and lower frequency of orbitofrontal lesions (12 months)	Vasa et al. 2004
Obsessions	Mesial prefrontal and temporal lesions (12 months)	Grados et al. 2008
Obsessive-compulsive disorder	Frontal and temporal lobes (3–9 months)	Max et al. 1995b
Anxiety disorder/probable anxiety disorder	Superior frontal gyrus (6 months) Frontal white matter (trend) (6 months)	Max et al., in press
Mania/hypomania	Frontal lobe and temporal lobes (3–24 months)	Max et al. 1997b

Schedule and the frequencies of PC symptoms after severe TBI. In severe TBI children, persistent personality change was significantly associated with severity of injury, particularly impaired consciousness longer than 100 hours, and a concurrent diagnosis of secondary attention-deficit/hyperactivity disorder (SADHD) but was not significantly related to any psychosocial adversity variables. Persistent PC was also significantly associated with adaptive and intellectual functioning decrements. In view of the findings of adaptive and intellectual functioning findings, the rationale for dementia as an exclusion criterion for the diagnosis of PC should be reevaluated.

More recent studies show that severity of injury is a significant predictor of PC in the first 2 years after TBI (Max et al. 2005a, 2006). Furthermore, PC is associated with superior frontal gyrus lesions in the first year. This lesion correlate is consistent with models of affective regulation implicating the dorsal prefrontal cortex (Mayberg 1997). In the second year after TBI, PC was significantly associated with frontal white matter lesions and preinjury adaptive function (Max et al. 2006). This may suggest that while affective regulation problems initially associated with superior frontal lesions may decrease as other gray areas subsume this function, such plasticity in the face of lesioned white matter tracts does not yield improved function. Furthermore, these findings suggest that akin to the notion of preinjury cognitive reserve, preinjury functional reserve (e.g., higher preinjury adaptive function) is important in determining whether a child will have PC persisting through the second postinjury year.

When PC is present, it typically encompasses the most impairing symptoms in a particular child even if other syndromes such as attention-deficit/hyperactivity disorder (ADHD) or oppositional defiant disorder (ODD) may co-occur. Many of these children are slow to learn from their mistakes. One reason for poor learning in children with PC is that the children almost invariably have poor insight regarding their condition. That is, parents report believable affective instability, aggression, disinhibition, apathy, or paranoia, but children deny such behavior. When they acknowledge the behaviors, most children do not appear to comprehend the grave implications thereof.

Secondary Attention-Deficit/Hyperactivity Disorder

Secondary attention-deficit/hyperactivity disorder or SADHD is the term used for ADHD that develops after TBI. SADHD is associated with increasing severity of injury and adaptive and intellectual function deficits as well as family dysfunction when children with mild to severe TBI are studied. When the samples are limited to severe or to severe/moderate TBI, adaptive deficits are still evident, but findings regarding intellectual function outcome are mixed (Gerring et al. 1998; Max et al. 2004). However, in these samples of constricted range of injury severity, variables that are not associated with SADHD are injury severity, family function at the time of assessment, socioeconomic status, family stressors, family psychiatric history, gender, and lesion area. An overlapping study of attention-deficit/hyperactivity symptoms found a similar relationship with severity and also found that overall attention-deficit/hyperactivity symptoms were associated with poorer preinjury family functioning (Max et al. 1998a). A referred sample of children dominated by severe TBI children had similar findings and the SADHD children had greater premorbid psychosocial adversity (Gerring et al. 1998). SADHD has been associated with lesions of the right putamen or thalamic lesions (Gerring et al. 2000; Herskovits et al. 1999) and orbital frontal gyrus lesions (Max et al. 2005b). These anatomical findings suggest that lesions in varied locations along specific cortical-striatal-pallidal-thalamic loops may generate a clinical syndrome of SADHD.

There is no doubt that SADHD can follow severe TBI (Brown et al. 1981; Gerring et al. 1998; Max et al. 2004). It can follow moderate TBI, but thus far this has been convincingly demonstrated only in the presence of preinjury

TABLE 28–3. Frequency of positively rated Neuropsychiatric Rating Schedule items among 37 consecutively admitted severe TBI subjects

	Item #	Subtype or symptom	Frequency	%
	1	**"Personality change"**	21/37	57
A	2	**Affective instability**	18/37	49
	3	Marked shifts from normal mood to depression	3/37	8
	4	Marked shifts from normal mood to irritability	15/37	41
	5	Marked shifts from normal mood to anxiety	2/37	5
	6	Rapid shifts between sadness and excitement	4/37	11
	7	Laughs inappropriately and/or excessively	9/37	24
	8	Sudden euphoria/elation	3/37	8
	9	Pathological crying	7/37	19
B	10	**Recurrent outbursts of aggression or rage that are grossly out of proportion to any precipitating stressors**	14/37	38
C	11	**Markedly impaired social judgment**	14/37	38
	12	Uninhibited/disinhibited (acts)	12/37	32
	13	Disinhibited vocalization/verbalization	15/37	41
	14	Lack of tact or concern for others; not sensitive to others' feelings/reactions	8/37	22
	15	Inability to plan ahead (lack of foresight, inability to judge consequences of actions)	10/37	27
	16	Sexually inappropriate (not part of a manic episode or delirium, dementia, or posttraumatic amnesia)	6/37	16
D	17	**Marked apathy or indifference** (little interest or pleasure in activities; apathetic, does not care about anything; lack of initiative)	5/37	14
E	18	**Suspiciousness or paranoid ideation**	2/37	5
	19	Explosive "subtype" predominates	12/37	32
	20	Perseveration	13/37	35
	21	Echolalia	1/37	3
	22	Immaturity	9/37	24

Note. The frequency of positively rated (occurring at least some point postinjury) Neuropsychiatric Rating Schedule items among 37consecutively admitted severe traumatic brain injury (TBI) subjects is shown. **Bold headings** correspond to subtypes of personality change due to TBI. The item numbers correspond to numbered items on the Neuropsychiatric Rating Schedule.

Source. Adapted from Max JE, Robertson BAM, Lansing AE: "The Phenomenology of Personality Change Due to Traumatic Brain Injury in Children and Adolescents." *Journal of Neuropsychiatry and Clinical Neurosciences* 13:161–170, 2001. Used with permission.

ADHD traits (Max et al. 2004). SADHD has also followed mild TBI and orthopedic injury (in the absence of brain injury) at similar rates (Max et al. 2004). The attribution of brain injury as the primary etiological factor for SADHD after mild TBI has been inconclusive.

A study by Schachar et al. (2004) provided some insight into the relationship of SADHD and inhibition deficit, measured with the Stop Signal Reaction Time task, in nonconsecutively injured mild to severe TBI and uninjured control children. An inhibition deficit, similar to that usually seen in developmental ADHD, was found only in severe TBI children who also had SADHD. SADHD was diagnosed by cutoff points on a behavioral questionnaire. Another study found that children with SADHD had worse memory skills compared with TBI children with preinjury ADHD (Slomine et al. 2005).

Oppositional Defiant Disorder

One study showed that ODD symptoms in the first year after TBI was related to preinjury family function, social class, and preinjury ODD symptomatology (Max et al. 1998b). Increased severity of TBI predicted ODD symptoms 2 years after injury. Change (from before TBI) in ODD symptoms at 6, 12, and 24 months after TBI was influenced by socioeconomic status. Only at 2 years after injury was severity of injury a predictor of change in ODD symptoms. The influence of psychosocial factors appears greater than that of severity of injury in accounting for ODD symptoms and change in such symptomatology in the first but not the second year after TBI in children and adolescents. This finding appears related to the persistence of new ODD symptoms after more serious TBI. Findings from a referred brain injury clinic sample were that children who developed ODD/conduct disorder following TBI, when compared with children without a lifetime history of this disorder, had significantly more impaired family functioning, showed a trend toward a greater family history of alcohol dependence or abuse, and had suffered a milder TBI (Max et al. 1998g).

Posttraumatic Stress Disorder

It is apparent that posttraumatic stress disorder (PTSD) and subsyndromal posttraumatic stress disturbances occur despite neurogenic amnesia. In one study, only 2 of 46 children (4%) with at least one follow-up assessment developed PTSD (Max et al. 1998d). However, the frequency with which

children experienced at least one PTSD symptom ranged from 68% in the first 3 months to 12% at 2 years in assessed children. The most consistent predictors of PTSD symptomatology are the presence of mood or anxiety disorder at time of injury followed by greater injury severity. Another group of investigators (Levi et al. 1999) found a significant relationship of parent- and child-reported PTSD symptomatology with severe TBI versus moderate TBI and orthopedic injury even after controlling for ethnicity, social disadvantage, and age at injury. However, family socioeconomic disadvantage was associated with greater PTSD symptomatology across groups. A third study found similarly that PTSD occurred in 13% of children with severe TBI recruited from a rehabilitation center (Gerring et al. 2002). PTSD by 1 year postinjury was associated with female gender and early postinjury anxiety symptoms. Posttraumatic symptoms at 1 year postinjury were predicted by preinjury psychosocial adversity, preinjury anxiety symptoms, injury severity, as well as early postinjury depression symptoms and nonanxiety psychiatric diagnoses. In this study, the PTSD criterion for "reexperiencing" was associated with a lower lesion fraction in the right limbic area, specifically the cingulum. This area is often activated in PTSD reexperiencing imaging studies (Herskovits et al. 2002). Furthermore, PTSD hyperarousal symptoms were associated with left temporal lesions and absence of left orbitofrontal lesions (Vasa et al. 2004).

Other Anxiety Disorders

Obsessive-compulsive disorder can occur following TBI in adolescence (Max et al. 1995b; Vasa et al. 2002). Frontal and temporal lobe lesions may be sufficient to precipitate the syndrome in the absence of clear striatal injury (Max et al. 1995b). New onset of obsessions is associated with psychosocial adversity, female gender, and mesial frontal and temporal lesions (Grados et al. 2008). A wide variety of other anxiety disorders have been documented after childhood TBI. These include overanxious disorder, specific phobia, separation anxiety disorder, and avoidant disorder (Max et al. 1997a, 1997c, 1998f). No statistically significant increase has been demonstrated in any single anxiety disorder compared with preinjury frequencies, but there was a trend in this regard for overanxious disorder (Vasa et al. 2002). However, a significant increase in anxiety symptoms after injury compared with before injury has been demonstrated. Preinjury anxiety symptoms and younger age at injury correlated positively with postinjury anxiety symptoms (Vasa et al. 2002). Other investigators reported that severity of brain injury and postinjury level of stress were associated with mood/anxiety disorders (Luis et al. 2002). Lesions of the superior frontal gyrus were significantly associated with postinjury anxiety symptoms, whereas frontal white matter lesions were associated at a trend level (Max et al., in press).

Mania/Hypomania

A number of case reports have been published on the development of mania or hypomania after childhood TBI (Sayal et al. 2000). However, there is only one report of this disorder from a child TBI cohort. Four of 50 children (8%) from a prospective study of consecutive children hospitalized following TBI developed mania or hypomania (Max et al. 1997b). The phenomenology regarding the overlapping diagnoses of mania, ADHD, and PC or the "frontal lobe syndrome" is an important consideration in differential diagnosis (Max et al. 2000). Increased severity of injury, frontal and temporal lobe lesion location, and family history of major mood disorder may be implicated in the etiology of mania/hypomania secondary to TBI. Lengthy episodes and similar frequency of irritability and elation may be characteristic.

Depressive Disorders

One prospective study that used standardized psychiatric interviews found that 9 of 50 children had a preinjury lifetime history of major depressive disorder, depressive disorder not otherwise specified, adjustment disorder with depressed mood, or adjustment disorder with mixed anxiety and depressed mood. Follow-up for 2 years revealed that 7 of these 9 children at some point displayed a clinically significant disorder of one of the above types. In fact, of 5 children who developed a depressive mood disorder in the first month after TBI, 3 had preinjury depressive disorders, 1 had a first-degree relative with major depression, and 1 had a preinjury anxiety disorder (J.E, Max, "Depressive Disorders After Pediatric Traumatic Brain Injury." Unpublished data, Iowa City, Iowa, July 1998). These data imply that a substantial proportion of children who manifest depressed mood after TBI have a preinjury personal history of depressive disorders and that most of the remaining children have identifiable risk factors for a new-onset depressive disorder. A retrospective psychiatric interview study (Max et al. 1998f) found that one quarter of severe TBI children had an ongoing depressive disorder and one-third of the children had a depressive disorder at some point after the injury. Another group found that TBI increases the risk of depressive symptoms especially among more socially disadvantaged children and that depressive symptoms were not strongly related to postinjury neurocognitive scores (Kirkwood et al. 2000).

Psychosis

Only two cases of new-onset nonaffective psychosis have been reported in studies of consecutive admission of 224 children with TBI that used standardized psychiatric interviews (Brown et al. 1981; Lehmkuhl et al. 1990; Max et al. 1997a, 1998f). There has been interest in the possibility that early TBI increases the risk of psychosis in adult life (Wilcox and Nasrallah 1987). A more recent large study of the association of multiplex schizophrenia and multiplex bipolar pedigrees found that rates of TBI were significantly higher for those with a diagnosis of schizophrenia, bipolar disorder, and depression than for those with no mental illness (Malaspina et al. 2001). Members of the schizophrenia pedigrees, even those without a diagnosis of schizophrenia, had greater exposure to TBI compared with members of the bipolar disorder pedigrees. Furthermore, within the schizophrenia pedigrees, TBI was associated with a greater risk of schizophrenia consistent with synergistic effects between genetic vulnerability for schizophrenia and TBI. The study concluded therefore that post-TBI schizophrenia in multiplex schizophrenia pedigrees does not appear to be a phenocopy of the genetic disorder.

Autism

The absence of autism after childhood TBI is notable. However, other forms of brain injury (e.g., brain tumors) have been implicated in the new onset of autism in childhood (Hoon and Reiss 1992).

Clinical Decision Making

The following vignettes illustrate some of the more common and important clinical differential diagnostic processes faced by clinicians working with children who have survived TBI. Personality change due to TBI (PC) is a disorder with which psychiatrists generally have less familiarity but is a disorder that should frequently enter the differential diagnosis.

Clinical Vignettes

Change in Personality Style

> A 12-year-old girl suffered a mild brain injury in an accident in which her mother was killed. The girl had been wild and boisterous before the injury but had no definite psychiatric disorder. After the injury she went through a period of appropriate mourning not complicated by depression. At assessments 6 and 12 months after TBI, she was much more quiet, thoughtful, and responsible than she had been before the injury. She displayed no evidence of PTSD. Her friends and family noticed this difference and accepted that she had begun to take on more of a maternal role in the family. The girl said that she felt that accidents can happen easily and this was why she developed a more cautious approach to life.

Comment: When personality styles change after a TBI, this need not necessarily be related to the direct effects of brain damage. Furthermore, PC is not a DSM-IV-TR (American Psychiatric Association 2000) personality disorder. Rather it is a syndrome dominated by a new onset of potentially severe affective instability, aggression, or disinhibition/markedly impaired social judgment and occasionally by apathy or paranoia. These symptoms may be so severe and pervasive that observers may conclude that the child has undergone a "change in personality." However, personality per se is not measured when making the diagnosis.

ADHD and ODD Versus PC

PC overlaps symptomatically with other disorders, including most commonly with ADHD and ODD (Max et al. 2000). One does not make the diagnosis of PC if the symptomatology can be sufficiently explained by ADHD or ODD. For example, children with comorbid ADHD and ODD have problematic hyperactivity, impulsivity, and/or inattention, as well as oppositional behavior, and may be easily angered. The diagnosis of PC is added in these children when poor anger control is more marked than oppositional behavior per se, when disinhibited behavior is a problem itself, and of course when these behaviors are a change from before a serious TBI.

> *Case 1.* A child with a mild TBI with preinjury ADHD and ODD had intense irritability (not caused by brain damage) before the injury. This was unchanged at an assessment 3 months after the injury. The child did not receive a diagnosis of PC.

Comment: If the child's irritability had increased only marginally and/or there may have been other psychosocial stress, the child's affective instability would continue to be attributed to causes other than brain damage.

> *Case 2.* A child with a severe TBI with preinjury ADHD and ODD had clinically significant moderate irritability (not caused by brain damage) before the injury. After the injury and for 6 months, he experienced significant worsening of his irritability. There were no obvious major psychosocial stressors and his school reentry program was well suited to his abilities. A significant component of his affective instability 6 months after injury was attributed to brain injury, and thus he received a diagnosis of PC, affective instability subtype.

Comment: If the clinician thinks that a substantial proportion of the basis for the child's symptom being rated is related to direct brain damage, the affective instability should be considered part of a PC syndrome.

Major Depression and PC or Postconcussion Symptoms

> A child with a mild TBI who was treated overnight at the hospital developed a month-long problem with intense irritability and anger but no violent outbursts. This made home life miserable. He had headaches and attentional difficulties during most of this month. The syndrome had resolved after approximately 1 month postinjury. Before the injury he had an easygoing temperament (according to an assessment immediately after the injury, before problems were seen to develop). There were no significant psychosocial stressors in the first month after injury. He did meet criteria for a major depressive disorder during the first month. The syndrome did not depend on irritability for the diagnosis. He was sad and persistently drew pictures of graves and tombs, expressed hopelessness, and had vegetative signs of depression. He thus received a diagnosis of postconcussional syndrome as well as a diagnosis of major depressive disorder.

Comment: This is an example of the affective instability subtype of "transient PC" (i.e., without the duration criterion of 1 year) that can occur after mild TBI. It would be recognized as a postconcussional syndrome (i.e., related to brain injury) by clinicians treating individuals with TBI. A judgment call was made that the child's entire presentation could not be adequately explained by the diagnosis of major depressive disorder alone. The presence of headaches influenced this decision as did the severity of attentional difficulties even though decreased concentration is a symptom overlapping with major depressive disorder.

PTSD Versus PC Versus PTSD and PC

> A child age 5 years 3 months presented 29 months after being involved in a motor vehicle accident. The vehicle in which he was riding was struck at 30 miles/hour, while stationary, by another vehicle. He was strapped in his car seat

and cried loudly immediately upon impact and then sucked his thumb. There was no apparent loss of consciousness and no treatment given by paramedics. His mother, the driver, suffered whiplash and headaches and had a prominent bruise across her chest from the seat belt. Her symptoms resolved within 4 months. The child was easygoing before the accident. After the accident he developed clinically significant headaches; feelings like spiders crawling on his scalp; mild regression in expressive language, requiring speech/language therapy; affective lability, mostly with family members rather than at preschool; aggression to his mother, himself, and his dog; callous comments on the physical attributes of strangers; a wish to die; and a preoccupation with car accidents, including believing that each car trip would be associated with another accident and that death was imminent. This persisted despite 2 years of play therapy, parent-child interactional therapy, and medication trials of fluoxetine, and then paroxetine combined with risperidone. Neurological examination, computed tomography (CT) scan, and magnetic resonance imaging (MRI) scan were normal; electroencephalography (EEG) showed nonepileptiform spikes in the left temporal lobe, and standardized psychological testing was unremarkable.

Comment: PTSD is clearly present and is associated with significant depressive symptoms and affective instability. The child's affective instability, aggression, and disinhibited comments are indistinguishable from PC. The case is confusing because there is no unequivocal evidence for TBI given the lack of loss of consciousness, difficulty assessing posttraumatic amnesia at this young age, and normal CT and MRI scans. Furthermore, despite the severity of symptoms, the child has for the most part limited the expression of his disruptive behaviors to family members. However, the diagnosis of PC is probably warranted because of the clinical constellation of headache, expressive language regression, and the nonspecifically abnormal EEG. The lack of clear documentation of a mild TBI in a child as young as this child is not completely surprising, although his mother's postconcussion symptoms suggest that the accident was of sufficient force to make a plausible case for similar injury in the child. Treatment with an anticonvulsant mood stabilizer such as valproic acid may be helpful.

Adjustment Disorder Versus PC

A child with a moderate TBI (e.g., depressed skull fracture that was elevated without complications) suffered mild attentional problems for 2 weeks after the injury. The next 8 months were uneventful. At that point his parents began experiencing marital conflict. The child became irritable and angry and destroyed some property.

Comment: The child's affective change was not considered to be a direct consequence of brain injury because of the clear serious stressor and the relatively uncomplicated 7½-month period before symptoms emerged. It is incumbent on the clinician to weigh the possibilities that symptoms directly related to brain damage may occur, most likely soon after injury, though there is a possibility that children will "grow into" their disability/syndrome as a lesioned area is expected to take over an important function later in development (Goldman 1971). Another delayed-onset mechanism may involve the rare late onset of a seizure disorder in less than 5% of children with severe TBI. A history of seizures would clarify the clinical decision.

School Failure

Case 1. A child with a severe TBI experienced a new-onset ADHD and significant problems with pragmatics of communication including narrative discourse. Regulation of mood states was unremarkable. Six months after injury he began to be challenged more at school and could not keep up with his class. He became irritable, angry, and sad and was diagnosed with an adjustment disorder with mixed emotional features.

Comment: In this case the child's affective instability was thought to be an indirect result of his TBI; that is, cognitive difficulties ultimately led to school failure and he responded to this with irritability and sadness.

Case 2. A child with a severe TBI experienced a new-onset ADHD and significant problems with pragmatics of communication including narrative discourse. Regulation of mood states was impaired in the hospital and remained so until an assessment 12 months after the TBI. Six months after injury, the child began to be challenged more at school and could not keep up with his class. He became even more irritable and angry and sad but did not meet criteria for a major depression.

Comment: In this case the child's affective instability was thought to be a direct result of his TBI; that is, poor affective regulation and cognitive difficulties led to school failure and complicated his teacher's efforts to work with him.

Treatment: Psychopharmacology

Personality Change Due to TBI: Affective Instability and Rage Subtypes

There are no studies of treatment of children with PC, therefore the following guidelines are anecdotal. Clinically, it is important to differentiate the subtypes because treatment approaches are different. The affective instability and aggressive types co-occur frequently (Max et al. 2001) and respond similarly to treatment. Mood-stabilizing medications such as carbamazepine and valproic acid can be particularly effective when combined with a behavior modification program targeting aggression. Adding a selective serotonin reuptake inhibitor (SSRI) to a mood stabilizer may be helpful as well. This may be counterintuitive for clinicians who work with children because of the well-known side effects of irritability and restlessness with SSRIs. Adults with affective instability (e.g., pathological laughter and pathological crying) have responded well to SSRIs (Robinson et al. 1993).

Personality Change Due to TBI: Disinhibited, Paranoid, and Apathetic Subtypes

The "disinhibited" subtype is particularly difficult to treat pharmacologically or behaviorally. School aides may be required to supervise the children closely. Parent education and support is particularly important to maximize overall family function. The paranoid subtype is rare. Careful assessment is necessary to determine whether a child with paranoid thoughts is truly impaired by these symptoms and whether the symptoms actually influence the child's behavior. Use of neuroleptic medication such as risperidone may be helpful in the acute hospitalization or rehabilitation unit if the child or adolescent is overtly paranoid and the symptoms are impeding compliance with treatment regimens. The potential risks regarding modification of neuronal recovery have been elucidated in animal models (Kline et al. 2008). The apathetic subtype is also rare and may respond to stimulant medication or SSRIs.

There may be periods when the child has intense affective instability, aggression, hyperactivity, and inattention and meets criteria for overlapping syndromes of PC, ADHD, and mania or hypomania (Max et al. 1997c). Mood stabilizers may be helpful, and if stimulants are being used, they should be reevaluated although the mania/hypomania should not be considered a contraindication to stimulant use (Max et al. 1995a).

Attention-Deficit/Hyperactivity Disorder

Some reports of stimulants administered to children with TBI who have attention and concentration deficits show positive results while others show negative results (Jin and Schachar 2004). There is anecdotal evidence that children diagnosed with SADHD respond to stimulant medication. Popular belief that children with brain damage do not respond to this treatment is unfortunate and may impede the appropriate treatment of children who could benefit from therapy. This belief may derive, in part, from the fact that even when SADHD has been treated with a stimulant, the child with a severe TBI may still have other psychiatric disorders that may require management as well as have adaptive function and cognitive impairments that require other interventions. Methylphenidate is generally the first choice of clinicians paralleling use in children with developmental ADHD. The literature on a decreased seizure threshold accompanying methylphenidate use in people with brain injury is extremely weak. There have been a number of studies demonstrating the safety of methylphenidate in rehabilitation centers that treat individuals with severe TBI (Wroblewski et al. 1992). The risk of seizures after closed head injury is small, and methylphenidate has been considered a safe choice of drug. There have been no studies of tricyclic antidepressant medication or bupropion for SADHD. Caution should be observed when prescribing the former class of antidepressants especially in terms of cardiac conduction side effects. The use of bupropion is generally avoided because of the risk of seizures. This may be an unnecessary avoidance in this population, but there are no research data to guide usage in children with TBI.

Depression

There are no treatment studies of depressive disorders after child TBI. Clinical experience suggests that use of SSRIs is effective as they have been shown to be when used for childhood depression in the absence of TBI. There is anecdotal evidence of effectiveness of amitriptyline in a child with comorbid posttraumatic migraines who could not tolerate an SSRI.

Treatment: Psychosocial Interventions

There are only a few studies of psychosocial treatments for complications from childhood TBI (Singer et al. 1994; Wade et al. 2005, 2006a, 2006b). Family problem-solving interventions have resulted in a decrease in children's internalizing symptoms, anxiety, depression, and withdrawal symptoms (Wade et al. 2006b). The online provision of family problem-solving interventions decreased injury-related burden, parental psychiatric symptoms, parental stress, and antisocial behavior but did not reduce depressive symptoms in the child (Wade et al. 2005). The focus on the family in these treatment studies is appropriate given that preinjury family function is a significant predictor of child outcome as well as postinjury family function. Therefore, family needs should be assessed soon after injury and at various junctures thereafter. Education, clinical, and advocacy services should be offered to families who are in need. This may improve child outcome by empowering the family to manage the child appropriately as well as limit secondary complications from delay in the diagnosis and treatment of medical, psychiatric, cognitive, and academic problems in the postacute and chronic phase after TBI.

Until more comprehensive treatment studies are done to justify specific guidelines for treatment of emotional or behavioral problems (e.g., phobias, PTSD, ODD/conduct disorder) after TBI, general principles of psychosocial treatment should be applied. An important and specific psychoeducational preventative and treatment intervention is to warn about and modify some families' apparent overindulgence of their injured child after injury. When this occurs, it tends to be self-limiting unless complicated by a parent's excessive sense of guilt. Other families at the opposite extreme may insist on prematurely reexposing their children to the proximal hazard that resulted in their TBI (e.g., three-wheeler racing). These parents may be more likely to accept the recommendations of a neurosurgeon than a psychiatrist.

Prevention

The prevention of accidents should be the first objective in the battle to limit the societal and personal costs of pediatric TBI. Education regarding the use of bicycle helmets, improved motor vehicle safety, efforts to decrease alcohol-related motor vehicle accidents, and programs to decrease the risk of child abuse and neglect are just some of the ways to prevent or limit the damage caused by pediatric TBI (Kraus 1995).

KEY CLINICAL POINTS

- Traumatic brain injury (TBI) in children and adolescents is a major public health problem. In particular, severe TBI may have neurological sequelae including seizures that can complicate behavioral outcome.
- Academic and cognitive function impairments make school reentry and long-term educational success a great challenge. The challenge is magnified when these impairments are associated with psychiatric problems.
- Psychiatric disorders are common in children both before and after TBI. Postinjury psychiatric disorders are predicted by a variety of injury and psychosocial variables that can be measured soon after injury. Therefore, children with TBI who are at high risk for impairing psychopathology are readily identifiable before the manifestations of the problems.
- The advantage of classification of psychiatric disorders into specific conditions versus T-scores on domains of behavior such as internalizing or externalizing disorders opens the possibility of specific, rational pharmacological and psychological treatment during the rehabilitative phase.
- The close relationship of family dysfunction and psychiatric disorders supports the case for family intervention research that may improve not only the family's function but also the child's function.
- More research on biopsychosocial factor correlates of injury risk and psychiatric outcome should lead to more effective primary and secondary prevention efforts.

Recommended Readings and Resources

Brain Injury Association of New York: Project LEARNet. 2008. Available at: http://www.projectlearnet.org. Accessed October 4, 2010. The Brain Injury Association of New York has produced a comprehensive website that deals in detail with academic, social, behavioral, biological, and family issues related to child and adolescent traumatic brain injury. The resource is for teachers, parents, children, and other professionals.

Dise-Lewis JE, Calvery ML, Lewis HC: BrainSTARS (Brain Injury: Strategies for Teams and Reeducation for Students). Wake Forest, NC, Lash and Associates Publishing/Training, 2002. This manual is an invaluable resource for educators, clinicians, and parents of children and adolescents with traumatic brain injury.

Max JE, Ibrahim F, Levin H: Neuropsychological and psychiatric outcomes of traumatic brain injury in children, in Cognitive and Behavioral Abnormalities of Pediatric Diseases. Edited by Nass R, Frank Y. New York, Oxford University Press, 2010. This book covers a wide variety of pediatric disorders including brain disorders, and the chapter cited has an in-depth review of neuropsychological outcome of pediatric traumatic brain injury.

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CHAPTER 29

Elderly

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INDIVIDUALS AGE 65 YEARS AND OLDER ACCOUNTED for nearly 13% of the United States population in 2005, and this figure will increase to 20.3% by 2040 (U.S. Bureau of the Census 2008). Additionally, individuals ages 85 years and older represent a rapidly growing segment of the United States population (Table 29–1). As a result, increasing attention must be paid to health care issues in the elderly. This chapter focuses on specific issues relevant to older patients with traumatic brain injury (TBI).

Etiology and Risk Factors

Although motor vehicle accidents represent the most common cause of TBI in younger individuals, falls account for the highest proportion of TBIs in older individuals (Thompson et al. 2006). This is largely because of the increased risk of falls in the aging population (Table 29–2). Falls cause 70% of accidental deaths in people older than age 75 years and represent the fifth leading cause of death in the elderly.

Influence of Age on TBI Outcome

Acute Outcome

The acute postinjury phase is characterized by an increased frequency of space-occupying lesions, secondary medical complications, and overall mortality. Comparing patients older than and younger than 65 years old, Pentland et al. (1986) reported a threefold increase in intracranial hematomas in mild to moderate injuries; in severe injuries, there was no difference between age groups. However, another study comparing patients 60 years and older with patients ages 20–40 years with severe injuries (i.e., a Glasgow Coma Scale [GCS] score of 5 or less) noted a higher incidence of multiple brain lesions, hematoma, and contusions in the elderly patients (Pennings et al. 1993). Mortality in the older patient group was 79%, with one-third of these mortalities attributed to pulmonary, cardiac, or multisystem organ failure. By comparison, mortality in younger patients was 36%, all attributed to primary brain injury. Rothweiler et al. (1998) prospectively followed 411 hospitalized patients with mild to severe TBI ages 18–89 years for 1 year postinjury. Patients 60 years and older took longer than 7 days on average to become responsive to commands compared with less than 24 hours in younger patients. Additionally, the older patients were more likely to have complications such as cardiac arrest, ventriculitis, and sepsis. Thus, although mild injuries were associated with only slightly increased mortality and poorer outcomes in older versus younger patients, moderate and severe TBI were associated with substantially increased morbidity and mortality in the elderly. This may be related to both physiological aspects of aging and limitations of the GCS in assessing severity of injury in older patients. These findings suggest that a GCS score alone may underestimate the severity of brain injury in patients with age-related cognitive and physiological changes.

TABLE 29–1. Population ages 65 years and older: United States, 1995–2040

Population	1995	2005	2020	2040
≥65 years (millions)	33.5	36.2	53.2	75.2
Percentage of total population	12.8%	12.6%	16.5%	20.3%
≥85 years (millions)	3.6	4.9	6.5	13.6
Percentage of total population	1.4%	1.7%	2.0%	3.7%
Percentage of population >65 years	10.8%	13.5%	12.1%	18.0%

Source. U.S. Bureau of the Census 2008.

TABLE 29–2. Factors associated with increased risk of falls

Sensory
Impaired vision
Impaired proprioception
Impaired vestibular function
Peripheral neuropathy
Musculoskeletal
Muscle weakness, arthritis
Cardiovascular
Postural hypotension
Cardiac arrhythmias
Central nervous system
Dementia
Depression
Movement disorders

Source. Adapted from Tinetti 1997.

Functional Outcome

There are conflicting data regarding the influence of age on functional outcome after TBI, perhaps related to methodologies, which have traditionally used stratification techniques to compare patients within different age ranges. In a meta-analysis of studies involving a total of 5,600 patients, Hukkelhoven et al. (2003) noted that the interaction between age and outcome fits a linear, continuous relationship rather than a categorical model, with a 10-year increase in age associated with a 46% risk of poor functional outcome. Older patients may experience neurological deterioration after discharge, leading to nursing home placement, in contrast with the tendency of younger patients to improve neurologically after discharge (Pentland et al. 1986). Comparing patients older than and younger than 55 years matched for injury severity and gender, Cifu et al. (1996) observed that the older patient group had a significantly longer mean length of rehabilitation stay, higher total rehabilitation charges, and a slower rate of improvement on functional measures. Nonetheless, there was no difference between groups in discharge disposition (community vs. institutional setting). In this study, the mean GCS score was approximately 10 in both groups, suggesting a preponderance of moderately severe injury. Therefore, although older patients required significantly longer and more costly inpatient rehabilitation stays, their postdischarge dispositions were comparable with those of younger patients. Comparing psychosocial outcomes at 1 year postinjury in patients of various ages, Rothweiler et al. (1998) found that patients ages 60 years and older were significantly more disabled than those younger than 50 years of age, and those age 50 years or older were significantly more disabled than those younger than 30 years. Significantly more patients older than 60 years required a change to a more supervised living situation than those younger than 50 years. Therefore, there is evidence that older patients may be able to achieve substantial gains, though at a much higher cost because of protracted inpatient rehabilitative treatments. These studies followed patients with a predominance of moderate to severe injuries.

Rapoport and Feinstein (2001) compared subjects ages 60 years and older with those ages 18–59 years who had mild TBIs. Contrary to expectations, the older group had better functional and psychological outcomes at 1-month follow-up. Severity of injury is therefore an important factor to consider when predicting age-related variance of TBI outcomes (Table 29–3). In cases of isolated TBI uncomplicated by multiple trauma, elderly patients appear to have the potential for functional outcomes comparable with those of younger patients, though achieving such improvements may take longer and require greater expense (Mosenthal et al. 2004). In another study designed to evaluate the isolated influence of TBI in the elderly, Testa et al. (2005) compared functional outcomes of patients with TBI and orthopedic injuries, stratifying their group by age range (18–49 vs. 50–90). Older patients were more likely to have decreased independence and employment than younger patients, and this effect was greater than that observed in the orthopedic control group. An important consideration, however, is the prevalence of such isolated TBIs in the elderly. Rather than making broad generalizations regarding the effects of age on TBI outcome, one must consider the interaction of age and mechanism of injury. Thus, the functional outcomes of mild TBI due to falls may be nearly equivalent in elderly and young patients, whereas functional outcomes of more severe TBI with multiple trauma due to motor vehicle accidents may vary substantially with age.

Cognitive Outcome

Cognitive functioning exerts a substantial influence on functional independence in all age groups. Goldstein et al. (2001) compared elderly TBI patients with community-dwelling control subjects approximately 2 months after mild and moderate TBI. The TBI subjects had poorer performance on tests of language, memory, and executive functioning than the healthy control subjects. Aharon-Peretz et al. (1997) noted greater cognitive impairment in elderly TBI subjects compared with healthy control subjects. However, they also noted similar cognitive impairment in a comparison group of orthopedic inpatients and hypothesized that preexisting cognitive impairment may have predisposed both TBI and orthopedic patients to falls that resulted in their hospitalization. In contrast, Rapoport et al. (2008) found no differences in cognition at 1 and 2 years postinjury between patients age 50 years and older with and without TBI.

Another factor that is not directly related to TBI is the role of medications, particularly polypharmacy, in the elderly. Advanced age and associated age-related medical illnesses can lead to the prescription of a variety of medications, including psychoactive drugs, which increase the likelihood of drug-drug interactions (Zhan et al. 2001). However, even appropriately prescribed nonpsychoactive medications such as antiparkinsonian, cardiac, and anti-inflammatory agents may adversely affect cognition (Moore and O'Keeffe 1999).

Summary

Elderly patients who sustain TBIs are generally at risk for higher mortality as well as poorer cognitive and functional outcomes because of TBI. In particular, secondary organ

TABLE 29–3. Traumatic brain injury (TBI) outcome and advanced age

Author	Study group age (years)	Effects of older age on functional outcome
Pentland et al. 1986	65+ vs. <65	Greater neurological deterioration leading to nursing home placement
Cifu et al. 1996	55+ vs. <55	Increased length of stay in inpatient rehabilitation stay, slower rate of improvement
		No difference in discharge disposition
Rothweiler et al. 1998	60+ vs. <50	Increased referral to supervised living
Ritchie et al. 2000	>65	Increasing nursing home placement at lower severity of injury
Rapoport and Feinstein 2001	>60 vs. 18–59 (mild TBI)	Better functional and psychological outcomes at 1 month postinjury
Hukkelhoven et al. 2003	14–85	40%–50% increased risk of poor outcome with every 10 years of increased age
Mosenthal et al. 2004	18–64 vs. 65 and older	Slightly less 6-month improvement postdischarge of questionable clinical significance
Testa et al. 2005	16–49 vs. 50–89	Greater dependence, lower employment at 1–2 years postinjury

failure is much more common and appears to contribute to increased mortality in older versus younger TBI patients. In addition, older patients tend to require longer, more costly rehabilitative treatments, though they may benefit substantially from such interventions. An additional concern is the concomitant use of psychoactive medications and other drugs that may have an adverse effect on cognition.

Pathophysiology of Aging and TBI

Age-related physiological changes contribute to the increased vulnerability of older patients to adverse consequences of TBI. These changes may involve brain structure and function that magnify the effects of head trauma and reductions in physiological reserve that predispose older patients to secondary organ failure.

Neurobiology of Aging

The human brain achieves full maturity in the second or third decade of life, and age-associated histological changes develop after age 40 years (Powers 2000). Age-related cerebral atrophy may result from a loss of neurons, decrease in neuronal volume, and loss of synapses. Synaptic density declines with age, but the number of cortical neurons in many areas may remain stable through advanced age (Haug and Eggers 1991). Neurotrophic factors such as nerve growth factor are essential to the normal development and maintenance of cholinergic neurons. In humans, there is evidence of decreased synthesis of nerve growth factor in the aging brain (Hefti et al. 1989). Thus, the aging brain may be less able to mount an effective regenerative response to brain trauma via neurotrophic factors. Age-related cerebrovascular changes also lead to a progressive reduction in cerebral perfusion and associated reductions in regional cerebral metabolism (Tumeh et al. 2007). Overall brain shrinkage due to cerebral atrophy increases the space between the brain and skull, exposing dural vessels to greater shearing forces in TBI (Cummings and Benson 1992).

Neurochemical Changes

It therefore stands to reason that preinjury age-related reductions in central cholinergic functioning may render elderly patients more vulnerable to the neurochemical effects of TBI. These changes are summarized in Table 29–4.

Cholinergic Systems

Human postmortem studies indicate that presynaptic cholinergic mechanisms are disrupted following TBI (Dewar and Graham 1996). Acetylcholine innervation is widely distributed throughout the brain, mainly originating in the nucleus basalis of Meynert in the basal forebrain. Although no consistent loss of acetylcholine content is found in the brains of healthy elderly humans, cerebrospinal fluid levels of the degradative enzyme acetylcholinesterase are increased with advancing age (Hartikainen et al. 1991; Muller et al. 1991). Thus, there is a general age-related impairment in cholinergic activity that may render elderly patients more susceptible to the disruptive effects of TBI on cholinergic systems.

Aminergic Systems

Disruption of aminergic systems has been implicated in the development of working memory deficits following TBI (McAllister et al. 2004). Loss of noradrenergic neurons in the locus ceruleus begins in the fourth decade of life and progresses in a linear fashion (Mann et al. 1983). Decreased activity of the noradrenergic synthetic enzymes tyrosine hydroxylase and dopamine β-hydroxylase also occurs in the aging brain (Powers 2000). Age-related loss of dopaminergic neurons in the nigrostriatal pathways begins in the fifth decade of life, leading to as much as 35% loss by age 65 (Mann et al. 1984). Moreover, density of D_2 receptors declines after age 18 (Antonini et al. 1993). In aging patients, decreased density of D_2 receptors is associated with cognitive dysfunction that is suggestive of frontal systems impairment (Volkow et al. 1998). This age-related deterioration of pre- and postsynaptic dopaminergic functioning may also account for the heightened

TABLE 29–4. Neurochemical changes associated with aging

Neurotransmitter	Location	Change	Receptor location	Receptor alterations
Acetylcholine	Nucleus basalis of Meynert	↓ or →	Neocortex	↓ M_1 and M_2
				↓ N
	Medial septal region	?	Hippocampus	↓ M_1, M_3, M_4
				↓ N
Serotonin	Raphe	?	Neocortex	↓ 5-HT_1, 5-HT_2
Norepinephrine	Locus ceruleus	↓	Neocortex	↓ α-adrenergic
				↓ β-adrenergic
Dopamine	Substantia nigra	↓	Basal ganglia	↑ Postsynaptic D_1
				↓ Postsynaptic D_2
				↓ Presynaptic D_1
				↓ Presynaptic D_2

Note. 5-HT=serotonergic; D=dopaminergic; M=muscarinic; N=nicotinic; ↓=decreased; ↑=increased; →=no change; ?=unknown.

Source. Adapted from Powers 2000.

sensitivity of older patients to cognitive impairment secondary to dopamine antagonists such as antipsychotic medications (Byerly et al. 2001). Brain levels of the degradative enzyme monoamine oxidase-B increase with age, which may reduce monoaminergic transmission (Fowler et al. 1997).

Densities of 5-HT_1 and 5-HT_2 receptors are decreased in elderly humans (see Table 29–4). Density of type 1 receptors is decreased by up to 70%, and type 2 receptor density is reduced by 20%–50% (Mendelsohn and Paxinos 1991). This reduction in central serotonergic functioning has been proposed as a potential contributor to the development of disturbances of mood and behavior in elderly patients (Meltzer et al. 1998).

Summary

Aging brain demonstrates mild to moderate neuronal loss, with much of the volume loss caused by neuronal and synaptic atrophy. Additionally, neural plasticity diminishes with advancing age. These factors, in addition to reduced neuronal responsiveness to injury-induced neurotrophic factors, may contribute to less favorable outcomes from TBI in the elderly. Neurochemical changes in the aging brain may lead to increased risk of post-TBI cognitive and affective disturbances.

TBI and Dementia

Chronic repetitive TBI is the putative cause of dementia pugilistica, or "punch-drunk" syndrome, which is associated with β-amyloid deposits similar to those seen in Alzheimer's disease (AD) (Roberts et al. 1990). A postmortem study found cortical β-amyloid deposits in 30% of patients ages 8 weeks through 81 years who died within 4 hours to 2.5 years following TBI (Roberts et al. 1994). Older age was associated with a greater likelihood of deposits. These findings suggest that the TBI may share common neuropathological features with AD. However, epidemiological studies do not consistently support a causal relationship between TBI and AD. In a study of 236 community-dwelling elderly persons, TBI alone was not associated with increased risk of AD, but the presence of both the apolipoprotein E epsilon 4 allele and a history of TBI was associated with a 10-fold increase in risk of AD (Mayeux et al. 1995). A prospective population-based study of 6,645 subjects ages 55 years and older in Rotterdam, the Netherlands, found that a history of head trauma with loss of consciousness was not associated with an increased risk of AD (Mehta et al. 1999). This relationship was not affected by apoE genotype, multiple head injuries, or duration of unconsciousness. The study was limited by a relatively brief interview between baseline and follow-up of 2.1 years (SD 0.8). A retrospective cohort study of 1,283 patients in Olmsted County, Minnesota, who sustained TBIs also found that the incidence of subsequent AD was no different from that expected in the general population, but the time between TBI and onset of AD was 10 years versus an age-adjusted median of 18 years (Nemetz et al. 1999). A systematic review and meta-analysis of 15 case-control studies identified a 58% greater prevalence of prior TBI in patients with AD (Fleminger et al. 2003). Stratification by gender revealed that the excess risk was present only in men (odds ratio 2.29, 95% confidence interval 1.47, 2.06).

Influence of Apolipoprotein E on Outcome

Apolipoprotein E (apoE) regulates lipid transport and metabolism in the liver and central nervous system, distributing cholesterol and phospholipids to neurons after injury. In this capacity, it may mediate neuronal repair, regeneration, and survival (Horsburgh et al. 2000). In humans, there are three common isoforms of apoE encoded by different alleles: ε2, ε3, and ε4 (*APOE*E4*). The *APOE*E4* allele, a known risk factor for AD, appears to influence outcome after TBI. A prospective study of 93 TBI patients found that the presence of the *APOE*E4* allele was associated with a twofold increase in risk of a poor outcome (death, vegetative state, or severe disability) when adjusted for age,

severity of injury, and computed tomography (CT) findings (Teasdale et al. 1997). A subsequent replication following 1,094 patients with TBI found no association between *APOE*E4* and outcome, although there was an interaction between genotype and age at injury, with the allele negatively influencing outcomes in younger patients (Teasdale et al. 2005). Several studies have observed an association between *APOE*E4* and greater postinjury impairment (Friedman et al. 1999; Lichtman et al. 2000). In a human postmortem study of 90 patients who died of TBI, 52% of patients with β-amyloid deposition had the *APOE*E4* allele, compared with only 16% of those with no deposits (Nicoll et al. 1995). However, one study found no relationship between genotype and cognitive functioning at 1 and 2 years postinjury (Rapoport et al. 2008). Head trauma may trigger deposition of β-amyloid, particularly in patients with the *APOE*E4* allele. The clinical implications of this finding are as yet unclear.

Clinical Presentation

The clinical presentation of TBI in older patients differs from that of other populations because of age-related physiological changes and the different circumstances related to their injuries. Cognitive and neurological sequelae of TBI in elderly patients may have a more insidious yet malignant onset and progression due to the high prevalence of subdural hematomas in even mild or moderate injuries. In this scenario, a patient may present with several weeks or months of progressive cognitive impairment. The patient may either have had a witnessed or unwitnessed fall or other head trauma that was not thought to warrant medical attention. The risk of social isolation in the elderly increases the likelihood that head trauma will either not be witnessed or the subacute evolution of signs and symptoms will not be observed.

Another presentation may involve the presence of orthopedic injuries resulting from a fall or cardiovascular pathology that precipitated a fall. These more emergent conditions may lead the primary treatment team to focus on acute stabilization, particularly in intensive care or surgical settings. Neuropsychiatric consultation may be requested later in the course of treatment as a result of emerging confusion or agitation that is attributed to complications of hospitalization rather than a preadmission TBI. Careful history taking using collateral information sources may assist in the identification of an occult TBI.

Assessment

Clinical History

The GCS may be a less reliable measure of severity of injury in older individuals because of numerous factors, including sensory deterioration and preexisting dementia (Powers 2000). Moreover, because many fall-related TBIs may be unwitnessed, the duration of time before initial assessment may be more variable in this age group, further limiting the utility of the GCS. As a result, additional history must be obtained to clarify the extent of the insult and its effects on the patient. Particularly important is the establishment of a preinjury baseline. Age-related bias may lead clinicians to assume that post-TBI cognitive deficits are merely reflective of a preexisting dementia. In addition, previous brain injuries or cerebrovascular insults may have occurred over the course of the individual's lifetime.

A detailed and accurate history of preinjury physical, cognitive, and psychological status is crucial. Frequently, such history must be obtained from relatives and friends. However, the protean manifestations of TBI in the elderly are further complicated by the increased physiological variability between older individuals. Therefore, the clinician must use collateral information to develop an estimate of the patient's preinjury functioning as well as preinjury rate of functional decline. This process can help determine the influence of the injury on the patient's functional trajectory.

Neuroimaging

Given the high incidence of posttraumatic subdural hematomas in older patients, structural neuroimaging studies such as CT and magnetic resonance imaging may help identify such pathologies in verified or suspected TBI. Single-photon emission computed tomography or positron emission tomography may also provide useful information regarding alterations in regional cerebral perfusion and metabolism not detectable by structural neuroimaging. However, age-related changes in the brain may make interpretation of both structural and functional imaging results difficult, particularly because cerebral perfusion may be altered by normal aging (Tumeh et al. 2007). The use of functional neuroimaging to differentiate between TBI and dementia in the elderly has not been well studied at this time.

Neuropsychological Assessment

Neuropsychological testing may help distinguish cognitive disturbances caused by TBI from age-related cognitive changes. Age-related decline in memory performance is characterized by a fairly narrow range of impaired performance in acquisition and retrieval of newly learned information (Small et al. 1999). Moreover, decreased processing speed in healthy elderly subjects seems to be narrowly circumscribed and not attributable to general deficits in executive function, inhibition, and working memory (Salthouse 2000). The cognitive deficits associated with TBI are more pervasive and may thus be distinguished from normal aging. Neuropsychological testing may also help distinguish cognitive effects of TBI from that of AD; specifically, patients with AD demonstrated poorer recognition memory than those with TBI (Goldstein et al. 1996).

Summary

Assessment of the brain-injured older patient begins with maintaining a high index of suspicion for TBI even when the initial presentation or reason for consultation does not specify this history. Obtaining detailed collateral history of the presenting syndrome is critical, as is a history of prior

injuries and cognitive functioning. Structural as well as functional neuroimaging provides important data regarding the effects of TBI on the brain, as does neuropsychological testing. Age-related alterations in brain structure and function require consideration of these changes when interpreting results. These factors that confound the use of formal testing and neuroimaging in the elderly accentuate the importance of a detailed pre- and postinjury history to determine the role of TBI in an older patient's functional problems.

Treatment

The necessity for a multidisciplinary biopsychosocial approach to management of TBI rehabilitation is present for all age groups. However, in older patients, even more attention must be paid to age-specific factors that affect the physiology, psychology, and social circumstances of brain-injured patients.

Pharmacological Treatment

Pharmacological interventions should take into consideration the increased sensitivity of elderly patients to medication side effects, particularly anticholinergic side effects. Attention must also be paid to physiological changes that alter the pharmacokinetics of medications (see Table 29–5). Increases in body fat composition may increase elimination half-life of lipid-soluble medications, whereas decreased serum proteins may lead to increased bioavailability at equivalent serum levels. Additional factors include decreased gastric emptying and resulting slowed absorption and decreased renal and hepatic excretion.

Environmental Interventions

Environmental interventions should address age-associated sensory decline. Areas should be well-lit and free from excessive noise and other stimuli that may overwhelm and confuse the patient. Caregivers should be trained to approach the patient directly and speak clearly in brief, succinct sentences. Reinforcement of communication through repetition is vital. Management of older TBI patients may be similar to that of elderly patients with primary dementias. Neuropsychological testing may help identify areas of deficit and areas of preserved function. This may assist in the development of environmental and communication modifications to enhance function.

TABLE 29–5. Age-related physiological changes and pharmacokinetic implications

Function	Pharmacokinetic effect	Clinical implications in relevant drugs
Absorption	↓ Rate of absorption	Delayed onset, incomplete absorption, reduced effect
↑ Gastric pH		
↓ Gastric emptying		
↓ Mesenteric blood flow		
Distribution	↑ Volume of distribution for lipophilic drugs	↑ Time until steady-state plasma concentration
↓ Muscle mass	↑ Elimination half-life of lipophilic drugs	↓ Duration of effect of single doses
↓ Total body water		Slower titration
↑ Total body fat		
Plasma protein binding	↑ Free fraction of highly protein-bound drugs	↑ Potency and toxicity at lower doses
↓ Albumin		Reduced dosage
↓ γ_1-acid glycoprotein		
Hepatic metabolism	↑ Elimination half-life of hepatically metabolized drugs	↑ Time till steady-state plasma concentration
↓ Liver volume	↑ Ratio of parent drug to demethylated derivative	Reduced dosage
↓ Hepatic blood flow		Slower titration
↓ Oxidative metabolism		
↓ *N*-demethylation		
→ Conjugation		
Renal clearance	↑ Elimination half-life of active hydrophilic drugs	↑ Time till steady-state plasma concentration
↓ Renal blood flow		Reduced dosage
Glomerular filtration rate		Slower titration

Note. ↓=decreased; ↑=increased; →=no change.

Source. Adapted from Zubenko GS, Sunderland T: "Geriatric Neuropsychopharmacology: Why Does Age Matter?" in *Textbook of Geriatric Neuropsychiatry,* 2nd Edition. Edited by Coffey CE, Cummings JL, Lovell MR, et al. Washington, DC, American Psychiatric Press, 2000, pp 749–778. Used with permission.

Psychotherapy

For the patient struggling with adaptation to new cognitive and functional impairments, supportive psychotherapy may be helpful in easing distress and obviating the need for psychotropic medications. This approach is addressed more completely in Chapter 36, Psychotherapy. Psychotherapy may be modified readily to accommodate the specific circumstances and needs of elderly patients and may prove quite effective for depressive disorders, particularly when combined with pharmacotherapy.

Family and Caregiver Work

The increased risk in older patients of functional impairment resulting from TBI may lead to drastic changes in role functioning in families that have often had stable roles for decades. Educating families and caregivers regarding the practical implications of these changes may reduce caregiver distress. In particular, engaging families with support groups that provide mentoring and education regarding the process of adjusting to TBI may reduce burnout. Caregivers and patients must be helped in the process of grieving lost functioning. As in the dementias, behavioral disturbances are a major cause of caregiver distress and an obstacle to successful community functioning. Likewise, such disturbances may accelerate the need for institutional placement, primarily mediated through the impact of behavioral problems on caregiver distress (Yaffe et al. 2002). Therefore, providing caregivers with psychoeducational and supportive interventions may enable them to better cope with their new roles and challenges.

Management of Neuropsychiatric Syndromes

Depression

Depression is an independent risk factor for mortality in advanced age and accounts for substantial functional impairment (Reynolds et al. 2008). It may be characterized by more irritability and apathy, with less overt sadness. The changes in role functioning that often occur with aging may be exacerbated by the abrupt loss of functional capacity because of TBI. Greater dependence on others for cognitive and, at times, physical tasks may engender feelings of loss and helplessness. Antidepressant therapy may be effective, though it is important to differentiate between depression and TBI- or dementia-related apathy syndromes to avoid unnecessary exposure to psychoactive medications. Dosing and titration should be adjusted based on the time-honored philosophy of "start low, go slow" in recognition of heightened sensitivity to medication side effects and potential drug-drug interactions with other nonpsychotropic medications.

Agitation and Psychosis

Agitation in elderly TBI patients may represent an exacerbation of a preexisting dementia-related behavioral disorder or frontal disinhibition resulting from the injury itself. Mood stabilizers and atypical antipsychotics appear to be well tolerated in elderly dementia patients, though with appropriate decreases in dosage and rate of titration. Clarifying the symptom may be important to effective treatment. Increased sensitivity to side effects of sedation, tremor, and ataxia are common in older patients with any neurological disease. Atypical antipsychotic medications may reduce irritability and aggression in elderly patients with dementia. This is also true of elderly patients with behavioral complications of TBI. Care must be taken to provide the optimum degree of therapeutic benefit with a minimum of side effects. The atypical antipsychotic medications have been well studied in treatment of dementia-related agitation and psychosis. The modest overall efficacy of these drugs must be weighed against the small but statistically significant risk of increased mortality and cerebrovascular adverse events (Schneider et al. 2006).

Cognition

Acetylcholine has been recognized as a principal neurochemical mediator of learning and memory (Thiel 2003). However, dopaminergic functioning has also been identified as an important component to the neurochemistry of cognition (Nieoullon and Coquerel 2003). Cholinergic therapies such as donepezil may improve cognitive functioning in patients with TBI (Khateb et al. 2005; Zhang et al. 2004). These medications are well tolerated and therefore may be used to treat cognitive difficulties in elderly and younger TBI patients alike.

Cognitive deficits may also respond to treatment with dopamine agonists. Both methylphenidate (Whyte et al. 2004) and amantadine (Sawyer et al. 2008) have been shown to improve attention, concentration, and processing speed in TBI patients. Amphetamine has been found to enhance functional recovery in a chart review study (Hornstein et al. 1996). In older patients who demonstrate reduced initiative and attention, these medications may be useful adjuncts to environmental stimulation.

Conclusion

The elderly represent a rapidly growing population with a specific set of risk factors for TBI that differs from that of the general population. Moreover, older patients are at high risk for less favorable outcomes and secondary complications. The thoughtful application of principles of geriatric medicine will improve the assessment and management of this complex patient group. Nevertheless, timely and appropriate rehabilitative and neuropsychiatric interventions may provide older patients with substantial functional and cognitive benefits.

KEY CLINICAL POINTS

- Elderly patients are more likely to be injured in falls than in motor vehicle accidents.
- Traumatic brain injury (TBI) generally leads to much greater morbidity and mortality in the elderly, often due to secondary organ failure rather than the primary brain injury. This difference is less prominent in mild TBI.
- Elderly patients may achieve improvements similar to those seen in younger patients, although this may require greater time and expense.
- Age-related neuronal loss and reductions in neural plasticity may contribute to less favorable TBI outcomes for elderly patients.
- The association of TBI with development of Alzheimer's disease and the influence of apolipoprotein E genotype on cognitive outcomes have been replicated in some but not all studies.
- Assessment as well as management of TBI in the elderly requires a broad understanding of normal age-related biopsychosocial changes and of how the TBI affects this equilibrium.
- Medication management of neuropsychiatric complications of TBI requires attention to the benefits and risks of pharmacological interventions, with particular attention to optimizing cognition.

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CHAPTER 30

Alcohol and Drug Disorders

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THE GREATEST RISK FACTORS FOR TRAUMATIC BRAIN injury (TBI) are alcohol/drug use and alcohol/drug disorder (A/DD). TBI is often an irreversible adverse consequence of the pharmacological effects and addictive use of alcohol and drugs. Of critical importance is that TBI is preventable. The prevention can include many aspects, but long noted of primary importance is the treatment of A/DD before the onset of the TBI (Brismar et al. 1983; Brooks 1984; Field 1976; Sparadeo and Gill 1989).

The coexistence of TBI with A/DD requires concurrent treatment of both disorders. A/DD complicates the treatment of TBI and vice versa. Acceptance of both categories of disorders as independent and interactive enhances the total treatment of the patient (Kreutzer et al. 1996; "Treatment and Rehabilitation" 1981).

Clinicians working with individuals who have acute or chronic sequelae of traumatic brain injury must be knowledgeable and skilled in the identification of A/DD whenever it exists in combination with TBI (Ksiazkiewicz and Bloch-Buguslawska 1998). If only one condition is the focus of the treatment, incomplete treatment and poor prognosis are likely to result for either condition. Because of the interplay between TBI and A/DD throughout the clinical course, treatment strategies must be developed that recognize the independence of and interaction between the two categories of disorders (Freund 1985). Research suggests that alcohol/drug dependence may play a mediating role in the outcomes of TBI (Bogner et al. 2001; Corrigan 1995). Proper treatment of both conditions may serve to lessen additive effects.

Treatment protocols can be implemented from the time of first contact during the acute intervention through chronic maintenance. Those who are actively involved in the treatment must be skilled in the intervention, referral, and, in some cases, the actual long-term management of both TBI and A/DD. Although a specialist may be employed for either category of disorder, he or she must know the ramifications of both disorders. For instance, the addiction specialist must know and work with the limitations of the alcohol- or drug-addicted patient with brain injury, and at the same time, the brain specialist must know the effects of both treated and untreated alcoholism and drug addiction on the patient with TBI. The two specialists, then, must work to coordinate the treatment of both disorders (Substance Abuse Task Force 1988).

Prevalence of the Problems

Between 29% and 52% of individuals admitted to a hospital with a TBI test positive for blood alcohol. Moreover, 58% of all surgical admissions and 72% of all hospital contacts, defined as visits to the hospital or emergency department, involve this same patient population. The reported prevalence of a history of alcohol dependence (addictive drinking) in patients with TBI ranges from 50% to 60% (Corrigan 1995), which suggests that the majority of those involved in TBI at any time had a serious problem with alcohol use before the onset of the injury. In an evaluation of substance use and dependence in TBI and spinal cord injury (SCI) patients, 81%–96% of individuals reported pretrauma drinking, whereas 42%–57% were heavy drinkers. This high degree of association strongly suggests that alcohol and TBI are causally related. Individuals who suffer an alcohol-related TBI are at greater risk for a second alcohol-related TBI (Winqvist et al. 2008). Early identification of at-risk populations for TBI/SCI may be possible. If an A/DD is identified and treated in the early stages, TBI, spinal cord injury, or both may be prevented (Kolakowsky-Hayner et al. 1999).

The role of drugs other than alcohol is not well documented because often specific testing and history taking for drugs are not part of either routine clinical practice or research studies. Many hospital records do not mention the implications of drug histories when clear evidence exists. The reasons for poor documentation are complex and include poor skills in assessing the importance of drugs and alcohol as well as ignorance that effective treatment

for alcohol and drug disorders exists. Research protocols do not often include measurement of urine or blood for illicit or prescription medications. The common occurrence of multiple drug and alcohol use or addiction in high-risk populations for the development of TBI (namely, adolescents and young adults) makes routine assessment for alcohol and drug use mandatory in these populations when traumatic injury occurs. Conversely, it has been proposed that a major diagnostic error occurs in the presence of TBI veiled by the effects of alcohol. Many individuals are brought to the hospital by police after slight bodily injury. Physicians may miss the symptoms of a TBI or misattribute observed symptoms to the effects of alcohol in an intoxicated individual. It is essential that physicians look carefully for signs or symptoms of a TBI in an intoxicated individual.

The prevalence rate for alcoholism in the United States is approximately 15%. The long-term diagnosis of alcoholism can be made in 29% of men and 7% of women in the United States. The mean age at onset of alcoholism is 22 years in men and 25 in women, according to the Epidemiologic Catchment Area study (Miller 1991b). The reported prevalence rate for drug addiction in the general population ranges from 9% to 20%. The majority of drug-addicted individuals are addicted to alcohol, and substantial numbers of alcoholic individuals are addicted to at least one other drug, namely, cannabis, cocaine, benzodiazepines, opiates, and/or hallucinogens, in decreasing order of frequency (Miller 1991b; Schuckit 1990). Despite these astonishing numbers, physicians often miss the diagnosis. In one evaluation of primary care physicians (Miller 2002), 94% were unable to identify a substance disorder as one of five diagnostic possibilities in case studies of patients with the early signs of an alcohol disorder. When case studies described early signs of a drug disorder in teenagers, 41% of pediatricians failed to provide substance disorder as one of five diagnostic possibilities. Also, nearly three-fourths of patients seeking treatment for a drug disorder did not receive guidance from their primary care physician. These results highlight the importance of physicians knowledgeable in addiction medicine to perform clinical examinations and assessments on drug use and history.

The prevalence rate for A/DD in psychiatric populations is 50%–75% and 25%–50% in medical populations. Treatment populations of addictive disorders show consistently high rates of multiple combinations of A/DD. The average age for men in treatment is 30–35 years, and the average age for women is 25–30 years. The proportion of men to women in typical treatment populations is 75% to 25% and 60% to 40% in membership surveys of Alcoholics Anonymous (AA) (Helzer and Pryzbeck 1988; Ries and Samson 1987).

Survey data provide evidence that alcohol and drugs are often involved with TBI. One hundred thousand people die annually in accidents in the United States. Motor vehicle accidents are the leading cause of death for teens in the United States, accounting for more than one-third of the deaths in this age group. In 2007, more than 4,200 teens between the ages of 15 and 19 were killed and almost 400,000 were treated in emergency rooms for injuries sustained in motor vehicle accidents (Centers for Disease Control and Prevention 2009). Fifty percent of all fatal accidents in the United States are motor vehicle accidents. Of these fatal motor vehicle accidents, 50% are associated with alcohol and drugs. Seventy percent of fatal injuries are from head trauma, and two-thirds of TBIs involve motor vehicle accidents. In fact, motor vehicle accidents appeared to be the most common cause of TBIs in a study of 322 patients at a rehabilitation center; however, violence-related injuries were found to occur most frequently in patients reporting substance dependence (Drubach et al. 1993). Similarly, 50% of all violent deaths from any cause are alcohol or drug related. However, the survival rate for people with severe TBI has increased to 60% since the 1980s. Most long-term survivors are young adult men (Sparadeo and Gill 1989; Sparadeo et al. 1990; Substance Abuse Task Force 1988).

The high degree of association of alcohol/drug use and addiction and TBI in young populations is clear. Despite what is known about the relationship between A/DD and TBI, there is much that is still unknown. Studies of prognosis and outcome after brain injury frequently exclude individuals who are addicted to drugs, alcohol, or both before accidents, even though this practice produces significant and relevant distortions of data (Sparadeo and Gill 1989; Substance Abuse Task Force 1988). Data regarding the impact of A/DD on mortality rates in patients with TBI unexpectedly have shown a decrease in the mortality rate. Despite the obvious associations between alcohol and trauma, very little is known regarding the pathophysiological implications of ethanol on TBI. Experimental animal studies suggest that ethanol may have a neuroprotective effect, though these results are conflicting and warrant more prospective studies (O'Phalen et al. 2008; Shandro et al. 2009).

Intervention in the Acute State

The first clinical caveat is that if alcohol or drug addiction, or both, is implicated in TBI, it is likely to have been a problem preceding and leading up to the injury (Ponsford et al. 2007). Precautions should be taken to address the medical and psychiatric sequelae of acute and chronic drug and alcohol use. Frequent complications include drug–drug interactions, drug overdose, increased sensitivity to medication effects, and seizures either from drug intoxication or from drug and alcohol withdrawal. Other possible complications include behavioral dyscontrol, hallucinations, delusions, anxiety, depression induced by intoxication and withdrawal from drugs and alcohol, and drug seeking because of the presence of an addictive disorder (Miller 1991b; Schuckit 1983) (Table 30–1).

The second clinical caveat is that behaviors such as lethargy, agitation, confusion, disorientation, and respiratory depression after acute intoxication and overdose are similar to those following brain injury. Importantly, some intoxicated patients are discharged from the emergency department when in fact they have undiagnosed brain injuries. In a study of 167 patients (Gallagher and Browder 1968), alcohol obscured changes in consciousness, leading to misdiagnosis or delayed diagnosis of complications of brain trauma. In 21 patients, a subdural hematoma was

TABLE 30–1. Psychiatric sequelae from drugs and alcohol

Drug-drug interactions
Drug overdose
Increased sensitivity to medication effects
Seizures from either drug intoxication or drug or alcohol withdrawal
Hallucinations
Delusions
Anxiety
Depression induced by intoxication and withdrawal from drugs
Alcohol and drug seeking from the presence of an addictive disorder

diagnosed only at postmortem (Galbraith 1976), and others have reported similar results (Rumbaugh and Fang 1980). In contrast, alcohol intoxication has a minimal effect on Glasgow Coma Scale scores of patients with TBI, except the most severely injured (Sperry et al. 2006).

Diagnosis of Alcohol and Drug Disorders

Once acute stabilization is achieved, the patient and family should be further evaluated for the presence and severity of an A/DD. Alcoholism and drug addiction are diagnosable according to established criteria in DSM-IV-TR (American Psychiatric Association 2000; Table 30–2). Three of the seven criteria for the dependence syndrome reflect the behaviors of addiction: 1) preoccupation with acquiring alcohol or drugs, 2) compulsive use of drugs despite adverse consequences, and 3) a pattern of relapse or inability to cut down on use despite adverse consequences. Two of the seven criteria reflect development of tolerance and dependence on alcohol and drugs. Any three of the seven criteria are required to make the diagnosis of alcohol or drug dependence, or both. Pervasive loss of control over use of alcohol and drugs sufficient to meet the criteria for the dependence syndrome in DSM-IV-TR is often evident in the histories of patients with TBI. The manifest loss of control often is reflected by the circumstances surrounding and including the actual trauma that culminates in the brain injury.

It has been well documented that the most effective clinical approach to both diagnosis and treatment of an alcohol or drug disorder involves the acknowledgment of substance dependence as a disease state rather than as a moral or character problem. Twin and adoption studies provide adequate support for the powerful role of inheritance in alcohol or substance disorders (Pickens and Svikis 1991). A parallel may be drawn between substance disorders and other inherited diseases such as hypertension, in which a person has little control over the development of the disorder but is solely responsible for treatment of the disorder. By using this approach in a clinical setting, patients often are able to overcome the common feelings of shame and blame associated with alcohol or drug dependence, accept responsibility for treatment, and adopt a commitment to long-term recovery. The use of medications for the treatment of withdrawal from alcohol or drugs and to assist patients with achieving abstinence may aid in the belief that alcohol or drug dependence is, in fact, a disease (Miller 2001).

TABLE 30–2. Criteria for substance dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) tolerance, as defined by either of the following:
  (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
  (b) markedly diminished effect with continued use of the same amount of the substance

(2) withdrawal, as manifested by either of the following:
  (a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for withdrawal from the specific substances)
  (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

(3) the substance is often taken in larger amounts or over a longer period than was intended

(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use

(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects

(6) important social, occupational, or recreational activities are given up or reduced because of substance use

(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

Specify if:

With physiological dependence: evidence of tolerance or withdrawal (i.e., either Item 1 or 2 is present)

Without physiological dependence: no evidence of tolerance or withdrawal (i.e., neither Item 1 nor 2 is present)

Course specifiers:

Early full remission

Early partial remission

Sustained full remission

Sustained partial remission

On agonist therapy

In a controlled environment

Source. Reprinted from *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision, pp. 197–198. Washington, DC, American Psychiatric Association, 2000. Used with permission. Copyright © 2000 American Psychiatric Association.

Alcohol dependence and drug dependence are independent diagnoses. As independent disorders, each has a characteristic course and predictable consequences. The application of exclusionary criteria for A/DD is required before establishing other psychiatric disorders using DSM-IV-TR (Tamerin and Mendelson 1969).

There is little objective evidence that alcohol or drugs are used to "medicate" or ameliorate a mood state or an underlying or additional psychiatric disorder, including one caused by TBI (Miller and Goldsmith 2001). The preponderance of the studies show that alcohol and drugs cause psychiatric symptoms and worsen already existing symptoms from psychiatric disorders, especially those associated with TBI. Although patients with alcoholism and those with drug addictions report drinking and using drugs because of anxiety and depression, objective and controlled studies fail to confirm the hypothesis that alcohol and drugs are used to improve mood and thinking. The conclusions from many studies are that continued alcohol and drug use results in the appearance and worsening of psychiatric symptoms in proportion to the amount and duration of alcohol and drug use (Mayfield and Allen 1967; Schuckit et al. 1990).

Family history is the best predictor for the onset of alcoholism and drug addiction in a given individual. A positive family history for alcohol and drug disorders can increase the index of suspicion for the presence of an A/DD in a TBI patient. Also family members may have A/DDs that require diagnosis, intervention, and treatment. Untreated family members with an addiction can have an adverse effect on the patient with A/DD and TBI that can interfere with the overall treatment (Cermak 1991; Miller et al. 1990).

Screening tests are available for alcohol disorders that can be modified for drugs by inserting *drug* for the word *alcohol*. The Brief Michigan Alcoholism Screening Test (Brief MAST; a modified version of the Michigan Alcoholism Screening Test; Selzer et al. 1975; Figure 30–1) correlates with the clinical diagnosis of alcoholism. The CAGE questionnaire (Mayfield et al. 1974; Figure 30–2) is also a useful bedside screening test that correlates well with a diagnosis of alcoholism (positive response to one question means probable alcohol dependence). The MAST and the CAGE questionnaire can be self-administered and take only a few minutes to complete. Both correlate highly with the DSM-III-R (American Psychiatric Association 1987) criteria for the substance use disorders, and they are commonly used and well-established screening instruments. Fuller et al. (1994) recommended the CAGE questionnaire or the Brief MAST be administered to any individual who has sustained a TBI. Ashman et al. (2004) recommended the CAGE questionnaire, and the face-valid drug subscale of the Substance Abuse Subtle Screening Inventory–3 (SASSI-3) may be useful in screening for alcohol and drug dependency in those who have suffered a TBI.

In an effort to improve the diagnosis of alcohol and drug disorders within TBI populations, many studies have focused on tools that serve as valid A/DD identifiers in the traumatic, and often, disabled state of patients with brain injuries. Through the combination of blood alcohol levels (BALs), quantity and frequency of alcohol or drug consumption, or both, and the Brief MAST, a comprehensive tool for recognizing substance disorders in TBI patients can be shaped. The partnership of these assessment tools has been effective in a study by Cherner et al. (2001), who examined issues that obscured the measurement of the effects of alcohol in TBI populations. The SASSI-3 and the Addiction Severity Index have also been recommended for the detection of an alcohol or drug disorder, or both, in individuals who have TBIs (Fuller et al. 1994). However, in an assessment of the utility of the SASSI-3 in individuals with TBIs, scores were most accurate when coupled with BALs. The SASSI-3 was found to be extremely sensitive to A/DD in TBI patients, whereas the BAL was more specific (Arenth et al. 2001).

Identification of the neural basis of pathological craving for alcohol and drugs may also serve as a vital tool for diagnosing patients with a substance dependency (Dackis and Miller 2003). Neuroimaging studies have identified limbic system pathways that are responsible for both normal and pathological cravings in human and animal studies. Changes in limbic system pathways have been identified in studies in which human and animal subjects have had chronic exposure to alcohol or drugs. It has been proposed that a change in homeostasis occurs. A new set point, or alleostasis, may be responsible for intense cravings that occur long after "liking" a drug. Structural neuroimaging studies have also revealed alcohol-induced brain atrophy, occurring in both limbic and frontal lobe structures. After a period of abstinence, the degree of atrophy in these regions tends to diminish, especially when abstinence occurs at a younger age. Further research on these issues may someday equip clinicians with an essential tool for the diagnosis and treatment of substance dependency (Netrakom et al. 1999).

Treatment of Alcohol and Drug Withdrawal

The first step in the treatment of A/DD is for the patient to discontinue the active use of alcohol and drugs. During this initial abstinence, the influence of alcohol and drugs on mood, cognition, and behavior, as well as the degree of drug-seeking behavior, can be assessed. A differential diagnosis for coexisting psychiatric disorders can also be assessed longitudinally apart from the effects of alcohol and drug intoxication and dependence (Blankfield 1986; Miller and Mahler 1991).

The principles used in the treatment of withdrawal from alcohol and drugs in addicted patients with TBI are similar to those used in patients without TBI, with some important exceptions. The identification of alcohol and drug intoxication and withdrawal follows the general principles of pharmacological dependence. The use of blood and urine toxicology is important to identify presence and levels of alcohol and drugs for assessment of intoxication and anticipation of withdrawal. The use of vital signs, particularly blood pressure, pulse, and temperature, is critical in determining the presence and severity of the withdrawal state (Miller 1991b).

The medications used in the treatment of withdrawal in TBI can be similar to those used in patients who have

Questions	Circle Correct Answer
1. Do you feel you are a normal drinker? (Normal means that you drink less than or as much as most other people.)	Yes (0) No (2)
2. Do friends or relatives think you are a normal drinker?	Yes (1) No (2)
3. Have you ever attended a meeting of Alcoholics Anonymous (AA)?	Yes (5) No (0)
4. Have you ever lost friends or girlfriends/boyfriends because of drinking?	Yes (2) No (0)
5. Have you ever gotten into trouble at work because of drinking?	Yes (2) No (0)
6. Have you ever neglected your obligations, your family, or your work for two or more days in a row because of drinking?	Yes (2) No (0)
7. Have you ever had delirium tremors (DTs) or severe shaking or heard voices or seen things that weren't there after heavy drinking?	Yes (2) No (0)
8. Have you ever gone to anyone for help about your drinking?	Yes (5) No (0)
9. Have you ever been in a hospital because of drinking?	Yes (5) No (0)
10. Have you ever been arrested for drunk driving or driving after drinking?	Yes (2) No (0)

FIGURE 30–1. Brief Michigan Alcoholism Screening Test (MAST).

Note. If this is used as a self-administered written instrument, the scoring system should not be shown on the form. The scores on the Brief MAST correlate well with the full MAST. A score of 6 or above could identify an alcoholic patient.

Source. Reprinted from Selzer ML, Vinokur A, van Rooijen L: "A Self-Administered Short Michigan Alcoholism Screening Test (SMAST)." *Journal of Studies on Alcohol* 36:117–126, 1975. Copyright by Journal of Studies on Alcohol, Inc., Rutgers Center of Alcohol Studies, New Brunswick, NJ 08903. Used with permission.

1. Have you felt you ought to **C**ut down on your drinking?
2. Have people **A**nnoyed you by criticizing your drinking?
3. Have you ever felt bad or **G**uilty about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves and get rid of a hangover? (**E**ye opener)

Scoring: Two or more positive responses suggest sufficient evidence of alcohol abuse at some point during lifetime to warrant further investigation

FIGURE 30–2. CAGE questionnaire.

Source. Reprinted from Mayfield D, McLeod G, Hall P: "The CAGE Questionnaire: Validation of a New Alcoholism Screening Instrument." *American Journal of Psychiatry* 131:1121–1123, 1974. Used with permission.

only drug or alcohol addiction, or both. However, the doses should be reduced to allow for the increased sensitivity of brain-injured patients to medication and drug effects. Individuals with TBI appear to have reduced tolerance to a wide variety of medications, particularly the sedatives used in treatment of withdrawal and agitation. The optimal level of medications for withdrawal can be assessed in an individual on an as-needed basis according to the clinical status of the patient. The patient's behavioral and vital signs can be assigned parameters for medication treatments (Miller 1991b).

For instance, for detoxification from alcohol, a dose of benzodiazepines can be given for systolic blood pressure greater than 150 mm Hg, diastolic pressure greater than 100 mm Hg, or both. For detoxification from benzodiazepines, a standing schedule can be designed for 2–3 weeks on the basis of estimates of doses taken during chronic use preceding withdrawal. For alcohol withdrawal, benzodiazepines should have a shorter-acting half-life (e.g., lorazepam) to avoid persistent sedation for patients with brain injury. However, for benzodiazepine withdrawal, the intermediate-acting preparations (e.g., diazepam) are preferred to avoid sharp peaks and troughs from short-acting preparations and persistent sedation from long-acting preparations that occur during the taper (Alexander and Perry 1991; Miller and Gold 1989; Miller et al. 1988). Previous research suggests that an important relationship may exist between prescription medications and outcomes for TBI patients with an A/DD. In a study by Chatham-Showalter et al. (1996), brain-injured patients with positive blood alcohol levels tended to be on higher dosages of narcotic medications and benzodiazepines. These individuals were also given medications for longer periods when compared with individuals who did not have positive BALs. Further investigation on the effects of prescription medication on TBI patients with an A/DD is necessary because of the poorer prognosis often associated with individuals in this group.

In general, benzodiazepines are used to treat alcohol withdrawal (Table 30–3) and phenobarbital or benzodiazepines are used to treat sedative-hypnotic withdrawal (see Table 30–3), including withdrawal from benzodiazepines (Table 30–4). For cocaine, other stimulants, and cannabis withdrawal, medications usually are not required. For opiates, either clonidine or methadone can be used in 2-week or 4-week tapering schedules. As stated, other schemes for detoxification can be used, but only in lower doses for the drug-sensitive individual with TBI. Assessment for other drug usage by a patient is indicated through history and clinical examination (Miller 1991b).

Pharmacological interventions must take into consideration possible drug-drug interactions with known and unknown drugs, both illicit and prescription medications. Persistent history taking from the patient and family and drug screens of urine and blood are essential in identifying the influence of alcohol and drugs in the precipitation of the brain injury and possible responses of the patient to pharmacological and behavioral managements. For instance, benzodiazepines may interact acutely with alcohol or other sedatives, or both, to further depress conscious-

ness. On the other hand, acute withdrawal from alcohol that is not adequately treated with benzodiazepines may progress to agitation, delirium, and even death. The combination of clinical assessment and laboratory diagnosis is needed to manage these difficult clinical issues (Miller and Gold 1991).

Complications

Psychiatric Symptoms

The effects of alcohol and drugs on mood and behavior are numerous. In general, alcohol and other depressant drugs can cause depression, suicidal and homicidal thinking during intoxication, anxiety, hyperactivity, hallucinations, and/or delusions during withdrawal. Cocaine and other stimulant drugs can cause anxiety, hallucinations, and delusions during intoxication, and/or depression and suicidal thinking during withdrawal. As a consequence of addictive disorders, individuals can be withdrawn, asocial, antisocial (including violent behavior), hysterical, passive-aggressive, dependent, and/or narcissistic. Often, these personality features diminish after abstinence from alcohol and drugs and specific treatment of the addictive disorder. The aim of treatment of the addictive disorder is to alter attitudes and behaviors that are detrimental to personality (Blankfield 1986; Mayfield 1979; Miller and Mahler 1991; Schuckit 1983). Brenner et al. (2008) found that individuals with a history of problematic alcohol and drug use were at higher risk to be hospitalized following TBI.

Length of Stay

The length of stay in the hospital for the individual with TBI is affected by the presence of alcohol or drugs. The TBI patients who are users of alcohol or drugs have a longer period of hospitalization. Sparadeo and Gill (1989) reported that patients with a negative BAL had an average stay of less than 3 weeks, with only 9.5% staying longer than 3 weeks and a maximum length of stay of 45 days. For patients with a positive BAL, twice as many patients (19.4%) stayed beyond 3 weeks, and the maximum length of stay was 102 days.

Agitation

The incidence of agitation is not significantly greater for patients with a positive BAL; however, the duration of agitation is significantly longer (Brismar et al. 1983). Agitation is a serious complication for recovery from TBI in these patients because it interferes with nursing care, physical therapy, occupational therapy, speech therapy, and medical and surgical intervention. Importantly, families and staff are generally disturbed by agitated patients (Sparadeo and Gill 1989; Substance Abuse Task Force 1988).

Cognitive Status

Of considerable interest is that individuals who were intoxicated before brain injury have lower global cognitive scores at the time of discharge than do those who were not intoxicated. One could speculate that the trauma is more significant in those who are compromised by alcohol and drugs through a number of mechanisms. There is significantly and persistently reduced intellectual function in alcohol- and drug-addicted patients who use alcohol and drugs on a regular basis over time (Tarter and Edwards 1985).

TABLE 30–3. Drug doses equivalent to 600 mg of secobarbital and 60 mg of diazepam

Drug (by class)	Dose (mg)
Benzodiazepines	
Alprazolam	6
Chlordiazepoxide	150
Clonazepam	24
Clorazepate	90
Flurazepam	90
Halazepam	240
Lorazepam	12
Oxazepam	60
Prazepam	60
Temazepam	90
Barbiturates	
Amobarbital	600
Butabarbital	600
Butalbital	600
Pentobarbital	600
Phenobarbital	180
Secobarbital	600
Glycerol	
Meprobamate	2,400
Piperidinedione	
Glutethimide	1,500
Quinazoline	
Methaqualone	1,800

Note. For patients receiving multiple drugs, each drug should be converted to its diazepam or secobarbital equivalent.

Intellectual deficits in A/DD populations appear to be in large measure reversible in those patients without known brain trauma, and IQs improve with abstinence over time. The improvement in memory, abstraction, calculations, and other cognitive abilities occurs rapidly in the first 3–6 months of abstinence from alcohol and more gradually thereafter. Studies have shown improvement in intellect continuing at 2 years of abstinence, and clinical experience suggests that improvement continues beyond this initial period (Chelune and Parker 1981; Parsons and Leber 1981). There is usually some loss of intellectual functioning in TBI. Cognitive deficits are commonly seen in attention and concentration, short-term memory, and speed of processing information. There are often significant impediments to long-term recovery from TBI (Sparadeo and Gill 1989).

The effects of TBI and alcohol and drug abuse may be additive. Baguley and colleagues (1997) compared heavy

TABLE 30–4. Signs and symptoms of benzodiazepine withdrawal

Symptoms of hyperexcitability
Agitation
Anxiety
Hyperactivity
Insomnia
Neuropsychiatric symptoms
Ataxia
Depersonalization
Depression
Fasciculation
Formication
Headache
Hyperventilation
Malaise
Myalgia
Paranoid delusions
Paresthesia
Pruritus
Tinnitus
Tremor
Visual hallucinations
Gastrointestinal symptoms
Abdominal pain
Constipation
Diarrhea
Nausea
Vomiting
Cardiovascular symptoms
Chest pain
Flushing
Palpitations
Genitourinary symptoms
Incontinence
Loss of libido
Urinary urgency, frequency

social drinkers, individuals with a TBI who did not drink heavily, and a group with a history of both a TBI and heavy social drinking. Significantly more cognitive impairments were observed in those with a TBI who were also heavy social drinkers compared with the other two groups. Kelly et al. (1997) found that full-scale IQ and verbal IQ scores were significantly lower in participants who screened positive for alcohol consumption or dependence, or both, at the time of TBI compared with those injured who screened negative for alcohol and compared with healthy control subjects.

Barnfield and Leathem (1998) studied New Zealand prison inmates and found high rates of substance disorders, TBIs, and recurrent TBIs. Furthermore, greater cognitive impairment was found in those individuals experiencing both an A/DD and a TBI. Similarly, individuals with a TBI who tested positive for cocaine on hospital admission showed significantly lower scores on the Rey Auditory Verbal Learning Test than those with TBI testing negative for cocaine (Barnfield and Leathem 1998).

Neuropathological Effects

The partnership of alcohol and TBI has been shown in numerous studies to cause measurable neuropathology in the brains of both human and animal models. In quantitative magnetic resonance imaging comparisons, patients experiencing a combination of both TBI and substance dependence exhibited greater atrophic changes when compared with individuals with either a TBI or an A/DD and healthy control subjects. TBI and A/DD groups also had significantly lower scores on the Glasgow Coma Scale when compared with TBI patients without A/DDs and healthy control subjects (Bigler et al. 1996). In animal studies, ethanol exposure at the time of brain injury has been shown to cause severe respiratory depression; this increase in postinjury apnea may lead to further injury or even death (Zink and Feustel 1995; Zink et al. 1993). The presence of ethanol intoxication at the time of brain trauma may potentiate responses both physiologically and metabolically that could play a causal role in secondary brain injury (Zink et al. 1998).

Hemodynamic depression, blood-brain barrier disruption, and derangements in homeostasis are some additional effects of intoxication at the time of brain injury. Upregulation of *N*-methyl-D-aspartate and downregulation of γ-aminobutyric acid receptor function may also arise because of chronic exposure to alcohol. Many factors, however, dictate the outcome of ethanol and brain trauma; proximity of intoxication to the time of injury, degree of use, and the effects of other injuries all may play a mediating role (Kelly 1995).

Economic Effect

A positive BAL is associated with higher costs for medical care. Longer length of stay, increased agitation, higher intensity and level of care, complications of treatment for TBI, and increased morbidity from alcohol and drug effects lead to greater expense in caring for alcohol- and drug-addicted or drug-using patients. Early identification and treatment of alcohol and drug problems can reduce expenses and allow greater numbers of patients to be treated (Miller and Ries 1991; Sparadeo and Gill 1989; Substance Abuse Task Force 1988).

Intermediate and Long-Term Treatment

Principles

Generally, the most widely used treatment for A/DD employs the 12-step approach, which considers addiction to be an independent disorder. This approach includes principles of

TABLE 30–5. Resources for treatment of addictive disorders

Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) and similar groups
Support groups patterned after AA and NA
Individual, group, and family alcohol and drug counseling
Outpatient and inpatient alcohol and drug treatment programs
Environmental control and behavior modification
Psychopharmacology

TABLE 30–6. Techniques for therapy of traumatic brain injury (TBI)

People with TBI may digress or change course during conversation.

1. Redirect them using appropriate cues and reinforcers.
2. Teach prevention skills to the person with TBI that can be used in more than one life setting to maximize generalizability.
3. Focus on a specific prevention goal.
4. Be redundant.
5. Never assume understanding or memory from previous session.
6. Always repeat the purpose, duration, and guidelines for each meeting.
7. Summarize previous progress and then restate where the previous meeting left off (Sparadeo et al. 1990).

TABLE 30–7. Comparative effects of brain injury and drugs/alcohol

Possible effects of brain injury	Pharmacological effects of drugs/alcohol
Poor memory	Poor memory
Impaired judgment	Impaired judgment
Fine and gross motor impairments	Fine and gross motor impairments
Poor concentration	Poor concentration
Decreased impulse control	Decreased impulse control
Impaired language skills	Impaired language skills

recovery derived from Alcoholics Anonymous (AA), cognitive-behavioral therapies, group and individual modalities, and long-term management of the addictive disorders in AA or Narcotics Anonymous (NA; Table 30–5). The results of treatment outcome studies indicate that the 12-step method is an effective form of treatment for A/DD (Harrison et al. 1991). Overall abstinence rates for 1 year were 68% in 1,663 outpatients and 60% in 8,087 inpatients in a study derived from 35 different treatment sites (Hoffman and Miller 1992). The abstinence rates increased to 82% and 75%, respectively, with regular attendance at AA. Effective treatment strategies for chemical dependency in TBI populations should focus on behavioral, cognitive, and gestalt issues. The supportive network of AA and NA offer therapy on all of these levels (Kramer and Hoisington 1992).

In a study of 9,750 patients, motor vehicle accidents and moving traffic violations were significantly reduced in patients who received treatment for alcohol or drug addiction, or both, when rates before and after the treatment of the addictive disorder were compared. Of further interest is that the use of medical and psychiatric services dropped significantly and job performance improved significantly in those who received addiction treatment.

Experience in applying these treatment techniques to individuals with TBI is limited. Novel programs tailored to the needs of these individuals are being used, although clinical success awaits documentation in outcome studies. Attempts are under way to integrate standard care for TBI patients (see Table 30–6) with standard treatment for addictive disorders (McLaughlin and Shaffer 1985; Miller and Mahler 1991; Substance Abuse Task Force 1988; Tobis et al. 1982).

Clinical experience suggests that individuals with TBI have specific persistent problems that may interfere with participating with other patients without TBI in mainstream programs (Jong et al. 1999). The major difference is that the pharmacological effects from alcohol and drugs are reversible, whereas the effects from brain injury may not be totally reversible (Table 30–7).

It is imperative to achieve and maintain progress in addiction treatment to gauge any success in the treatment of the neuropsychiatric deficits from trauma. Basic principles used in working clinically with brain-injured individuals can be used in their addiction treatment as well. Individuals with TBI require concrete and structured programs that are tailored to their mental capacities. The addiction therapist must be knowledgeable in the assets and liabilities of individuals with brain injury and skilled in applying traditional addiction treatment to their specific needs. Physicians, including psychiatrists and other therapists, must be knowledgeable in the priority of alcohol and drugs in the life of addicted patients and skilled in referring and collaborating with the addiction treatment team to provide a consistent, cogent, and effective treatment plan.

Research suggests that there is usually a window of opportunity for assisting those with a substance disorder to stop the abuse immediately after a TBI. Readiness to change in this time frame could prove useful if substance dependence is identified at the time of injury and treated appropriately (Bombardier et al. 1997). Wehman et al. (2000) proposed another form of assistance for young adult men, the group displaying the highest risk for the duality of TBI and substance use disorders. Because of high rates of unemployment in young adult men with a history of both TBI and A/DD, the authors suggested a supported employment approach to assist these individuals on reentry into the workforce. This program may help alleviate frustrations in TBI and A/DD populations and assist in the transition toward a more normal lifestyle.

Treatment Strategy and Process

The following sections illustrate a program that provides a therapeutic milieu for the brain-injured patient to learn about and discuss his or her alcohol and drug problems.

Abstinence

The overall aim is for the individual with TBI to achieve and maintain abstinence from alcohol and drugs. The common denominator for recovery for alcohol- or drug-addicted individuals is loss of control over alcohol and drugs. The focus of treatment should be on abstaining from alcohol and drugs of addiction and what changes the patient must make to accomplish this goal. The process begins by admitting and optimally accepting that the use of alcohol and drugs results in adverse consequences to the individual. The success in maintaining abstinence by the addicted individual will be limited without the fundamental recognition by the therapist of the psychopathological processes in addictive use of drugs. The therapist must collaborate in the goals with the patient and be prepared to clarify for the patient the importance of abstinence from alcohol and drugs to recover from both addiction and TBI. At times, supportive confrontation may be necessary to dispel the denial inherent in the addictive process (Miller 1991a; Roman 1982; Vaillant 1983).

Confrontation of Denial

Denial is a major feature of the psychopathology of addictive disorders. Denial is both conscious and unconscious and appears to originate from multiple sources. The denial system stems in part from the pharmacological (organic) effects of alcohol and drugs and in many ways is indistinguishable from a dementia syndrome from other causes. The pharmacological effects of alcohol and drugs include impairment in judgment, insight, planning, and motivation, functions that are subserved by the frontal lobe. The result is a poorly motivated, addicted individual with little insight and judgment with regard to therapeutic intervention. The temporal lobes are also affected by alcohol and drugs such that short-term memory and the acquisition of memory for new events are impaired, resulting in faulty recall of associations between alcohol and drug use and the adverse consequences. Pharmacological disruption of the temporal lobe also leads to distortions in thinking and emotions that further augment the denial associated with continued substance use (Blanchard 1984).

The denial can be effectively confronted using the evidence of the adverse consequences from addictive use of alcohol and drugs. The associations can be made for the patient by the therapist in the concrete manner that is already used in the approach to the individual with TBI. The therapist is advised to remain in the "here and now" and concentrate on what must be done for the patient to abstain from alcohol and drugs. It is counterproductive to dwell on antecedent causes that are ultimately not directly related to the addictive use of alcohol and drugs. The addiction to alcohol and drugs is an independent and autonomous condition that is not generated by other causes. This is a crucial concept that must be incorporated into successful addiction treatment. Otherwise, distraction away from the central problem of addiction to other problems that are unrelated or secondary to the addiction will prevent the addicted patient from focusing on the addictive use of alcohol and drugs (Miller and Mahler 1991; Stead and Viders 1979).

The timing and method of confrontation about deficits, including alcohol and other drug problems, should be carefully coordinated with the interdisciplinary TBI treatment team. Educational points should be presented in the most effective cognitive and sensory mode. This information is best obtained from a TBI team member knowledgeable in cognitive deficits (Kreutzer et al. 1990).

Group Therapy

In group therapy, the primary treatment intervention is performed in a group setting in which confrontation of denial and induction of acceptance of the individual's addiction are best accomplished. The group consists of peers who also have addiction(s) and brain injury and is led by professionals who are skilled in addiction therapy. The focus of the group is on the loss of control of alcohol and drug use and the attendant adverse consequences. Group members share their experience, strength, and hope with each other in a supportively confrontational atmosphere (Langley 1991; Miller and Mahler 1991).

The group should have a prescribed structure and format that are facilitated by the therapist and actively used by the patients. Group members generally speak one at a time, with limited cross-talk when patients "advise" other patients. Individuals are encouraged to speak from their own experiences and show how these may benefit others. The identification of one patient with another is central to the therapeutic process. The identification between individuals with both addiction and TBI is conducive to dissipating the destructive denial and to initiating constructive therapeutic changes. The shame, guilt, and hopelessness associated with addiction and TBI can be replaced through the mutual care and consideration of one individual toward another. There are no good studies illustrating the interactions between group members that produce the dramatic cohesion that can occur within the group. Thus far, it has been impossible to explain how individuals with severe addiction and mental problems work together to produce this therapeutic milieu.

The clinical experience in this type of group process has been predominantly in addiction treatment. However, preliminary experience suggests that group therapy can be adapted to those who also have TBI. Special techniques that are commonly used in people with brain injury can be applied in addiction groups. The psychological approach to the person with brain injury shares commonalities with that used for the addiction patient. Techniques such as keeping it simple, focused, and concrete are useful in both populations. Being directive and supportive are also useful in treatment of individuals with addiction and TBI (Sparadeo et al. 1990).

Cost-effective treatment options for individuals with TBI and a substance use disorder have been proposed by Delmonico et al. (1998). The authors suggested group psychotherapy to help manage the frustration, poor impulse control, depression, anxiety, and many other common symptoms associated with TBI and A/DD. The average financial status of individuals with TBI and an A/DD requires a form of therapy that is affordable and long term. This psychotherapeutic group approach addresses preexisting coping skill deficits and psychological conditions while requiring minimal subsidy.

Corrigan et al. (1995) recommended community-based intervention for substance dependence in persons with TBI. By combining a staff of individuals experienced in both TBI treatment and substance disorder therapy, a cost-effective program can be implemented. Community teams should treat patients on the basis of a theoretical model of changing addictive behaviors through community integration.

Treatment strategies that are both affordable and successful at bringing about recovery for substance dependents are imperative. Survival rates of persons with a substance dependency can be greatly improved through obtaining abstinence or complete recovery. Persons who do not achieve continual abstinence are at a much higher risk of mortality. Whether treatment is by means of group therapy, psychotherapy, community intervention, or some other form, all programs should focus on abstinence, which has been proven essential to the long-term health of those with a substance use disorder (Miller 1999).

Treatment Setting

The addiction-focused groups can be adjunctive in milieus that treat people with TBI. The addiction groups can be combined with the other therapies as an integral part of the overall therapy of those with TBI. Because more than 50% of individuals with TBI are likely to also have alcohol and drug addiction, the addiction groups can be incorporated as an essential therapeutic component for many patients in a given setting. Although it is not necessary for all members of the treatment staff to be skilled in addiction treatment, it is desirable that they have minimum knowledge regarding the nature of the illness and its effect on recovery from TBI. For instance, physicians and nurses must be able to identify drug seeking and differentiate it from other medical and psychiatric problems. In this way, addiction can be confronted and treated, and iatrogenic participation in addictive use of drugs can be minimized in the clinical care of these patients (Minkoff 1989).

All interventions should be directive in nature, short term, goal directed, and behaviorally anchored. The effects of severe brain injuries are typically so devastating to the family system that many family members "leave the field" when they come to appreciate what has occurred. Social isolation is common for people with TBI. The family system must be assessed and reassessed because it will fluctuate markedly in the first 4 years after TBI. The clinician should accentuate positive gains by using frequent social praise (Sparadeo et al. 1990).

Duration of Treatment

The duration of the addiction groups can be extended over time in a graduated fashion. The first month may have three 1-hour groups per week, on a Monday-Wednesday-Friday schedule. The remaining months may have one group per week in the setting, particularly if there is a prolonged stay. Also, it is important that the individuals attend AA or NA meetings, either in the treatment setting or in the community. The service structure of AA offers assistance with holding meetings in institutions through the Cooperation With Professionals Committee. Also, some AA and NA meetings in the community are oriented toward having individuals attend on a regular basis (Chappel 1993) (see Appendices 30–1, 30–2, and 30–3 in this chapter).

Generally, it is recommended that a patient with alcoholism and drug addiction undergo continuous treatment indefinitely. Both of these are chronic illnesses that can be characterized by a relapsing course in the untreated state. The relapse rate is highest in the first 3–6 months after cessation of alcohol and drug use, with up to 80% of individuals returning to alcohol and drug addiction in the untreated state. With treatment intervention, the abstinence rate can be increased to 70%–80% and higher with attendance at AA or NA meetings (Hoffman and Miller 1992). Abstinence rates are unknown for addicted individuals with TBI in long-term recovery.

Hoffman and Miller's (1992) treatment outcome study, as well as others in noninjured addicted individuals, further demonstrates improved cognition, emotional status, and attitudes toward self and others. The interpersonal relationships and responsibility toward self and others are improved in those with alcohol and drug addiction who continue in a sustained recovery program that includes attendance at aftercare for addiction treatment and AA. Personal responsibility is the cornerstone in recovery from addictive diseases (Alcoholics Anonymous 1976).

In a study by Miller et al. (1999), continuation in a sustained recovery program was a better predictor of posttreatment outcomes than lifetime depression or other pretreatment, clinical, or demographic variables. In fact, patients with a history of depression were more likely to be active in outpatient treatment and peer support groups when compared with patients with substance dependence without a history of depression. One-year abstinence rates overall were 61% for patients taking part in outpatient treatment, 62% for patients without prior history of depression, and 60% for patients with a history of depression, thus indicating that abstinence rates were not significantly affected by depressive histories. Therapeutic interventions should focus on these findings when assessing plans for recovery.

Use of Medications in the Recovered Alcoholic or Addicted Patient With TBI

Studies do not find that standard psychiatric pharmacological and nonpharmacological treatments for depression and anxiety occurring in the setting of addiction are efficacious in reducing either the depression or the anxiety associated with addiction (Miller 2003). DSM-IV-TR (American Psychiatric Association 2000) requires exclusion of substance-induced disorders even before diagnosis or treatment. Antidepressants, antianxiety agents, and psychotherapy do not relieve the depression and anxiety induced by alcoholism or drug addiction or influence the overall course of the addictive use of alcohol and drugs. The same findings hold for other psychiatric disorders. Hallucinations and delusions induced by the addictive use of alcohol and drugs do not respond to conventional psychiatric pharmacological or nonpharmacological ther-

apies, especially if the use of alcohol and drugs continues (Miller 1991b; Schuckit 1990).

Studies do confirm that specific treatment of the addictive disorders alleviates the addictive use of alcohol and drugs and the consequent psychiatric comorbidity. A period of observation of days to weeks may be necessary to examine important causal links in the genesis of psychiatric symptoms from addictive disorders and to establish independent psychiatric disorders (Miller 1991b; Tamerin and Mendelson 1969).

Most psychotropic medications can be used to treat independent psychiatric disorders in alcohol- and drug-addicted individuals with a TBI. Beyond the detoxifying period in the abstinent state, there is little evidence that the psychiatric disorders in those individuals with addictive disorders respond differently to most psychotropic medications. The caveat is that because of the addiction potential, alcoholic or addicted individuals are more likely to overuse and lose control of virtually any medications compared with individuals who are not addicted, particularly those medications with already established addictive potential (Miller 1991b).

The dose of psychotropic medications should be reduced because individuals with brain injury commonly show heightened sensitivity to both stimulants and depressants. The selection of medications can be similar to those for other psychiatric disorders, including diffuse brain damage from other causes. Miller (1991b) suggested the guiding principle of aiming for the lowest doses to reduce untoward effects while maximizing therapeutic efficacy.

The physician views medications as powerful and inherently good despite the potential for toxicity. Some psychiatrists do not view themselves as physicians or minimize their role as doctors if they do not prescribe medications for a clinical disorder. Moreover, clinicians skilled in the treatment of addictive disorders advocate that the patient who is addicted to alcohol or drugs needs a clear sensorium and access to feelings to make fundamental changes in attitudes and behaviors for continued abstinence. Medications may impair cognition and blunt feelings, albeit sometimes in a subtle way. A parallel illustration is the crucial point stressed by psychotherapists who advise judicious use of mood-altering chemicals that might interfere with the process of psychotherapy. This is a clinical caveat that pertains to the person with TBI as well (Miller 1991b).

The person with alcohol or drug addiction and TBI must take an active initiative in changing attitudes and feelings and must abandon the long-held belief that alcohol, drugs, or both can "fix" or "treat" life problems and uncomfortable psychological states during recovery. Clinically acknowledged, anxiety and depression can be motivating feelings to change without which the patient has little awareness of the need to change. A commonly used expression to explain this practice among recovering individuals is "no pain, no gain." The aim of pharmacotherapy to suppress symptoms such as anxiety and depression in the recovering addicted patient must take into consideration that these symptoms may be vital to the recovery and survival of the patient with alcohol or drug addiction. Enormous misunderstanding has arisen between physicians and patients with addiction and TBI because of a divergence in purpose and perspective toward medications and the lack of knowledge and skill in both (Miller 1991b).

There are several pharmaceutical agents specifically approved to manage alcohol dependence. They comprise two categories: anticraving medications and aversion medications. The anticraving medications include naltrexone and acamprosate. These are both opioid agonists and are noted to decrease the intoxicating effects of alcohol and reduce the urge to drink. Disulfiram is an aversion medication. It interacts with alcohol and causes multiple distressing side effects, including nausea, vomiting, headache, and flushing. All of these pharmaceutical interventions are noted to be more effective when coupled with a 12-step program.

The current standard of care for addictive disorders is nonpharmacological beyond the detoxification period. Several studies have shown that treatment of the addictive disorder with abstinence alone results in improvement in the psychiatric syndromes associated with alcohol and drug use or addiction. Severe depressive and anxiety syndromes induced by alcohol resolve within days to weeks after the onset of abstinence. Manic syndromes induced by cocaine resolve within hours to days, and schizophrenic syndromes with hallucinations and delusions resolve within days to weeks with abstinence as well (Mayfield and Allen 1967; Schuckit 1990).

Additional studies are needed to confirm the clinical experience that psychiatric symptoms, including anxiety, depression, and personality disorders, respond to the specific treatment of addiction. The cognitive-behavioral techniques used in the 12-step-based treatment approach have been shown to be effective in the management of anxiety and depression associated with addiction (Miller 1991c).

Long-Term Recovery in Alcoholics Anonymous

Available data demonstrate abstinence rates from alcohol and other drugs, including cocaine, of 60%–80% after 2 years in both alcohol- and drug-addicted individuals who are in treatment programs on the basis of a 12-step approach with referrals to AA. Surveys also show recovery rates with continuous abstinence of 44% at 1 year, 83% between 1 and 5 years, and 90% at longer than 5 years with membership and attendance at meetings in AA (44% of alcoholic individuals in AA are also addicted to drugs; see Appendices 30–1 and 30–2). A controlled study by Keso and Salaspuro (1990) revealed that the best treatment outcome is obtained when professional treatment and AA are combined. Studies are not yet available that examine the efficacy of psychiatric treatments in enhancing treatment outcome in addicted patients with psychiatric comorbidity, including TBI (Chappel 1993; Group for the Advancement of Psychiatry 1991; Schulz 1991; see Appendices 30–1 through 30–3).

Conclusion

Alcohol and drug use disorders are a major risk factor for TBI. The coexistence of TBI with A/DD requires concurrent treatment of both disorders. If only one condition is the focus of the treatment, incomplete treatment and poor prognosis are the likely outcomes for both conditions. A/DD complicates the treatment of TBI, and vice versa. Clinicians working with individuals who have acute or chronic sequelae of TBI must be knowledgeable and skilled in the identification of A/DD whenever it exists in combination with TBI. Because of the interplay between TBI and A/DD throughout the clinical course, clinicians must develop treatment strategies that recognize the independence of and interaction between the two categories of disorders. Such strategies must include early identification, family intervention, and the use of group, family, and individual therapies in combination with judicious psychopharmacological approaches.

KEY CLINICAL POINTS

- Alcohol and drug use are common causes of traumatic brain injury (TBI). Alcohol and drug dependence are common sources of this use and carry a high risk for TBI.
- Prevention of TBI in substance users involves early detection of alcohol and drug dependence and referral for treatment.
- Prescription medications are drugs associated with TBI.
- Individuals with TBI who continue to use alcohol and drugs (including prescription medications) respond to, and should be referred to, addiction treatment and 12-step programs.

Recommended Readings

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Appendix 30–1

Letter to Alcoholics Anonymous Sponsor of Member With Traumatic Brain Injury

The following is a letter to an Alcoholics Anonymous (AA) sponsor explaining the special characteristics of the alcohol- or drug-addicted individual with brain damage. A sponsor in AA (or Narcotics Anonymous [NA]) is someone who also is an alcoholic- or drug-addicted individual in recovery who assists the sponsoree in learning about the AA or NA program and "working" the steps of AA or NA (Henry 1988).

Dear Sponsor:

As a 12-stepper in AA or NA, you know fully well the horror chemical dependency thrusts into a person's life. Without concerted and persistent effort toward recovery, personal, family, and social dimensions of life are deeply threatened and treacherously undermined. In the case of the person you are now sponsoring or are considering whether to sponsor, the addiction has been further compounded by a head injury that has, to some degree, caused damage to the brain. Because of this damage, the very physiological organ responsible for memory, language, reasoning, judgment, and behavior (among other skills and abilities) has been compromised. Consequently, problems have emerged that are a direct result of the trauma to the brain, and these problems now are inevitably overlapping and interacting with the individual's addictive nature.

At this stage in his or her recovery from the trauma, the individual with whom you are working has undoubtedly regained many of those diminished abilities. However, in all probability, there are lasting effects ("sequelae," in medical terminology) that remain and that you may now be witnessing. These residual problems may be manifested in obvious or subtle ways, and an explanation of their nature may be helpful.

The purpose of this letter is to acquaint you with some of the more common cognitive (i.e., having to do with perceiving, organizing, interpreting, and acting on information) and emotional problems that head-injured people face as a direct result of brain trauma. With a good medical recovery it is not at all unusual for these individuals to appear unimpaired unless one takes a close look, and your work as a sponsor certainly will require close interaction. These comments, then, are offered in a spirit of gratitude for your help to this person who must now come to grips with himself on several levels; who must now, en route to recovery from addiction, untangle a complex knot of problems, including the changing pretraumatic lifestyle, while dealing with the confusion and psychological pain that recently shattered cognition brings.

The human brain has specific sections that specialize in specific functions. If damage to any of these areas is severe enough, those functions—as well as higher level ones that they support—may be lastingly limited. Many of these regions of the brain interface to enable the performance of complex skills such as reading, or remembering and following through on lengthy directions. Because the brain's functioning is so dependent on the interrelationship of parts, and because any of those parts may be hurt in a trauma, many sorts of problems can result. The more prominent and frequently occurring ones, discussed in cognitive and emotional areas, are as follows:

Cognitive

Attention

This includes maintaining attention for normal periods and the ability to shift attention to different areas after concentrating on one set of ideas. Also included here are difficulties screening out distractions (voices, noises, and visual things) in the environment, as well as suppressing one's own preoccupations while there is other work to be done.

Suggestions: Settle for smaller amounts of quality time rather than attempting longer amounts that may prove too fatiguing to the sponsoree. Cue him when he seems stuck in prior topics (e.g., "We're talking about now . . .") or when he seems to have drifted away ("Tune back in now, okay . . ."). Gradually lengthen the time of expected attention and concentration as increasing abilities permit.

Appendices reprinted courtesy of the National Head Injury Foundation (Substance Abuse Task Force: "White Paper." Washington, DC, National Head Injury Foundation, 1988, pp 53–59).

Memory

The most common type of deficit resulting from brain injury is of short-term memory. This appears as difficulty holding onto several pieces of information while having also to think through each item (e.g., cooking while also staying mindful of the children's nearby play). Other common problems are in remembering to follow through on assigned tasks at specified times and in remembering recent experiences and conversations. Fortunately, memory for pretraumatic episodes are most often unimpaired by this time in the person's medical recovery.

Suggestions: Expect the person to use journals and date books—and to review them frequently and independently—to cue himself about past and future events. If such memory aids are necessary, consider this simply another component of the program to be worked; do not shy from expecting self-responsibility. If the person is overloaded by doing two or more things simultaneously, encourage him to prioritize tasks and work out a time management schedule honoring that limitation.

Language

Both ability to understand others and to express one's own ideas clearly are often affected. In both cases, a slower speed of processing language is at play. Also, delays in recalling the words needed to articulate a thought are common. When speaking, the head-injured person may ramble and talk in a disorganized, circular kind of way, often failing to come to the point or himself losing it in the details of the conversation.

Suggestions: Encourage the person to ask questions and request clarification of information whenever needed to compensate for a slower rate of comprehension. For situations in which it is appropriate, encourage the head-injured person also to ask speakers to slow down, to repeat points, and to explain ideas in different words. Support may be required to downplay feelings of embarrassment to do these things. As a speaker, the sponsoree may need cues to see the need for making his point more clearly, simply, or briefly; working out a system for your providing such cues that you both feel comfortable with might be useful. As a general rule, encourage him to take time to think about what he wants to say, to plan how to say it, and to be unrushed in finding the words he needs.

Reasoning and Judgment

Basic skills such as cause-effect reasoning and/or the ability to make inferences are often reduced. Thinking may be excessively concrete, giving rise to confusion and misinterpretation of others' remarks (e.g., "Come off your high horse…"). Similarly, problem-solving skills are often marred by impulsive decision making, difficulty in considering several solutions to problems and in envisioning potential consequences of actions. Failure to note voice or facial cues of others that convey nonverbal messages also increases the chance of inappropriate remarks. Common, too, are related problems in inhibiting inappropriate behavior, determining what situations require which behaviors, and reflecting on the propriety of what he has just said or done.

Suggestions: As an overall rule, do not avoid openly addressing the issues raised by the above-mentioned behaviors or misunderstandings. Apply the very same gentle but firm advice-giving anyone working in a recovery program may require. It may be helpful to point out specific incidences as examples of behaviors that need to be avoided, or situations from which one can learn to "think first before saying or doing something." As you would with anyone looking to you for help, follow your good instincts to provide support in the amount, kind, and frequency that leads this particular person with this particular personality to the best levels of independence he can achieve.

Executive Functions

Executive functions refer to those abilities to initiate, organize, direct, monitor, and evaluate oneself. Self-insight is a crucial component. Owing to the very high-level nature of these skills and to the vulnerability of the part of the brain responsible for their operation, they are frequently impaired in the person who has suffered a head trauma. As a result, even with other skills and abilities intact, the use of these executive functions in a directed, purposeful manner may be lacking, making the overall picture of brain operations rather like a full-member, competent orchestra without a conductor to organize and lead their many mixing harmonies; or, like a ready and able work crew without a foreman to coordinate and direct their labor.

Suggestions: If impairments in executive functions are apparent in the person you sponsor, it may well become especially important for you to assume a role of guiding some of these operations within the context in which you work together. To an extent, you would do this anyway; it is a large part of sponsorship. For a head-injured person, however, the need for such help may be deeper and more substantial. Your skills as a conductor, or foreman, may be particularly required. A little more firmly offered advice in decision making, for example—or better perhaps, encouragement to make one's own sound decisions with you available to monitor, affirm, give feedback, and gently correct when necessary. As noted earlier, in most cases it would be perfectly okay to talk openly about the need for your help in this regard because of the limitations imposed by the head injury. But be careful, of course, not to foster unnecessary dependence; increased well-being through healthy, clear-minded independence is always, as you know, the ultimate goal.

Emotional

There is an array of emotional problems typically related to head injury. These include irritability, poor frustration tolerance, dependence on others, insensitivity, lack of awareness of one's affect on others, and heightened emotionality. There may be tendencies toward overreaction to stressful situations, some paranoia, depression, withdrawal, or denial of problems. No single head-injured person evidences all of these problems, of course, and most would show only subtle signals of some of these psychosocial difficulties. They are mentioned, however, to familiarize you with some of the emotional problems that often accompany brain trauma, and to alert you to their similar-

ity to those characteristics of many persons with histories of alcohol and drug addiction.

Suggestions: In your sponsoring of a head-injured person who may exhibit some of the above problems, the art of playing issues straight is recommended. Your sponsoree should know what problems you see impeding his progress toward greater recovery. Because his well-being is the goal, your responsibility is as it would be with any other such partnership. Tactful but clear identification of problems, complete with acceptance of them as risks to continued sobriety or clean time that will necessitate work, is an appropriate attitude to adopt. Whether these sorts of problems are attributable to an addictive personality, or to the head injury, or to both, open, honest acknowledgment of the work to be done and the support needed to do it is what recovery is all about. The sponsorship concept, moreover, is a very plausible means of addressing those sorts of problems.

Please also be aware that there are three main avenues of assistance further available to you.

If the person with whom you work has received treatment from a rehabilitation center specializing in brain trauma, do not hesitate to contact the staff for advice. They may be aware of approaches or strategies that work well with your individual.

For materials on brain injury and chemical dependency, contact the Brain Injury Association of America, 105 North Alfred Street, Alexandria, VA 22314 (www.biausa.org/Pages/home.html).

You are one of the main supports of the recovering chemically dependent, head-injured person. You deserve great thanks. The comments in this letter are not meant to frighten or dissuade you from sponsorship, but rather to provide you with basic information with which to enhance your preparedness and diffuse any unnecessary anxieties you may feel. Trust yourself in your work; your status as a 12-stepper well respected for your patience, intelligence, and straightforwardness. The recovering head-injured person receiving your help is fortunate to have you in his corner.

Kurt Vonnegut wrote that "Detours are dancing lessons from God." You understand chemical dependency and recovery. Confronting a major life obstacle, you have learned to dance. Your sponsorship of the head-injured person with whom you are beginning involvement represents help for someone whose life has been shattered in a particularly devastating way, whose detour is indeed formidable. May your help in teaching that person to dance be gratifying, and blessed, and an occasion for joy and learning for you both.

Reference

Henry K: A letter to sponsors of chemically dependent head injured persons, in Task Force on Chemical Dependency. Southborough, MA, National Head Injury Foundation, 1988, pp 53–57

Appendix 30–2

Original Twelve Steps of Alcoholics Anonymous

1. We admitted we were powerless over alcohol; that our lives had become unmanageable.
2. Came to believe that a Power greater than ourselves could restore us to sanity.
3. Made a decision to turn our will and our lives over to the care of God as we understood Him.
4. Made a searching and fearless moral inventory of ourselves.
5. Admitted to God, to ourselves, and to another human being the exact nature of our wrongs.
6. Were entirely ready to have God remove all these defects of character.
7. Humbly asked Him to remove our shortcomings.
8. Made a list of all persons we had harmed and became willing to make amends to them all.
9. Made direct amends to such people wherever possible, except when to do so would injure them or others.
10. Continued to take personal inventory and when we were wrong, promptly admitted it.
11. Sought through prayer and meditation to improve our conscious contact with God as we understood Him, praying only for knowledge of His will for us and the power to carry that out.
12. Having had a spiritual awakening as the result of these steps, we tried to carry this message to alcoholics and to practice these principles in all our affairs.

Appendix 30–3

Traumatic Brain Injury Explanation of the Twelve Steps

The following are the 12 steps of Alcoholics Anonymous that have been written for the traumatic brain injury (TBI) patient who has cognitive and mood disturbances. These steps can be understood by those who need concrete examples for understanding and using the 12 steps in the recovery program for the TBI patient.

1. Admit that if you drink and/or use drugs your life will be out of control. Admit that the use of substances after having had a TBI will make your life unmanageable.
2. You start to believe that someone can help you put your life in order. This someone could be God, an Alcoholics Anonymous group, counselor, sponsor, etc.
3. You decide to get help from others or from God. You open yourself up.
4. You will make a complete list of the negative behaviors in your past and current behavior problems. You will also make a list of your positive behaviors.
5. Meet with someone you trust and discuss what you wrote in step 4.
6. Become ready to sincerely try to change your negative behaviors.
7. Ask God for the strength to be a responsible person with responsible behaviors.
8. Make a list of people your negative behaviors have affected. Be ready to apologize or make things right with them.
9. Contact these people. Apologize or make things right.
10. Continue to check yourself and your behaviors daily. Correct negative behaviors and improve them. If you hurt another person, apologize and make corrections.
11. Stop and think about how you are behaving several times each day. Are my behaviors positive? Am I being responsible? If not, ask for help. Reward yourself when you are able to behave in a positive and responsible fashion.
12. If you try to work these steps, you will start to feel much better about yourself. Now it's your turn to help others do the same. Helping others will make you feel even better. Continue to work these steps on a daily basis.

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Part V

TREATMENT

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CHAPTER 31

The Family System

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Thomas Kay, Ph.D.

TRAUMATIC BRAIN INJURY (TBI) IS AN EVENT THAT affects and alters an entire family, not only the person with the injury. It is our hope that this chapter will serve as an introduction to service providers across disciplines to sensitize them to the needs of families so that the role of family intervention can be spread out and shared across the rehabilitation team and into the community.

The Family System: Homeostasis and Involvement

The effect of TBI on the family system merits study for five important reasons:

1. Inevitably, TBI causes profound changes in every family system.
2. These changes dramatically influence the functional recovery of the person with brain injury.
3. The effect of TBI continues over the life cycle of the family, long after the initial adjustment to disability is made.
4. The lives of individual family members may be profoundly affected by a brain injury in another family member.
5. Family assessment and intervention are crucial at all stages of rehabilitation and adjustment after TBI, even when a pathological response is not present.

Families are systems with sets of relationships and roles that develop to maintain an effective balance in the day-to-day world. This homeostasis is broken at the moment one person in the family sustains a brain injury. The struggle of the family to "right itself" and establish a new homeostasis after TBI in one member is parallel to the process of rehabilitation and adjustment in the person with the injury. In the way that recovery is never complete for the individual after brain injury, the family as a unit can never return to its former "self." Assisting families in the process of reestablishing equilibrium, with new sets of roles, relationships, and goals, is the purpose of family assessment and intervention. Because of the range of physical, cognitive, and behavioral-affective changes that can result from TBI, the injured person is often more dependent on family members and therefore more intertwined in and affected by family dynamics. Consequently, the family's relative success or failure in establishing a functional equilibrium plays a significant role in determining the relative independence of the person with brain injury, making family interventions critical to the rehabilitation process.

Although it is generally agreed among professionals that families should be involved in the rehabilitation process, family involvement is often limited to keeping families informed of treatment plans and periodic appearances at team conferences, in which families may be updated on progress and encouraged to participate in carrying out the team's care plan. This approach both lacks the active input of the family in defining the rehabilitation goals and process and fails to appreciate the needs of the recovering family system.

The model developed in this chapter does not involve primarily tertiary professional intervention in the event of crisis but instead a prospective, preventive, primary intervention model that calls for the psychodynamic and interpersonal expertise of the professional team to be brought to bear in helping families cope from the moment of injury through long-term adjustment. In fact, this chapter is less concerned with delineating traditional manifestations of problems in the family and more concerned with articulating the effect of TBI on families, how they respond, what they need, and what interventions are appropriate across the life of the individual, family, and injury.

In the long run, however, TBI is distinguished from other catastrophic injuries in terms of effect on the family by the following facts: 1) cognitive, emotional, and behavioral sequelae, which alter the personality and capacities

of the injured person, are constant; 2) the deficits are permanent, and the family must establish new patterns and goals to incorporate a member with brain damage; and 3) the demographics of TBI (primarily affecting young, adult men) dictate that, unlike strokes or dementing diseases affecting primarily the elderly, TBI affects families who are generally young and in the early stages of their development.

Research Literature on Families

Kay and Cavallo (1991) described an "evolution" of TBI family research that includes four main phases. Phase I consisted of the earliest research, in which family members were studied as "windows" on the person with brain injury. These studies were useful in documenting the cognitive, affective, and personality changes after brain injury and the persistence of symptoms over time. In phase II, studies primarily documented the effects of brain injury on the individual and also noted the effect of the injury on significant others. These studies, however, did not have the family as their primary focus.

In phase III, beginning in the late 1970s but peaking in the mid- to late 1980s, families—or at least individual family members—became a primary focus of research. By documenting the severity of injury, presence of a range of neurobehavioral symptoms, and the reactions of family members, these studies began to identify the factors that led to distress and burden on primary caregivers. Briefly summarized, subjective burden of family members tends to increase, not decrease, over time; it is most related to changes in personality, emotions, and behavior, of which the person with brain injury is least aware; it is the neurobehavioral manifestations of TBI and not the neurological severity per se that affect family members; and the adjustment of family members plays a large role in determining the subjective burden they experience. For an overview of burden literature, see Cavallo (1997).

Although the bulk of work on caregiver burden was done in the mid- to late 1980s by Brooks and colleagues (for reviews, see Brooks 1991; Livingston and Brooks 1988), other researchers continue to explore this area (e.g., Cavallo 1997; Cavallo et al. 1992; Groom et al. 1998; Koskinen 1998; Machamer et al. 2002; Marsh et al. 1998, 2002; Sander et al. 2007; Wells et al. 2005; Wood et al. 2005).

In phase IV of the research literature, predominantly from the late 1980s to the present, the focus shifted from individual family members to families as systems and the effect of TBI on roles, relationships, and the family's status in society. For example, Kozloff (1987) used network analysis to document that the size of the social network of the person with the brain injury decreases, multiplex relationships increase (i.e., family members serve more and more functions as nonrelatives drop out), and families with higher socioeconomic status are more able to maintain existing relationships. Maitz (1989) compared families with a member with TBI to a group of families who did not have a person with TBI living with them but in which one of the members either had a sibling with TBI or a sibling married to a person with TBI. Maitz found, using formal measures of family functioning, that families with a member with TBI had less (and more variable) cohesiveness and more variability in conflict resolution than those families who did not have a person with TBI living with them and showed a correlation between marital conflict and decreased cohesiveness. Peters et al. (1990) found that good dyadic adjustment (between person with TBI and spouse) was associated with less financial strain, low spousal ratings of patient psychopathology, and less severe injuries.

Moore et al. (1993) approached long-term outcome after TBI from a family life cycle model. They looked at a variety of family stressors in relation to distress in families. Perceived financial strain and age of the oldest child were found to be the factors most significantly related to an increase in distress in families. In an investigation of family response to injury in the acute stage of recovery, Curtiss et al. (2000) used Olson's circumplex model (Olson 1993; Olson et al. 1982) to examine changes in family response structure and coping responses pre- and post-TBI. Curtiss et al.'s results were consistent with Olson's circumplex model: significant changes in family structure and coping styles post-TBI were found, with differential changes on the basis of preinjury family structure.

There is also an emphasis in this literature on exploring mediators to predict the caregiver's adjustment to a family member with brain injury. Rather than trying to predict adjustment levels by characteristics of the injury and of the caregiver's situation, the research draws from cognitive-behavioral theories about the connection between mood and the perception of reality and interpretations of experience (i.e., belief systems). Similarly, these models of family adjustment to TBI assert that the appraisal process largely dictates experience. Studies move away from solely identifying injury-related predictors to family adjustment and focusing on mediators that reside in the individual before the traumatic event. Kosciulek and his colleagues (Kosciulek 1994, 1997a, 1997b; Kosciulek and Lustig 1998; Kosciulek and Pichette 1996) found positive appraisal and family tension management ability to be predictive of successful family functioning and identified factors that enabled families to successfully adapt, such as support from friends. Minnes et al. (2000) found that reframing and seeking spiritual support as coping mechanisms after TBI were significantly related to more positive outcomes in family members. Similarly, Ergh et al. (2002) found social support to be a significant factor moderating family functioning and caregiver burden after TBI. The more social support a family reported, the more functional the family was. Social support also moderated caregiver distress: in the absence of social support, caretakers were more vulnerable to the effects of time since injury, level of impairment, and lack of awareness on the part of the injured person. Ergh et al. (2003) found that whereas neurobehavioral disturbances are related to reduced life satisfaction in caregivers, social support (actual and/or perceived) moderated this relationship; the cognitive problems of the family member with TBI and his or her unawareness of his or her deficits cause distress only in caregivers with low social support and are associated with caregiver life dissatisfaction. Carnes and Quinn (2005) found that decreased psychological distress for families of individuals with TBI was related to good family functioning, which itself was influenced by social sup-

port. Wade et al. (2004a) also found that greater interpersonal supports for parents of individuals with TBI reduced the stress and burden.

Cognitive variables have been found to be significantly associated with psychological adjustment levels, and especially with coping skills (e.g., use of problem-solving skills and positive reinterpretations of problems), low use of avoidant coping skills, and magical thinking (Blais and Boisvert 2005). Coping behavior may assume a mediating role between these stressful events and family psychological functioning (Benn and McColl 2004). Anderson et al. (2002) found that family resources (those that are inherent in the family unit, such as good problem solving and open communication) mediated the relationship between stressors (neurobehavioral problems) and psychological distress, and that high levels of unhealthy family functioning were related to high levels of distress in spouse caregivers, who reported extraordinary behavioral, communication-oriented, and social problems in their injured partners. According to Blais and Boisvert (2007), the main personal characteristics associated with psychological adjustment and/or marital satisfaction of individuals were effective attitude toward problems, infrequent use of avoidant coping strategies, and positive perception of a spouse's communication skills. Here "perception" is critical in that it is not the degree of severity of the injured family member but how the family receives it that facilitates the adjustment process. The family member's psychological adjustment is related to his or her attitude toward the cognitive or behavioral problems the person with the injury manifests.

Differing Perceptions

Some studies have focused on differing perceptions within the family of a person with TBI on the basis of factors such as kinship, role, and gender. A group of researchers (Gervasio and Kreutzer 1997; Kreutzer et al. 1994a, 1994b; Serio et al. 1995) examined a variety of these factors potentially related to family functioning after TBI. Major findings included that outcome predictors as well as perceived unmet needs of family members differed for spouses as compared with parents of individuals with TBI. Cavallo (1997), in comparing wives and mothers of individuals with TBI, found that although mothers were caring for more severely injured individuals with TBI, wives were reporting significantly more subjective burden related specifically to affective-behavioral and cognitive functioning of the individual with TBI. No differences related to residual physical problems were found between the two groups.

In studies of differing perceptions of residual problems and family functioning when individuals with TBI are compared with family members and/or professional staff working with them (Cavallo et al. 1992; Gan and Schuller, 2002; Lanham et al. 2000; Malec et al. 1997), some basic concurrence of findings has emerged, as outlined below:

1. The amount of agreement between individuals with TBI and their families, staff, or both tends to differ based on the types of problems they are being asked to endorse.
2. The amount of agreement between individuals with TBI and their families, staff, or both differs overall. Some have high agreement; some have low agreement, with families, staff, or both endorsing more problem areas; and some have low agreement, with the individuals with TBI endorsing more problem areas.
3. In general, when family members are endorsing more problems than the individual with TBI, the problems tend to be in the affective-behavioral realm.

Most significantly for this review, however, these studies generally represent a shift from generalizing about how all families respond to investigating differential responses within and among families.

Children With Brain Injury

In an interesting study of children with TBI, Yeates et al. (1997) investigated the preinjury family environment as a predictor of outcome in children with TBI. They found that preinjury level of family functioning had a significant effect on 1-year outcome, even after injury-related variables were accounted for. Another study of children with TBI by Max et al. (1998) confirmed this finding. Max and colleagues looked at preinjury psychosocial factors, injury factors, and postinjury factors (such as coping of family members and the development of psychiatric disorders in the child with TBI) as they related to family functioning in the first 2 years after TBI in children. The major findings were that the best predictor of family functioning after an injury was the preinjury family functioning as well as whether the child developed a psychiatric disorder.

Armstrong and Kerns (2002) examined the needs of parents of children with brain injury and found that they reported a substantial number of unmet health and medical needs as compared with parents with diabetic and orthopedically injured children. The authors claimed that this phenomenon illustrated the unique crisis of a child with TBI and the unique distress the parents experience. The Wade group (Wade et al. 2002, 2004a, 2004b, 2006a, 2006b, 2006c) found that although overall family stress and caregiver burden declined over time after both pediatric brain injuries and orthopedic injuries, families of children with severe brain injuries continued to experience high levels of stress and burden years after injury when compared with families of children with orthopedic injuries, and that as time since injury increases, parents' worries about the future of their children increase. Anderson et al. (2005) also found high levels of stress as long as 30 months postinjury, which was predicted by severity, functional impairment, and postinjury behavioral disturbances on the part of the child. Prigatano and Gray (2007) found that parents of children with brain injury report severe stress at all levels of severity, primarily related to concerns about poor school performance, lack of friends, apathy, and behavioral problems.

Professional Intervention and Support

The research literature on the success of family intervention is small and relatively recent. One study that demonstrates the potential value of professionally based support is that of Albert et al. (2002), who examined the effects of offering an experimental social work liaison program for

families of discharged rehabilitation inpatients with brain injuries of mixed types. In addition to offering education and emotional support, social workers offered practical advice about services and financial matters, and families were free to call at any time. Six months after patient discharge, the caretakers who participated in the program showed decreased burden on six of nine scales when compared with caregivers who were tracked and interviewed but did not have access to the liaison program. Carnevale (1996) outlined an approach called the Natural-Setting Behavior Management Program that trained individuals with TBI and their families to implement home-based behavior management programs. The results of the study support the success of this approach in managing behavioral issues after TBI. However, in a sobering follow-up article, Carnevale et al. (2002) found that neither education alone nor education combined with the Natural-Setting Behavior Management Program was effective in relieving caregiver burden. Kreutzer et al. (2002) discussed the development of the Brain Injury Family Intervention, a curriculum that includes intervention topics, self-evaluation tools, and treatment strategies. Other examples of family interventions include educational programs (Sinnakaruppan et al. 2005), a liaison nurse acting as a point of contact for the family member, screening for abnormal levels of stress or anxiety (Hawley et al. 2003), ongoing long-term supports (Armstrong and Kerns 2002; Ponsford et al. 2003), interdisciplinary family intervention programs (Lefebvre et al. 2007), family empowerment programs (Forsyth et al. 2005), and some combination of these elements (Aitken et al. 2005). Although many of these programs received positive evaluations from the participants and there was some recorded increase in staff-family communication, few of these programs were studied with any scientific rigor for effectiveness in alleviating burden and stress in caregivers (Boschen et al. 2007).

Cultural Diversity

No discussion of family issues after TBI is complete without the inclusion of the role of cultural background, which in the broadest sense includes race, religion, ethnicity, language, socioeconomic status, and sexual orientation. Any or all of these factors may influence etiology, symptom manifestation, beliefs about the causation of disability, expectations regarding recovery and rehabilitation, participation in the rehabilitation process, and more (Fitzgerald 1992).

Consideration of cultural background is especially important as the United States increasingly becomes a multicultural nation. Early 2000 census data, for example, revealed that overall, 18% of the U.S. population speaks a language other than English at home (in states such as California, New Mexico, Texas, New York, and Hawaii, it is approximately one-third of the population) (Schmitt 2001). In the 1990 census data, that figure was 14%, which was a 38% increase over the 1980 census figures (Barringer 1993). Despite this shift, there is little information in the TBI literature about the impact of language and culture on families after TBI or how to address the needs of these families in clinical situations. The most comprehensive review and discussion of these issues in the TBI literature appears in Cavallo and Saucedo (1995). This article provides information on the epidemiology of TBI in culturally diverse populations and includes discussions of assessment, treatment, and factors that must be considered during service provision.

Rosenthal et al. (1996) looked specifically at how racial and ethnic status affects functional outcome and community integration after a TBI using data from the TBI Model Systems National Database. They found no significant differences between whites and minorities (described as blacks, Hispanics, and Asian/Pacific Islanders) at time of admission to and discharge from inpatient rehabilitation and at 1 year postinjury in basic functional skills. However, at 1 year postinjury, they did find worse outcomes for minorities in return to work or school, in addition to decreased social contacts. They postulated that these differences may relate to the socioeconomic status of minorities in the United States. However, Yeates et al. (2002) found that the differences in black and white families in their reactions to TBI were independent of socioeconomic status. Nabors et al. (2002) also found that black and white caregivers were similar in patterns of adjustment after TBI. There were no differences in family functioning, perceived level of support, perceived level of burden, or overall importance of family needs between the two groups. However, the black caregivers did report having fewer needs met, more limited health care insurance, and lower total household income relative to the white caregivers. Finally, Hart et al. (2007) found that across races, caregiver emotional health is affected by the functional level of the individual with brain injury. African American caregivers may be at risk for worse emotional consequences due to worse outcomes for the individual, yet may underutilize professional services.

Impact on the Family

Clinical experience bears out the research and descriptive literature cited in the preceding sections. Physical problems, although at times quite severe and necessitating specific family routines or limitations, are usually dealt with most successfully by the family in the long run, in large part because these problems are predictable, can be planned for, are within the awareness of the person with the brain injury, and are visible to and acknowledged by others. Cognitive problems, such as impaired attention, concentration, and memory, are more troublesome because they are less predictable and can invade all spheres of interaction and because their functional implications often are beyond the anticipation of the person with the brain injury. On the other hand, families often can be extremely creative in providing the external structures to minimize the effect of such deficits on everyday life. Emotional, behavioral, and personality changes, however, such as anger outbursts, self-centeredness, impulsivity, disinhibition, and social insensitivity, are extremely difficult to cope with because they can appear suddenly and unpredictably, have (even if not intended) a direct emotional impact on the recipient, are often embarrassing to others, and are extremely difficult to control. Not only do these types of problems increase stress in internal family

life, but they also lead to family isolation as fewer friends visit, social outings decrease, and the immediate family bears increasing responsibility for the social network of the person with brain injury. For example, a young father with brainstem and frontal lobe injuries after a high-speed motor vehicle accident and extended coma will typically have physical, cognitive, and behavioral changes. He may learn to compensate for an ataxic gait by walking slower, using a cane on uneven surfaces, and avoiding activities requiring speed and agility. He may learn to compensate in part for severe memory deficits by keeping a detailed memory book, writing down all telephone messages, keeping lists and checking things off as he does them, and posting visual cues around the house for things he needs to do. Adaptations to these physical and cognitive deficits may enable him to be a semiproductive and reliable helper at home. However, if he is behaviorally disinhibited, his outbursts of rage at his wife and children may make him difficult to be around, and his unpredictable and embarrassing disparagement of guests may make it impossible to have friends over, essentially isolating the family and leading to severe emotional and interpersonal problems within it.

In a qualitative study, Yeates et al. (2007) had clinicians identify individuals with brain injury lacking awareness of executive dysfunction and problems with social pragmatics and attempted to identify themes in the reconstruction of the family and the individual's sense of selfhood after brain injury. One theme that emerged involved the struggle on the part of the person with brain injury and the family to make sense of the changes associated with the injury; a sense of "no one being prepared" for the trauma prevailed. According to the perceptions of these families, services to provide sources of crucial information were not available, or perhaps did not provide adequate explanations about what happened and what to expect in the future. Another theme that emerged was the person with a brain injury being viewed as naïve and vulnerable to either the damage in his or her brain or life's dangers of which the person is unaware. Some families constructed the self of the injured individual as lacking agency (e.g., "I think it's her brain injury; she's not aware of the problems that she's got") and as protected by others' knowing better (e.g., "I'm currently more aware of what's going on than he is"). A third theme involved the confusion of the families in terms of knowing what changes were attributable to the brain injury or to the person with a brain injury just being the person he or she always was. Each relative reported that taking up one meaning or another had consequences for each person's own position in relation to the family member with brain trauma. For example, one wife observed her husband inappropriately touching a family friend: did this indicate that he is a "letch," with the attendant uncertainty about the implications of this behavior for their relationship, or was the behavior an indication that her husband is struggling against the effects of his brain injury?

Most difficult was the process in the relatives of trying to orient themselves to the positions that their injured family member would take up with respect to his or her sense of self and abilities. From the viewpoint of the injured individual, the continuity of his or her preinjury self seemed to be contested. These discrepant views of an individual's identity cause mutual feelings of tension and anxiety—and not just in the injured individual. The burden the family faces with respect to relating to the individual stems not only from functional problems in the injured individual, such as impaired memory, but also from the pervasive feeling that the close family member has suddenly become a stranger, with family members struggling to try to repatriate the person into "the world they had created" preinjury. This burden manifests itself in three ways: 1) families complain about lacking service providers to give them adequate information—perhaps no amount of information can be experienced as adequate; 2) families feel responsible for the vulnerable, childlike person the injured individual has become, with the accompanying "he/she will grow out of it" frame of mind; and 3) families believe that the health of the relationship rests solely on them, thus setting themselves up for feelings of guilt as difficulties accrue (Yeates et al. 2007). This experience of the discrepancy between the actual self (after TBI) and the ought-to-be self can lead to depressive states (Cantor et al. 2005).

These generalizations tend to apply to all "families" in which two or more persons are living together. Specific variations occur, however, depending on whether the person with TBI is a parent or a child, and brain injury in the family affects spouses, parents, children, and siblings in different ways. These variable effects on family roles are considered in the following section.

Family Structure and Role Change

The impact of TBI on various members of the family system has been documented in a number of ways in the literature cited earlier. For excellent first-person accounts from family members, see Williams and Kay (1991). In this section, we provide clinical observations of caregivers who are spouses, parents, children, siblings, and extended family.

Impact on Spouses

In many ways, the spouse, usually the wife, bears the greatest burden when the partner sustains a brain injury. An equal adult partnership has been broken, and the uninjured spouse is often thrust into the role of caregiver—both for the injured partner and for the family when there are children. The result is often financial burden, loss of support, and isolation. Younger spouses may become more dependent on their families of origin, especially if the injured partner is unable to independently carry out household responsibilities. In-law conflicts may erupt between the parents of the injured person and his or her spouse over care issues. In premarital, committed relationships, boyfriends or girlfriends may be excluded and shut out from contact by protective family members who "circle the wagons" against someone not perceived as being part of the family; this can have poisonous effects for years. In traditional families in which the husband was the "family executive," the wife may be thrust into managing and decision-making roles for which she is not prepared. (Increasingly, it is common for the wife to play this executive role.) Spouses often express the feeling of being

"single parents": "My husband and I used to have two children; now I feel like I have three." Even in situations in which the injury is less severe and the injured partner is able to return to some type of work, it often is far below preaccident levels, and major lifestyle changes are required of the family. With social sympathy and concern flowing mainly toward the injured partner, the caretaking spouse often feels his or her needs go totally neglected, and this can lead to bitterness, despair, or burnout. When there are children, the spouse may be without an equal parenting partner, and in fact competition may develop between the children and the injured partner for the spouse's attention.

Especially in more severe injuries, spouses may feel married to a different person, one he or she no longer loves or feels attracted to. Spouses face an enormous conflict between commitment and guilt if they consider leaving the relationship. This is particularly the case when the couple is young and have either no children or young children. The spouse often realistically faces the choice of sacrificing his or her life to the injured partner or leaving the relationship to develop a new family. These are difficult moral and personal choices, and the professional is best advised to help the spouse sort out the options rather than imposing his or her own value system. In less tragic cases, enough of the personality and competence of the injured person remain on which to build a mutually satisfying commitment.

The situation in which the uninjured partner is considering divorce poses ethical and treatment dilemmas for the clinician. When the identified patient is clearly the person with TBI, it may be appropriate to find another therapist to help the partner, or the couple, deal with the divorce issues. When the identified "patient" is the family, however, it is appropriate for the clinician to work with the whole system—or the parental subsystem—to help the family face these issues. Unlike many mutually agreed-on divorces, however, divorces after TBI are often more unilaterally sought (by the uninjured partner), and the process of negotiating this transition is a combination of supporting the uninjured spouse (who is often ridden with guilt) and negotiating new support systems for the reluctant, angry, and frightened person with TBI—tasks usually more comfortably handled by two persons.

Countertransference issues often arise in working with young families of individuals with severe injuries if the personal value system of the clinician is at odds with the decisions of the uninjured partner, or the therapist's fantasies of improvement and happiness collide with the realities of the marital relationship. These feelings can arise in either direction: the therapist may unconsciously encourage the partner perceived as trapped to find a way out or unconsciously discourage a desperate spouse from abandoning the injured partner. Awareness of his or her personal feelings is crucial for the therapist, and transfer of the case is appropriate if the decisions of the uninjured partner make it impossible for the clinician to be fully supportive. Sorting out these countertransference issues, from realistically helping the partner to think through the consequences of his or her choices to knowing when to turn the case over to a colleague, is a crucial but tricky process, requiring self-searching by the therapist and, often, consultation with a colleague.

Even when marriages do survive, sexuality and intimacy are often difficult (see Chapter 25, Sexual Dysfunction). Persons with brain injury may have decreased capacity for intimacy and either heightened or lowered sexual drive and may be impaired in their ability to perform sexually (for physiological or psychological reasons). Wives in particular may be pressed to meet the sexual demands of the injured spouse, with little satisfaction for themselves. It is not uncommon for sexual relationships to stop entirely; when the spouse chooses to stay in the marriage, he or she may seek out (with much guilt and need for support) sexual relationships outside the marriage.

Impact on Parents

When a child is injured, special burdens and pressures exist for the parents. When a young child living at home is injured, the mother usually takes on the role of primary nurturer and caregiver. This may create tension within the marital relationship, and underlying cracks or strains in the relationship may become manifest. Husbands may unconsciously compete with the injured child for the wife's limited resources. When couples are composed of persons with complementary coping styles, the stress of caring for a severely injured child may drive them to opposite extremes of reaction and threaten the relationship; for example, the father may bury himself in his work while the mother drops everything (including any attention to her husband) and devotes all her energy to the injured child. Parents may also find it difficult to apportion their time and energy to other children or to elderly parents whom they may care for. Even when they work well together around the crisis, parents may find their lives dominated by the needs of the injured child and may be in jeopardy of neglecting their own marital relationship (e.g., no longer spending time together separate from their children) or may be cut off from adult social activities with friends.

When the injured child is an adult who had been living independently, parents often are thrown back into an earlier developmental phase of caring for a dependent child, with the complication that the grown child resents and resists the dependency. This is an extremely difficult position for both parents and child, especially when the child is male, recently past adolescence, and striving for autonomy. Driving, independent living, dating, and establishing friends and intimate relationships become volatile family issues. Parents often have great difficulty accepting the permanent changes in their children and in fact may complicate the rehabilitation process by refusing to give up unrealistic expectations ("My son *will* become a lawyer!"). Conflicts may develop between the parents over what is reasonable to expect of their adult child with brain injury. When adult children move back in with their parents for a period after a brain injury, it is not uncommon for old psychological terrain of the struggle for independence to be traversed again. How this was negotiated the first time around in adolescence is often predictive of how things will go the second time around. Sensitive clinicians can be extremely helpful to families during this period by normalizing the conflicts around independence and individuation and helping negotiate a series of compromises that respect both the needs of the parents to be protective and the needs of the adult child to start regaining independence.

Special issues attend the parent-school relationship for younger children through adolescents. These issues are addressed in the section Special Issues later in this chapter.

Impact on Children

Children of parents with brain injury face special problems over which they have little control. Younger children may suddenly find that they have lost the nurturance and guidance of a formerly loving and competent parent. The injured parent may be unpredictable, irritable, or even in competition with them for the uninjured parent's attention. Older children at home usually have increased responsibilities, less attention from the other parent, and an awkward home situation into which they are uncomfortable bringing their peers. Depending on the preexisting relationship, the child may be drawn emotionally closer to or driven farther away from and resent the injured parent. Older children may have more capacity to understand what has happened but also more freedom to create distance. It is not uncommon for school or behavioral problems to surface in children who are depressed, angry, or guilty about their new family situation.

When an older parent incurs a brain injury, adult children who are out of the house are inevitably faced with the issue of taking on increased responsibility. Because of their own adult responsibilities, children are often limited in how much assistance they can actually contribute, with inevitable feelings of guilt. Adult children are often torn between the needs of their partners and children and those of their parents. Conflicts often develop between the caregiving adult child and his or her spouse, with resulting imbalance and conflict within the family. Conflicts can also erupt among siblings with an injured parent over perceptions of uneven participation in caregiving. Interventions with spouses of adult children with parents with TBI are often the most effective way to stabilize the support system for the injured parent. Therapists need to be realistic, however, in assessing how much any one child is willing and able to give and help other siblings deal emotionally with perceived inequalities.

Impact on Siblings

With most attention being paid to the child with the injury, uninjured siblings often become unrecognized victims of shifts in the family system after TBI. When the siblings are young and living at home with the injured child, the parents characteristically reorient all of their attention and energy toward the child with the brain injury. Children who suddenly feel lack of attention from their parents often act out their needs in ways not initially seen as related to their sibling's injury. This acting out may take the form of failing grades or getting into trouble at school. Parents need support in finding a balance in allocating limited resources among their children. Older children at home may, like children of injured parents, have more domestic responsibilities and perhaps also a socially awkward situation into which they are embarrassed to bring friends. Siblings of different personality styles and relationships with the injured child may also respond in different ways; one sibling may become closer to the injured child while another moves away in anger.

Older siblings who are not living at home experience stresses similar to those of adult children of injured parents. The demands of their own lives, perhaps including a spouse and children, compete against the need and desire to help their injured sibling. Typically, one adult sibling is designated as the primary caregiver, especially if the injured sibling is unmarried and the parents are distant or too old to take on a primary caregiving role. Support from the sibling's family is essential for him or her to play an effective role.

Impact on Extended Family

The impact of TBI on extended family networks is seldom discussed. The reality is that, especially in a mobile, urban society, kinship bonds often are more tenuous than they used to be, and aunts, uncles, and cousins seldom play a significant role in the primary care of any person with brain injury. (This does not hold in cultural groups in which a high value is placed on networks of extended families.) From our perspective, it is helpful for the nuclear family, whenever possible, to involve the extended family as early as possible in learning about the injury, the recovery process, and how to normalize the new person who emerges. Nuclear families that are able to tap into the support systems of extended families, even once or twice a year for respite, have a great advantage. Families often are unable to elicit the active support of relatives, however, because extended family members who do not live with the injured person often do not understand, are less sympathetic toward the family stresses, or are simply more wary of becoming involved. It is extremely useful for professionals working with families to include extended families in family meetings, especially early on, to establish a basis for a wider support network.

Family Responses to TBI: Stage Theories

The family's process of adjusting to TBI evolves over time; it involves becoming aware of the nature, extent, and permanence of neurobehavioral deficits and establishing a new set of family roles, structure, and routines to adapt to these changes. Successful clinical intervention with families requires the professional to be aware of where in this process of adjustment the family is; this determines what the family is able to hear and what kind of support is needed.

There are a number of useful ways to conceptualize the continuum of changes that families pass through. These are expressed as various stages, although it is clear that there is no objectively and universally true sequence.

A number of authors have proposed stage theories of family adjustment after TBI. Rape et al. (1992) described a number of these and identified six major stages incorporated in most (but not all) of the stage theories they analyzed:

1. Initial shock
2. Emotional relief, denial, and unrealistic expectations
3. Acknowledgment of permanent deficits and emotional turmoil

4. Bargaining
5. Mourning or working through
6. Acceptance and restructuring

Rape et al. (1992) noted that the hypothesized stages lacked empirical validation, often failed to meet the criteria for defining explanatory epigenetic stages, and contained conceptual problems (e.g., why some families adapt whereas others become stuck at one of the stages). They proposed integrating a family systems perspective into stage theories to solve some of these problems, and they advocated longitudinal research.

Prominent among the stage theories specific to TBI is Lezak's (1986) six-stage model of family adjustment after TBI, which introduces substages into the integration phase. After the injured person returns home, the family passes through a series of perceptions, expectations, and reactions, beginning with minimizing problems, expecting full recovery, and feeling happy about the person's survival (I), through bewilderment and anxiety (II), discouragement and guilt (III), and depression, despair, and feeling trapped (IV). Families who ultimately move beyond their sorrow go through two final stages of grieving (V) and reorganization-emotional disengagement (VI). Lezak emphasized that many families are unable to move beyond chronic depression and despair.

Kübler-Ross (1969) proposed an intrapsychic model of an individual's response to the prospect of death and dying, which is often applied to TBI, and described the process of the family as a system, or each individual family member, proceeding through the stages of denial, anger, bargaining, depression, and acceptance. Although it is absolutely true that each family member goes through some or all of these feelings in coping with TBI, we believe that there are some problems, indeed some dangers, in applying this model too simplistically to a family's response to TBI. First, the fact that the mourned person still lives and is present interferes with the normal grieving process in and of itself. Second, the denial so often noted in families of persons with brain injury often is treated as something to be dislodged by therapists if families do not heed therapists' prognostications early in the rehabilitation process about the permanence of deficits. The reality is that early denial—especially continuing to believe in the possibility of significant recovery—is an effective buffer against depression (Ridley 1989), may be necessary for the family to regroup, and should be respected by professionals. Third, the notion of a steady final stage of acceptance—in the sense of an emotionally peaceful embracing of the way things are—is neither realistic nor, perhaps, desirable to expect. Transitions in the family's life cycle bring episodic loss and rekindle the mourning process. It is also adaptive for families to keep their level of dissatisfaction alive because it can fuel needed periods of advocacy at different points of the injured person's life. Most important, harm has been done to families in turmoil years after an injury by professionals who expect that because families are not demonstrating "acceptance" after so much time, a psychopathological process must be occurring. The reality is that living with an adult with brain injury brings cycles of adjustment, disequilibrium, and reestablishment of a new balance on a periodic basis, and this recycling never ends. The Kübler-Ross stages are best seen as an individual's internal responses that are likely to be replayed numerous times over the course of the life cycle. The family system's process of adjustment is too complex to reduce to such a set of stages.

That the grieving process after disability does not simply reach a steady state of acceptance has been recognized by those working outside the area of TBI. Olshansky (1962), for example, introduced the notion of "chronic sorrow" to describe the continued experience of sadness and ongoing adjustment that parents of children with mental retardation feel. Wikler (1981), working within the same framework, recognized that such chronic sorrow is punctuated by periods of more intense grieving at critical developmental junctures. The experience of grief in relatives of persons with serious mental illness, as examined by Miller (1996), provides a window into the experience of families of individuals with TBI. Unique to having a family member who has a serious mental illness is that the loss and grief experience of the family is cyclical in nature: the periodic "reappearance of the former self" creates a prolonged period of grieving. The principal element of this sense of grief involves a sense of loss of a person who is "there but not there." Robinson et al. (2005) wrote about psychological reactions in couples to a diagnosis of dementia. Although there are key differences between dementia and TBI, specifically the progressiveness of dementia as opposed to the suddenness of TBI, the dynamic that ensues for both dementia and TBI in the social context of the individual is very similar. For Robinson et al. (2005), families who experience chronic trauma cycle through the stages multiple times. Their adaptation is not linear. The authors found that there was an ongoing process of making sense and adjusting to loss and that the adaptation experience was cyclical in nature, marked by noticing changes in the person, making sense of these changes as a couple, and gradually accepting what was happening and its relation to their expectations and experiences as a couple. They also described the movement of adjustment as a process of oscillation between acknowledging losses and developing coping strategies. The authors described the insidious nature of dementia in that there is a continued presence of the person. These concrete reminders of "how it used to be" are also integral to the experience of families of individuals with brain injury.

Kiser and Black (2005) pointed out that adaptation to stress or crisis typically relies on the stage model to conceptualize and describe the phenomenon. The acute stage follows the transitional stage, and the third stage is entry into more stable family patterns or longer-term adaptation. Davis et al. (2003) found that the term "crisis" for individuals with brain injuries and their families was not an accurate descriptor for their experiences. Unlike more traditional crisis models, these individuals and their families had to cope with their "initial crisis" on a long-term basis, perhaps lifelong because adjustment meant fundamentally redefining identities. The crisis is not time limited; it is never ending, varying in intensity over time yet never absent. And it leaves the families with a "precarious homeostasis" whereby the critical moment may recede until the next imbalance occurs. The deficits caused by the brain injury leave the individual with the brain injury

with fewer resources to cope with and surmount the particular problems. There is, therefore, a greater need for intervention from supporting family members. In this sense, according to Davis et al. (2003), the terms crisis and models of crisis and, by implication, the concept of family burden need to be redefined in the context of the brain injury, the experience of which is not a discrete temporary moment. The authors deemed this perpetual crisis as more akin to a "transcrisis" state in which the injury and crisis experiences are chronic and long term. Citing research, Davis et al. (2003) observed that this characterization of family experience and difficulty adapting to the chronic stress of brain injury is harshly underscored by findings that show that physical violence in the family unit increases up to 26% in one 7-year follow-up of a family's life after brain injury.

A Model of Family Assessment and Intervention

Families are thrown into crisis at the moment a person is injured. Professional intervention should not be reserved for severe management problems or dysfunctional families. Family intervention should be proactive, flexible, health and prevention oriented, and responsive to the needs of families within the context of a progressive reestablishment of family equilibrium after brain injury.

The quality of family functioning has direct impact on the process of rehabilitation. "Dysfunctional" families may fail to join forces with the rehabilitation team, deliver conflicting messages, or respond to behaviors in ways that undercut the team's approach, all of which result in the patient's being caught between the family and treating professionals in a way that undermines the rehabilitation process. However, much of what professionals perceive as dysfunctional in families is the result of families being uninformed, underinvolved, and not having basic needs met, all of which may be preventable with appropriate interventions.

We propose a three-dimensional model of intervention (Table 31–1): *where* the intervention is aimed (concentric circles of intervention), *what* the intervention is (levels of intervention), and *when* it occurs (stages of intervention). Each of these dimensions itself contains three progressive levels.

Concentric Circles of Intervention

In evaluating the family of a person with brain injury, our model suggests thinking of that family as composed of three sets, or units, nested within each other (Figure 31–1): 1) the individual family members, 2) the family as a system, and 3) the relationship of the family to the community. Each of these systems must be assessed independently, and different interventions can be made at each level depending on what stage the family is in. (The concept of concentric circles, as an alternative to the more traditional "unstable triad" of person, family, and society as bearing responsibility for the long-term care needs of persons with TBI, was first proposed by DeJong et al. 1990.)

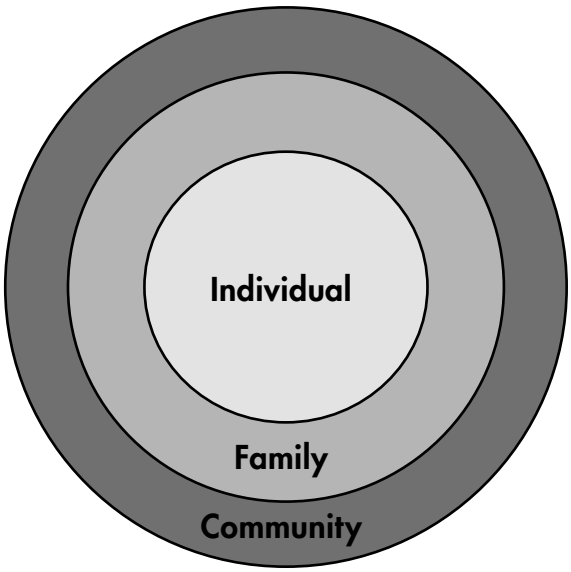


FIGURE 31–1. Concentric circles of intervention.

The clinician should evaluate individual family members in terms of their personality structure, their expectations for the injured person and the family, the individual strengths and weaknesses they bring to the family, and how they respond both to the person with the injury and to the current family situation. Individual family members may have particular attitudes, limitations, or strengths that become crucial in the rehabilitation process (e.g., a mother's need for her son not to hold a menial job, a father's need to not let others make decisions for his family, or a sibling's commitment to support an injured child). Individual family members may be at risk or in crisis, or may simply need support because they are shouldering a large share of the family's responsibilities. At times, the most effective family intervention is a targeted intervention with an individual family member.

The family system must be considered as a unit above and beyond its individual members. What are the structures and roles in this family, and how have they shifted as a

TABLE 31–1. A model of family assessment and intervention after traumatic brain injury

Concentric circles of intervention
Individual family members
The family as a system
Relationship of family to community
Levels of intervention
Information and education
Support, problem solving, and restructuring
Formal therapy
Stages of intervention
Acute care
Rehabilitation
Community reintegration

result of the injury? What are the patterns of relationship and communication, and how are problems solved? How cohesive is the family unit, and what is the degree of enmeshment or disengagement? How flexible is the family in responding to challenges? What specific cultural norms does the family hold that may differ from those of members of the rehabilitation team, and will those color expectations of what is important to achieve? (See Williams and Savage 1991, for examples of cultural values applied to TBI rehabilitation.) What values does the family hold that will influence goals and expectations? (Strong cultural differences may exist among families, especially recent immigrant families.) Often, the failure of the rehabilitation team to appreciate strongly held family norms, values, or needs leads to conflict and an impasse in the rehabilitation process. Assessing the family system is crucial, and often strategic interventions within the family structure are critical to enabling a family to move on and cope more effectively.

The family's relationship to the community also must be assessed, and, often, crucial interventions need to be made not within the family system itself, but at the interface of the family and its community. The community is both the professional community of services that needs to be accessed and the psychosocial community of friends, recreation, and extended family. The history of a family's relationships to these communities is the best predictor of how they will respond in the crisis situation of TBI. In the early stages, intervention at this level almost always involves negotiating a good working relationship between the family (often as represented by one or two key members) and the rehabilitation team. Forging a strong working alliance is crucial for successful rehabilitation. In later stages, families must learn to deal with the world of multiple, often bureaucratic, community services, and if they are to overcome the natural tendency toward isolation, they must reestablish functional social and recreational opportunities. One often overlooked community relationship in the early stages is the family's need to establish quick communication with the world of insurance and legal matters. For families with injured children, the educational world is the major community relationship. Effective family intervention pays attention not only to the internal matters of the family but also to the family's relationship to various aspects of the community.

Special issues exist for recent immigrant families, often in large urban centers, who are locked into enclaves of culturally homogeneous families. Mainstream services often do not extend into such communities or are unknown or rejected. Language barriers often limit how effective outside professionals can be. In these situations, it is extremely helpful to identify a bilingual person within the family's community who can act as a translator throughout the process of community integration. Many large cities fund agencies to provide bilingual social workers or case managers for families from ethnic subcultures with special needs.

New York University Head Injury Family Interview

Appropriate family assessment depends on increasingly sophisticated and valid instruments and techniques for assessing family system functioning (for a review of existing approaches, see Bishop and Miller 1988; Struchen et al. 2002). Most family assessment instruments are inadequately sensitive to particular issues specific to TBI. The New York University Head Injury Family Interview was designed to survey family members systematically about the effect of TBI on the person with the injury and on the family system (Kay et al. 1988, 1995).

TABLE 31–2. New York University Head Injury Family Interview

Demographic and preinjury form
Demographic information
Accident/medical information
Preaccident history
Psychiatric history
Neurological history
Follow-up interview
Routine medical care
Rehabilitation services
Psychotherapy
Living arrangements
Legal issues/insurance
Community service use
Significant other interview
Problems and changes
Problem checklist
Activities of daily living
Socialization and home activities
Patient competency rating
Interview for person with the brain injury
Problems and changes
Friendship and intimacy
Employment status
Homemaker status
Educational status
Problem checklist
Patient competency rating
Impact on the family
General
Questions for spouse
Questions for parents
Questions for adult siblings
Questions for younger siblings
Questions for adult children
Questions for younger children

The Head Injury Family Interview is a five-part structured interview designed for both research and clinical uses (Table 31–2). It includes five sections covering premorbid, accident, rehabilitation, and community resource utilization. It gathers information from both the person with the brain injury and significant others and provides a method for documenting the effect of the brain injury not only on the injured person but also on other family

members. Most questions are hierarchically organized, beginning with open-ended questions (e.g., "What changes have you noticed since the injury?"), proceeding through structured areas (e.g., "Have you noticed any physical changes?"), and ending with focused questions (e.g., "Do you have problems with balance?"). Many of the main areas of inquiry are asked both of the person with the injury and of a significant other. Specific sections are provided for impact on parents, spouses, siblings, and children.

Levels of Intervention

A second principle of our model is that family intervention need not equal family therapy. Effective family intervention requires that the clinician think in terms of levels of intervention that are appropriate to the situation (Muir et al. 1990). Our model defines three levels of intervention: 1) information and education; 2) support, problem solving, and restructuring; and 3) formal therapy. Figure 31–2 illustrates how these three levels of intervention—in ascending order from the most basic to the most complex—cut across the dimensions of individual, family, and community (the concentric circles of intervention described in the previous section).

At the most basic level, families in which a brain injury has occurred need information and education at all stages of intervention (see next section), from acute care to community reentry. In the earliest acute phase, education is the most crucial intervention, although long-term prognostication is impossible. Families need to know what has physically happened to the injured family member and his or her brain, what treatments are being given and why, what can be expected over the next few days and weeks, how to understand unusual behavior (e.g., confusion, agitation, and disinhibition) and how to respond to it, how to anticipate and respond to cognitive deficits (e.g., disorientation, severe memory problems, and lack of language), what treatment options should be considered, and what their insurance and legal options are.

The timing of providing information is also crucial, as is judging how much information the family is able to take in. In early stages of recovery, families need to sustain hope and cannot be overwhelmed with dire warnings and pessimistic projections. The seeds of long-term limitations are quietly planted early, but the skilled clinician will know when the family is ready to have them nurtured. Likewise, it is unethical to steer families toward program decisions without making them aware of the full range of options. Since the 1980s, an enormous amount of informational material (of variable quality) has been developed for families, and the Brain Injury Association of America is an excellent resource for such materials (see contact information in the section Brain Injury Association of America and Other Support Organizations). Most good rehabilitation facilities develop specific educational programs for families to inform them about TBI in a systematic way (Rosenthal and Hutchins 1991). Educational programs that include open discussions also can be an excellent indirect and nonthreatening way to enable families to face their own emotional reactions in a way they would not if offered the more direct opportunity of group sessions run by psychologists or psychiatrists.

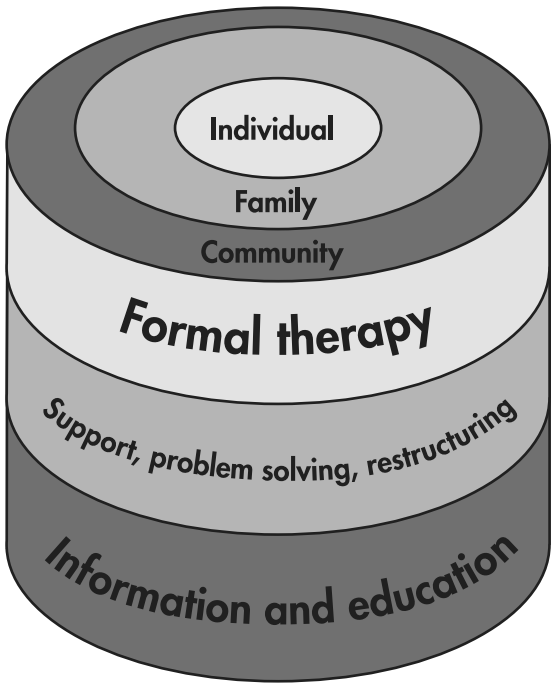


FIGURE 31–2. Levels of intervention.

Support, problem solving, and restructuring can be effective family interventions at individual, system, or community-relations levels. For example, the overwhelmed wife of a husband with a brain injury may need structure and guided problem solving in deciding how to manage a family on limited resources. A large family whose mother returns home after a brain injury may need to sit down as a group and negotiate how family responsibilities should be reapportioned and deal with the inevitable feelings and conflicts generated by that process. The family that feels trapped at home with an impulsive and aggressive teenage son may need help in finding creative ways to maintain social relationships in the community or even how to take vacations. This level of intervention requires an active therapist who knows the realities of adjusting to brain injury and builds on the strengths and problem-solving capacities of the family and its individual members. As noted earlier, in the section on review of research, there is increasing evidence that social support moderates how families function and how much burden caregivers experience. Sometimes, helping families negotiate transportation, figure out a way to pay for a piece of equipment, or find a weekend social program for their child is a more needed and effective intervention than ideas and psychological discussion.

Formal therapy becomes appropriate when severe problems render the family system, or some part of it, dysfunctional. The stress and family changes inherent in TBI may cause family members to need individual therapy (often because the injured person is a family member previously seen as strong, such as a sibling or child). Individual family members who benefit from psychotherapy usually begin with issues related to brain injury but often end up dealing with longer-standing personal or family-of-origin

issues. This is what distinguishes this level of intervention from the previous two: all families benefit from education and problem solving; some family members require longer-term formal treatment because of issues outside the event of TBI. The same holds true for the family as a system. Families that were dysfunctional before the injury may require formal family therapy after the injury, with the added complication of learning to adjust their family structure. Decisions about the nature of this family therapy, and the extent to which the person with brain injury will be able to fully participate, should be on the basis of individual circumstances and the injured person's neurobehavioral competence.

Stages of Intervention

The impact of TBI on the family can be conceptualized in three broad stages: 1) acute stage, 2) rehabilitation stage, and 3) community reintegration stage, being fully aware that the third stage is open-ended and itself contains numerous subphases. This broad division, however, is useful in conceptualizing the nature of interventions that must be made during each stage. Figure 31–3 illustrates the concept that at each of these temporal stages, interventions can be conceptualized at the three levels (information and education; support, problem solving, and restructuring; formal therapy) and within the three concentric domains (individual, family, community) described in the preceding sections.

In the *acute stage,* in which the primary issues are survival, medical stabilization, and minimization of permanent damage, the family generally coalesces, suspends normal routines, and orients all of its energy toward the care of the injured person. This is a period of crisis intervention when education and information are crucial. Emotional support and permission to break standard family routines also are important. Later within this stage, when survival is assured, the family must quickly evaluate treatment options and insurance realities. Family intervention should be aimed at helping the family to cope effectively on numerous fronts while still in shock, including practical daily realities, emotional distress, and major decision making.

The *rehabilitation stage* is defined as the intermediate stage during which formal restorative treatment, inpatient or outpatient, is the primary family focus. This is a time when high expectations for recovery predominate, and the family begins the task of receiving the injured person back into the family system and making the necessary structural adjustments. Family roles are reorganized, and the goal is the restoration of as much physical and cognitive functioning as possible after brain injury. During this stage, there is initially relief at survival and great hope for recovery, which the therapist should support, while gradually tempering hope with cautious reality. Even when therapists realistically assess severe limits of long-term functioning, families may be angered and alienated if this message is presented prematurely or too starkly. It is much better to help families gradually realize (rather than be told) emerging limitations through experience. It is during this stage when major family role restructuring often takes place, and individuals may need help in adjusting to their new roles. Toward the end of the rehabilitation stage, it will begin to become apparent that even though formal treatment is ending, complete recovery has not occurred, and the family faces the prospect of living with a permanently disabled person. This is a crucial time for intervention, when the therapist begins to deal with the anxieties and fears of the family.

The *community reintegration stage,* as noted in the subsection Concentric Circles of Intervention, refers both to the person with brain injury and to the family system as they struggle to reenter community life under drastically changed circumstances. This phase is the lengthiest and most difficult and involves integration in two senses. First, the injured person is completing formal treatment and is, as much as possible, becoming gradually reintegrated into the community (e.g., socially and vocationally). Second, this is a time of reintegration for the family system. Expectations for complete recovery begin to recede as the reality of permanent neurobehavioral impairment in the injured person becomes apparent, and the family system attempts to strike a new, more permanent balance to allow its various members to proceed with their own lives. There is enormous variability during this final phase, which itself is composed of a series of stages of internal adjustment. The individual recovering from the injury attempts to return as much as possible to a level of maximum engagement and productivity in the community, while the family settles into longer-term patterns and equilibrium that allow them to resume their family life cycle with an altered identity. This is when discouragement, depression, despair, and mourning begin to occur, often over the first few years after the end of rehabilitation. Family interventions usually become more needed, more intense, and longer term. The crucial turning point occurs when, after all formal rehabilitation ends, the family as a system faces the challenge of being able to reconstitute as an effective and functional system with a new balance and identity. Not all families are able to do so. In families who cannot, the life cycle is seriously disrupted, and individual members may be blocked from making natural life transitions in a healthy way. For example, a busy professional couple may be unable to reorganize their time and finances to care for a severely injured son who lives at home, and that role may fall to a teenage daughter. If she becomes trapped in that role, she may stay home after high school and devote herself to caring for her brother, with the result that her own development (college, career, boyfriends, marriage) may be seriously blocked. Depending on her nature, she may either become seriously depressed or sacrifice herself for the sake of the family to her long-term "detriment." In working with such families, clinicians must be careful to sort out what is detrimental in their eyes from what is detrimental in the eyes of different family members. The decision to intervene when the self-sacrifice is in the service of homeostasis raises difficult countertransference and ethical issues, which must be dealt with honestly both by the therapist and directly with the family. Often, it is when a family member reaches a developmental transition (e.g., when the caregiving daughter's friends begin to marry) that the family becomes destabilized and productive intervention can begin.

Even when families do make the transition and their life cycle resumes, transitional points can bring episodic

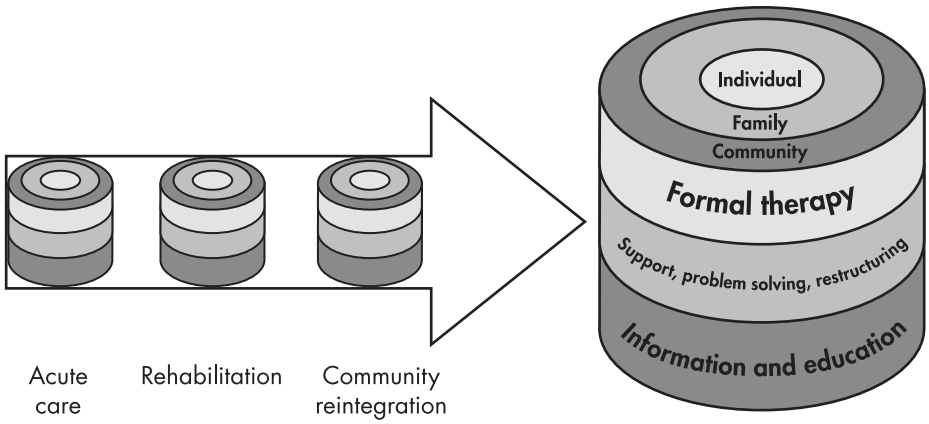


FIGURE 31–3. Stages of intervention.

loss and mourning (see Family Responses to TBI: Stage Theories). For example, a family may adapt quite well to a severe TBI in a young child, but when his or her peers begin Little League and the child does not, or when dating, high school graduation, college, and marriage do not occur as they naturally would, there is sadness for the family and a retouching of old hurts and losses. It is crucial during this period to help families build on their strength and dignity, and especially important to enable the person with the brain injury to find a productive and meaningful place in the family, with peers, and in the community.

The relationship of the family to the community is particularly important during this stage. Families need to learn to draw comfortably on the existing resources of extended family, friends, employers, churches, and other community organizations and to resist the tendency to become isolated, ashamed, and self-conscious or to shield the community from the injured person (although the conscious motive is usually the opposite). Family interventions should include a circle of support that is often wider than would initially be comfortable for the family. Family-to-family programs, self-help groups, family outreach and advocacy, and community networking are all concepts that the savvy family therapist uses (Williams and Savage 1991). Family intervention at this final stage of reintegration should move beyond the confines of the office into the community.

Long-Term Issues

In the acute care and rehabilitation phases, as well as early in the community reintegration phase, most professional intervention provided to the family takes place within a medical model of service provision. As noted in the preceding section, once the family moves into the community reintegration phase, medical model supports become less available and, possibly, less useful, and the family's relationship to the community and community-based supports becomes more salient. In the past, community-based supports after TBI took the form of either informal family and community organizations (e.g., churches) or TBI-specific self-help groups that provide services such as educational materials, support groups, and mentoring or family-to-family programs, all of which are useful and important. However, in recent years, a variety of professional long-term community-based supports have become available. In fact, as funding for short-term medical model rehabilitation services has become more restricted (because of the influence of the managed care environment), funding streams, usually in the form of Medicaid waivers or trust funds supported by fees on (for example) drunk drivers, have allowed for the proliferation of a variety of previously unavailable long-term community-based support systems (Digre et al. 1994; Rosen and Reynolds 1994; Spearman et al. 2001). Such supports—which are not equally available throughout the country—may include long-term service coordination (case management), in-home supervision and skill training, substance abuse services, and day programs.

Regarding community-based day programs (as opposed to medical model day treatment programs), probably the most widely known model is that of the Clubhouse, but in recent years other excellent models specific to the needs of individuals with TBI have developed. The Community-Based Day Rehabilitation model developed through the TBI Services Department at the Association for the Help of Retarded Children in New York City (www.ahrcnyc.org) serves as an example of an approach to providing long-term (lifelong if necessary) services to individuals with TBI within a day program environment. In this model, individuals attend a 6-hour-per-day program for as many days as they choose (Monday through Friday). They set individual goals with the assistance and guidance of staff and family members. These goals may change as the needs of the individuals change across their life span. The individuals may attend the program as long as needed. For some, it is an excellent stepping stone for vocational advancement; for others, it may potentially provide a lifelong learning and socialization environment. The program provides a variety of in-house cognitive, psychosocial, and skill groups and activities, but the primary work and socialization activities take place outside of the program site at a wide variety of settings within the community. Individuals choose the community activities they wish to be involved in and may go on a daily basis to community activities of their choice. They are accompanied into the

community by a small group of peers (usually three other participants) and a staff person. Activities vary but are always associated with skill development. The overall goals of the program are the development and enhancement of skills, use of compensatory strategies in an increased variety of settings, increased awareness, increased socialization opportunities, and community inclusion.

The key points are that these community-based supports are long term, supportive, person centered, and driven by the person being served. These types of supports are extremely helpful to families in the long run. The service coordination aspect alone relieves families of much of the logistical and practical, if not emotional, burdens. They also provide for ongoing interventions as needed. Some may even provide community living opportunities for individuals with an injury, which may help normalize as much as possible the family role and life cycle issues.

Over the long term, the issues families deal with tend to become more focused on quality of life rather than on the restoration of specific functions and abilities. Issues such as employment or productivity, intimacy, sexuality, and community inclusion become primary. In our experience, there is an ongoing sense of loss and visible grieving, not just by family members but also by the individuals themselves about their "lost self"—who they used to be, who they thought they were going to become, and their lost abilities and plans for the future. This may become less prominent with increased socialization opportunities and increased success in the community but rarely entirely disappears. In working with families whose member was injured 10, 15, or even 20 years earlier, we still see grief, anger, guilt, and even denial. The usual pattern is that these emotions erupt periodically and present in waves and appear to be the clinical manifestations of what we have described as episodic loss reactions or chronic sorrow (see Family Responses to TBI: Stage Theories).

Another interesting clinical observation is how family members will sometimes actively resist even positive change in the individual with TBI if it involves increased autonomy within the family and/or community or self-advocacy. Sometimes, what staff may see as progress in individuals with TBI in self-care, autonomy, or the ability to make decisions for themselves, the family sees as increased noncompliance with the newly established family routines, roles, and rules or as potentially dangerous situations. This may stem from fear for and protectiveness of the injured individual and from the many years of struggling to establish a new family homeostasis. Family members may have been forced to take on a greater role in the supervision and care of the injured individual. This may have become the new and accepted dynamic in the family, and disrupting it, even by positive change or opportunities, may lead to a need for further family restructuring and education. Families need support and guidance through this process.

Dealing With "Unrealistic" Family Expectations

It is not uncommon for families to express goals, hopes, and expectations for the person with the brain injury that, in the judgment of the clinician, are simply not possible. When families react to such feedback with resistance, skepticism, or even anger, clinicians often see the family as being unaware, or in denial, and in need of education. Such scenarios often generate significant negative feelings and even outright conflict. How much is this the family's problem or the clinician's problem in knowing how to deal with the family?

Often, the clinician can diffuse such potential conflict and find a way of working with the family around the goals in question without placing the family in a position of giving up hope. Doing so requires a good bit of clinical savvy and use of language that permits the clinician to participate in exploration of certain goals and their feasibility without abandoning his or her clinical point of view. The following principles are meant as possible tools for the clinician to use to work his or her way through difficult situations in which the family is expressing expectations and goals that appear unrealistic from the clinician's point of view.

Principle #1: Ask the Person With the Injury What He or She Wants. Sometimes, clinicians become so caught up dealing with family expectations and demands that they fight the battle of what is realistic without ever inquiring what the injured person wants. Even though parents may be insistent that their injured son will go back to law school, the eager-to-please son may be harboring his own doubts about whether he still wants to do so. Sometimes, it takes a number of sessions privately with the injured adolescent or young adult to help the person sort out what his or her goals are and how they may be different from the goals of the rest of the family.

Principle #2: Realities Are Subjective, and They Differ. Remember what any good marital therapist knows: each person's set of perceptions is absolutely real for them. To forcefully challenge the person's perceptions is tantamount to invalidating the person. Perceptions are driven not by cold, clear observation of obvious facts but by interpretations of cues that pass through a series of emotional filters. Families who express goals for the person with TBI that seem wildly unrealistic to a clinician are expressing hopes that may be coming from sacred places. These hopes must be dealt with gently and with respect. At the very least, do not immediately and offhandedly dismiss these hopes as unrealistic; it will be experienced as a crushing blow by the family, and you may lose them to work with. Show an interest in the goals and a willingness to discuss them.

Principle #3: We Do Not Know. Many families have had experience with professionals who made pronouncements that turned out to be false (e.g., "Your loved one will not survive"; "He survived, but he will not come out of the coma"; "He came out of the coma, but he will not communicate meaningfully"; "He communicates, but he will not walk"; "He walks, but he will not be independent"). Even in less severe cases, we really do not know what any given individual will be capable of—in both directions. Patients who look like they will make good recoveries languish; patients with severe impairments make achievements never

dreamed possible. Clinicians develop a set of expectations on the basis of probabilities derived from experience. However, if it is true that 95% of people with a given level of deficit will not go back to work, then 5% will. How does one know if this family represents the exception and not the rule? Clinicians owe it to the family to keep their minds open.

Principle #4: Never Underestimate Motivation. We have seen people with severe brain injury being told in no uncertain terms they will never be able to work again—only to do so—and injured students being told that college would be impossible—who earned their degrees. In these cases, the professionals did not so much misjudge the severity of the injury as underestimate the motivation of the injured person and the family. This does not mean that all families will succeed at what they put their minds to; it does mean that clinicians should not short circuit the power of families who have a strong need to achieve a goal until they have given themselves a chance to try. Just as it is impossible to force a person with brain injury and his or her family to move in a direction they do not want to go, so, too, it is wise to see what motivates a patient or family and ride it as far as possible. The following principles are ways of encouraging a family's motivation, by endorsing the *spirit* of their goal, without necessarily endorsing the ultimate goal itself.

Principle #5: Elaborate and Collaborate: Find a Way of Endorsing the "Spirit of the Goal." Elaboration and collaboration can be done in two major ways: break the goal down into steps and take one at a time, and find the spirit of the goal and substitute reasonable alternatives.

(1) Break the goal down into steps and take one at a time. In practice, because families are often unrealistic about future goals soon after brain injury, it is most often the case that the spirit of the goal is identified first and then broken down into transitional steps that can be taken one at a time, as illustrated by the following example. A bright young woman in college had the (realistic) goal of becoming a doctor. After a TBI, she has significant memory and executive deficits. Her parents believe it is still possible for her to succeed and want her to resume college and take the Medical College Admission Test. The clinicians are absolutely convinced this is not possible. What options do the clinicians have?

One option is to confront the parents, saying that the goal is unrealistic. This is likely to provoke resistance and conflict. If the implications of their daughter's deficits were obvious, the parents would not be taking this stance in the first place. They are not likely to meekly respond by saying, "Oh, you're right, we never noticed that." Their expectations express deep-seated needs and hopes on their part, coupled with a willingness to believe that recovery, therapy, and determination will enable their daughter to achieve her goal.

A smarter, more complex response is to first talk about what is required in medical school and in the practice of medicine and to relate those requirements to the changes in the young woman because of the injury that can be observed by the parents and clinicians. This engages the parents in a collaborative process of discovery to see how they respond to the explicit consideration of demands and capacities. Some families, in the face of such explicit comparison (which they probably have never done), begin on their own to modify their expectations. Other families admit skepticism but are clear about wanting to move forward. Other families may in fact be in full-blown denial—but again, contradicting them only fuels the denial (because it is acting as a defense mechanism).

When families remain determined to pursue goals professionals view as unrealistic, the best course of action is to break that goal down into component parts, and say "OK, let's take it one step at a time, and see how far we can go." It is perfectly fine for the clinician to express concerns that certain aspects of the demands may become too difficult for the injured person to handle. The process is then to implement the first step with support, see how it goes, and keep implementing steps as long as the person is succeeding. Ongoing monitoring and discussion are essential to evaluate progress and potential.

The medically aspiring young woman might enroll for a single course in a local community college (a far cry from applying to medical school, but that goal is not being explicitly rejected). Can she manage course reading? Can she take notes? What assistance does she need on examinations and papers? After she has taken one or two courses, the decision may be made for her to return to her college—or perhaps transfer to one with better support for students with disabilities. There she can take a science course or two and see how it goes.

The progression is obvious. By breaking the "unrealistic" goal down into steps, the professional can support each individual step and let the decision about how realistic medical school emerge from the process itself, rather than being mandated a priori. When it is in fact unrealistic, both the injured person and his or her family will gradually realize that and be more at peace with letting go of the goal because they gave it their best shot.

(2) Find the spirit of the goal and substitute reasonable alternatives. Many times, it is possible to discover the motivation behind a particular goal that may be unrealistic and satisfy the underlying need by substituting another, more reasonable goal. Most commonly, this process begins when an original goal has been broken down into steps and it becomes clear that the original goal is not achievable.

Many young persons with TBI become attached to and want to model themselves after therapists in their rehabilitation. One particular girl, a high school sophomore, loved her occupational therapist (OT) and on returning to school announced that becoming an OT was her career goal. The girl had severe visual problems, severe motor integration problems, and poor short-term memory. Her family was, at least superficially, supportive of her goals and told others of her plans.

There are two mistakes the professional can make in this scenario, at both extremes. The first is telling the girl and her family, point blank, that becoming an OT is an impossible goal. (This does not preclude serious discussions with the parents about what the obstacles would be.) This would prematurely deprive the girl of a much-needed aspiration and the reconstruction of her self-esteem by

denying her a model with whom to identify. It could do significant harm. The other mistake is the opposite: to fully endorse the goal and reassure the girl that everyone will do everything possible to help her achieve that goal. That would feed into her unawareness or denial of the implications of her deficits, or both, and set her up for a particularly devastating failure.

The best path is the process of discovery (e.g., "OK, what do you need to do to go to OT school?" "What kinds of classes do you need to be able to pass? Let's give one a try"). When students return to school after severe brain injury, there is a benign tendency to grade them by their effort, not their achievement. In this example, it is important that the grade given the girl be a realistic one on the basis of the course expectations. It will probably become clear over the course of a semester that a diet of science is not realistic.

It is at this point that one is ready to explore the spirit of why the girl wanted to be an OT. Helping others, making suffering go away, or enabling a person to learn and succeed may emerge as the driving forces. It is then possible to explore other career or volunteer options that can meet those needs and give the girl an experience doing them in a supervised setting. But exploring the spirit of the goal in search of an alternative cannot take place until the injured person—as well as his or her family—is ready to let go of the original goal.

Principle #6: Use Controlled Failure (the Dignity of Risk). As much as clinicians would like to save clients and their families additional pain, that is not always possible. There are times when all else fails and the injured person and family insist on embarking on a path that the clinician deems unrealistic. This may range from applying to college to returning to a job. Often, the reality is that the only way a family will confront the impossibility of a goal is to try it and fail. The key is to set up a safety net in the event the person fails. The wrong thing to do is simply say, "OK, give it a try," then shrug your shoulders and walk away. Setting up support services for the person, keeping clinical contact as he or she starts the process, identifying in advance what the difficult areas will be, and having a contingency plan if all comes crashing down are the responsible clinical approaches. That way, the injured person is protected as he or she comes to terms with what the clinician knew: that the goal was unrealistic. Then again—the patient might fool the clinician and succeed.

The one exception to allowing controlled failure is when the cost of failure could be catastrophic in terms of human or financial well-being. A trader responsible for millions of dollars a day, an air traffic controller, or a surgeon should not be let loose to "see what happens," no matter how reliable the safety net. However, even in high-risk situations, it is often possible to create a supervised, less risky, job. Doctors, for example, can perform limited parts of examinations under supervision. But when the cost of failure is potentially too high, the risk of uncontrolled experimentation simply cannot be taken.

Principle #7: Be Prepared to Challenge Overprotective Families That Are Negatively Unrealistic. A separate problem, but one that falls under the category of unrealistic families, is the overprotective family that underestimates the capacities of the injured person. Most often, this occurs with persons with more severe injuries who have realistically significant limitations. However, the family, in the desire to protect the vulnerable family member, fails to appreciate capacities that the person has or risks that are reasonable to take. This usually occurs with people with frontal lobe injuries whose judgment may be compromised or people with unstable medical conditions such as partially controlled seizures. The unpredictability of the injured person's behavior triggers an overprotective fear response on the part of the family. Such families may block efforts at continuing education, job trials, dating, or independent travel or living.

A number of strategies may be helpful to the clinician in this case. First and foremost is turning attention away from the person with the TBI to the fears of the family members in a position of decision making. An honest discussion of (usually parental) fears, coupled with a practical discussion of the risks involved (how realistic the risks are and what steps could be taken to minimize them), is often helpful. Second, it is often productive to sit down together with the person with TBI and the family to discuss goals and see if it is possible to set up a series of compromise steps that will allow a discovery of what is realistically possible.

For example, a young woman with a severe brain injury may be interested in learning to travel independently between her home and a job trial site. Her family, which may be all in favor of her having a job, may veto the goal of independent travel on the grounds that it is unsafe. To discuss this decision in the abstract may be unproductive. More helpful might be the approach taken in principle #5 as outlined in the preceding section: elaborate and collaborate. A multistep approach to travel training might be put forth explicitly as a compromise measure: it satisfies the injured person's desire to see how independent she can become in travel while satisfying the family's need to maintain a level of protection. Thus, the client might be guided to the work site, then develop a map and set of steps to follow, then accompanied one more time but encouraged to make her own decisions, then accompanied but tailed only, and so forth. Between each step, family members could be told how things went, and their consent could be sought for taking the next step.

As with any program of deconditioning, the idea is to introduce at each step a goal that has a high probability of success and that arouses a minimum amount of anxiety. Such an approach sidesteps the major conflict of whether the family will allow the injured person to travel alone and introduces a stepwise process of gradual challenge in which the family is never asked to lose control of the process. Allowing families to retain a sense of control and safety in decisions about the injured person is a key concept in dealing with unrealistic expectations.

The preceding principles are not all-inclusive. They are meant to represent some of the guidelines professionals can use when confronted with families whose goals are thought to be unrealistic. The key is to join with the family to develop a process of moving toward a goal to discover how realistic it is or to see if it can be reshaped in some way that works for the injured person. Simply telling the family that goals are unrealistic almost never works. It does not deter family members, and clinicians lose their ability to work with the family.

Special Issues

Family Issues in Mild TBI

A special set of dynamics applies to mild TBI (see Chapter 15, Mild Brain Injury), which deviates somewhat from some of the principles outlined in this chapter. Mild TBI refers to injuries with brief or no loss of consciousness, no long-term focal neurological abnormalities, usually normal computed tomography scans and magnetic resonance imaging studies, and a constellation of symptoms, including headache, irritability, fatigue, sleep disturbance, depression, anxiety, poor self-esteem, general inability to function, and poor attention, concentration, and memory (Kay 1986). Psychological overlay can accumulate with time and increases dysfunction, which usually reflects a complex interaction among organic, personality, and environmental factors. In many cases, a legitimate, if subtle, brain injury underlies and drives the dysfunction, which is layered over with maladaptive psychological reactions, many of which result from inappropriate environmental responses (Kay 1992).

In moderate to severe brain injury, although the family tends to rally around, support, and advocate for the injured person, one often sees a picture of initial concern followed by increasing alienation in families after mild TBI. This shift is the result of the injured person's apparent normalcy in the presence of his or her anxiety, depression, loss of self-esteem, and increasing dysfunction over time.

An essential part of any neuropsychiatric treatment of such complex and difficult cases is immediate family involvement. Family responses and reactions to the apparent discrepancy between severity of injury and severity of symptoms can either induce or exacerbate a dysfunctional postconcussional syndrome. The family needs information and education about the nature and consequences of concussion and how to understand and help the patient manage his or her symptoms. Also, any alienation that develops between the injured person and the family should be healed. Often, this involves addressing old issues, either intrapersonal or within the family system, which are in fact contributing to the excessive level of dysfunction. It is a mistake to see the obvious emotional overlay in such cases and dismiss the injured person as malingering or the problems as purely psychosomatic ones. The individual cannot be helped back to a level of productive functioning without addressing what is often a deteriorated family situation.

Parents and the School System

The normal relationship of parents and school is dramatically altered when a child has a TBI. The keys to successful adjustment for a student with TBI—from prekindergarten through high school—are contact, communication, consistency, and flexibility.

Contact

Unless the school is familiar with students with TBI and has special procedures in place (which is unusual and unlikely), the parents will need to be the ones to initiate contact with the school around the special needs of their child. This should start long before the child is ready to return to school—soon after the accident has occurred while the child is still in the acute or rehabilitation stage. The school should be apprised of the child's injury and school materials made available to rehabilitation professionals at the appropriate time. When the child is nearing discharge home, the parents need to make sure the rehabilitation team is putting together recommendations for school needs and help the team contact the appropriate school personnel. The parents should ask to sit down and meet with school staff in advance of the child's return and not be afraid to bring with them a member of the rehabilitation team or other expert in the community on TBI and education. Depending on the severity of the injury, the time since injury, and the student's stamina, the return to school may need to be gradual. Again, the parents should take the lead in contacting the school to work out these decisions. As the child's school career progresses, there may be need for special evaluations or special services. Parents should be assertive in contacting the school about such special needs. They should not be afraid to identify advocates within the community and include them in school meetings. This does not mean there needs to be an adversarial relationship between the parents and the school. Quite the opposite: the goal is to establish a collaborative working relationship in which both school staff and parents are focusing on what is in the child's best interest. The message, however, is that the parents should be prepared to initiate contacts with the school around the child's needs.

Communication

Three levels of communication are critical when a child returns to school after a TBI: 1) between parents and school, 2) among those persons working with the child within the school, and 3) between the school and professionals working with the child outside the school. First, parents need to take the initiative to meet on a regular basis with the teacher(s) and service providers within the school. This is particularly true on the child's school reentry, at the beginning of each school year or semester, or both (when teachers and classes may be changing). Periodic team meetings with all involved persons should be the goal. More frequent face-to-face or telephone contact with the classroom or research room or homeroom teacher is appropriate. For younger children, a communications book in which the teachers, parents, and therapists write notes, requests, and concerns is often extremely helpful. Assignments should be checked for clarity so parents can monitor homework when necessary. Second, it is equally important that the child's school program be integrated—that is, that all the teachers and therapists are communicating with each other about their goals and the strategies they are using. When parents sense communication is not happening internally and services are becoming fragmented, it is appropriate for them to request that the school arrange time for the persons involved with the child to meet on a regular basis. Third, it is also important that there be communication between the school and those professionals treating the child outside the school setting.

For example, physical therapists and occupational therapists within and outside the school should communicate about their goals and strategies to learn from each other. It is also important that there be an open line of communication between the school and physicians, especially around behavioral issues, when seizures are suspected or when medication is an issue. Physicians need input from the school on the child's behavior, and the school needs to know when medical changes have been made. It is the parents' responsibility to allow and foster such open communication.

Consistency

A child with TBI thrives most when there is consistency of approach between school and home. This is true in both cognitive and behavioral domains. When parents are involved in helping with homework, which they often are, they should discuss with teachers and therapists which compensatory strategies work best, and there should be consistency of implementation of these strategies across home and school settings as well as consistency across internal school settings. (For example, the history teacher, the science teacher, and the parents all should be using the same approach in helping a child with executive deficits develop a topic and outline for a paper.) Behaviorally, it is even more critical that difficult behaviors be dealt with in consistent ways at home and at school. This requires communication and problem solving on the part of parents, teachers, and school professionals. In the absence of such communication and consistency, the child's behavioral problems are likely to become worse.

Flexibility

It is critical that parents and school personnel be flexible in their approaches to children with TBI. Children are developing rapidly, especially in their earlier years, even as they undergo recovery from the injury and the changing demands of new teachers, classes, routines, and schools. What is needed and working one semester may change the following semester or next school year. The child with TBI is especially at risk for breakdown at major transition points, including new teachers, moving from one classroom to multiple classes, and changing schools. As children grow older and as the demands for more abstract and integrative thinking as well as for more independent and self-generated work increase, the need for academic assistance may increase. Individualized education programs may need to be revised on a more frequent basis than for other children. Teachers and parents should remain flexible in the approach they are taking with the child and communicate regularly to maintain consistency.

Legal Issues

Legal issues are touchy, and most professionals are wary of addressing them with families. Although it is certainly inappropriate for medical professionals to become involved in personal family matters regarding suing for damages and choosing lawyers, there are ethical responsibilities about informing families about long-term care needs of the injured person and helping families avoid critical mistakes early on that will permanently prevent the injured person from receiving the resources he or she deserves. In our opinion, there are two circumstances in which medical professionals are justified in counseling families about legal issues.

First, not all personal injury lawyers are sophisticated in bringing injury cases to settlement or trial. They may terribly underestimate the long-term disability of the person and simply not be aware of what the long-term costs will be in terms of lost wages and care needs. This is especially true in severe injuries in which executive dysfunction may not be apparent in protected environments (including the lawyer's office) and in cases of mild brain injury. We have seen many families who were counseled by lawyers to settle early for sums of money grossly inadequate to care for the person in the long term and who bitterly look back on their legal advice wishing they knew then what they know now. When a clinician senses this is happening, we believe there are ethical grounds for discussing the situation with the family and urging them to seek consultation from a law firm more savvy and experienced in handling TBI cases.

Second, special situations exist with children who sustain a TBI at an early age. Many children "grow into" their deficits as the demands of school become greater and more complex and require more frontal lobe processing. Often, it is difficult to assess the long-term effect of a TBI on a child until he or she has worked his or her way through the school system. Many lawyers familiar with TBI in children prefer to wait years to try the case, except when the damages are immediately catastrophic and apparent. The failure to wait may mean families will accept a small settlement and then have an adolescent who is unable to support him- or herself and is genuinely in need of longer-term support. However, the risk of waiting to try the case is that other intervening events or variables over the years may cloud the picture and make it much more difficult in later years to tease out the impact of an early injury. In our opinion, in cases in which the child is too young for the true effect of the injury to be determined, and if the family is being pressured to accept a small, immediate settlement, there are ethical grounds for the clinician to discuss the legal issues with the family and to urge discussion of the issues with a lawyer as well.

Military Families

The conflicts in Afghanistan and Iraq have resulted in a whole new population of individuals with brain injury returning to their communities and their families. Most of these injuries are described as *polytrauma* (Department of Veterans Affairs 2005; Lew et al. 2007), which is defined as injury to the brain and several other body areas or organ systems, primarily caused by blast injuries, which are often the cause of skull fractures, amputations, and mild TBI, which then make the soldier more prone to posttraumatic stress disorder (Trudeau et al. 1998; Warden 2006). Pure TBI (without other injuries and comorbid psychological ramifications) is rare. It is too early for there to be a large body of literature exploring the unique family issues for returning military personnel with brain injury, and in fact a review of the literature on family adjustment of soldiers with brain injuries uncovered no literature focused on family adjustment. The little information available is primarily anecdotal and published in newspapers and magazines. For example, an AARP magazine article, "When Wounded Vets Come Home"

(Yeoman 2008), focused on parents being thrust into the role of long-term caregiving. The author wrote:

> For many of the newly injured, most in their late teens and 20s, the logical direction to turn for care is toward Mom and Dad. Many of the wounded are single. Others are married to partners who can't or don't want to care for gravely injured spouses. As a result, across the nation, parents end up scrubbing burn wounds, suctioning tracheotomy tubes, and bathing adult children. They assist with physical and occupational therapy. They fight for benefits. They deal with mental health crises and help children who have brain injuries to relearn skills. They drive back and forth to VA [Veterans Affairs] hospitals for outpatient appointments. In short, they put their lives on hold. (Yeoman 2008, pp. 62–63)

An article by Grafman et al. (1996), which focused on frontal lobe injuries in Vietnam veterans, found that veterans with TBI were reported by family members or close friends to be more violent than veterans without brain injury, that these behaviors took a significant toll on the daily life of family and friends of the veteran with TBI, but that family and friends were not likely to seek help but rather resigned themselves to coping the best they could.

These descriptions are eerily similar to descriptions of family involvement and response in the early TBI literature described in the beginning of this article (phases I and II in the evolution of TBI family research). However, we must ask what are the possible areas that are unique to families of military personnel who have TBI, usually in the context of these polytrauma injuries and the military culture. For examples, Okie (2006) described the challenges of providing veterans with medical, vocational, and emotional support in the context of the stigma injured soldiers tend to attach to seeking help.

Brain Injury Association of America and Other Support Organizations

The National Head Injury Foundation was founded in 1980 by Marilyn Price Spivack and Martin Spivack and a small group of families and professionals in Framingham, Massachusetts, because of the unmet needs of their brain-injured daughter. Today known as the Brain Injury Association of America, it has grown into a national advocacy organization headquartered in Vienna, Virginia, with affiliated chapters in most states. The association encourages active participation of persons with brain injury, family members, and professionals; provides educational materials to families and professionals; organizes support groups at the local level; and acts as an advocacy organization at the state and national level for public policies and laws that support persons with brain injury and their families. At the professional level, the Brain Injury Association of America provides numerous opportunities for involvement through committees, task forces, and national conventions. The Brain Injury Association of America can be reached via its website (www.biausa.org), by phone (703-761-0750; toll-free hotline, 800-444-6443), or by mail (Brain Injury Association of America, 1608 Spring Hill Road, Suite 110, Vienna, VA 22182). All associated state chapters can also be found through the website or by contacting the Brain Injury Association of America directly.

Family Individuality and Coping

Chapters such as this one can be written only by generalizing about families. A fitting way to end is with the caveat that each family is different. The effective clinician responds to the conscious and unconscious needs of an individual family and does not project onto the family his or her value system of what healthy adjustment is. Precisely because the person with brain injury is dependent on a network of significant others for his or her successful adaptation to disability, successful family intervention must proceed from within the framework of the unique family system. The rehabilitation team will not successfully impose goals, limits, or routines that are alien to the family. It is the role of the family therapist to help families meet needs, establish a new balance and identity that works for them, and negotiate a productive alliance between the rehabilitation team and the family. This can be done only by starting—and ending—with a healthy respect for the family's individuality.

KEY CLINICAL POINTS

- TBI causes profound changes in every family system. The family must deal with changes in the person with TBI; in the roles of multiple family members; and in dependency, intimacy, finances, and expectations. They must deal with these changes over the course of the life of the person and the family.
- In general, stress or burden on family members is greatest for emotional, behavioral, and personality changes such as anger outbursts or social insensitivity; moderate stress or burden accompanies cognitive deficits such as memory and concentration problems; and physical problems are dealt with most successfully.
- Family needs will differ depending on the role of the injured person in the family, when in the life cycle the injury occurred, the person's current stage in the life cycle, and where he or she is in the recovery and rehabilitation process.

- Family intervention after brain injury should consist primarily of providing education, information, support, and assistance with problem solving and restructuring.
- It is the role of the professional to facilitate the resources and solutions needed by families to adjust and reestablish a sense of balance.

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CHAPTER 32

Systems of Care

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IN TERMS OF SHEER NUMBERS OF CASES, PATIENTS with mild and moderate traumatic brain injury (TBI) far outnumber the severely injured, and frequently these are essentially physically independent individuals struggling with isolated psychiatric problems of depression, posttraumatic stress disorder, anxiety reactions, and less severe cognitive and behavioral disturbances. Appropriate psychological and psychiatric care, as detailed in the chapters of this textbook, is essential. For the more severely injured patient with TBI, however, a more complex pattern of care is typical. The aim of this chapter is to provide a general overview of the treatment environment that will be the backdrop for most neuropsychiatric care. It is hoped that as more awareness of these parallel resources emerges, a better integration between them will occur, to the benefit of the patients and families enduring the consequences of TBI. In this chapter we also describe public and private sources of funding and the efforts of state governments (in part as a source of funding) to address gaps in the system and encourage the development of needed services.

Rehabilitation and Community Systems

Need for Systems and Concept for Systems

Too often psychiatric or behavioral health care for individuals with TBI has been provided in isolation from and in disregard for existing rehabilitation systems. This isolation has led to redundancy of care as well as failure by each system to garner the full value of the expertise in the other. In this chapter we explore critical elements of the existing TBI service delivery system, recognizing that this system still fails to provide comprehensive and coordinated care for the great majority of individuals who experience TBI because of financial or geographic barriers that prevent the individuals' access to services. This failure reflects the disjointed policy and funding of American health service delivery pointedly discussed in the Institute of Medicine's *Crossing the Quality Chasm: A New Health System for the 21st Century* (2001). Yet a system has emerged over the last 30 to 35 years, spurred by the demands of families in need of services, growing recognition of the size and cost of TBI, and growth in available treatment approaches based in part on federally funded research in TBI. Elements of the system include various settings of care, clinical disciplines, and funding and policy guidelines. Operation Iraqi Freedom and Operation Enduring Freedom (Afghanistan) (OIF/OEF) and the identification of brain injury as the signature injury of these wars have affected all elements of this system (Tanielian 2008).

Just as no two brain injuries are entirely alike in terms of resulting disabilities, the course of treatment, rehabilitation, and supports vary with each person with a TBI. With the possible exception of some mild injuries, current thinking requires that individuals with TBI, with its multiple and varied impairments, be treated and supported by a diverse group of clinicians, other professionals, and providers in a variety of settings in order to achieve optimum results. The clinician who undertakes to provide psychiatric or behavioral health care, as well as those who provide ongoing supports, to this population should have a basic understanding of this range and sequence of services and supports as well as specific resources available in his or her region of practice. Psychiatric interventions thus can be integrated into the broader context; and, in the instances where the psychiatric clinician is primary in coordination of care, he or she can efficiently and appropriately refer to these services for his or her patients with TBI.

As some behavioral health issues emerge after the individual is discharged from a hospital or rehabilitation setting, families, caregivers, and community support providers at that point may need assistance with appropriate and ongoing treatment and supports. An ideal system is one that not only addresses the upfront acute and rehabilitation care and transition but also has capacity for ongoing interventions, crisis management, and supports that can be put in place to assist the individual in any setting, whether at home, school, work, or community.

The genesis of the system concept of care for TBI, to the extent it can be delineated, lies with two seminal grants in 1977 by the Federal Rehabilitation Services Administration to New York University and Stanford University. These centers were the first to systematically investigate the long-term treatment and support needs and outcomes of survivors of severe TBI. These investigations concluded that the treatment of TBI required a multidisciplinary approach, applied both longitudinally over the course of initial recovery as well as in multiple settings beyond the traditional hospital-based care delivery sites previously extant (Berroll et al. 1982). Since that time, the experience and reports of these model system centers has stimulated an enormous growth over the past generation of multiple treatment options and approaches for TBI. This federal support of the systematic processes of care requirements, outcomes, and other treatment and needs research has continued to this day and has expanded to the current 16 grant-supported model system research centers across the United States. These centers, supported by the National Institute of Disability on Rehabilitation and Research, continue to contribute to the scientific and clinical foundation of care for persons who sustained a TBI (Bushnik 2008).

Patients with TBI typically have a broad array of physiological deficits and functional impairments, each of which may require treatment by specific specialists. Because many of these impairments require coordinated interventions, it is imperative that an overarching schema of care be developed and implemented that comprehensively addresses all significant deficits to ensure efficient and optimum recovery. This schema should not only encompass the 12–36 months postinjury during which "active" recovery is generally thought to proceed but should also end with implementation and maintenance of an appropriate life management plan for those persons with TBI who require it.

Over the past 20 to 30 years, as experience with the varying requirements of persons with TBI has grown, a more or less standard array and sequence of services has evolved. (Although general patterns are evident in acquired brain injury service delivery, great individual differences exist from patient to patient in specific composition, intensity, and timing of such services.) The entirety of this deliberate interaction among many types of clinicians and sites of services has become referred to as the *system of coordinated supports and services.* Supports and services include any and all of the medical, therapeutic, rehabilitative, community-based, psychosocial, economic, educational, vocational, and other services necessary to enable the person with TBI to function in the community independently and productively (Bureau of Maternal and Child Health 2001). Although initial care and rehabilitation may be delivered by the medical components of health care systems—usually funded by insurance or Medicaid—transitional, educational, vocational, and long-term supports are generally supported through public systems designed specifically for TBI or for persons with other disabilities. The goal of these systems should be to offer the "right services at the right time" to address current needs and to produce effective outcomes.

The descriptions of the components of the comprehensive system of care and services that follow include information about the sources of financial support and public policy that support these systems. In addition, later in this chapter there is a more comprehensive discussion of the public funding and support of the delivery of necessary care and services.

These publicly funded systems of services were developed by states in the 1980s in response to advocacy by families and individuals with TBI. Each state approached service delivery within the context of its existing systems for individuals with disabilities, behavioral health, or vocational needs. This approach resulted in states enacting legislation establishing registries for purposes of surveillance and/or linking individuals with recent injuries to services and developing a funding stream to support an array of services. Because there was no federal definition for TBI, those pioneering states adopted their own definitions for TBI for data and service eligibility purposes as well as definitions for types of rehabilitation and community supports and services to be delivered and paid for by state and federal funds, primarily through state Medicaid programs. In 1985, Missouri and Massachusetts state legislatures appropriated state funds for an array of services to address needs not covered by insurance following hospitalization, including transitional services, prevocational services, in-home supports, day programs, and supported employment. Pennsylvania enacted legislation that same year that allocated a portion of funds from traffic fines to pay for rehabilitation care (Digre et al. 1994).

In 1991, Kansas became the first state to apply to the U.S. Department of Health and Human Services for a home- and community-based Medicaid waiver to pay for rehabilitation and community supports to individuals with TBI who are Medicaid eligible in lieu of institutional care (Spearman et al. 2001). Most states that have implemented services have followed Pennsylvania's approach by establishing trust fund legislation supported by dedicated funding and or expanding Medicaid through waivers and state plan services. In 1993, the National Conference of State Legislatures produced *What Legislators Need to Know About Traumatic Brain Injury,* with support from the Milbank Memorial Fund, that summarized state legislation and approaches for prevention, trauma systems, rehabilitation, and long-term and community supports to help other state legislatures to address the need for TBI systems (Wright 1993).

While states were beginning to address services needed by individuals with TBI, work was being carried out at the national level to create public awareness and to create national priorities for prevention, research, and rehabilitation care and supports. The National Head Injury Foundation (NHIF), now known as the Brain Injury Association of America, established in 1980 by the parent of brain injury

survivor Marilyn Spivack, was the driving force behind these early initiatives (Brain Injury Association of America 2010; Spivack 1993). Through the work of NHIF, interagency agreements were established with the U.S. Office of Special Education and Rehabilitation Services to acknowledge TBI and to help expand capacity for TBI treatment through those programs (Spivack 1993).

In 1985, the National Council on Research, the Institute of Medicine, and the Committee on Trauma Research produced *Injury in America, A Continuing Public Health Problem,* which stated, "Injury is a public health problem whose toll is unacceptable" and delineated a set of recommendations for national and state public policy initiatives (Committee on Trauma Research, Institute of Medicine, National Research Council 1985). Included in those recommendations was one to expand the role of the Centers for Disease Control (CDC) to include research, prevention, surveillance, and interagency coordination. As a result, CDC expanded its name and mission (to become the Centers for Disease Control and Prevention) and established the National Center for Injury Prevention and Control. CDC has over the years awarded grants to states and other entities to establish injury prevention, education, and surveillance programs. It is through these initiatives that CDC determines the prevalence and incidence figure for TBI. Currently, 30 states have grants for one or more core funded programs to gather data from registries, emergency departments, and/or to link individuals to services (Centers for Disease Control and Prevention 2008). A current review of TBI research and programs funded by the Centers for Disease Control and Prevention has been published (Langlois et al. 2005).

In response to this growing awareness of the need to address the multifaceted issues facing many persons with TBI in a comprehensive way, Congress enacted the TBI Act of 1996, reauthorized in 2000 and again in 2008 (Traumatic Brain Injury Act of 2008). The intentions of this act included supporting the conduct of expanded studies and the establishment of innovative programs with respect to TBI. The act authorizes funding to the U.S. Department of Health and Human Services for purposes of improving and expanding prevention, public education, surveillance, and access to services and supports. Under the law, appropriations are authorized to the department's Health Resources and Services Administration (HRSA) to provide grants to states to improve access to rehabilitation and other services for individuals with TBI and their families. Funding from this program has resulted in states creating service infrastructure and expanding screening, outreach, and services to underserved or unserved populations, including victims of domestic violence, returning service members and veterans, and individuals with co-occurring conditions. Since 1997, 48 states, the District of Columbia, and two territories received at least one state agency grant (Traumatic Brain Injury Act of 2008). The 2000 amendments included a new provision for authorization of funding for state protection and advocacy (P&A) systems to expand their client and systems advocacy services to individuals with TBI. HRSA administers grants to 57 state and territorial P&A systems that receive funding under this program. The P&A grant program is a formula-based program that allows 57 states, territories, and the Native American Protection and Advocacy Project to assess their state P&A systems' responsiveness to TBI issues and provide advocacy support to individuals with TBI and their families (Traumatic Brain Injury Act of 2008). The National Institutes of Health (NIH) and the CDC were assigned responsibilities in the areas of research, prevention, and surveillance. The 2008 reauthorization of the TBI Act, P.L. 110–206, included a new provision directing the CDC and NIH in consultation with the Department of Defense and the Department of Veterans Affairs to submit a report to Congress on methods for collecting and disseminating compatible epidemiological studies on the incidence and prevalence of TBI in the military and veterans populations who return to civilian life (Traumatic Brain Injury Act of 2008).

In pursuance of the 1996 legislation (P.L. 104-166), the NIH convened a consensus conference on TBI rehabilitation methods in 1998. The panel concluded "rehabilitation services, matched to the needs of persons with TBI, and community-based non-medical services are required [in addition to strictly medical services] to optimize outcomes over the course of recovery. Public and private funding for rehabilitation of persons with TBI should also be adequate to meet these acute and long-term needs, especially in consideration of the current health care environment where access to these treatments may be jeopardized by changes in payment methods for private insurance and public programs" (National Institutes of Health Consensus Development Program 1998, under "Abstract").

In addition to federal legislation, public policy supporting community services for individuals with TBI has also been influenced by federal court decisions. In 2008, two important lawsuits were settled on behalf of individuals with TBI who desired community-based services in lieu of institutional or nursing home care. A lawsuit was filed in the northern district of California by six individual plaintiffs, including individuals with TBI, as well as the Independent Living Resource Center of San Francisco, to prevent unnecessary institutionalization of people with disabilities residing at Laguna Honda Hospital and Rehabilitation Center, a public hospital, in San Francisco, CA. (Co-counsel on the case included the Disability Rights California, American Association of Retired Persons Foundation Litigation, Bazelon Center for Mental Health Law, Disability Rights Education and Defense Fund [DREDF], and a law firm that provided pro bono services.) On September 18, 2008, a federal judge granted final approval of the settlement agreement calling for the city to establish a program to coordinate services across city departments to enable individuals with disabilities who live at or who are referred to Laguna Honda to receive community-based housing and services (*Chambers v. City of San Francisco and County of San Francisco 2008*).

A class action lawsuit initiated by the Brain Injury Association of Massachusetts in 2007 was also settled in 2008 *(Hutchinson v. Patrick* 2008). The suit alleged that the state failed to provide adequate services for individuals with TBI who wanted to live in community settings in lieu of structured residential or nursing home settings. The lawsuit was filed on behalf of the approximately 2,000 individuals with TBI residing in nursing homes. The judge

ruled in favor of the plaintiffs. Both judges found in their decisions that the city of San Francisco and the state of Massachusetts violated the Americans With Disabilities Act (ADA), which requires individuals with disabilities be provided services in the least restrictive environment of their choice. The U.S. Supreme Court previously had upheld this view in the *Olmstead* decision in 1999, which stated that unnecessary institutionalization violates the ADA. The *Olmstead* decision directed states to initiate efforts to offer individuals with disabilities community choices in lieu of institutional services *(Olmstead v. L.C.* 1999).

These federal and state initiatives have resulted in expanding services and in setting principles for providing an array of TBI rehabilitation treatment, services, and supports in the least restrictive environment and in a manner that empowers an individual with TBI to self-direct his or her treatment. However, achieving this goal is rare because the service delivery system tends to be a patchwork of services that differ from state to state, and even within states.

Voluntary national guidelines have been established for managing trauma, acute care, and rehabilitation programs in various settings, including inpatient hospital, skilled nursing facilities, outpatient, home- and community-based, residential, and vocational rehabilitation programs. These guidelines reflect the research indicating that after initial trauma and neurosurgical management of the acute TBI (and associated injury), early comprehensive rehabilitation is perhaps the most important aspect of the care continuum for recently injured individuals with TBI. Numerous studies have linked early rehabilitation intervention following stabilization with greater functional recovery after TBI (Aronow 1987; Cope and Hall 1982; Mackay et al.1992), including links between intervention directly after medical stabilization and shorter lengths of stay (Finset et al. 1995), higher functional levels at discharge (Bureau of Maternal and Child Health 2001; National Institutes of Health Consensus Development Program 1998), lower disability levels at discharge (Rappaport et al. 1989), and higher likelihood of discharge to the home (National Institutes of Health Consensus Development Program 1998). Similar studies suggest that benefits are derived from postacute services and other later services (Cope 1995, 1996). Although research may support the merits of comprehensive rehabilitation services, private insurance often does not pay for the rehabilitation over an extended period of time. One state, Texas, has enacted legislation requiring insurance to provide cognitive rehabilitation services (Texas Traumatic Brain Injury Advisory Council 2008).

Given this wide array of programs and needs, and the multiple gaps in actual availability of such programs, a critical challenge for any clinician involved in coordinating care and services relates to the identification and appropriate application of an amalgam of these treatments for any individual with a TBI. These options may be limited either because of lack of the specific clinical services in the area where the individual resides or lack of financial support (insurance and public reimbursement) for certain indicated elements (or indicated duration) of care. Rural areas in particular may not have sufficient rehabilitation professionals. In Missouri, where 32% of the population lives in rural counties, data indicated that there is a scarcity of rehabilitation professionals (i.e., physiatrists, mental health providers, rehabilitation therapists), facilities (i.e., hospitals offering comprehensive rehabilitation therapies), and services (i.e., support groups) in rural areas of the state. The results suggest that 1) future rehabilitation researchers need to evaluate the impact of accessibility to rehabilitation services and resources on the outcome of people with TBI, and 2) TBI health policy administrators need to consider how to increase rehabilitation resources for people with TBI in rural areas, including the use of rural-based training programs, rural debt-forgiveness training programs, and telehealth systems (Johnstone et al. 2002). An emerging trend in recent years is to use telehealth or tele-rehabilitation as a method for providing assessment, treatment, and supports to individuals who live in rural areas (Forducey et al. 2003). This approach provides a convenience to the patient and his or her family by allowing him or her to receive services close to home. It also provides an opportunity for the rehabilitation professional to provide service to local professionals who may not be experienced in treatment of persons with TBI (Schopp et al. 2005, 2006).

Individuals with TBI tend to be ineligible for public mental health or behavioral health services because of their diagnosis. These systems tend to provide a safety net for people with severe mental illness or those who are medically indigent. TBI is often not considered a covered diagnosis, yet individuals served by these systems may have behavioral or cognitive problems associated with TBI that may be identified as a secondary condition or not identified at all (Hux et al. 2009). The Alaska Behavioral Health Division routinely screens all behavioral health participants (those receiving public substance abuse or mental health services) for TBI. Over the past 5 years, the agency has found that at least one-third of these patients screen positively for TBI (Alaska Brain Injury Network 2008).

The RAND Corporation conducted a comprehensive study, based on data from April 2007 to January 2008, of the postdeployment health-related needs among OIF/OEF veterans and stated, "Our nation urgently needs a better understanding of the full range of problems (emotional, economic, social, health, and other quality-of-life deficits) that confront individuals with post-combat PTSD, major depression, and TBI" (Tanielian 2008, p. xxxi). Such knowledge is required both to enable the health care system to respond effectively and to calibrate how disability benefits ultimately are determined. What also needs to be understood is who is at risk for developing mental health problems and who is most vulnerable to relapse, and how to target treatments for these individuals.

Other public systems that may provide or fund, to some degree, services for individuals with TBI include programs for persons with developmental disabilities, vocational rehabilitation, Medicaid, and children with special health care needs. A challenge for these systems is to have interagency collaboration and coordination policies that promote readily identifiable points of entry, maximization of resources, and ease of accessibility for individuals with TBI and their families. These challenges have prompted some states to develop information and referral

services and service coordination or resource facilitation services to help individuals to navigate these complex systems and supports.

Although acute medical and surgical care is typically comprehensively covered, there is incremental difficulty in obtaining funding and access for inpatient, outpatient, residential, cognitive, and behavioral rehabilitation as well as mental health services. Best results for individuals with TBI served in these settings are obtained when all members of the rehabilitation team, as well as families, understand available resources and plan proactively and collaboratively with state and community services.

Clinicians should develop familiarity with the total conceptual array of indicated services as well as the particular availability and capabilities of such services in their community. They should also become knowledgeable about the various funding options for persons with TBI, in particular those reimbursement practices that prevail in their communities.

Several states do contract for or administer service coordination (also known as case management, resource facilitation, or care coordination) for individuals with TBI (Sample and Langlois 2005; Seymour et al. 2008). Some states collaborate with trauma centers, acute hospitals, and rehabilitation programs to assist with transitioning from postacute care to home and community services and supports. An evaluation of the Missouri Early Referral Program suggests that referring persons with TBI and their families to government-funded TBI programs as soon as possible after the injury "is an important step in improving functional outcomes." Specifically, data suggested that individuals who were referred at an earlier stage in their recovery from TBI experienced better functioning in the community and in social settings over time (Reid-Arndt et al. 2007).

Professionals Who Treat Individuals With TBI

A variety of professionals in both private and public service delivery systems are involved in the comprehensive treatment of TBI, starting with treatment provided at the scene of injury by emergency medical services technicians or first responders and prehospital care. Individuals who are seriously injured are more likely to be transported to a trauma center, where a full array of medical and rehabilitation teams of physicians and other clinicians are readily available to attend immediately to and continue to provide the required treatment, care, and rehabilitation necessary to restore physical, emotional, and cognitive functioning. In its most comprehensive form, care is typically delivered initially in a formalized coordinated hospital-based inpatient treatment setting under the direction of a rehabilitation physician; but as recovery proceeds, and persons with TBI move to outpatient settings, individual clinicians may evolve to providing care in a more or less autonomous manner.

Depending on severity of the brain injury and other associated injuries, virtually the entire spectrum of medical specialties may be called upon. Neurosurgeons are the primary physicians managing the acute component of care for patients with severe TBI. Patients with mild TBI often are attended to by the generalist, emergency room physician, or neurologist who may take primary accountability. Once an individual is medically stable, other specialties or clinicians may be involved to provide physical, occupational, cognitive, and speech/language therapies. A neuropsychologist may assess cognitive functioning and be involved in cognitive therapies, counseling, and behavior management or treatment. A rehabilitation team may also be comprised of a social worker, nurse, vocational rehabilitation specialist or counselor, recreational therapist, orthotist and prosthetist (for occasional associated amputations), and rehabilitation engineer. This team of professionals should work together to coordinate assessment and evaluation of the individual's strengths and weaknesses and to establish short-term and long-term goals for recovery and reintegration. The plan should also include transitional services and strategies for community reintegration.

Psychiatry generally is not involved in this immediate trauma management period, but many of these medical issues persist into the postacute period and thus have interplay with psychiatric and rehabilitation concerns. Without venturing a complete listing, such medical conditions as delayed or recurrent subdural collections, hydrocephalus, posttraumatic epilepsy, fracture malunion or delayed healing, and infections all may require the care of these more acutely focused specialists for months and even years postinjury. Thorough reviews of these issues are available and should be referenced for details on this portion of the care process (Feliciano et al. 1996; Horn and Zasler 1996; Jennet and Teasdale 1981).

Often, issues such as third-party liability, workers' compensation regulations, governmental program eligibility, competency, and in some cases divorce and child custody and child protective services issues, all lead to a very high rate of attorney involvement in TBI cases. It is in the patient's best interests for the rehabilitation team, especially the member providing service coordination, to understand the important role attorneys can play in facilitating (or impeding) treatment and recovery. It is unnecessary to elaborate upon the particular expertise and focus of each of these clinical specialties. However, it is important to discuss a number of general aspects of these clinicians' care delivery.

First, it should be recognized that the treatment of patients with TBI is a specific area of clinical expertise for each of these disciplines. Just as the expertise of neuropsychiatry is a subspecialty of general psychiatry, so must each of these professionals have the necessary experience and training to provide care adequately to individuals with TBI. One should exercise caution in assuming that a generalist clinician of any specialty or discipline can adequately assess or treat the person with TBI; effort should be made to identify appropriately qualified providers. The Academy of Certified Brain Injury Specialists (ACBIS) offers a voluntary national certification program for both entry-level staff and experienced professionals working in brain injury services (www.acbis.pro). ACBIS provides staff and professionals the opportunity to learn important information about brain injury, to demonstrate their learning in a written examination, and to earn a nationally recognized credential.

It is also critical to realize that each of these professionals is highly likely to interact with the patient and his or her family in an intensely personal and educational manner. Virtually all of these clinicians have had at least some training in basic supportive psychology/counseling processes and actively participate in the education and counseling of the patient and family. Many of the attitudes and beliefs that patients with TBI and their families develop about their injury and condition are derived in large part on the prolonged input of these multiple participants in the care process. Thus, it is important to the psychiatrist both to be aware of this process and to understand what messages are being communicated. For example, it is not uncommon for many rehabilitation professionals (particularly those early in their careers with limited experience) to promote unrealistic expectations of recovery to both patients and family members. Doing so has the potential to create a nontherapeutic or even destructive dynamic. One of the authors has seen examples of entire families "held hostage" for years to unremitting 24-hour-a-day treatment programs by parents of patients with TBI. These situations often result in sibling and spouse depression, anxiety, and divorce or broken families. Alternatively, such clinician involvement can create a powerful opportunity to support a comprehensive psychiatric management plan for a person with TBI and his or her family.

It is also useful to utilize these professionals as sophisticated observers of patient and family behaviors. Doing so is critical to both gaining accurate diagnostic information and monitoring treatment responses to counseling, behavioral, or psychopharmacological interventions. Many of these clinicians will also be able to productively participate in behaviorally based treatment programs if directed. These professionals generally perceive these behavioral and psychological monitoring and support functions to be appropriate aspects of their more specialized clinical roles in the care of the patient with TBI.

Finally, as implied by the above paragraphs, it is critical to consider the inputs, interfaces, and contributions of this array of professionals of differing backgrounds in considering the neuropsychiatric assessment and treatment planning for each case of TBI. Although doing so may initially require that the clinician devote more time for gathering information and background and for developing working relationships with the total treating team, the reward of more comprehensive and effective treatment more than compensates for this effort.

Settings of Care

As we noted earlier, the treatment and rehabilitation of the patient with TBI takes place in a variety of settings designed to address the particular needs of each patient at specific points in the recovery process (see Figure 32–1). It is important to appreciate that each patient will follow his or her own appropriate sequence of programs, and this need not be a linear progression. Many patients may skip components of care; some proceed at times from left to right in the diagram instead of conversely. Other patients need to have multiple opportunities for certain types of treatment, whereas often services are needed intermittently. It is important to recognize the general indications for each type of care manifested by each patient. As each TBI differs from person to person, depending on the location of the injury, severity, age, preinjury functioning, substance abuse history, education, and other contributing factors, the extent and duration varies individually, as well as when they may need them in their recovery and reintegration process. A challenge in service delivery is to offer *the right services at the right time*—and to be responsive when problems arise.

In addition, the patient with a TBI and/or the patient's family, as appropriate, should be at the center of planning for his or her goals, objectives, and identifying the type of services and supports needed. Increasingly, state TBI and other disability programs are adopting such principles as person-centered planning or personal futures planning as a process for supporting the patient in identifying his or her own needs and desires. When possible, these planning teams identify natural supports, generic services, and other supports that offer assistance within the home and community, which may be in addition to paid supports and services financed through public and private programs. Although it is usually desirable for patients to live in their own homes and communities to receive services, they may be referred out of area for certain types of care (e.g., specialized behavioral management or structured residential care in absence of such resources in their own community). Individuals with TBI may start their treatment and care in medical settings but will transition to public and private community services for ongoing rehabilitative support, community reintegration, and return to home, school, and work.

Figure 32–1 is a simplification of the many variations of treatment, rehabilitation, and support programs that exist in various communities. The Brain Injury Association of America (BIAA) identifies national and local resources in its National Directory of Brain Injury Rehabilitation Services on the BIAA website (Brain Injury Association of America 2010).

Most state chapters of BIAA have compiled supplemental information in state and regional level resource directories, and some have staff devoted to information and referral functions. These staff may be of great assistance to providers, persons with TBI, and their families in locating appropriate services. In addition, the National Association of State Head Injury Administrators produces a National Directory of State Contacts and has information available on service delivery in each state (www.nashia.org).

Some states contract with their state BIAA for information and referral services, whereas other states may provide such information through their own state TBI programs. A number of states operate programs that include service coordination that serve as a point of entry to the service system. States participating in the federal HRSA TBI program must have a designated lead state agency and an advisory board responsible for planning, assessing resource needs, and coordinating policies and programs within their state. The Commission on Accreditation of Rehabilitation Facilities (CARF) is the accepted accrediting body for the various forms of brain injury rehabilitation programs. It accredits programs under eight general categories (see Table 32–1).

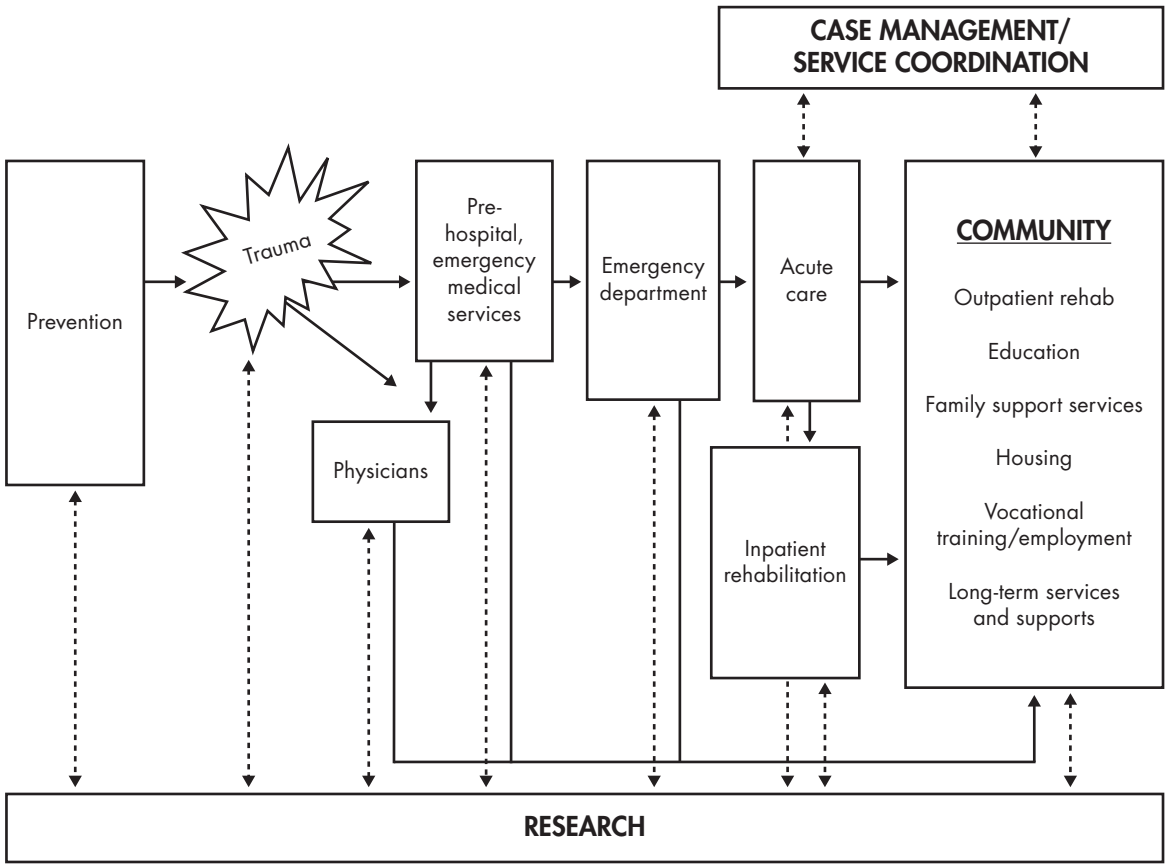


FIGURE 32–1. Simplified schematic of treatment flow for individuals with traumatic brain injury: acute care, rehabilitation, and community services and supports.

Solid lines refer to the path that an individual with traumatic brain injury may take after an injury, including prevention initiatives that may reduce the severity of the injury (e.g., helmets, seat belts). Dotted lines show the relationships and mutual collaboration among the various components of the service delivery system.

Source. Reprinted from King A, Vaughn SL: *Guide to State Government Brain Injury Policies, Funding, and Services,* 2nd Edition. Bethesda, MD, National Association of State Head Injury Administrators, 2005.

TABLE 32–1. Categories of Commission on Accreditation of Rehabilitation Facilities–certified medical rehabilitation programs

Inpatient rehabilitation hospital
Inpatient rehabilitation long-term acute care (hospital)
Inpatient rehabilitation skilled nursing
Outpatient
Home and community based
Residential
Long-term residential
Vocational

An Internet-based directory of CARF accredited programs is available at the CARF website. These accreditation requirements for both inpatient units as well as for specialized downstream TBI programs mandate an array of required therapy services as well as physician direction by a qualified specialist. A specific set of program evaluations is also mandated (Commission on Accreditation of Rehabilitation Facilities 2010).

Acute Care

The premise underlying the development of state trauma systems was that an organized system of trauma care would ensure that critically injured patients are appropriately triaged and transferred, when indicated, to the appropriate high-quality definitive care, or both, without delay. Despite its conceptual simplicity, implementation of the necessary infrastructure for system development is exceedingly complex (Ziran et al. 2008).

Trauma centers are categorized by the American College of Surgeons into five different levels based on their resources, trauma volume, education, and research. Over the past 25 years trauma systems increasingly have been formally developed to expedite the immediate evacuation of severely injured patients to tertiary-level facilities with comprehensive trauma-focused medical and surgical capabilities. According to the American College of Surgeons, there are 105 Level I trauma centers.

These trauma systems, with Level I and II centers being the appropriate triage destination for severe injury, are expected to have 24-hour-a-day surgical, intensive care unit, and imaging capabilities, and virtually immediate avail-

ability of subspecialties required for trauma care—in particular, neurosurgical services for patients with TBI. However, a recent study found that few trauma systems met the criteria deemed necessary for a fully functional and comprehensive system (Health Resources and Services Administration 2002). Furthermore, large portions of the United States, particularly rural and frontier areas, do not have access to trauma services (Health Resources and Services Administration 2006). It is assumed that these systems should improve survival and recovery from severe trauma, but conclusive evidence is lacking because adequate research has yet to be done. The lack of adequate Level I trauma centers both in numbers and quality is traced to a variety of factors (Institute of Medicine 2007). A 2000 study of state trauma systems found that their benefit is greatest with motor vehicle crash–related injuries (Nathens et al. 2000). The Institute of Medicine recently published a series of reports based on their evaluation of the status of state trauma systems. The institute's advisory committee concluded that there is a national crisis in emergency care. Their publications identified the most important issues facing the nation's emergency care system and made a series of recommendations for how best to deal with those issues (Institute of Medicine 2007). A 2002 study of state trauma systems conducted by the HRSA concluded that there has been demonstrated progress in obtaining trauma systems across the country, although there is concern about financial stability of infrastructure and the ability to recruit and maintain adequate staffing of physicians and nurses. According to the 2002 study, only 38 states have legal authority to designate trauma centers (Health Resources and Services Administration 2002).

Evidence-based guidelines for acute neurosurgical and medical care that delineate those immediate care procedures shown to improve clinical outcomes were first published in 1995 by the Brain Trauma Foundation (BTF) (Bullock et al. 1996). These guidelines were developed by the BTF in cooperation with the American Association of Neurological Surgeons, and the preparation of companion guidelines by the BTF for prehospital management of TBI was supported by the National Highway Traffic Safety Administration (Faul et al. 2007).

The CDC found in its study of the BTF guidelines for prehospital treatment of TBI that adoption of the guidelines for treating individuals with severe TBI would result in substantially decreased deaths and large savings in medical and rehabilitation costs and particularly societal costs avoided by decreased morbidity (Centers for Disease Control and Prevention 2010).

In 2008, through grant funding from the Department of Defense and Veterans Brain Injury Center (DVBIC), the American Association of Neuroscience Nurses developed *Nursing Management of Adults With Severe Traumatic Brain Injury,* which provides recommendations based on current evidence to help registered nurses, intensive care unit personnel, and institutions provide safe and effective care to severely injured patients with TBI (Mcilovy and Meyer 2008).

In 2009, the U.S. Department of Defense and U.S. Department of Veterans Affairs issued the *VA/DoD Clinical Practice Guidelines for Management of Concussion/Mild Traumatic Brain Injury (mTBI)* (U.S. Department of Veterans Affairs and U.S. Department of Defense 2009).

In addition to acute medical and surgical care, rehabilitation evaluation and preliminary interventions should take place within a short time following onset in these settings as well; ideally this should occur within a neurological intensive care unit setting during the first several days after injury.

From this point, determination of subsequent rehabilitation pathways is provisionally made on the basis of extent of injury and nature of recovery. Most commonly, for persons with severe TBI, the next treatment site is rehabilitation. The full array of in- and outpatient programs is typically only required in severe cases of TBI. Mild and moderate cases typically do not require the inpatient components of this care spectrum, but may require significant outpatient physical, occupational, and psychological therapies; vocational and educational programs; and significant neuropsychiatric assistance.

Acute Inpatient Rehabilitation

Inpatient acute rehabilitation programs offer medical monitoring and care of 24-hour-a-day nursing staff who have specialized expertise in issues relevant to severely disabled patients (e.g., pulmonary, bowel, bladder, and nutritional management; skin and wound care management). Patients in this setting may require management of residual medical/surgical issues and engagement in a full array of rehabilitation activities (physical therapy, occupational therapy, speech and language therapy, psychology). Typically, a variety of medical and surgical subspecialties also are routinely available as consultants in these settings. Because of the relative high cost of these programs, patients typically are referred to less acute levels of rehabilitation as soon as their medical and nursing care requirements are sufficiently resolved.

Subacute Rehabilitation

Subacute programs for persons with TBI are designed for those very severely impaired patients who—because of the extent of their injury, slowness of recovery, or other medical reasons—are unable to participate in full therapy programs. These programs are appropriate for patients who are in a "minimally responsive state" in which further arousal has not yet occurred but may be anticipated, leading to subsequent entry into acute rehabilitation. Patients in these programs are characterized by relative medical stability but with high levels of nursing care needs. Therapies are provided at a lower level of intensity than in acute rehabilitation units, and often in the earliest stage of rehabilitation the focus is on relatively passive preservation of function via skin and joint maintenance programs, development of appropriate nutrition (e.g., gastrostomy tube feeding protocols), bowel and bladder management programs, and so forth. These subacute units or programs are typically distinct wards within acute hospitals or specialized programs within extended care or skilled nursing facilities.

Neurobehavioral Treatment, Interventions, and Supports

Some individuals with disruptive behaviors such as significant agitation and/or aggression may be treated with appropriate medications, whereas other individuals may be able to manage their own behavior with appropriate simple structured environments and other interventions. Treatment for neurobehavioral issues occurs in diverse settings, from a structured residential setting to crisis interventions, prevention, and supports in home and community settings. On occasion severe disruptive behavior occurs. Intervention may then be done in a neuropsychiatric unit, although more typically and appropriately it is in neurobehavioral programs specifically designed for patients with TBI. These programs may be subunits within inpatient units in rehabilitation hospitals, in skilled nursing facilities, or in residential programs. They are characterized by relatively high staff-to-patient ratios, with staff that have specific expertise in neurobehavioral management. The programs also have physically or architecturally designed "secure" physical plants, which prevent patient elopement or self-injury. There are a limited number of private programs offering neurobehavioral services, but private reimbursement for such services through health insurance is typically available to only a few of the individuals who need it.

As for many other patients with TBI, most must receive services funded by public programs when such programs are available. A limited number of states have explicitly addressed this population. Examples of state programs include the states of Massachusetts and Minnesota, which developed specialized neurobehavioral programs for patients with TBI that offer combined cognitive, behavioral, and pharmacological treatments. The Massachusetts program is a locked program with capacity for voluntary admissions or commitments. The program was initially funded with state dollars, although it was designed with the ability to serve individuals with third-party pay, including Medicaid. Minnesota also developed a 15-bed specialty unit 1993, which has expanded to include outpatient clinic and specialty/consultative services, to address this need.

Both of these states viewed the behavioral unit as one piece of the continuum with other less restrictive services as a necessary part of the system. Massachusetts learned very quickly that without other services the behavioral unit became the only place where people were placed, which then quickly filled, thus creating a long waiting list for the program. This unit became the first step in development of a menu of neurobehavioral services that includes community living programs and in-home family assistance programs.

Since 1995, the New York State Department of Health has funded statewide regional resource development programs to provide administrative case management and the development of a cadre of providers in the region who would participate in the state's Home and Community Based Services (HCBS) Medicaid waiver. It was soon recognized that specialized resources were needed to provide training and technical assistance to providers to enable them to provide appropriate behavioral interventions. The state developed a statewide behavioral resource project to provide this training and technical assistance. The program created behavior screening and assessment protocols and worked with staff throughout the state to develop and implement behavior programs and to provide crisis management support. This approach has demonstrated that it is cost effective to treat patients with significant behavioral problems in the community as long as the patient is not a threat to self or others (Feeney et al. 2001).

Residential Treatment

For a number of patients without extensive medical or nursing care needs, treatment in an acute rehabilitation program is unnecessary, but for those with sufficient functional deficits, residential treatment and group residence programs exist that take place on "campuses" of various sorts, including rural "ranches," urban or suburban residential settings, dormitories, and apartments. These programs have therapy areas as well as facilities such as kitchens and workshops to provide avocational/vocational training opportunities. These programs are staffed by professional clinicians of various disciplines as well as by laypersons that are provided in-program training in essentials of TBI rehabilitation management. Nursing services are typically provided (although usually not on a 24-hour-a-day basis) so that medical monitoring and dispensing of medications can take place. There is no on-site physician involvement although typically there is a medical director (consultant) who rounds on the patients on a regular basis (usually weekly to monthly). These programs provide a safe and structured environment (often with graduated levels of autonomy which participants move through during recovery) to prepare for return to home or other long-term living arrangements.

During the 1980s such programs were considered the preferred model for providing rehabilitation to prepare the patient with TBI to return successfully to independent living in the community. Currently there is a growing preference for providing person-centered individualized rehabilitation in the patient's natural setting rather than expecting the patient to translate what he or she has learned in the residential program to the community. Insurance reimbursement and public funding for these residential programs has become increasingly limited. Public funding is increasingly directed to supporting individuals in their own home and in the community. However, for selected patients, these residential programs remain the optimal locus of treatment.

Outpatient Day Hospital or Program

For many medically stable patients, it is possible to return home but still receive a full array of multidisciplinary therapy via a TBI day hospital or program. Such programs may or may not be attached to a hospital-based acute rehabilitation program within their outpatient department. At their best, these programs include specifically designed comprehensive activities and services for patients with TBI. These programs should have an identified medical director and a

rehabilitation team that includes therapists, social workers, and other professionals as needed. The patient with TBI, and family as appropriate, are increasingly included in the rehabilitation process by participating in the development and review of rehabilitation goals and progress for each.

Outpatient Therapy

Very commonly, patients with TBI, following more comprehensive treatment programs, will require one or more individual therapy service for isolated residual functional deficits. Patients with mild to moderate injuries also may only require one or a few isolated therapy services. These individual physical, occupational, speech, and psychological services are provided in a traditional manner within a hospital outpatient department or via individual office-based or home-health treatments.

Vocational Services

Employment is considered a successful outcome for most patients after their injury. A recent study found that approximately 40% of people hospitalized with TBI reported that they had stopped working at 1 year after injury, 36% reported the same hours, and smaller percentages reported working more or fewer hours. A limitation of this study is that, among those who reported working the same hours, it is unknown whether they kept the same job or changed jobs. The study also found that women were more likely than men to stop working, especially at younger ages. However, within the older age group, men were more likely to have stopped working (Corrigan et al. 2007).

Individuals seeking employment services generally apply for such services through their state vocational rehabilitation agency, which receives federal funds through the Rehabilitation Act of 1973, as amended, for vocational rehabilitation, supported employment, independent living, and client assistance. To be eligible for services, a person has to have a physical or mental impairment that is a substantial impediment to employment, be able to benefit from vocational rehabilitation services in terms of employment, and require vocational rehabilitation services to prepare for, enter, engage in, or retain employment.

Vocational programs can provide work evaluation, including onsite evaluation; assessment for and provision of assistive technology, such as customized computer interfaces for persons with physical or sensory disabilities; job counseling services; and medical and therapeutic services.

States that report successful job placement for individuals with TBI cite the importance of interagency planning and coordinating supports to assist the individual in maintaining a job. Supported employment and follow-along services often are used to provide the ongoing job coaching and cueing supports that may be needed.

Special Educational Services

In 1975, Congress passed legislation, the Education for All Handicapped Children Act (P.L. 94-142), that mandated public schools to provide free and appropriate public education for children with disabilities (up to age 22 or graduation from high school). The act provides federal funding for special education and related services for those children and youth with disabilities who are eligible and require such services. Related services refer to an array of services that may be needed for a student to benefit from special education. These services may include transportation, speech and language therapy, physical and occupational therapy, psychological services, and counseling. However, if it is determined through an appropriate evaluation that a child has one of the 14 disabilities identified in law, but only needs a related service and not special education, the child is not considered as a child with a disability in accordance with the law.

The law has been reauthorized several times over the years, with the last reauthorization passing in 2004. In 1990, the reauthorization bill changed the name to Individuals with Disabilities Education Act (IDEA) and also added TBI as a disability for purposes of reporting. Before the addition of TBI as a disability reporting category, children and youth with TBI may have received special education and related services but may have been reported under other disability categories, such as specific learning disability, other health impairment, emotional disturbance, or mental retardation. Because of the low reported numbers of students with TBI who are receiving special education and related services, state educational agencies often refer to TBI as a low-incidence population—even though the numbers of children and youth with TBI may be much higher according to trauma and TBI registries.

Students with TBI who are not eligible for special education services under IDEA may be eligible for accommodations through Section 504 plans as authorized by the Rehabilitation Action of 1973. Section 504 prohibits discrimination against individuals with disabilities in a program receiving any federal funding. A student that has medical documentation may qualify for a 504 education plan that specifies accommodations necessary for learning. Accommodations could include the need for periodic breaks caused by fatigue associated with TBI, special seating in the classroom to eliminate distractions, repeated directions or written instructions to accommodate for memory, and structured environments to support appropriate behaviors.

Beginning in the 1980s states began to develop materials and consultative services to assist school districts in assessment and in developing appropriate individualized education programs (IEPs) and educational strategies to accommodate the needs of students with TBI. In 1987, the Kansas State Department of Education in partnership with the University of Kansas developed a model for offering preservice training to undergraduate and graduate students, in-service training to educators and families, and technical assistance and consultative services to educators. The project developed mini-teams throughout the state to provide these services. Several states have replicated this program, including Hawaii, Oregon, Nebraska, Tennessee, Iowa, and Pennsylvania.

Community and Family Supports and Services

Many people make a good recovery after a severe TBI. However, a number of individuals have considerable dif-

ficulty with community integration after their rehabilitation and may need further services and supports (Feeney et al. 2001). These services include social, personal care, residential, transportation, assistance and training in activities of daily living, prevocational and supported employment, and service coordination. Without community and family supports, patients with TBI are often at risk for inappropriate placement in nursing homes. Often the payment for rehabilitation ends within a few months after the injury, whereas the period for recovery may extend to years. In addition, ongoing rehabilitation is often needed to maintain function. Such "maintenance" rehabilitation is often not reimbursed by insurers because it is beyond the scope of their benefits.

To address these needs, states and other community providers have developed an array of programs that vary from state to state and also geographically within states. These public programs are generally financed from state revenues; trust funds that are created from dedicated funding sources, usually related to traffic fines; and federal funds. Almost half of the states have trust fund programs that range from less than $1 million to $17 million annually (Federal TBI Program's Traumatic Brain Injury Technical Assistance Center at the National Association of State Head Injury Administrators 2006).

Nearly half of the states have also implemented HCBS Medicaid waivers specifically for individuals with TBI and/or have included individuals with TBI in other waivers, such as waiver services for individuals with developmental disabilities, physical disabilities, and self-directed waiver. These waivers are designed to provide community services in lieu of institutional or nursing home services and generally include an array of services, including therapies, speech/language, physical, occupational, behavioral, cognitive services; personal care; in-home support; home modifications; transportation; supported employment; case management; respite; and assistive technology (Hendrickson and Blume 2008).

Twelve million people in the United States are unable to live independently, and 6 million are under 65 years of age (Feder et al. 2000). However, the United States currently has no universal public or private mechanisms to pay for long-term care services (O'Keefe 1994). Many seriously injured persons with TBI who are unable to return to an independent living environment depend on informal supports provided by family and friends. When informal supports and personal finances are not available or have been exhausted, there is a patchwork of federal, state, and local programs that provides some home- and community-based services; however, services are limited and fragmented.

To address this problem Congress included provisions for long-term services and supports in the health care reform legislation, the Patient Protection and Affordable Care Act, which was signed into law March 23, 2010. These provisions include the Community Living Assistance Services and Supports (CLASS) Act, the Medicaid Community First Choice Option, and funding to extend Money Follows the Person (MFP) grants to states through September 2016 (Patient Protection and Affordable Care Act, P.L. 111-148). The CLASS Act, initially introduced as a separate bill by the late Senator Edward Kennedy, is a voluntary public long-term care insurance program to help support individuals with significant functional limitations. The U.S. Department of Health and Human Services was to have issued regulations on the CLASS Act by October 1, 2012. Under the Community First Choice Option, states may offer community-based attendant services and supports as an optional State Plan service to Medicaid recipients, regardless of diagnosis, who require institutional level of care. MPF grants, authorized under the Budget Deficit Reduction Act of 2005, are a federal initiative designed to assist states in transitioning individuals from hospitals and institutional settings to community settings (White House 2010).

Mental Health Services

Mental health conditions often are present before injury or manifest after injury in the patient with TBI. These may include depression, anxiety, personality changes, and social inappropriateness. Mental health services may be provided as a short-term benefit available through health insurance or another funding stream. Under such circumstances, the person with TBI can receive services from any appropriate provider. However, finding an appropriate provider often is a challenge because comprehensive education and training about TBI has not been routinely included in medical school or specialized training of psychiatrists or other mental health professionals. In addition, one of the key problems for persons with TBI attempting to access available services has been establishing that they are appropriate recipients of such services—this has often been true for mental health services. Insurance coverage has restrictions on the benefits that may rule out its use as a source of payment for mental health benefits even when a provider is located.

Similar problems apply to the publicly funded mental health services available through state and local mental health programs designed to meet the needs of persons with chronic mental illness. As public mental health systems have reduced or nearly eliminated the use of large state-operated psychiatric institutions, admissions have been restricted to those who are defined as appropriately matched to the services available within the institution and the community-based aftercare system. These state facilities and systems are becoming overburdened with court commitments and forensic patients. Many states have determined that persons with TBI have needs that cannot be met within their psychiatric facilities, or they are not eligible under their commitment laws. Advocates for persons with TBI have agreed because they wish to avoid the perceived stigma associated with mental illness. Such advocates supported the development of specialized programs for persons with TBI who have behavioral problems that jeopardize their ability to live successfully in the community rather than advocate for access to an apparently inappropriate mental health system. These programs have been described earlier in this chapter in the section Neurobehavioral Treatment, Interventions, and Supports.

Family and Other Caregivers

Families are often responsible for caring for a member with TBI. As such, families and other caregivers need information, resources, training, and respite to carry out this role.

As the result of state legislation, the California Department of Mental Health contracts with 11 nonprofit caregiver resource centers that serve and support families and caregivers of persons with adult-onset brain impairments, including TBI. Services are designed to deter institutionalization, allow caregivers to maintain a normal routine, and promote quality care. Services provided to family and caregivers include respite, short-term counseling, support groups, and education. A second goal of the program is to enhance the capacity of individuals with TBI and family caregivers to self-manage significant behavior challenges.

Recognizing the need to assist families who frequently serve as caregivers, Congress passed the Lifespan Respite Care Act of 2006 authorizing state grants to help families with children and adults with disabilities to access affordable respite care (Lifespan Respite Care Act of 2006). The U.S. Administration on Aging (AoA) administers the program. On May 5, 2010, the President signed the Caregivers and Veterans Omnibus Health Services Act of 2010 directing the U.S. Department of Veterans Affairs to provide training and assistance to family caregivers of veterans with severe disabilities (Caregivers and Veterans Omnibus Health Services Act of 2010).

Sources of Funding and Public Policy Aspects

Public and private funding for rehabilitation of persons with TBI is needed to meet acute and long-term needs. Access to initial care and subsequent rehabilitation for persons with TBI varies depending upon insurance coverage, treatment personnel, family and community characteristics, geographical location, knowledge of available resources, and the ability to navigate the medical care and rehabilitation system successfully. The outcome of injury depends not only on its severity but also on the speed and appropriateness of treatment.

Health Insurance

Health insurance often provides very few benefits beyond acute medical care needed by a person with a serious TBI. Private insurance pays primarily for acute care, and coverage decisions are generally based upon a narrow definition of *medical necessity* (Goodall et al. 1994). Limits typically are applied to the number of hospital days, skilled nursing facility days, and the number of therapy sessions. Additional exclusions may exist for home health care, outpatient services, and all forms of long-term care. Health insurance policies rarely specify benefits for rehabilitation. Companies may negotiate an "extra contractual agreement" to cover such services (Spearman et al. 2001). As the majority of Americans participating in employer and Medicaid-sponsored health plans have become enrolled in managed care plans, these preexisting limitations in health insurance coverage typically have continued, if not increased (DeJong and Sutton 1998).

The Patient Protection and Affordable Care Act provides some protections for individuals with disabilities, including the prohibition of denying health care coverage due to preexisting conditions, prohibition of lifetime benefit limits, prohibition of annual benefit limits, and extension of coverage to young adults on their parents' health plan to age 26. The health reform law also defines an essential health benefits package that all qualified health plans sold in individual and small group markets must cover at a minimum. This benefit package includes emergency services, hospitalizations, rehabilitative services and devices, prescription drugs, and mental health and substance use disorders, including behavioral health services. (Patient Protection and Affordable Care Act, P.L. 111-148).

Automobile Liability Insurance

Automobile accidents are a frequent cause of TBI especially in teenagers and young adults; therefore, automobile liability is an important source of payment for rehabilitation for such TBI survivors. Traditional automobile liability insurance is based upon the concept that the party at fault for an accident is financially responsible for damage and injuries resulting from the accident. The owner of the car purchases insurance as protection from lawsuits. However, for the driver at fault and his or her passengers, automobile insurance does not cover the driver and passengers in the car driven by the party at fault. The party at fault and his or her passengers must seek reimbursement through their private health insurance or through Medicaid. Long delays associated with establishment of fault and obtaining settlements from the insurance companies is another problem. Such delays can adversely affect access to necessary rehabilitation (Spearman et al. 2001).

No-Fault Automobile Insurance

No-fault automobile insurance is an alternative to traditional liability insurance. The no-fault concept is designed to provide prompt payment for lost wages and medical expenses. Benefits are paid through one's own insurance company without long delays associated with litigation (Spearman et al. 2001). Massachusetts was the first state to enact a no-fault law, in 1970, with 25 other states soon following suit. However, as of 2010, 12 states had a no-fault law. Three states have a "choice" no-fault law. In those states motorists may reject the lawsuit threshold and retain the right to sue for any auto-related injury (Insurance Information Institute 2010). Most no-fault states place a fairly low cap on the amount paid for medical care and rehabilitation (Michigan is the single exception). This amount typically may be $50,000, an amount totally inadequate to meet the needs of most persons with TBI. Active lobbying by trial lawyers' associations has contributed to weak no-fault laws (Spearman et al. 2001). Additional costs must be met by obtaining a settlement from the insurance company insuring the driver who was at fault. The person with TBI can also obtain reimbursement from his or her health insurance once no-fault means are exhausted (A.T. Doolittle, personal communication, October 2001).

Workers' Compensation

Some individuals with TBI who were injured on the job are eligible for workers' compensation. Workers' compensa-

tion legislation was initially enacted by most state legislatures in the first part of the twentieth century. The purposes included the provision of adequate benefits to injured workers in addition to limiting employers' liabilities. The system was designed to make prompt payments at predetermined levels to relieve employees and employers of uncertainty and to eliminate wasteful litigation (General Accounting Office 1996). These benefits are among the most comprehensive of all insurance coverage. They include medical care, extended rehabilitation, and partial wage replacement. Some states provide retraining and job placement services when the injured worker is not able to return to work. Although this coverage provides a good opportunity for a person with TBI to resume his or her prior lifestyle, not many cases of TBI occur on the job, so few persons with TBI can benefit from this coverage (Cavallo and Reynolds 1999; Wright 1993).

Medicare

Medicare is a federal health insurance program covering services to persons aged 65 and older as well as 5.2 million persons under age 65 with disabilities (2008 data; Centers for Medicare and Medicaid Services 2009). Medicare pays primarily for acute care and a limited amount of postacute rehabilitation, nursing home, and home care. Medicare typically does not benefit many persons with TBI for two reasons. The first reason relates to the average age of persons with TBI. To be eligible for Social Security Disability Insurance (SSD) and therefore eligible for Medicare, one must have a sufficient number of quarters of earnings, and many persons who sustain a TBI do not meet this qualification. Second, those who become eligible for SSD must wait 2 years to become eligible for Medicare. Medicare eligibility therefore is not determined until after the postacute stage of injury, the period when TBI patients have the greatest need for rehabilitation services (Goodall et al. 1994). These barriers do not apply to most people over 65, who are already eligible for Medicare.

Medicaid

The program known as Medicaid (Title XIX of the Social Security Act) became law in 1965 as a jointly funded cooperative venture between the federal and state governments to assist states in the provision of adequate medical care to eligible persons in need of it. One category of eligibility for Medicaid in most states of particular interest in regard to TBI is beneficiaries of the Supplemental Security Income program, which provides cash benefits to low-income disabled persons younger than the age of 65 years and to elderly persons with low income. Medicaid is the largest program providing medical and health-related services to America's lowest-income people. Within broad national guidelines (provided by the federal government), each state establishes its own eligibility standards; determines the type, amount, duration, and scope of services; sets the rate of payment for services; and administers its own program. Just as coverage for rehabilitation is often limited in health insurance plans and other private insurance, the Medicaid program benefits may or may not be adequate to meet the needs of persons with a recent TBI. This shortcoming may result from a state's failure to cover specific needed services that are not mandated by federal law or by the state's limitations on amount, duration, and scope of covered benefits.

Despite Medicaid's limitations in coverage of many people with low income, Medicaid provides a more comprehensive array of benefits than Medicare. Medicaid coverage can include rehabilitative services in addition to acute services. Medicaid covers long-term care services that are not covered by Medicare. In addition, some states provide an array of services appropriate to meet the needs of persons with TBI through offering optional Medicaid services including case management, personal assistance services, and HCBS waivers (Digre et al. 1994; Goodall et al. 1994; Hendrickson and Blume 2008; LaForce and Wussow 2001; Spearman et al. 2001).

For the clinician managing cases with TBI, in light of this daunting array of (typically inadequate) potential funding resources, the services of an experienced social worker or other reimbursement specialist is of critical importance in ensuring that survivors with TBI receive the optimum care possible.

Conclusion

In terms of sheer numbers of cases, patients with mild and moderate TBI far outnumber severely injured patients, and frequently the former are essentially physically independent individuals struggling with isolated psychiatric problems including depression, posttraumatic stress disorder, anxiety reactions, and less severe cognitive and behavioral disturbances. Appropriate psychological and psychiatric care is essential. For the more severely injured patient with TBI, however, a more complex pattern of care is typical. This chapter gives a general overview of the treatment context into which most neuropsychiatric care is placed. It has been a source of long-lasting surprise to the authors to see the degree to which the psychiatric "mental health" care for the patient with TBI has been provided in isolation from and with disregard for the well-developed rehabilitation system developed over the past 25–30 years. This disconnection has frequently led to duplication of care as well as each system's failure to garner the full value of the expertise in the other. It is hoped that as more awareness of these parallel resources emerges, better integration between them will occur, to the benefit of patients and families experiencing the consequences of TBI.

KEY CLINICAL POINTS

- Three decades of research, supported primarily by the federal national model systems data, suggest that care of persons with traumatic brain injury (TBI) are best treated by a comprehensive multidisciplinary approach applied longitudinally over the course of time of recovery as well as in multiple settings. Such care should cover not only the 12–36 months after injury where "active" recovery occurs, but also implementation of an appropriate life care plan for those who require it. Such a system is now termed the system of coordinated supports and services.

- Two powerful organizations with knowledge of many TBI resources are the Brain Injury Association of America (BIAA) and the National Association of State Head Injury Administrators (NASHIA).

- Legal precedents have firmly established the right of TBI survivors to live in and receive services in a "least restrictive environment" (Chambers v. City of San Francisco and County of San Francisco 2008) and (Hutchinson v. Patrick 2008) in Massachusetts.

- Screens of behavioral health populations have determined that one-third or more of participants have a positive screen for prior TBI.

- TBI care in an ideal environment takes place in a sequence of differing formally designed and designated programs: inpatient, outpatient, community and home settings. However, because of gaps in clinical resources and financial support, perhaps the majority of TBI survivors receive less than optimum care.

- Services and funding for TBI care vary extensively from locale to locale. Each clinician responsible for directing care of persons with TBI needs to become familiar with both funding sources and the array of clinical resources and programs in their locality so proper referrals and coordination can be done. Clinicians should also be aware of highly specialized (e.g., neurobehavioral) programs, which are available for referral but perhaps not locally.

- Psychiatric expertise can often inform the care of multiple other clinicians involved in the TBI survivor's care and should be considered a potential resource for information about patients' adaptation and behavior as well as extensions of the psychiatric treatment plan itself.

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CHAPTER 33

Social Aspects

Andrew Hornstein, M.D.

FIFTY THOUSAND PEOPLE DIE OF TRAUMATIC BRAIN injury (TBI) every year in the United States, and over 5 million TBI survivors are left with permanent disabilities. Most TBI victims are young, and many survivors require lifelong services (Centers for Disease Control and Prevention 1999; Langlois et al. 2006). These facts highlight a major public health issue that has broad social as well as clinical implications. This chapter reviews some of the social implications. Areas to be covered are legislation affecting TBI patients, advocacy issues, insurance coverage, employment and vocational rehabilitation services, and litigation. Other important social aspects of TBI prevention and broader legal issues are covered in depth in other chapters in this volume (see Chapter 31, The Family System, Chapter 32, Systems of Care, and Chapter 34, Clinical Legal Issues).

Public Policy and Legislation

Clinicians are often only vaguely aware of how public policy affects their work. However, the care of patients with TBI exemplifies the profound effect that government actions can have on the kind of care available to patients. As Rosen and Reynolds (1994) pointed out, "public policy decisions have an impact on every aspect of an individual's life following a traumatic brain injury…[affecting], for example, the training and skill level of emergency medical technicians, the configuration of the trauma system, the type and amount of rehabilitation services allowable through insurance, and the services available for long-term supports" (p. 1).

Prior to 1980, there was essentially no public policy specific to TBI (Spivack 1994). Since the mid-1970s, there has been significant improvement in rates of survival from TBI, a result of better emergency care at accident sites, improved access to specialized trauma centers, and technological advances such as intracranial pressure monitors and magnetic resonance imaging scans (U.S. Department of Health and Human Services 1989). This led to a growing population of TBI survivors with a broad array of neurological deficits, some subtle but devastating to vocational or social functioning, some profound and necessitating institutional care. Few people other than TBI specialists understood the needs of these patients, and few resources were available to meet these needs. The U.S. health care system is weighted overwhelmingly toward the provision of curative interventions for clearly defined, usually acute conditions. However, the chronically disabled, such as TBI survivors, require a far greater variety of services than those provided in a hospital or clinic (Committee on Traumatic Brain Injury 2006). Unfortunately, such services have traditionally been relegated by public and private insurers to the category of "maintenance," for which very limited, if any, funds are available. This situation is well illustrated in Figure 33–1.

The burden of managing the daily needs of TBI survivors fell primarily on their families, who were further burdened by a paucity of information on TBI. The National Head Injury Foundation was founded in 1980 by family members of TBI survivors "to provided support, gather and disseminate information, and encourage program development" (Spivack 1994, p. 83). This organization evolved into the Brain Injury Association of America, which with its local and state chapters has been in the forefront of advocating for TBI survivors and their families. The Brain Injury Association has also become a vital source of information to TBI survivors and their families. It publishes an annual National Directory of Brain Injury Rehabilitation Services, periodicals for both the lay public and TBI professionals, and a series of resource guides on available public benefits.

The lobbying efforts of the National Head Injury Foundation succeeded in a number of states, leading to legislation and executive orders addressing specific needs of TBI patients. Among the first was the Statewide Head Injury Program of Massachusetts, established in 1985, which provided case coordination and training on TBI issues to schools, professionals, and the public. It also assisted with program development and direct funding of nonresidential services (Digre et al. 1994). At the federal level, active lobbying by the members of the National Head Injury

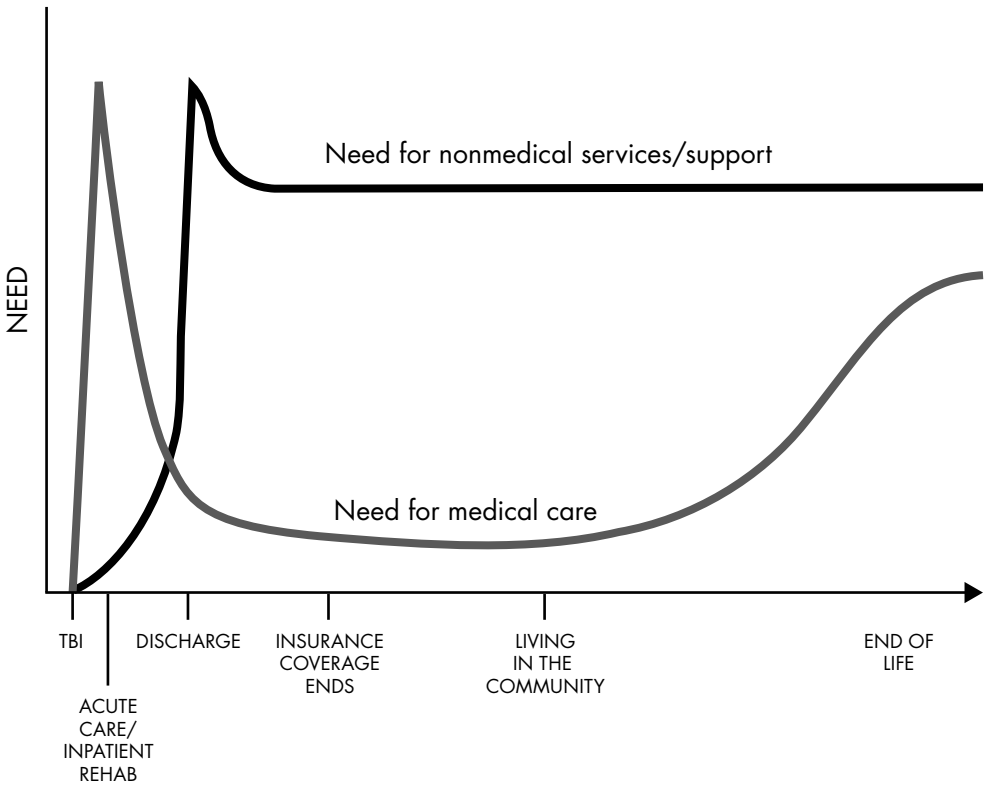


FIGURE 33–1. Continuum of needs after traumatic brain injury (TBI).

Source. Reprinted from Committee on Traumatic Brain Injury, Board of Health Care Services, Institute of Medicine of the National Academies: *Evaluating the HRSA Traumatic Brain Injury Program*. Washington, DC, National Academies Press, 2006, p. 60. Used with permission.

Foundation led to increasing interest by members of the United States Congress in the plight of TBI survivors and their families. In 1984, both the House of Representatives and the Senate passed resolutions directing various federal agencies dealing with the disabled to begin collecting data on the incidence of TBI, as well as to assess the status of services and research and to assess unmet needs. In addition to increased recognition of TBI as a growing public health crisis, there were administrative initiatives that led to productive cooperation between federal and state officials involved with TBI issues (Spivack 1994). In 1987, at the direction of Congress, a Federal Interagency Head Injury Task Force issued a report that recommended, among other things, consistent case definition and reporting of TBI, which had been lacking up until that time (U.S. Department of Health and Human Services 1989). Comprehensive regional head injury centers were also established, but funding constraints limited full implementation of the report's recommendations.

Recognizing the large and growing public health problem that TBI survival represented, Congress passed the Traumatic Brain Injury Act in July 1996 (P.L. 104-166). The act directed the federal Centers for Disease Control and Prevention to carry out intra- and extramural projects to reduce the incidence of TBI by conducting research on strategies for prevention of TBI and by implementing public information and education programs on such prevention. The act also directed the National Institutes of Health to conduct research on the following:

> (A)…[the] development of new methods and modalities for the more effective diagnosis, measurement of degree of injury, post-injury monitoring and prognostic assessment of head injury for acute, subacute, and later phases of care; (B) the development, modification, and evaluation of therapies that retard, prevent, or reverse brain damage after acute head injury, that arrest further deterioration following injury and that provide the restitution of function for individuals with long-term injuries; (C) the development of research on the continuum of care from acute care through rehabilitation, designed, to the extent predictable, to integrate rehabilitation and long-term outcome evaluation with acute care research; and (D) the development of programs that increase the participation of academic centers of excellence in head injury treatment and rehabilitation research and training.

In addition, the Traumatic Brain Injury Act provided matching funds for state demonstration projects designed to improve access to "health and other services regarding traumatic brain injury." The act called for the development of a uniform reporting system for TBI and also called for a consensus conference on TBI. The act allocated $3 million per year for 3 years for these activities.

The National Institutes of Health held a consensus development conference on rehabilitation of persons with TBI in October 1998. The panel, whose 16 members represented multiple disciplines involved with TBI and public health, elicited expert and consumer opinion, with a focus on the following questions:

1. What is the epidemiology of TBI in the United States and what are its implications for rehabilitation?
2. What are the consequences of TBI in terms of pathophysiology, impairments, functional limitations, disabilities, societal limitations, and economic impact?
3. What is known about mechanisms underlying functional recovery following TBI, and what are the implications for rehabilitation?
4. What are the common therapeutic interventions for the cognitive and behavioral sequelae of TBI, what is their scientific basis, and how effective are they?
5. What are common models of comprehensive, coordinated, multidisciplinary rehabilitation for people with TBI, what is their scientific basis, and what is known about their short- and long-term outcomes?
6. Based on the answers to these questions, what can be recommended regarding rehabilitation practices for people with TBI?
7. What research is needed to guide the rehabilitation of people with TBI? (National Institutes of Health Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury 1999).

The panel's conclusions are listed in Table 33–1.

TABLE 33–1. Conclusions of the National Institutes of Health Consensus Conference on Traumatic Brain Injury (TBI)

TBI is a heterogeneous disorder of major public health significance.
Consequences of TBI can be lifelong.
Given the large toll of TBI and absence of cure, prevention is of paramount importance.
Identification, intervention, and prevention of alcohol abuse and violence provide an important opportunity to reduce TBI and its effects.
Rehabilitation services, matched to the needs of persons with TBI, and community-based nonmedical services are required to optimize outcomes over the course of recovery.
Mild TBI is significantly underdiagnosed, and early intervention is often neglected.
Persons with TBI, their families, and significant others are integral to the design and implementation of the rehabilitation process and research.
Public and private funding for rehabilitation of persons with TBI should be adequate to meet acute and long-term needs.
Access to needed long-term rehabilitation may be jeopardized by changes in payment methods for private insurance and public programs.
Increased understanding of the mechanisms of TBI and recovery holds promise for new treatments.
Well-designed and controlled studies are needed to evaluate benefits of different rehabilitation interventions.
Basic and common classification systems of TBI are needed.
The evaluation of TBI interventions will require innovative research methods.
Funding for research on TBI needs to be increased.

Source. Adapted from National Institutes of Health Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury 1999.

The Traumatic Brain Injury Act of 1996 also mandated the Centers for Disease Control and Prevention to publish a study of the national incidence and impact of TBI. The Centers for Disease Control and Prevention's (1999) report presented available epidemiological data and concluded that TBI is a clearly important public health problem. The importance of primary prevention of the three main causes of TBI—transportation crashes, violence, and falls—was reiterated. Improved acute care and rehabilitation of TBI was called for, with specific focus on cognitive and emotional impairments. The need for improved data systems was also emphasized. The report described the decrease in TBI-related hospitalization rates over the past 20 years. It was suggested that this decrease reflects fiscally driven restrictions in hospital admissions, leaving larger numbers of patients with less severe TBI with only emergency care. Uniform state-based surveillance systems of emergency room visits were recommended to determine the true frequency of different types of TBI (Centers for Disease Control and Prevention 1999) and to better determine the relationship between the initial severity of injury and long-term outcome.

Title XIII of the Children's Health Act of 2000 (P.L. 106-310) authorized continued funding for TBI programs, with emphasis on protection and advocacy services and improvement of epidemiological data by means of state registries. The federal agency charged with implementing these programs, the Maternal and Child Health Bureau, states that its objective is to "Ensure that the estimated 5.3 million individuals and their families who live with the effects of TBI in the United States have access to comprehensive, coordinated systems of care that are person-centered and attend to their changing needs from the moment of injury throughout the rest of their lives" (http://mchb.hrsa.gov/; accessed March 30, 2009). Unfortunately, this same website reports that for fiscal year 2008, less than $9 million was appropriated to achieve these goals. While the intent of many of the federal TBI programs is to provide seed money to states to establish and fund their own initiatives, local administrators are often expected "to make something out of nothing" (Hendrickson and Blume 2008).

Medicaid

The major sources of public funding for TBI services are Medicaid, vocational rehabilitation, and independent living services (U.S. General Accounting Office 1998). Medicaid was established by the federal government in 1965 to provide health care for low-income and disabled adults and children. It provides health insurance for nearly 40 million Americans. Medicaid is a federally mandated program that is administered and partially funded by the individual states, with required services that all states must provide, such as inpatient and outpatient hospital care, physician services, and nursing facility care, as well as optional programs such as rehabilitation services and prescriptions.

Standard Medicaid programs do not provide funding for long-term community-based support services. In 1981, Congress passed the Home and Community Based Waiver,

allowing states to waive certain Medicaid regulations to provide long-term services in the community, so long as these services cost less than institutional care (Goodall and Ghiloni 2001). In 2004, there were 263 waiver programs nationally that provided more than 1 million individuals with such services as homemakers, personal care, and nonmedical transportation (Ng and Harrington 2008). At first, administrators of state programs for TBI patients were slow to invest the significant resources required to apply to the Health Care Financing Agency for waivers, especially as these services were designed primarily for individuals with physical rather than cognitive or emotional disabilities. However, regulatory changes in 1990 specifically eased the application process for TBI programs, and at present more than half of the states use some type of Medicaid waiver to provide services for those with TBI (Spearman et al. 2001). Given the decentralized nature of the Medicaid program, every state TBI waiver program is unique. Table 33–2 lists some of the waiver services various states provide.

Unfortunately, the benefits of these waiver programs are limited to only a small fraction of TBI patients. In a survey of state programs, 10,700 individuals were identified as receiving TBI waiver services nationally (Hendrickson and Blume 2008). A U.S. Government Accountabilty Office (2005) report cited the following barriers to TBI patients using waivers: 1) Many state programs are still weighted in favor of those with physical disabilities and are not equipped to recognize or deal with individuals with, for example, subtle but incapacitating executive dysfunctions; 2) effective advocates are very often needed to negotiate social service systems, especially for those TBI survivors with cognitive impairments; and 3) programs tend to exclude patients with problematic or aggressive behaviors; funding is only rarely available to provide the structured settings and professional supports necessary to properly manage TBI patients with behavioral problems. TBI waiver programs are expanding, however, with a doubling of participants in the last 3 years for which data are available (Committee on Traumatic Brain Injury 2006). It is hoped that this trend will continue as policymakers are made more aware of the utility and cost-effectiveness of long-term community-based care for TBI.

TABLE 33–2. Types of traumatic brain injury waiver services available

Case management
Residential rehabilitation
Transitional living
Independent living skills training and development
Adult day care and/or day treatment
Home and community support services (e.g., chores, supervision, companionship)
Substance abuse or mental health counseling
Psychological or behavioral counseling
Employment rehabilitation
Intensive behavioral support/crisis support
Home modifications
Specialized medical equipment and supplies/assistive technology
Nonmedical transportation
Respite care
Personal care/attendant services
Skilled nursing
Home-delivered meals

Source. Adapted from Spearman et al. 2001.

Employment

A series of studies in the 1980s documented the fact that severe TBI precluded return to competitive employment for the majority of survivors (Ben-Yishay et al. 1987; Brooks et al. 1987; Levin et al. 1979; McMordie et al. 1990; Rao et al. 1990). Despite methodological differences, the studies found the unemployment rate among survivors of severe TBI was generally in the range of 60%–80%. Factors correlated with poor employment outcome included severity of injury; degree of cognitive, physical, and psychosocial impairments; and vaguely defined "preinjury variables." To clarify the impact of various risk factors on return to work, Dikmen et al. (1994) conducted a prospective study of 366 TBI patients and 95 control subjects with somatic trauma. The results are illustrated in Figure 33–2.

The data in the figure show that 1 year after injury, 80% of TBI patients with Glasgow Coma Scale (GCS) scores of 13–15 returned to work, almost equal to that of control subjects. For patients with GCS scores of 9–12, less than 60% returned to work, and less than 30% of those with GCS scores of 8 or less were employed 1 year postinjury. Those with more severe injuries tended to show some improvement up to 2 years postinjury, whereas those with less severe injuries reached the asymptote by 1 year. Dikmen et al. (1994) emphasized the importance of severity of injury in having a reliable and powerful predictive effect, especially length of coma. Of those patients in their cohort who were not following commands 29 days after injury, only 8% were working 2 years after injury. The authors found that subjects over age 50, those with less than a high school education, and those with unstable premorbid work histories were significantly less likely to be employed after TBI. In their group, moderate injury to other body systems did not lead to significant unemployment by 6 months after injury. A limitation of Dikmen et al.'s study is the fact that the outcome measure is time to return to work; employment retention, shown to be highly problematic for TBI survivors (Machamer et al. 2005; Wehman et al. 1995), is not addressed. Later studies have replicated and expanded these data (Avesani et al. 2005; Gollaher et al. 1998; Hawkins et al. 1996). Sherer and colleagues found that a premorbid history of substance abuse results in an eightfold increase in post-TBI unemployment rates, all else being equal (Sherer et al. 1999). Limited insight into deficits (anosognosia) has been shown to impede return to work (Sherer et al. 1998; Trudel et al. 1998). In their thoughtful review, Wehman et al. (2005) pointed out, "Indeed, it does appear that self-awareness and acceptance of disability clearly have an impact on employment outcome. It is important to note that for many individuals with TBI, this insight will not be gained in a counseling session, but instead will be gained over time and through real work experience" (p. 116).

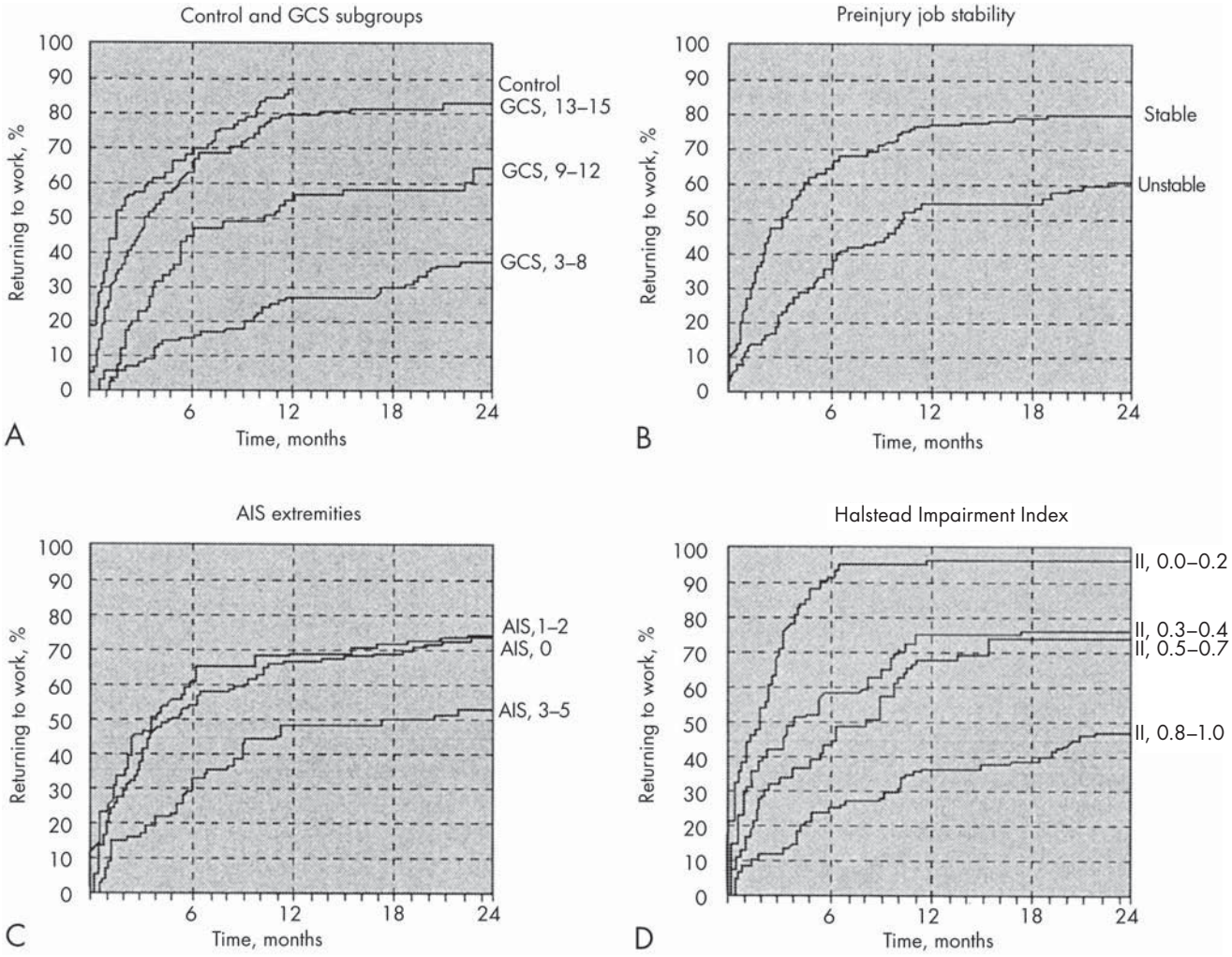


FIGURE 33–2. Return to work by severity of traumatic brain injury, by preinjury stability, by physical disability, and by neuropsychological status.

Estimated percentage first returning to work by subgroups defined on the basis of initial Glasgow Coma Scale (GCS) (top left), job stability (top right), Abbreviated Injury Scale (AIS) score for the extremities (bottom left), and neuropsychological performance at 1 month after injury, using Halstead Impairment Index (II) (bottom right).

Source. Reprinted from Dikmen SS, Temkin NR, Machamer JE, et al.: "Employment Following Traumatic Brain Injury." *Archives of Neurology* 51:177–186, 1994. Copyright © 1994 American Medical Association. Used with permission.

Predictably, depression has been found to correlate with poorer work outcomes (McCrimmon and Oddy 2006; Satz et al. 1998). Fraser and Wehman (2001), among many others, found cognitive barriers to be the major difficulty in returning to work. Although no specific neuropsychological test or variable has been shown to be clearly predictive of real-life employability, impairments of higher level cognitive skills, such as the ability to screen out distracting or irrelevant stimuli, the ability shift attention at will, the ability to plan and maintain a strategic sequence of activities, and the ability to inhibit responses, all have a profound impact on success in nearly every vocational setting (LeBlanc et al. 2000). Fraser and Wehman (2001) presented data, consistent with prior studies such as that of Eames (1988), showing that in their cohort, diverse emotional concerns and preexisting characterological or behavioral difficulties were each found to seriously adversely affect one-third of their patients. They cited the critical need for neuropsychiatric interventions, for example, pharmacotherapy and/or behavioral and cognitive strategies, for population-wide improvements in the employment of TBI survivors. In an interesting parallel to studies demonstrating the impact of premorbid factors, Walker et al. (2006) found that working in a professional or managerial position prior to brain injury was positively correlated with successful return to work. It is suggested that the skills or traits necessary for maintaining a more demanding career may contribute to better outcomes after TBI.

Mild TBI, however defined, has received less attention than the more obviously disabling varieties. Boake et al. (2005) found that even though no significant difference in employment status is apparent between patients with mild TBI and control subjects 6 months after injury, a majority of nonhospitalized mild TBI patients did not return to work for at least 1 month after injury.

Most of the literature on TBI and return to work focuses on competitive employment. Uysal et al. (1998) examined the effects of TBI on one's ability to function as a parent. In a group of parents 9 years after the injury, on average, the authors found more impairment in goal setting, skill development, nurturing, and involvement with children than in matched control subjects. Although the children of the families they examined were no more objectively dysfunctional than control subjects, TBI appears to impair one's ability to work as a parent.

Return to work has been used as a convenient end point for measuring recovery from TBI. It is clearly more than just a statistical tool, however. For many TBI survivors, the inability to work epitomizes their sense of loss and diminishment. The inability to resume their accustomed social role and to support themselves and their families exerts a highly corrosive effect on self-esteem. O'Neill et al. (1998) found employment status to be well correlated with perceived quality of life, social integration, and avocational activities. The workplace is also, in most cases, a major focus of one's social network. Unfortunately, many TBI survivors face the loss of medical or disability benefits if they do return to work, a major difficulty especially if they cannot work full time or work at their premorbid levels. Recent changes in Social Security statutes, outlined below, address this issue.

Disability Insurance

TBI survivors unable to work competitively must rely on disability insurance for maintenance of some income. The Social Security Administration is the largest disability insurance program in the United States, providing benefits for up to 50% of those qualified as disabled (Ranavaya and Rondinelli 2000). It funds two distinct programs. Social Security Disability Insurance (SSDI) was established in 1956 to provide pensions for workers over the age of 50 who are totally and permanently disabled. Benefits are available to workers who have contributed to the program through payroll and employer-paid taxes over a designated period of years, usually 5 of the preceding 10 years. Over 96% of jobs in the United States are covered by SSDI (Robinson and Wolfe 2000). The Supplemental Security Income (SSI) program was established by Congress in 1972 to provide income support to the indigent disabled. It is a combined state and federal program that differs in its details and benefits from state to state. Eligibility for SSI benefits does not depend on work history; all those below designated levels of income and assets are eligible if they meet disability criteria. Congress mandated that recipients of either program undergo periodic continuing disability reviews to certify ongoing disability and thus eligibility for benefits. In 1995, approximately 13% of reviews led to termination of benefits (Robinson and Wolfe 2000). The benefits provided by these government programs are rather austere, with SSDI replacing less than one-half the income of a person earning $25,000 annually and one-fourth the income of a person earning $60,000. SSI payments average only 60% of SSDI (Robinson and Wolfe 2000). While these federal programs clearly provide vital assistance to most of those with disabilities, the U.S. Government Accountability Office (2005) designated them a "high-risk area requiring urgent attention" from Congress, citing problems with lack of coordination between the approximately 200 government programs providing different forms of assistance for various populations in need. They also described lengthy processing times for applications, delays in provision of benefits, inconsistency in applying complex eligibility requirements, and absence of strategic planning for future needs.

Approximately 40 million Americans have some type of private long-term disability insurance, either purchased privately or acquired through the workplace (Ranavaya and Rondinelli 2000). Private disability insurance usually replaces 60% of an individual's usual income. However, these private policies are unique contracts between individuals (or groups) and the insurance company, thus making generalizations difficult. Increasing numbers of insurance companies are also issuing policies for long-term care, providing reimbursement for institutional or home care in case of incapacity as demonstrated by inability to perform a predetermined set of activities of daily living. Such insurance can be very helpful in the face of catastrophic incapacity, as with a severe TBI.

Vocational Rehabilitation

The history of federal legislative efforts on behalf of the disabled well illustrates the interacting themes of advocacy, public policy, and clinical impact. The federal government has promoted efforts to reemploy the disabled since 1918, when the Soldiers Rehabilitation Act authorized vocational rehabilitation programs for injured veterans of World War I. This effort was expanded in 1920 with the Civilian Rehabilitation Act and was set up as a permanent part of the Department of Labor with the Social Security Act of 1935 (Tate et al. 1998). Some of the more recent legislative efforts are discussed below, but a brief description of vocational rehabilitation is in order.

Vocational rehabilitation has been defined as any goods or services required to make people with disabilities employable. As a government program that evolved piecemeal over decades, vocational rehabilitation has no intrinsic definition, especially as it is (like Medicaid) a federal grant-in-aid program to the states, which authorize and define services as they see fit. Depending on the jurisdiction and the political climate, vocational rehabilitation services can include the following: medical services (e.g., surgery or prostheses), tuition reimbursement for formal or vocational education, testing (including neuropsychological testing), assistive devices and technological aids, counseling, and on-site job coaching, modification of the work environment, and cultivation of potential employers. The ways in which such services are provided has evolved over the past 30 years. Attempts to parse out which types of services are most effective have not yet shown any clear "best practice" (Fadyl and McPherson 2009; Hart et al. 2006). However, there is good evidence that vocational rehabilitation programs allow TBI survivors to return to work or productive activity earlier than without such interventions (Kendall et al. 2006; Wehman et al. 2005).

Under the growing influence of the National Rehabilitation Association and other advocacy groups for the disabled, government attitudes toward the provision of vocational and other services began to shift in the 1960s from top-down bureaucracies aiding those it labels as "handicapped" to a more consumer-oriented approach. The Rehabilitation Act of 1973 mandated that vocational rehabilitation processes begin with the formulation of an Individualized Written Rehabilitation Plan, with active participation of the client. Subsequent amendments to the Rehabilitation Act have mandated greater consumer control over the types of employment and employment services available, as well as supporting the use of assistive technologies and supported or part-time employment. The Ticket to Work and Work Incentive Improvement Act of 1999 attempts to remove serious disincentives to returning to work experienced by SSDI and SSI recipients. Beneficiaries who return to work can now retain Medicare part A health insurance for up to 7½ years. The availability of health insurance has been found to be a significant factor for successful return to work of TBI survivors (West 1995). Those who try returning to work but fail can have an expedited reinstatement of benefits without reapplication or waiting period. Disability benefits continue for the first 9 months of work, considered a "trial work period." The act also partially privatizes vocational rehabilitation services, allowing consumers to use approved private agencies whose reimbursement is in part tied to their success in getting people off disability (Golden 2001).

TBI patients have benefited from such services, with studies showing the specific utility of supported employment—the presence on the job site itself of an employment specialist to provide training, counseling, and support on an ideally long-term basis, with subsequent skills generalization and increased productivity by the patient (Wehman et al. 1990, 1995). Wehman et al. (1990) cited the cost of such services as $8,700 per placement. While an admittedly expensive investment of taxpayer dollars, alternatives such as chronic unemployment, dependence, and depression are far more expensive (Abrams et al. 1993). Wehman et al. (2005) also suggested alternative work arrangements, such as telework, self-employment, and independent contracting, as being viable strategies for getting TBI survivors with residual disabilities into productive activities.

The Rehabilitation Act of 1973 also guaranteed nondiscrimination against persons with disabilities in any federally assisted program or activity. This guarantee was expanded by the Americans With Disabilities Act of 1990 to include all employment, public services, public transportation, places of accommodation such as hotels, and telecommunications. All firms with 15 or more employees had to accommodate their disabled employees unless this would impose "undue hardship."

As of the early 1970s, Congress has been funding Centers for Independent Living—autonomous, community-based agencies that provide peer counseling, information and referral, training in independent living skills, and advocacy to the disabled (Tate et al. 1998). Depending on available funding, some centers provide housing assistance and other concrete services. These Centers for Independent Living are unique in that they are managed and often staffed by the disabled persons themselves, on the theory that they know better than bureaucrats (or physicians) what concrete services are needed. These centers and groups modeled on them teach TBI patients, among others, to be self-advocates, a role that can be deeply meaningful to people abruptly deprived by TBI of former capacities and often having to be dependent both on other individuals and on obtuse bureaucracies (Wehman 2001).

Litigation

The costs of care and rehabilitation for TBI are beyond the means of most people if these would have to be paid out of pocket (Sherer et al. 2000). As outlined earlier in this chapter, TBI patients and their families, to gain funding for treatment, typically have to deal with many insurance and governmental agencies, each with their own complicated sets of rules, requirements, and exclusions. The advocacy and clerical work required—for example, the establishment of contact with all available sources of funding, the verification of eligibility for benefits, and the collection of necessary data to justify services—are vitally important for most TBI patients but can easily consume much of a caregiver's time and energy. Psychiatrists working at TBI centers are often called to consult with distraught family members who are overwhelmed with the abrupt and horrifying impairment of a loved one, and who in the midst of shock and grief have to become highly effective advocates.

The challenges faced by patients and their caregivers become even more complicated when the TBI patient's injuries lead to litigation. It is estimated that most TBI patients become involved in litigation at some point, most often as plaintiffs suing for damages or for wrongful denial of benefits (Miller 2000; Taylor 1997). Patients and their families then face the additional task of finding a lawyer competent and experienced in dealing with the multiple clinical and legal aspects of brain injury. Cases involving brain injury are considered among the most complex and expert-intensive areas of civil law practice (Taylor 2000). Increasing numbers of personal injury lawyers are specializing in what is called "neurolaw," a subdiscipline of attorneys with special competence in understanding the complex clinical issues involved in TBI (Taylor 1997). The legal literature has numbers of articles and texts in the field of neurolaw (Miller 1998; Roberts 1996; Taylor 1997). Some of them (e.g., Miller 1998) can stand as thorough and sophisticated clinical reviews. The Brain Injury Association of America maintains a list of attorneys practicing neurolaw on its website (www.biausa.org).

Litigation is often the only way TBI survivors can obtain even basic financial security. For those whose lives have been permanently impaired by the negligence of others, there are few ways other than litigation to obtain any sense of justice or closure. However, it is important for clinicians working with TBI survivors to realize that litigation can have serious adverse effects for the survivor. Strasburger (1999) pointed out that few litigants are prepared for the forces of aggression that are released and sanctioned by the U.S. legal system. Ideally, seeking and obtaining compensation for multiple losses should be an empowering experience, especially for those who are

powerless to fully restore their premorbid lives. Unfortunately, even with successful outcomes, litigation can be highly deleterious to plaintiffs as well as defendants (Halleck 1997).

The goal of the U.S. legal system is to reduce all uncertain issues to clearly discernible dichotomies, guilty or innocent, for plaintiff or for defendant. A TBI survivor struggling with having to adapt to a life quite different from anything he or she could have imagined, whose life has become a series of novel and mostly unpleasant experiences, may have trouble conforming to forensic certainties. Patients suffering the sequelae of TBI often feel damaged, helpless, and victimized. The incidence of posttraumatic stress disorder (PTSD) among TBI survivors is difficult to estimate, given the great variety of clinical and cognitive pictures presented. One may assume, however, that the typical avoidant defenses seen in general trauma survivors are used. The injury may evoke emotional memories of prior instances of victimization (e.g., childhood abuse) leading to a complex PTSD (Raskin 1997). Judicial procedures can exacerbate these feelings and memories. Acute and chronic PTSD symptoms can be sharply exacerbated by the unraveling of avoidant defenses resulting from the survivor having to repeatedly recount his or her history in law offices and in court (Pitman et al. 1996). A patient struggling to accept disability may find the articulate skepticism of opposing attorneys difficult and may feel compelled to prove to others and to themselves that the symptoms with which they are struggling are indeed real. This can cause an increased focus on symptoms and a tendency to overstate disability. In other words, survivors may feel compelled to assume a sick role that interferes with recovery (Bellamy 1997; Halleck 1997). In my experience, patients who are depressed and suffer from self-doubt and self-criticism are the most vulnerable to this process of having to prove symptoms. Narcissistic patients who need to minimize and deny any disability, lest they appear "defective," are also vulnerable to preoccupation with their symptoms. This process can be conscious or unconscious and lead to a preservation of self-esteem at the expense of worsening symptoms (Strasburger 1999). It should be stressed that these patients are not malingering—that is, deliberately exaggerating symptoms for financial gain—but are rather trying to adapt as best they can to a stressful and, at times, inquisitorial process.

TBI survivors may well have cognitive symptoms that impair their ability to competently participate in their case. For example, posttraumatic amnesia may interfere with both the ability to recall events following the injury and the ability to recall appointments, names of witnesses, and documents needed. Difficulty with organizing thoughts makes preparation for depositions and meetings with attorneys difficult. Increased distractibility may make the coherent presentation of information problematic, especially in the face of skeptical cross-examination. Symptoms of TBI, like all symptoms, can be exacerbated by stress (Feinstein et al. 2001; Finset et al. 1999). TBI survivors can thus be caught in a vicious circle, their cognitive symptoms worsening their ability to deal with litigation, and the consequent stress worsening their cognitive symptoms.

Some authors conclude that the legal process itself is nociceptive, perpetuating pathology and disability in litigants (Bellamy 1997). In a meta-analysis of studies comparing litigating and nonlitigating TBI survivors, Binder and Rohling (1996) found that patients seeking compensation for injuries were more likely to show behavioral abnormalities and functional disability than control subjects, despite the fact that the litigating group had fewer neurological findings within 24 hours of injury and had a shorter period of posttraumatic amnesia. Time since lawsuit, rather than time since injury, has been found to be correlated with recovery, again implying that litigation itself is toxic (Binder et al. 1991). In a prospective study of 100 patients with mild TBI, no demographic, neurological, or premorbid differences were found between litigating and nonlitigating patients; the litigants were significantly more anxious, depressed, dysfunctional, and likely to have a poor outcome than nonlitigants (Feinstein et al. 2001). These conclusions remain controversial, however. Authors such as Thornhill et al. (2000) pointed out that TBI survivors with poor outcomes are more likely to seek damages than those who recover, accounting for the higher incidence of disability among litigants. They noted that among the patients in their prospective study who had impairments after mild brain injury, 80% were not involved in any litigation, implying that litigation is not a significant factor in poor outcome after TBI. In a study of survivors of severe TBI at 4 months and 10 years after injury, Wood and Rutterford (2006) found no difference on clinical measures between litigants and nonlitigants.

This controversy has a long and venerable history. Evans (1994), in his review article, detailed some of this history. The terms *railway spine* and *compensation neurosis* both date from the late nineteenth century, arising soon after the invention of both mechanized forms of transportation and insurance awards for accident victims. The determination of feigned or exaggerated symptoms after TBI remains difficult and controversial, even with the current availability of both structural and functional scanning techniques (Alexander 1998; Ricker and Zafonte 2000). The importance of differentiating frank malingering, PTSD, somatoform disorders, and the often subtle neuropsychiatric symptoms of TBI has led to the evolution of forensic neuropsychology. This challenging subject is beyond the scope of this chapter, and the interested reader is referred to review articles and books such as those of Iverson and Binder (2000), Larrabee (2005), Murray and Starzinski (2007), Reynolds (1998), and Rogers (1997).

Conclusion

TBIs have left ever-increasing numbers of survivors with serious disabilities. The cost of caring for these survivors is prohibitive for most families and has led to increasing numbers of government initiatives to provide assistance. After lobbying efforts by consumer groups such as the Brain Injury Association, the U.S. government passed legislation to specifically study the epidemiology of TBI and interventions to minimize morbidity and mortality. Medicaid waiver programs dedicated to TBI survivors, though of limited availability, provide extended rehabilitation and care. Social Security disability benefits provide a major source of income for TBI survivors. Vocational rehabil-

itation services, along with incentive programs in the Social Security system, are designed to help those disabled by TBI to become self-supporting. TBI survivors are often involved in litigation that can be difficult and painful but can also partially redress loss of income and perhaps even feelings of injustice.

The resources TBI survivors need to survive and to obtain clinical services are mostly funneled through major social institutions such as government bodies, insurance companies, and the judiciary. Social policy and effective advocacy profoundly affect the quantity and quality of resources available.

KEY CLINICAL POINTS

- Public policy can have a profound effect on the care available to patients.
- There have been thoughtful and meaningful legislative efforts specifically focused on traumatic brain injury. Their impact has been limited by budgetary constraints.
- Many survivors of traumatic brain injury, no longer able to work competitively, have to depend on public and private insurers for financial support, often at levels far below their premorbid incomes.
- Those injured through the negligence of others can seek redress and compensation by litigation. The process, however, can be quite stressful and daunting.

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CHAPTER 34

Clinical Legal Issues

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PATIENTS WITH TRAUMATIC BRAIN INJURY (TBI), especially those with personality change or who manifest difficulties in consciousness, judgment, mood regulation, memory, orientation, insight, and impulse control, can raise complex legal and ethical problems (Warriner and Velikonjad 2006). TBI creates situations requiring the patient, and thus the clinician, to interface with multiple systems. People with TBI frequently are involved in criminal, civil, or administrative legal situations. They may be involved as disability claimants, witnesses, victims, plaintiffs, criminal defendants, respondents, or petitioners, in a wide variety of circumstances. TBI has become associated with the wars in Afghanistan and Iraq, challenging systems of health care delivery, rehabilitation, and compensation. Readers of this chapter may find themselves working with people with TBI as treatment providers or as expert witnesses commenting on various types of competencies, petitioning for guardianship or conservatorship, supporting accommodations and services under the Individuals With Disabilities Education Act (1990) or the Americans With Disabilities Act (1997), testifying on the effects of the TBI on the person's life or predictions of future behaviors, or providing estimations of whether the injury's effects are being overstated, among many possible roles. TBIs, when initially seen, may require a report to authorities under a mandated reporter statute. Injuries that result in a persistent vegetative state may require ethical consultation if further care is felt to be futile and the substitute decision maker is requesting termination of further lifesaving or maintenance interventions. The basic legal and ethical concepts discussed in this chapter are applicable to other forms of brain injury or disorders.

We first address the issue of mandatory reporting, including *Tarasoff*-type notification, because a failure to adhere to the law can result in adverse consequences to the clinician as well as the patient.

Mandated Reporting, *Tarasoff,* and Shaken Baby Syndrome

Child abuse, and particularly what is called *shaken impact syndrome* or *shaken baby syndrome,* can result in fatal or near-fatal TBI (Richards et al. 2006). The occurrence is not rare; nonaccidental head trauma is the leading cause of infant death from injury (see Chapter 2, Neuropathology, in this volume), The effects of child abuse–related trauma to the brain may be mild, transient, or fatal. Infants are particularly susceptible because of the relative weight of their head and immature muscle control over head movement (Duhaime et al. 1992). Of roughly 50,000 reported cases of child abuse involving suspected acceleration, deceleration, and or impact trauma to the brain, 25% result in death. Risk factors for perpetrators of shaken baby syndrome include male gender, history of impulsive behavior, substance abuse, and history of childhood abuse. Child abuse may be the likely cause of injury in cases involving serious intracranial or intraocular bleeding, diffuse brain injury, and brain swelling, with little history or signs of external trauma (Reece and Sege 2000). No constellation of signs can be considered pathognomonic. There is considerable controversy over the minimization of nonabusive causes of retinal hemorrhage and subdural or intracranial bleeding in infants (Bandak 2005). Accidental head trauma can occur from minor falls. The cooccurrence with other evidence of child abuse, such as burns or bone fractures, should alert the health care provider to the need for a report of suspected child abuse.

All 50 states and the District of Columbia have mandatory reporting requirements for health care providers who become aware of child abuse under the Child Abuse Prevention and Treatment Act. All have mandatory reporting

for elder abuse or neglect and abuse of the cognitively or physically disabled. Some states also have reporting requirements for injuries from firearms, assault, sexual abuse, or domestic violence. The exact requirements will vary from jurisdiction to jurisdiction. Reasonable suspicion of abuse or neglect will trigger the reporting duty in most jurisdictions. Certainty is not required, nor is lack of it a defense for failing to report. Most states have absolute civil and criminal immunities for reports made in good faith, if there is a reasonable basis for suspicion of abuse. The legal requirement to report trumps claims of patient-physician confidentiality. For example, in California, health care providers must notify local authorities if they are providing medical services to a patient with a physical injury resulting from a firearm or assaultive or abusive conduct. Patient or parental consent is not needed to make a report. There are often special forms (e.g., Suspicious Injury Report Form) for the reporting. Failure to report in some states can be a misdemeanor and can result in action against a practitioner's license (e.g., California Penal Code sections 11160–11163.2). Some states do not require the mandated reporter to be the one providing services; for example, New York requires a report even on the basis of secondhand knowledge. Physicians may be liable in malpractice suits for failure to report (*Landeros v. Flood* 1976).

Domestic violence is subject to mandated reporting requirements in some jurisdictions. More than 80% of women presenting in an emergency department or to primary care with intimate partner violence have facial injuries (Banks 2007). Because facial injuries are common in intimate partner beatings, it is likely that TBI, particularly mild TBI, is not uncommon in the victims of domestic violence (Corrigan et al. 2003; Monahan and O'Leary 1999; Valera and Berenbaum 2003). Domestic violence is often repeated and chronic, increasing the risk for TBI. Screening for domestic violence is strongly encouraged in emergency departments and primary care facilities; if domestic violence is present, screening for TBI symptoms is potentially very useful, particularly if there are concerns about the victim's executive functioning. Mild TBI symptoms can too easily be attributed to posttraumatic stress disorder (PTSD) or Cluster B personality traits (Gagnon et al. 2006; Raskin 1997). Male perpetrators of domestic violence have a higher incidence of TBI than nonabusing spouses (Rosenbaum et al. 1994).

Mandatory reporting laws are not without controversy, particularly those relating to domestic violence (Appelbaum 1999; Lachs 2004; Rodriguez et al. 2001). The American Medical Association (2008), for example, opposes mandatory reporting for competent adult victims of intimate partner violence.

Clinicians may be asked to evaluate the safety of resuming driving after a person suffers a TBI. Some states also mandate physicians to report to the Department of Motor Vehicles or public health department patients who experience seizures or lapses of consciousness and who drive automobiles. In the majority of states, reporting is encouraged but not mandated (Aschkenasy et al. 2006). Again clinicians working with a person with TBI should consider the patient's individual circumstances and the law in their jurisdiction (Leon-Carrion et al. 2005). The loss of driving privileges, hence transportation, can impact rehabilitation efforts (Rapport et al. 2008).

The private version of mandated reporting is usually referred to as a *Tarasoff* warning (*Tarasoff v. Regents of the University of California* 1976). As with mandated reporting laws, the exact requirements of a *Tarasoff*-type notification vary from jurisdiction to jurisdiction, if it is even recognized (Mossman 2006). For example, North Carolina does not impose this duty on mental health clinicians (*Gregory v. Kilbride* 2002). The concept of a *Tarasoff*-type warning generally refers to the responsibility of a mental health clinician or physician treating a violent or dangerous patient to break confidentiality and to warn and protect any intended victim of planned violence. In some jurisdictions the existence of an intended victim may not be required, only the existence of a patient with generally dangerous propensities (*Lipari v. Sears* 1980, applying Nebraska law; *Petersen v. State* 1983, applying Washington law; *Estates of Morgan v. Fairfield Family Counseling Center* 1997, applying Ohio law). In the rehabilitation or clinical work with a patient with TBI in which irritability, impulsivity, and concrete thinking are severe problems, and explosive behavior has occurred and is threatened, the clinician may face the situation of contemplating the need to give a *Tarasoff* warning. Stalking among the brain-injured or cognitively impaired is poorly studied, but inquiries are indicated if the person with TBI is particularly obsessed with another. We encourage clinicians to consider the need to take measures to protect others early after a concern is first experienced rather than waiting for an emergency. No jurisdictions at present require any warning to family members when suicide is threatened, under a *Tarasoff* theory. Along with a *Tarasoff* warning, the clinician will want to consider the use of emergency mental health detention proceedings, if explosive behavior is escalating or imminent or if self-harm is likely. In working with the aggressive and impulsive brain-injured person, risk assessment and risk management must be an ongoing process. Consultation with the important people in the patient's life, after the patient provides consent, is useful both to gather additional information about risky behaviors and to develop strategies to manage them.

Assessment of Risk of Violence in the Person With TBI

The causal connection between brain damage, criminality, and violence remains uncertain (Baguley et al. 2006; Kandel and Freed 1989). Violent behavior spans a wide spectrum, from a normal response to a threatening situation to violence emanating directly from brain disorders such as Klüver-Bucy syndrome, hypothalamic tumors, or temporal lobe epilepsy (Strub and Black 1988). Frontal lobe injury appears to be associated with increased impulsivity and aggression (Heinrichs 1989). Violent behavior is the result of the interaction between an individual and a specific situation with multiple influencing factors. Some of those factors associated with brain injury and aggression include the presence of major depression after injury, frontal lobe lesions, premorbid history of mood disorder, poor premorbid social functioning, premorbid aggressive behavior, and a premorbid history of alcohol and substance

abuse (Tateno et al. 2003). A literature review sponsored by the American Neuropsychiatric Association Committee on Research emphasized the many limitations in the current studies of TBI and postinjury aggression (Kim et al. 2007). Psychiatrists should acknowledge limitations in their expertise concerning the possible connections between brain damage, criminality, and violence.

Focal orbitofrontal injury is specifically associated with increased aggression (Brower and Price 2001). The Vietnam Veterans Head Injury Study demonstrated a higher rate of aggressive behavior in patients following ventromedial frontal lobe lesions (Grafman et al. 1996). However, this study did not factor in the role of premorbid traits (Kim et al. 2007). As suggested in the previous discussion, behavioral dyscontrol is not rare following TBI (Brooks et al. 1986). TBI is not rare in persons with preexisting problems with impulsivity, substance misuse, risk taking, or antisocial behaviors. Behavioral dyscontrol often coexists with irritability, impulsivity, impaired judgment, impaired inhibition, and cognitive deficits following TBI (Damasio et al. 1999). Some patients with TBI, particularly those with behavioral dyscontrol, will present with aggressive behaviors (Dyer et al. 2006). Assessment of risk of violence is a clinical process along a continuum from no risk to absolute risk (Buchanan 2008). It is decidedly not a dichotomous sorting of populations into the violent and nonviolent. Though the data are inconsistent, most recent studies of violence to others risk assessment have generally found that mental illness by itself is not a potent risk factor for violence to others but that the addition of specific traits associated with mental illness can increase risk above population baselines. These factors include paranoid-like symptoms, sometimes labeled "threat-control override" symptoms, grandiose delusions, substance abuse, and impaired compliance with treatment (Choe et al. 2008; Swanson et al. 2006; Teasdale et al. 2006). Substance abuse is often increased following TBI, which increases the risk of aggressive behaviors (Corrigan and Cole 2008; Taylor et al. 2003).

Studies of the epidemiology of self-harm among people with TBI show increased risk (Simpson and Tate 2005, 2007a, 2007b). One study showed that people with severe TBI are four times more likely to commit suicide compared with the general population (Teasdale and Engberg 2001). People with mild TBI or concussion also had an elevated, but lower, risk of suicide (Teasdale and Engberg 2001). Other studies are contrary to this trend (Harrison-Felix et al. 2006). Suicidal ideation and attempts are also increased following TBI (Anstey et al. 2004). The risk of self-harm among TBI patients remained elevated over a 15-year follow-up (Fleminger et al. 2003). Drug overdose has been the most frequent method of suicide (Simpson and Tate 2005). The risk of suicide in the future is particularly high if the TBI was caused by a suicide attempt (Teasdale and Engberg 2001). General risk factors for self-harm in the entire population include the presence of depression, anxiety, substance abuse, recent loss, chronic medical condition, history of prior violence toward self or others, intent and plans for self-harm, hopelessness, and impulsivity (American Psychiatric Association 2003); Simpson and Tate 2002). Many of these risk factors are increased following TBI. Chronic pain syndromes, particularly headache, have been associated with TBI and may increase the risk of self-harm (Nampiaparampil 2008; Ratcliffe et al. 2008).

The use of seclusion or restraints, including chemical restraints, may be necessary and appropriate in the acutely suicidal or dangerous agitated patient, the confused patient, or the patient who wanders. Most regulations define bedside rails as restraints (Centers for Medicare and Medicaid Services [CMS] 2006; Gaber 2006). Under many guidelines, CMS conditions of participation, Joint Commission (2002) standards, and in some cases state law, restraints or seclusion can only be used after the failure of less restrictive alternatives has been documented (National Association of Protection and Advocacy Systems 2003).

Assessments of risk are best performed by the clinician using a mixture of clinical acumen and experience, as well as a review of the risk factors and weighting established by mathematical analyses (actuarial methods). A violence risk assessment specific to TBI has yet to be developed. The Historical Clinical Risk–20 (HCR-20) is widely used for the purpose of general risk of violence assessment (Webster et al. 1997). The communication of a moderate to high assessment of risk of self-harm or harm to others in the TBI patient needs to take place in the context of therapy, rehabilitation, and potential legal requirements.

Assessment of Competencies in the Patient With TBI

Competency is defined as "having sufficient capacity, ability…[or] possessing the requisite physical, mental, natural, or legal qualifications" (Black 1990, p. 284). This definition is deliberately vague and ambiguous because competency is a broad concept that encompasses many different legal issues and contexts. As a result, competency requirements and application can vary widely depending on the circumstances in which they are measured (e.g., health care decisions, executing a will, or confessing to a crime). The term *incapacity,* which is often interchanged with *incompetency*, refers to an individual's functional inability to understand or to form an intention with regard to some act, as determined by a health care provider (Mishkin 1989).

Competency refers to some minimal mental, cognitive, or behavioral ability, trait, or capability required to perform a particular legally recognized act or to assume some legal role. All persons regardless of their diagnosis are presumed competent once past the age of majority. The California Probate Code (section 811; see Appendix 34–1, this chapter) gives a useful structured overview for the court's determination of competency. In TBI patients, fluctuations in mental capacity are common, particularly in the days and even months after injury. The mere finding of residual cognitive function in a persistent vegetative state or the ability to answer general yes/no questions, as in the minimally conscious state, would not be sufficient to prove competency (Nakase-Richardson et al. 2008). Competency determinations look for specific knowledge relative to the task and ability to coordinate that information.

The legal designation of incompetency is applied to an individual who fails one of the mental tests of capacity and is therefore considered by law not to be mentally capable of performing a particular act or assuming a particular role. The adjudication of incompetence by a court is subject or issue specific. For example, the fact that a TBI patient is adjudicated incompetent to execute a will may not automatically render that patient incompetent to do other things such as consenting to treatment, testifying as a witness, consenting to sexual activity, driving, or making a legally binding contract. Generally, the law recognizes only those decisions or choices that have been made by a competent individual. The law seeks to protect incompetent individuals from the harmful effects of their acts.

Scrutiny should be given to determine whether there are specific functional incapacities that render a person incapable of making a particular kind of decision or performing a particular type of task. Willfully ignoring that a patient lacks competency may violate statutes as well as civil law (*Zinermon v. Burch* 1990).

Admissibility of Clinician Testimony Related to Brain Injury

As new technologies are developed, the question of their reliability and accuracy will come up when admissibility is sought in court proceedings. Clinicians must be prepared to have all of their methodologies scrutinized. The general test for the admissibility of expert or technical evidence under the Federal Rules of Evidence 702 is given by the decision in *Daubert v. Merrell Dow Pharmaceuticals* (1993) and *Kumho Tire Company, Ltd. v. Carmichael* (1999). Expert testimony must assist the finder of fact in understanding the evidence. In *Daubert,* the U.S. Supreme Court considered the admissibility of expert testimony as subject to four factors: general acceptance among the scientific community, the extent of empirical testing, publication of findings in peer-reviewed journals, and the error rate of the testing. Many states have taken the Federal Rules as a model, and the influence of *Daubert* is widespread. However, others use the *Frye* test of admissibility based on whether the findings or methodologies have general recognition in the scientific community (*Frye v. United States* 1923). Results of neuropsychological testing, computed tomography, single-photon emission computed tomography, positron emission tomography, or functional magnetic resonance imaging scans are not automatically allowed into court. Scans and neuroimaging are not direct visualizations of the brain tissue but are processed information, more analogous to maps (Kulynych 1996, 1996–1997). Juries can be strongly influenced by neuroimaging because of the belief that it is tangible scientific evidence. Inferences of causation based on technical tests may also be subject to challenge. Nor are psychologists or neuropsychologists automatically allowed to testify on medical matters regarding brain injury (Foster 1999; *Minner v. American Mortgage and Guaranty Co.* 2000). Even diagnoses such as postconcussional disorder have been challenged in court.

Malingering and Inaccurate Reporting of Symptoms

Malingering can be conceptualized as the intentional production of false or grossly exaggerated physical or psychological symptoms motivated by conscious external incentives (Mittenberg et al. 2002). All symptoms of TBI can be malingered: memory impairment, poor concentration, weakness, nightmares, apathy, anhedonia, headaches, irritability, and even seizures. Patients with persistent postconcussive complaints are typically scrutinized for malingering because of the largely subjective nature of the symptoms that are dependent on accurate self-report. PTSD symptoms pose similar challenges for clinical validation. Malingering is a diagnosis of exclusion based on contradictory or discrepant evidence that cannot be explained by the claimed disorder (Table 34–1). The widespread use of the Internet has allowed litigants to become quite sophisticated about medical symptoms and procedures. In the past 20 years, a number of sophisticated tests to detect deceitful responding or poor effort in the presentation of cognitive deficits have been developed. These include the Portland Digit Recognition Test, the Test of Memory Malingering, the Validity Indicator Profile, and the Word Memory Test (Binder 2002; Iverson et al. 1999; Tombaugh 2002; see also Chapter 8, Neuropsychological Assessment, this volume). These are based on the forced choice paradigm (Hiscock and Hiscock 1989). Neuropsychological tests vary in their sensitivity and specificity (Cullum et al. 1991). Malingerers can be coached to not appear deceitful on these tests.

Although DSM-IV-TR (American Psychiatric Association 2000) views the occurrence of factitious disorder and malingering as mutually exclusive, in clinical practice this is not the case. Regression and deceit are not logically incompatible.

TBI in the Criminal Justice System

Assaults are the fourth leading cause of TBI in the United States, accounting for about 10% of brain injuries (Centers for Disease Control and Prevention 1999; Langlois et al. 2006). Brain injury, often combined with impulsive behavior and substance abuse, is common in the criminal justice system.

Competency Issues

The basic concept of competency in the criminal justice system is that of competency to stand trial. Like all other competency measures, it is a measure of task-specific functionality, regardless of diagnosis (Slovenko 1995). Before any defendant can be criminally prosecuted, the court must be satisfied that the accused is competent to stand trial—that is, he or she understands the charges and is capable of rationally assisting counsel with the defense (*Dusky v. United States* 1960). Competency to stand trial is based on the historical principle that trying a defendant in

TABLE 34–1. Increased index of suspicion for malingering

Litigation context (e.g., financial compensation, evading criminal prosecution)
Marked discrepancy between clinical findings and subjective complaints
Inconsistency in impairments in different contexts
Poor effort on cognitive testing or neuropsychological testing
Lack of cooperation with evaluation and treatment
Antisocial and other Cluster B personality traits or disorders
Overdramatization and overstatement of complaints in interview and on psychological testing
History of recurrent accidents or injuries
Evidence of self-induced injuries
Vaguely defined symptoms
Poor work history
Inability to work but retains capacity for pleasurable activities

absentia was part of the era of European Absolutism, which the founders of the United States rejected (Abrams 2002). The prohibition against trying a person who was physically absent was extended to those who are mentally absent. The U.S. constitution has been understood to require that all criminal defendants have a minimum level of cognitive functioning, so that they are mentally present at their trial, in order to have a fair trial. This only applies to criminal trials and some quasi-criminal proceedings such as extradition or deportation; analogous concerns to the competency to stand trial do not exist throughout the civil law system. A reckless driver who is severely brain injured in a collision may not be subjected to a criminal trial if not competent but may still be sued and tried, and assessed damages, if a civil action is filed.

TBI can affect criminal competency to stand trial under many circumstances. People who are charged with a crime may have a prior history of TBI or suffered a TBI during the commission of a crime or in attempting suicide in a murder-suicide case (*Commonwealth v. Harrison* 1961). Significant impairments of cognitive and communicative abilities are likely to affect the decision regarding a defendant's competency to stand trial. Nevertheless, it is the actual functional mental capability to meet the minimal standard of trial competency and not the severity of the deficits that determines whether an individual is cognitively capable of being tried. The mere presence of cognitive impairments from a TBI does not automatically exempt a defendant from facing trial. The cognitive impairments must be of such severity that the person cannot communicate the facts of the events involved in the charges, or otherwise assist in his or her defense, or is unable to learn basic facts of the charges or proceedings. A finding of not competent to stand trial is typically followed by hospitalization or supervision and participation in a program to restore trial competency.

An interesting conundrum arose from a TBI acquired during the commission of a series of robberies one night in Washington, D.C. Robert Wilson and a companion stole a yellow Mustang at gunpoint and then robbed a pharmacy on Connecticut Avenue, taking money and barbiturates. During the subsequent high-speed chase, Mr. Wilson lost control of the car and crashed into a tree. His crime partner died in the crash. Mr. Wilson suffered multiple skull fractures. He was in a coma for 3 weeks. When he recovered consciousness, he had residual speech deficits, paralysis, and a complete amnesia for the events preceding the crash. Clearly, Mr. Wilson could not tell his account of why he might be innocent or provide any mitigating defenses. When Mr. Wilson was examined at St. Elizabeths Hospital to determine competency, the fact of his amnesia was felt to mandate a finding of not competent to stand trial. Because Mr. Wilson was not mentally ill, after his initial commitment, he was returned to court for disposition. At the second competency hearing, the judge ruled that Mr. Wilson was competent to stand trial. The U.S. Court of Appeals for the District of Columbia Circuit addressed whether a person totally amnestic for the crime with which the person is charged could ever be considered competent to stand trial, and if so under what circumstances (*Wilson v. United States* 1968). The D.C. Circuit Court remanded the case for further fact finding and ruled that a per se approach to amnesia was not appropriate. The court reasoned that a case-by-case approach was needed to evaluate whether sufficient collateral information existed that would allow the defendant to have a fair trial and effective assistance of counsel despite the amnesia. The court also required that if an amnestic defendant is found competent to stand trial, that after the verdict is reached, the trial judge must make a detailed written finding of fact whether the defendant's amnesia affected the fairness of the trial. While the holding in *Wilson* is not binding on courts in other jurisdictions, its thoughtful approach to the problems of TBI is useful for the mental health clinician in considering the evaluation of competency to stand trial of a person with TBI and amnesia for the charged offense in all jurisdictions (Tysse 2005).

Failure of the attorney or the court to consider the issues of competency in a brain-injured defendant can have disastrous consequences. Consequences and comorbidities of a brain injury, such as substance abuse, impulsivity, and memory impairment, can make compliance with probation or parole conditions, or requirements to register with the police, problematic, leading to additional prosecutions. Clinicians frequently are in the position of first raising the issue of trial competency to the attorney who has requested assistance.

Competence to Testify

Victims of crime who suffered a TBI may be the main witnesses to the crime. The need for their testimony in the prosecution can raise questions about the reliability of a brain-damaged witness's accuracy of recall, the weight that the finder of fact can place on the testimony, or even the ability to testify at all (Gudjonsson et al. 2000). Federal and state rules of evidence require a witness to possess the mental ability to perceive, recollect, narrate, and understand what it means to tell the truth (Federal Rules of Evidence [601] 2008). There is a presumption that all witnesses are competent to testify. Challenges to witness competency are primarily concerned with child witnesses and the cognitively impaired. Even if a witness is allowed to testify, the witness's credibility and the weight given to

his or her testimony can be challenged or impeached by either party. Nonparty witnesses cannot be compelled to have a psychiatric examination to assess competency to testify.

Diminished Capacity, Insanity, and Automatism

Defendants with TBI who are found competent to stand trial may seek acquittal on the basis that they were not criminally responsible for their actions because of insanity at the time the offense was committed. A generally accepted, precise definition of legal insanity does not exist. Over the years, tests of insanity have been subject to much controversy, modification, and refinement (Brakel et al. 1985, p. 707). In the United States, the two major tests used by jurisdictions for determining criminal responsibility or insanity are the *M'Naghten* (or *McNaghten*) test and the American Law Institute (ALI) test. The *M'Naghten* test (1943) was originally stated as whether the defendant was "laboring under such a defect of reason, from disease of the mind, as not to know the nature and quality of the act he was doing; or, if he did know it, that he did not know that what he was doing was wrong." Insanity tests based on *M'Naghten* are concerned primarily with the cognitive abilities of the accused. The ALI test (American Law Institute [1985] Model Penal Code, Section 4.01), which also has a volitional aspect, is generally enacted in the following terms: "A person is not responsible for criminal conduct if at the time of such conduct, as a result of mental illness or retardation, he lacks substantial capacity either to appreciate the criminality of his conduct or to conform his conduct to the requirements of law." Different jurisdictions use their own versions of one or the other of these standards. A criminal defendant with TBI could be found to be not criminally responsible under either test. The ALI test is perhaps more suitable for evaluating the responsibility of brain-injured persons with impulsivity, impaired judgment, and behavioral dyscontrol. The concept of "irresistible impulse" is rarely recognized in modern law, but in jurisdictions that follow the ALI standard, a failure of inhibition due to TBI may allow a finding of inability to conform one's behavior (Redding 2006). Impulse disorders that allegedly arise secondary to TBI, such as intermittent explosive disorder, kleptomania, pathological gambling, and pyromania, generally have not fared much better under an insanity defense than the "purely" psychological impulse disorders. Persons with these conditions do not meet the criteria for the cognitive prong of an insanity defense. Presumably, the volitional prong would be applicable, but it is usually insufficient by itself. Moreover, courts and juries tend to view criminal acts arising from impulse disorders as impulses not resisted rather than irresistible impulses.

Most jurisdictions recognize that acts done while unconscious or without conscious control should not be punished (Fenwick 1990; Wright et al. 1995). In addition to statutory and common law in many jurisdictions, Section 2.01(2) of the Model Penal Code (American Law Institute 1962) specifically excludes from the *actus reas* (the guilty act) the following: "(a) a reflex or convulsion; (b) a bodily movement during unconsciousness or sleep; (c) conduct during hypnosis or resulting from hypnotic suggestion; [and] (d) a bodily movement that otherwise is not the product of the effort or determination of the actor.…" This is referred to by the legal term automatism. Defendants with complex seizures may commit aggressive acts as part of a seizure, and those with generalized seizures may act violently in the postictal state. Other situations relevant to psychiatry in which the defense might be used arise when a crime is committed during a state of altered consciousness caused by a concussion after a brain injury. Episodic dyscontrol syndrome (Elliot 1978; Monroe 1978) has also been advanced as a neuropsychiatric condition causing involuntary aggression. In evaluating a defense of automatism, the psychiatrist should consider whether the actions were truly purposeless and lacked goal directedness, along with an absence of any evidence of premeditation, motive, or planning. There are, however, limitations to the automatism defense. Most notably, some courts hold that if the person asserting the automatism defense was aware of the condition before the offense and failed to take reasonable steps to prevent the criminal occurrence, then the defense is not available. For example, if a defendant with a known history of uncontrolled epileptic seizures loses control of a car during a seizure and kills another, that defendant will not be permitted to assert the defense of automatism.

The law recognizes that there are "shades" of mental impairment that obviously can affect criminal intent or *mens rea* but not necessarily to the extent of completely nullifying it. In recognition of this fact, the concept of diminished capacity was developed (Melton et al. 1997, pp. 204–208). The defense of diminished capacity is disfavored in many jurisdictions. The mere presence of a demonstrable brain injury is not sufficient to negate criminal responsibility, but it may be relevant to sentencing decisions (Morse 2006).

TBI Among the Convicted

Many persons in the forensic criminal system and the criminal justice system in general have suffered head injuries, which may or may not have been identified (Colantonio et al. 2007; Crespo de Souza 2003; Langevin et al. 1987; Martell 1992; Sarapata et al. 1998; Slaughter et al. 2003). Brain injuries are common in delinquent adolescent boys. In a large Danish study of male criminals with organic brain syndrome, findings suggested that males who started criminal activity before age 18, that is, who engage in reckless behavior, are more likely to develop organic brain syndrome than early starters who do not engage in reckless behavior. In males who started their criminal behavior early and developed organic brain syndrome, their pattern of criminality was more severe, with more violent recidivism (Grekin et al. 2001). Sexual offenders in one study were found to have a nearly 50% incidence of TBI (Del Bello et al. 1999; Langevin 2006). Lewis et al. (1986) studied 15 death row inmates who were chosen for examination because of imminent execution rather than evidence of neuropathology. In each case, evidence of severe brain injury and neurological impairment was found. Lewis et al. (2004) made similar findings of the frequency of head trauma among 18 condemned juveniles.

Because of the small numbers, the findings may not be generalized to all condemned inmates.

Recent Supreme Court decisions have greatly expanded the restrictions on the use of the death penalty. In the Supreme Court's decision in *Roper v. Simmons (*2005), the Court considered epidemiological and psychiatric evidence of "impetuous and ill-considered actions and decisions" in adolescents to support its decision that the death penalty is unconstitutional when applied to people who committed the capital crime before they were age 18. In *Atkins v. Virginia* (2002), the Supreme Court also ruled it unconstitutional to execute a person who is mentally retarded. In *Panetti v. Quartermann* (2007), the Supreme Court required that the person to be executed must possess a rational and factual understanding of the upcoming execution, as well as an understanding of the state's rationale for the execution in order to be competent to be executed. The ruling in *Panetti* expanded the concept of competency to be executed previously decided in *Ford v. Wainwright* (1986). Although there is no prohibition specifically against executing the brain damaged, brain-damaged persons facing a capital sentence may fall under one or more of the Supreme Court's populations excluded from the death penalty.

TBI in the Civil and Administrative Justice Systems

In 2005, the case of Terri Schiavo was widely publicized in the United States (Cranford 2005; Perry et al. 2005). Ms. Schiavo's brain injury was primarily anoxic, which may have been traumatic from a fall or metabolic. The cause was never clearly determined. Ms. Schiavo never created any advanced directives. After years of remaining in a vegetative state, her husband, Michael Schiavo, as her legal substitute decision maker, requested the end of artificial life-sustaining care. Her biological parents, however, objected and sought to end the husband's ability to control medical decision making (*In re Guardianship of Schiavo* 2001, 2003). No court agreed with the parents' position, so the parents appealed to the governor of Florida, the Florida legislature, and finally the U.S. Congress to pass a special law for their benefit. In October 2003, the Florida Legislature passed a special law that gave the governor the ability to override the husband's medical decision (so-called "Terri's Law"; Chapter 2003-418, Laws of Florida). Eventually, this law was declared unconstitutional by the Florida courts, and the husband's decision to terminate life support was carried out (*Bush v. Schiavo* 2005). The case highlighted the many heated political, legal, and ethical issues around medical decision making for those persons who are persistently incompetent.

Treatment Decisions, Advance Directives, and End-of-Life Decisions

During the first half of the twentieth century, the principle of patient autonomy was clearly recognized in the medical malpractice case, *Schloendorff v. Society of New York Hospital* (1914). Justice Benjamin Cardozo enunciated the principle of patient self-determination by stating that "every human being of adult years and sound mind has a right to determine what shall be done with his own body, and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages" (*Schloendorff* 1914).

TABLE 34–2. Informed consent: reasonable information to be disclosed

Although there exists no consistently accepted set of information to be disclosed for any given medical or psychiatric situation, as a rule of thumb, five areas of information are generally provided:
Diagnosis—description of the condition or problem
Treatment—nature and purpose of proposed treatment
Consequences—risks and benefits of the proposed treatment
Alternatives—viable alternatives to the proposed treatment, including risks and benefits
Prognosis—projected outcome with and without treatment

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Ethical and legal issues arise frequently for psychiatrists who treat TBI patients. Medical decision making, informed consent, resuscitation, "brain death," organ transplantation, the withholding and withdrawing of life support, and the allocation of medical resources all give rise to complex ethical and clinical legal problems (Burck et al. 2007; Jennett 2005; Luce 1990). Moreover, that which is considered ethical in clinical practice today may become a legal requirement tomorrow.

Under the doctrine of informed consent, health care providers have a legal duty to abide by the treatment decisions made by competent patients unless a compelling state interest exists. Legally, the term *competency* is narrowly defined and equated with cognitive capacity. There are no established criteria for determining a patient's competence. A basic level of decision-making capacity exists when the patient is able to understand the particular treatment choice proposed, make a treatment choice, and communicate that decision (Applebaum 2007).

Obtaining a competent informed consent to proposed diagnostic procedures and treatments can be both challenging and frustrating (Table 34–2). The capacity to consent, particularly after brain injury, may be present one moment and gone the next. Lucid intervals may permit the obtaining of competent consent for health care decisions.

The need to obtain competent, informed consent is not negated simply because it appears that the patient is in need of medical intervention or would likely benefit from it. Instead, clinicians must assure themselves that the patient or an appropriate substitute decision maker has given a competent consent before proceeding with treatment. Except in an emergency for an unconscious or incompetent patient, an authorized representative or appointed guardian must make health care decisions on behalf of patients with TBI if they cannot. If the patient is grossly

disordered, lacks health care decision-making capacity, is at risk of dying before proxy consent can be obtained, or presents an immediate danger to self and others, the physician or hospital is on firm ground medically and legally to temporarily override the patient's treatment refusal (California Business and Professions Code section 2397, see Appendix 34–1; also see *Cobbs v. Grant* 1972). The existence of an emergency cannot override a refusal under a durable power of attorney for health care or a declaration under the Natural Death Act. When patients agree to treatment, their competency to assent is often not questioned. Some jurisdictions have passed laws to relieve health care professionals from the burden of petitioning the court for an adjudication of incompetency and the appointment of a guardian. In California, when a patient in a skilled or intermediate care nursing facility is thought not competent, the treatment team can convene to make medical decisions according to the statutory protocol in agreement with reasonable medical standards (California Health and Safety Code section 1418.8; see Appendix 34–1). Other states have passed statutes allowing for the use of surrogate consent by next of kin in the absence of a court-appointed guardian. These statutes typically name the order of preference for obtaining surrogate consent, usually starting with the patient's spouse, then an adult child, then a parent. Table 34–3 lists some consent options for patients lacking the mental capacity for health care decisions.

The psychiatrist who treats a patient with TBI suspected of having neuropsychiatric deficits should conduct a thorough assessment of cognitive functioning. The sole objective of such an evaluation should be the determination of the TBI patient's ability to meet the minimal requirements for consent. At the very least, a mental status assessment of the patient's language comprehension, memory, judgment, insight, affect, orientation, and attention span should be performed (Folstein et al. 1975). Scores below 19 on the Mini-Mental Status Examination are associated with a finding of incompetency to consent to treatment (Kim and Caine 2002). A formal tool, the MacArthur Competence Assessment Tool for Treatment, has been developed for assessment of competency for treatment decision making. This does not give a definitive answer but provides standardized questions (Grisso and Appelbaum 1998). Some TBI patients may be cognitively intact but manifest such severe affective lability that they are rendered mentally incompetent.

The use of advance directives such as a living will, health care proxy, or durable medical power of attorney is recommended to avoid ethical and legal complications associated with requests to withhold life-sustaining treatment measures (Simon 1992; Solnick 1985). Federal regulations define advance directives as "written instructions, such as a living will or durable power of attorney for health care, recognized under State law, relating to the provision of health care when the individual is incapacitated" (42 C.F.R. 489.100, 2006). Living wills do not give decision-making powers to another person; they specify treatments to be given or withheld in the event of incapacity. In contrast, durable powers of attorney for health care name a substitute decision maker in the event of incapacity. The Patient Self-Determination Act (1990) requires hospitals, nursing homes, hospices, managed care organizations, and home health care agencies to advise patients or family members of their right to accept or refuse medical care and to execute an advance directive (LaPuma et al. 1991). The Uniform Health-Care Decisions Act (1993) provides a set of model standardized advance instructions, but very few states have adopted this act. A do not resuscitate order is one form of an advance directive.

TABLE 34–3. Common consent options for patients lacking the mental capacity for health care decisions

Proxy consent of next of kin
Adjudication of incompetence; appointment of a guardian
Institutional administrators or committees
Treatment review panels
Substituted consent of the court
Advance directives (living will, durable power of attorney, and health care proxy)
Statutory surrogates (spouse or court-appointed guardian)[a]

[a]These laws authorize certain persons, such as a spouse or court-appointed guardian, to make health care decisions when the patient has not stated his or her wishes in writing.

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In the ordinary power of attorney created for the management of business and financial matters, the power of attorney generally becomes null and void if the person creating it becomes incompetent. In this situation, the need arises for a special durable power of attorney for health care.

Federal law does not specify the right to formulate advance directives; therefore, state law applies. State legislators have recognized that individuals may want to indicate who should make important health care decisions in case they become incapacitated and unable to act in their own behalf. All 50 states and the District of Columbia permit individuals to create a durable power of attorney (i.e., one that endures even if the competence of the creator does not) (*Cruzan v. Director* 1990, n. 3). A number of states and the District of Columbia have durable power of attorney statutes expressly authorizing the appointment of proxies for making health care decisions (*Cruzan v. Director* 1990, n. 2).

In a durable power of attorney or health care proxy, general or specific directions set forth how future decisions should be made in the event one becomes unable to make these decisions. The determination of a patient's competence is not specified in most durable power of attorney and health care proxy statutes. Because this is a medical or psychiatric question, the examination by two physicians to determine the patient's ability to understand the nature and consequences of the proposed treatment or procedure, the ability to make a choice, and the ability to communicate that choice are minimally sufficient. This information should be documented in the patient's file.

Guardianship and Conservatorship Proceedings

TBI patients may lack capacity or competency in other areas in addition to medical decision making, such as con-

trolling their finances, determining where to reside, or hiring helpers. A guardianship is a method of substitute decision making for individuals who have been judicially determined as unable to act for themselves (Brakel et al. 1985). Historically, the state or sovereign possessed the power and authority to safeguard the estates of incompetent persons, the doctrine of *parens patriae*.

This traditional role still reflects the purpose of guardianship today. In some states, there are separate provisions for the appointment of a "guardian of one's person" (e.g., health care decision making) and for a "guardian of one's estate" (e.g., authority to make contracts to sell one's property) (Sale et al. 1982, p. 461). Terminology varies widely from jurisdiction to jurisdiction. A further distinction, also found in some jurisdictions, is general (plenary) versus specific guardianship (Sale et al. 1982, p. 462). As the name implies, the latter guardian is restricted to exercising decisions about a particular subject area. For instance, the specific guardian may be authorized to make decisions about major or emergency medical procedures, with the disabled person retaining the freedom to make decisions about all other medical matters. General guardians, by contrast, have total control over the disabled individual's person, estate, or both (Sale et al. 1982, pp. 461–462).

Guardianship arrangements can also be of use for TBI patients (Overman and Stoudemire 1988). Laws governing competency to control financial decisions or make medical treatment decisions in many states are based on the Uniform Guardianship and Protective Proceedings Act or the Uniform Probate Code (Mishkin 1989). The general concept of incompetency is defined by the Uniform Guardianship and Protective Proceedings Act (1997) as "impaired by reason of mental illness, mental deficiency …to the extent of lacking sufficient understanding or capacity to make or communicate reasonable decisions."

Generally, the appointment of a guardian is limited to situations in which the individual's decision-making capacity is so impaired that he or she is unable to care for personal safety, protect assets, or provide such necessities as food, shelter, clothing, and medical care, likely resulting in physical injury or illness (*In re Boyer* 1981). Guardianship or conservatorship proceedings can be uncontested or even voluntary. When such efforts are contested, the standard of proof required for a judicial determination of incompetency is clear and convincing evidence. Although the law does not assign percentages to proof, clear and convincing evidence is in the range of 75% certainty (Simon 1992).

Prior to the institution of advance directives for patients who are in a vegetative state, relatives would petition for guardianship to make end-of-life decisions. This was the legal basis for the case of Karen Ann Quinlan, in which the right of third parties to end care was at issue (*In re Quinlan* 1976). A similar question was litigated in the case of Nancy Cruzan, who suffered a TBI in an automobile crash (*Cruzan v. Director* 1990). Ms. Cruzan did not have any advance directives, only a history of verbal comments about how she wanted to be treated if incapacitated. Her parents were already her guardians and wished to terminate further treatment. The U.S. Supreme Court repeated the right of competent persons or, if incompetent, their guardians or next of kin, to determine their care at the end of life. However, the Supreme Court decided the Cruzan case on the issue of what standard of proof a state could require to demonstrate the wishes of the now incompetent person. A similar decision was reached in a California case requiring clear and convincing evidence of the person's wishes (*Conservatorship of Wendland* 2001).

Fitness for Duty and Return to Competition Following TBI

After experiencing a brain injury, many people want to resume full activities, regardless of whether their fitness to do so is an accurate assessment or is due to denial of their symptoms. Fitness-for-duty (FFD) examinations evaluate whether a symptomatic employee can perform his or her job in a safe and effective manner meeting standards for minimally acceptable performance and conduct. The exact parameters of the evaluation should be clarified prior to the evaluation. Clinicians may also be retained to review a prior FFD evaluation. FFD evaluations may need to be repeated as the TBI potentially resolves. FFD evaluations for police officers or others who carry firearms, for persons with occupations that leave little room for irrational or impulsive behaviors, or for physicians following a TBI require a difficult balancing of current strengths, behaviors, or deficits and future risk. Obtaining collateral information from coworkers, supervisors, and family regarding symptom expression, particularly when the evaluee is fatigued or when rapid decision making is needed, will be useful within the limits of consent. Neuropsychological testing is a useful supplemental source of information. There is nothing conceptually different about an FFD following TBI from other psychiatric FFD evaluations; however, the finding of cognitive deficits and/or behavioral dyscontrol is more problematic in persons where the deficits may place them or others in danger in the future (American Psychiatric Association 2004). FFD in military personnel is discussed separately below.

There has been increasing concern about brain injuries in athletes (Cantu 1986, 1998; Collins et al. 1999; see also Chapter 27, Sports Injuries, in this volume). A study from the University of North Carolina estimated a concussion rate for high school football players of 33.09 per 100,000 athlete exposures (Guskiewicz et al. 2000; Schulz et al. 2004). Sports in which players are at risk for concussion or head injury include football, boxing, ice hockey, wrestling, gymnastics, lacrosse, soccer, and basketball. Once a concussion has occurred, the player becomes as much as three times more likely to sustain a second concussion (Guskiewicz et al. 2003). Coaches, team physicians, and athletes experience tensions from wanting or needing to get back into the game opposed to the need for rest to heal from the concussion. In 2000, a Chicago Bears running back, Merril Hoge, who had to retire early due to TBI, successfully sued the team physician for failing to warn him of the dangers of returning to play prematurely. The jury verdict was over $1.45 million (Hecht 2002).

Guidelines have been developed to assist in determinations of when and under what circumstances an athlete can be safely returned to competition after a concussion

(Kelly et al. 1991). The American Academy of Neurology (1997) guidelines stratify concussions into three grades, with recommendations. Premature return before the first concussion has resolved can result in "second impact syndrome," which can be fatal (Cantu 1998). Returning to competition prematurely may also increase the likelihood that the athlete will develop persistent postconcussive symptoms (see also Chapter 27, Sports Injuries).

Military Fitness and Disability Evaluations

TBI from exposure to blast injuries caused by improvised explosive devices (IEDs) is sadly becoming more frequent among members of the military in Operation Iraqi Freedom and Operation Enduring Freedom (Bhattacharjee 2008; Hoge et al. 2008; Okie 2005; Taber et al. 2006; Trudeau et al. 1998; Warden 2006). In one survey, about half of military personnel treated at an Echelon II medical unit (a casualty receiving company after emergency care) in Iraq had head injuries from IEDs or mortar (Murray et al. 2005). TBI also occurs from gunshot wounds, motor vehicle injury, and other sources of head trauma. Many service members are able to return to duty after light duty. However, results from the Defense and Veterans Brain Injury Center at Walter Reed Army Medical Center indicate that about half of their sample had moderate or severe TBI (Warden et al. 2005). The combination of PTSD and TBI, or "polytrauma," is also increasing (French and Parkinson 2008; Schneiderman et al. 2008) (see also Chapter 26, Traumatic Brain Injury in the Context of War).

If a unit commander or physician feels that a member of the armed forces is unable to fulfill his or her duties due to physical or mental impairments, the service member is referred to the Physical Disability Evaluation System. Department of Defense (1997) directives and those regulations specific to each branch direct this process. The Physical Disability Evaluation System encompasses a complex set of laws, regulations, instructions, and policies (Ritchie et al. 2006). The first step is generally a referral for a fitness-for-duty evaluation. This may result in a finding of FFD or not. If there is a finding of unfitness, if it is due to a condition such as a personality disorder, disorders of impulse control, or a learning disability, including attention-deficit/hyperactivity disorder (ADHD), that predated service, the service member will receive an administrative separation. If the service member is unfit for retention due to a medical or psychiatric condition other than a personality disorder, he or she is then referred to a Medical Evaluation Board (MEB)/Physical Evaluation Board (PEB) for a further evaluation and disability rating. Distinguishing and apportioning preexisting personality traits, impulsivity, and ADHD from acquired TBI can be difficult. Suitability for retraining and placement in limited duty is also possible if recommended by a Specialty/Medical Retention Board. The MEB prepares a thorough evaluation generated by the service member's treating physician to assess military-specific duty impairment, social impairment, and vocational impairment. If retention is not recommended, the service member is referred to the PEB. Fitness for duty is performance based depending on the service member's specific duties, not on the diagnosis or severity of the disorder, except to the degree that the disorder impairs performance of duties. It must be objective and factual.

For mental disorders, the service member's effect on "the welfare of other members were the member to continue on active duty or in an Active Reserve status" can be considered by the board. If a determination of unfitness for duty is made, the PEB rates the disability according to the Department of Veterans Affairs Schedule for Rating Disability Scale. Department of Defense Instruction 1332.38 (1996) provides in part that "any military member on active duty or in the Ready Reserves who is found to be unfit will be retired, if eligible for retirement, or, if not so eligible, separated." The level of rating, years in the service, and preexisting factors will determine whether the service member receives a disability retirement with monthly benefits or a lump sum separation severance package. A minimum disability of 30% is required for eligibility for a retirement disability. A member can appeal the findings and the rating. Although the Department of Defense and the Department of Veterans Affairs both use the same rating scale, there are significant differences between the two systems. The military services only evaluate unfitting disabilities, whereas the Department of Veterans Affairs compensates for all service-connected disabilities; the military services' ratings are permanent, whereas Department of Veterans Affairs disability ratings are subject to change (Ritchie et al. 2006).

On February 18, 2007, the *Washington Post* began publishing a series of articles raising concerns about the processes used to evaluate disability in injured military service members. Because of concerns about inequities in the medical retirement process, congressional hearings were held, and P.L. 110-181, the National Defense Authorization Act for Fiscal Year 2008, was enacted. As directed by the law, Instruction Section 1612 MEB/PEB of Recovering Servicemembers was promulgated. In accord with this instruction, on June 30, 2008, the Department of Defense created a new Physical Disability Board of Review to review disability ratings of wounded service members and provide another avenue of administrative recourse for wounded veterans. The new board's task is to reassess the accuracy and fairness of the combined disability ratings assigned to service members who were discharged as unfit for continued military service by the military departments with a combined disability rating of 20% or less and were not found to be eligible for retirement. Section 1612 MEB/PEB also provides for more standardized procedures across service branches, National Guard, and the Department of Veterans Affairs.

Personal Injury Evaluations

Civil litigation in brain injury cases generally requires the evaluation and testimony of psychiatrists (neuropsychiatrists) as well as neurologists, psychologists, neuropsychologists, and other mental health professionals. Psychiatrists can become involved in litigation as witnesses in one of two ways: as treaters or as forensic experts. In evaluating the TBI patient, both the treating psychiatrist and the expert psychiatric witness will need to coordinate their efforts with other medical and nonmedical professionals. Obtaining additional

information from others who are also assisting the patient fosters both good treatment and credible testimony. The vast majority of TBI involves mild TBI. The Centers for Disease Control and Prevention (2003) surveillance project estimated that 75% of all TBI is included under their criteria for mild TBI. Many of the symptoms of mild TBI are common in the uninjured population, and the evaluation of many symptoms of TBI depends on self-report (Iverson and Lange 2003). Proving or disproving the component symptoms of mild TBI constitutes a considerable portion of TBI-related litigation (Hall et al. 2005). Studies of the effect of litigation or compensation claims on recovery from mild TBI are inconsistent (Bernstein 1999; Hammond et al. 2004; Kibby and Long 1996).

The possibility of malingering should be kept in mind (see Table 34–1) (Larrabee 2003a, 2003b). Malingering is not limited to the fabrication of symptoms; most often, it is manifested by the exaggeration of symptoms. Litigants also may consciously deny or minimize a significant past history of mental illness or impairment (Greiffenstein et al. 2002). Thus, the psychiatrist should consider a broad array of information. The forensic psychiatrist should review all data carefully before reaching a conclusion. The collateral source information list in Table 34–4, although not exhaustive, indicates major areas for inquiry.

The role of neuropsychological testing must be critically evaluated in each case. The interpretation of neuropsychological tests is not totally objective. The qualifications and experience of the neuropsychologist are important variables. Tests of behavior in neuropsychological testing are subject to the control of the person performing the task. Thus, the consideration of motivation is critical. Also, low test scores may be caused by factors other than brain damage (Table 34–5). For example, the impact of somatic therapies and psychopathology as confounding factors in neuropsychological testing has been noted (Cullum et al. 1991; Finlayson and Bird 1991). Doctors, not tests, make diagnoses. A neuropsychological test score, by itself, cannot point to a specific cause of the litigant's injury. In litigation, whether legal causation exists between an injury and alleged incapacity (harm) is a matter for the finder of fact to determine.

Base-rate neuropsychological deficits typically exist in the normal population. If impairments are noted without evaluation of the claimant's prior history and level of neuropsychological functioning, overinterpretation of test data can occur. The critical review of educational and work records to determine prior level of intellectual functioning is important in establishing baseline preinjury performance.

A number of psychiatric disorders may mimic and complicate the assessment of TBI or may be the result of the TBI. Some of the more common TBI mimics include conversion, factitious, somatization, and depressive disorders presenting with symptoms of neurological and cerebral dysfunction. Conversion disorder symptoms classically mimic neurological disease. Dissociative symptoms may present with amnesia or atypical memory loss. Depressive pseudodementia is a commonly recognized clinical disorder in the elderly. PTSD manifesting symptoms of difficulty in concentration and psychogenic amnesia can also mimic brain injury. The occurrence of PTSD in TBI patients with amnesia for the trauma has been questioned (Klein et al. 2003). Similarly, anxiety disorders may be associated with memory complaints secondary to the inability to concentrate. Substance misuse may have preceded the injury or developed subsequently, further complicating the treatment or assessment (Corrigan and Cole 2008).

Additionally, TBI litigants may be prescribed psychoactive substances, either for their symptoms of brain injury or for concurrent psychiatric and medical disorders. Antipsychotics, antidepressants, lithium, and, particularly, benzodiazepines can produce side effects that mimic neurological and brain disorders. Psychoactive substances may produce serious memory difficulties, either directly on brain chemistry or indirectly through sedation. It is common for practitioners to prescribe two or more drugs concurrently, particularly when the claimant appears refractory to treatment during the course of litigation. Various combinations of medications may interact to produce a host of side effects that involve the central nervous system. Psychoactive drug abuse is distressingly common in

TABLE 34–4. Collateral information sources

Other physicians and health care providers (e.g., reports, direct discussions)
Hospital records
Family
Other third parties
Prior litigation documents
Military records
Educational records
Police records
Juvenile arrest records
Witness information
Work records
Work products (e.g., letters, work projects)
Legal discovery (e.g., depositions, legal documents)
Prior medical and psychiatric records
Prior psychological and neuropsychological evaluations

TABLE 34–5. Major factors affecting neuropsychological test findings

Original endowment, congenital disorders
Environment (e.g., education, occupation, and life experiences)
Motivation (e.g., effort)
Fatigue or sleep deprivation
Physical health
Age
Psychological distress
Psychiatric disorders (e.g., affective and somatoform disorders)
Medications (e.g., anticonvulsants and psychotropics)
Intoxication, substance abuse
Conscious error production or slowed performance
Qualifications and experience of neuropsychologist
Errors in scoring
Errors in interpretation

these cases, especially when the TBI litigant complains of persistent headache and other pain. Comorbidity and drug effects also should be considered when evaluating the results of neuropsychological test assessments. Questionable results will be obtained in the neuropsychological testing if the effects of concurrent psychiatric disorders and medications are not considered.

In litigation, it is the degree of functional impairment, not the psychiatric diagnosis per se, that determines the amount of the monetary awards for damages. In combination with current and future medical expenses, compensable damages from head trauma can be substantial. The psychiatrist must understand the difference between impairment and disability. The term *mild TBI* does not imply that the consequences are necessarily mild (Centers for Disease Control and Prevention 2003). An impaired individual may not necessarily be disabled in all areas. Psychiatric impairment is considered disabling only when a psychiatric disorder limits a person's capacity to meet the demands of living. A traumatic blow to the eye of a company president that causes visual impairment may not significantly impair occupational functioning. The same injury to a major league baseball player would likely be totally disabling and end his career.

Similarly, a TBI patient may have moderate impairment but only mild disability in social or occupational functioning because of the development of compensatory coping mechanisms. Most psychiatric clinicians have seen TBI patients who have mild impairments but who are seriously disabled. For claimants presenting the latter clinical picture, the psychiatrist should pay particular attention to the possible presence of concurrent Axis IV psychosocial and environmental problems, comorbidity, substance abuse, medication effects, and litigation issues on the clinical presentation of the TBI claimant.

Standard impairment assessment methods should be used in combination with the DSM-IV-TR Axis V global assessment of functioning. The credible psychiatric assessment of functional impairment will avoid strictly subjective, conclusory pronouncements about the claimant's impairment and the need for future treatment. Instead, whenever possible, the TBI claimant's functional impairment and future treatment needs should be evaluated according to standard impairment measures, such as the American Medical Association's (2008) *Guide to the Evaluation of Permanent Impairment*. This guide closely follows the Social Security Administration's guidelines for the assessment of disability. Assessment of permanent impairment should not be made until maximum medical improvement has been achieved.

Social Security Disability Evaluations

The Social Security Administration provides benefits to those who are unable to work or engage in substantial gainful activity (SGA). In 2008, SGA is indexed at earning $940 per month or more. Those who have previously worked are provided benefits under the Social Security Act Title II (Social Security Disability Insurance) and those who have never worked or only worked sporadically receive benefits under Title XVI (Supplemental Security Income). Title XVI is need based, whereas Title II is not. The procedures for determining eligibility are the same under both titles. Social Security follows a sequential evaluation analysis to determine if a long-term disabling condition exists, if the condition is severe and imposes limitations on the ability to engage in SGA, and if the limits are incompatible with working in the national economy. Children are eligible for Social Security benefits if they have a condition that is the equivalent of an adult condition that would prevent working. Patients with TBI can be found disabled under the Social Security procedures, particularly if the injury impairs persistence, concentration, ability to interact with the public, or ability to follow instruction. Reports and records by a treating clinician are given added weight in the determination of disability.

In the Social Security disability evaluation, TBI, including mild TBI, would be rated under the listing 12.02 "Organic Mental Disorders" or 11.18 "Cerebral Trauma," which are defined by the presence of one or more of the following symptoms of dysfunction of the brain:

> 1. Disorientation to time and place; or 2. Memory impairment, either short-term (inability to learn new information), intermediate, or long-term (inability to remember information that was known sometime in the past); or 3. Perceptual or thinking disturbances (e.g., hallucinations, delusions); or 4. Change in personality; or 5. Disturbance in mood; or 6. Emotional lability (e.g., explosive temper outbursts, sudden crying, etc.) and impairment in impulse control; or 7. Loss of measured intellectual ability of at least 15 I.Q. points from premorbid levels or overall impairment index clearly within the severely impaired range on neuropsychological testing, e.g., the Luria-Nebraska, Halstead-Reitan, etc. (Social Security Administration, 2008, section 12.02, "Organic Mental Disorders")

These are the A criteria for the impairment. The applicant would meet the B criteria if the applicant also has marked impairments in activities of daily living; in maintaining social functioning; in maintaining concentration, persistence, or pace; or has repeated episodes of decompensation, each of extended duration. Alternatively, if the applicant shows a current history of 1 or more years of inability to function outside a highly supportive living arrangement, with an indication of continued need for such an arrangement, the applicant would meet the C criteria. If the applicant meets the A criteria and either the B or C criteria, the applicant is considered as meeting the listing requirements for receiving benefits. If the applicant has comorbid disorders that add to the disabling impairments, such as depression (12.04 "Affective Disorders"), PTSD (12.06 "Anxiety Related Disorders"), generalized seizures (11.02 "Convulsive Epilepsy"), partial seizures (11.03 "Nonconvulsive Epilepsy"), or other physical impairments, the applicant may equal the listing when all the impairments are considered together. If the impairments do not meet or are not equivalent in severity to the criteria of any listing, an assessment of residual functional capacity (RFC) to do substantial gainful activity (SGA) is performed. The RFC will suggest among other factors whether the applicant is able to do simple or repetitive work, tolerate supervision, and work alone or in public. Vocational experts are an integral part of the determination. If the RFC, along

with the applicant's age, education, and past work experience, indicates the applicant cannot do SGA, he or she will be awarded benefits (Social Security Administration Regulation 20 C.F.R Part 402).

Private Disability Evaluations

TBI is a significant cause of disability among young persons in high-income countries (Maas et al. 2008). Private disability insurance is a form of contract and is governed by the specific terms of the insurance contract. The adjudication of claims for mild TBI is a source of dispute and litigation because of the amounts of money involved, the importance of a favorable finding to all parties, the difficulty in showing objective signs or symptoms of mild TBI, the occurrence of overstatement and malingering, and the difficulty of linking specific symptoms with impairment in the ability to perform the material and substantial occupational duties. In the past, private disability policies were sold that were occupation specific; that is, if the disability prevented the insured person from working in the specified occupation, it did not matter in what other fields the person was able to work. Such policies tend to be rare at present because of cost. Neuropsychological testing with a forensically trained neuropsychologist is important, particularly if symptom exaggeration is suspected. The clinician evaluating a claimant with TBI must clarify what the exact terms of the insurance contract require for the findings of impairments and relate the impairments to the ability to function in specific occupations.

Workers' Compensation Treatment and Evaluations

TBI is a significant source of workplace injury. In one recent study, approximately 6 out of every 1,000 lost-time claims were associated with mild TBI (Kristman et al. 2008). The building and construction trades are the leading industries in which TBI occurs, and falls appear to be the most common cause of occupational TBI (Kim et al. 2006; Wrona 2006).

All states and the U.S. federal government have systems referred to as workers' compensation to compensate people who are injured in the course of their employment. Negligence and fault, unless extreme or willful, are not factors in workers' compensation. Injured workers are typically barred from bringing personal injury lawsuits by statute, unless certain conditions exist such as the employer not paying into the insurance system or the employer disabling safety devices or otherwise willfully creating a hazardous work environment. The goal of the workers' compensation system is to treat and rehabilitate the injured workers and return them to productive employment if possible (Keyser-Marcus et al. 2002). If there is permanent impairment of the injured worker's ability to compete in the labor market, there is a need for an evaluation of the extent of the residual impairment in calculating fair compensation (Franulic et al. 2004). This evaluation is usually done by an agreed-upon examiner or an examiner who is not providing treatment.

KEY CLINICAL POINTS

- People with traumatic brain injury (TBI) frequently are involved in criminal, civil, or administrative legal situations.
- Clinicians may act as treaters of TBI patients or expert witnesses in competency determinations, guardianship, or conservatorship litigation.
- The Individuals With Disabilities Education Act and the Americans With Disabilities Act often require testimony regarding the extent of TBI effects.
- Clinicians often provide testimony regarding workers' compensation cases. Negligence and fault are not factors. The purpose is to treat and rehabilitate the injured worker.
- TBI can affect criminal competency to stand trial. It is the functional mental capacity to meet minimal standards of competency to stand trial, not the deficits, that determines whether an individual is cognitively capable of being tried.

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Appendix 34–1

California Probate Code Section 811

(a) A determination that a person is of unsound mind or lacks the capacity to make a decision or do a certain act, including, but not limited to, the incapacity to contract, to make a conveyance, to marry, to make medical decisions, to execute wills, or to execute trusts, shall be supported by evidence of a deficit in at least one of the following mental functions, subject to subdivision (b), and evidence of a correlation between the deficit or deficits and the decision or acts in question:

(1) Alertness and attention, including, but not limited to, the following:

(A) Level of arousal or consciousness.

(B) Orientation to time, place, person, and situation.

(C) Ability to attend and concentrate.

(2) Information processing, including, but not limited to, the following:

(A) Short- and long-term memory, including immediate recall.

(B) Ability to understand or communicate with others, either verbally or otherwise.

(C) Recognition of familiar objects and familiar persons.

(D) Ability to understand and appreciate quantities.

(E) Ability to reason using abstract concepts.

(F) Ability to plan, organize, and carry out actions in one's own rational self-interest.

(G) Ability to reason logically.

(3) Thought processes. Deficits in these functions may be demonstrated by the presence of the following:

(A) Severely disorganized thinking.

(B) Hallucinations.

(C) Delusions.

(D) Uncontrollable, repetitive, or intrusive thoughts.

(4) Ability to modulate mood and affect. Deficits in this ability may be demonstrated by the presence of a pervasive and persistent or recurrent state of euphoria, anger, anxiety, fear, panic, depression, hopelessness or despair, helplessness, apathy or indifference, that is inappropriate in degree to the individual's circumstances.

(b) A deficit in the mental functions listed above may be considered only if the deficit, by itself or in combination with one or more other mental function deficits, significantly impairs the person's ability to understand and appreciate the consequences of his or her actions with regard to the type of act or decision in question.

(c) In determining whether a person suffers from a deficit in mental function so substantial that the person lacks the capacity to do a certain act, the court may take into consideration the frequency, severity, and duration of periods of impairment.

(d) The mere diagnosis of a mental or physical disorder shall not be sufficient in and of itself to support a determination that a person is of unsound mind or lacks the capacity to do a certain act.

(e) This part applies only to the evidence that is presented to, and the findings that are made by, a court determining the capacity of a person to do a certain act or make a decision, including, but not limited to, making medical decisions. Nothing in this part shall affect the decision-making process set forth in Section 1418.8 of the Health and Safety Code, nor increase or decrease the burdens of documentation on, or potential liability of, health care providers who, outside the judicial context, determine the capacity of patients to make a medical decision.

California Health and Safety Code 1418.8

(a) If the attending physician and surgeon of a resident in a skilled nursing facility or intermediate care facility prescribes or orders a medical intervention that requires that informed consent be obtained prior to administration of the medical intervention, but is unable to obtain informed consent because the physician and surgeon determines that the resident lacks capacity to make decisions concerning his or her health care and that there is no person with legal authority to make those decisions on behalf of the resident, the physician and surgeon shall inform the skilled nursing facility or intermediate care facility.

(b) For purposes of subdivision (a), a resident lacks capacity to make a decision regarding his or her health care if the resident is unable to understand the nature and consequences of the proposed medical intervention, including its risks and benefits, or is unable to express a preference regarding the intervention. To make the determination regarding capacity, the physician shall interview the patient, review the patient's medical records, and consult with skilled nursing or intermediate care facility staff, as appropriate, and family members and friends of the resident, if any have been identified.

(c) For purposes of subdivision (a), a person with legal authority to make medical treatment decisions on behalf of a patient is a person designated under a valid Durable Power of Attorney for Health Care, a guardian, a conservator, or next of kin. To determine the existence of a person with legal authority, the physician shall interview the patient, review the medical records of the patient, and consult with skilled nursing or intermediate care facility staff, as appropriate, and with family members and friends of the resident, if any have been identified.

(d) The attending physician and the skilled nursing facility or intermediate care facility may initiate a medical intervention that requires informed consent pursuant to subdivision (e) in accordance with acceptable standards of practice.

(e) Where a resident of a skilled nursing facility or intermediate care facility has been prescribed a medical intervention by a physician and surgeon that requires informed consent and the physician has determined that the resident lacks capacity to make health care decisions and there is no person with legal authority to make those decisions on behalf of the resident, the facility shall, except as provided in subdivision (h), conduct an interdisciplinary team review of the prescribed medical intervention prior to the administration of the medical intervention. The interdisciplinary team shall oversee the care of the resident utilizing a team approach to assessment and care planning, and shall include the resident's attending physician, a registered professional nurse with responsibility for the resident, other appropriate staff in disciplines as determined by the resident's needs, and, where practicable, a patient representative, in accordance with applicable federal and state requirements. The review shall include all of the following:

(1) A review of the physician's assessment of the resident's condition.

(2) The reason for the proposed use of the medical intervention.

(3) A discussion of the desires of the patient, where known. To determine the desires of the resident, the interdisciplinary team shall interview the patient, review the patient's medical records, and consult with family members or friends, if any have been identified.

(4) The type of medical intervention to be used in the resident's care, including its probable frequency and duration.

(5) The probable impact on the resident's condition, with and without the use of the medical intervention.

(6) Reasonable alternative medical interventions considered or utilized and reasons for their discontinuance or inappropriateness.

(f) A patient representative may include a family member or friend of the resident who is unable to take full responsibility for the health care decisions of the resident, but who has agreed to serve on the interdisciplinary team, or other person authorized by state or federal law.

(g) The interdisciplinary team shall periodically evaluate the use of the prescribed medical intervention at least quarterly or upon a significant change in the resident's medical condition.

(h) In case of an emergency, after obtaining a physician and surgeon's order as necessary, a skilled nursing or intermediate care facility may administer a medical intervention that requires informed consent prior to the facility convening an interdisciplinary team review. If the emergency results in the application of physical or chemical restraints, the interdisciplinary team shall meet within one week of the emergency for an evaluation of the medical intervention.

(i) Physicians and surgeons and skilled nursing facilities and intermediate care facilities shall not be required to obtain a court order pursuant to Section 3201 of the Probate Code prior to administering a medical intervention which requires informed consent if the requirements of this section are met.

(j) Nothing in this section shall in any way affect the right of a resident of a skilled nursing facility or intermediate care facility for whom medical intervention has been prescribed, ordered, or administered pursuant to this section to seek appropriate judicial relief to review the decision to provide the medical intervention.

(k) No physician or other health care provider, whose action under this section is in accordance with reasonable medical standards, is subject to administrative sanction if the physician or health care provider believes in good faith that the action is consistent with this section and the desires of the resident, or if unknown, the best interests of the resident.

(l) The determinations required to be made pursuant to subdivisions (a), (e), and (g), and the basis for those determinations shall be documented in the patient's medical record and shall be made available to the patient's representative for review.

California Business and Professions Code Section 2397

(a) A licensee shall not be liable for civil damages for injury or death caused in an emergency situation occurring in the licensee's office or in a hospital on account of a failure to inform a patient of the possible consequences of a medical procedure where the failure to inform is caused by any of the following:

(1) The patient was unconscious.

(2) The medical procedure was undertaken without the consent of the patient because the licensee reasonably believed that a medical procedure should be undertaken immediately and that there was insufficient time to fully inform the patient.

(3) A medical procedure was performed on a person legally incapable of giving consent, and the licensee reasonably believed that a medical procedure should be undertaken immediately and that there was insufficient time to obtain the informed consent of a person authorized to give such consent for the patient.

(b) This section is applicable only to actions for damages for injuries or death arising because of a licensee's failure to inform, and not to actions for damages arising because of a licensee's negligence in rendering or failing to render treatment.

(c) As used in this section:

(1) "Hospital" means a licensed general acute care hospital as defined in subdivision (a) of Section 1250 of the Health and Safety Code.

(2) "Emergency situation occurring in the licensee's office" means a situation occurring in an office, other than a hospital, used by a licensee for the examination or treatment of patients, requiring immediate services for alleviation of severe pain, or immediate diagnosis and treatment of unforeseeable medical conditions, which, if not immediately diagnosed and treated, would lead to serious disability or death.

(3) "Emergency situation occurring in a hospital" means a situation occurring in a hospital, whether or not it occurs in an emergency room, requiring immediate services for alleviation of severe pain, or immediate diagnosis and treatment of unforeseeable medical conditions, which, if not immediately diagnosed and treated, would lead to serious disability or death.

CHAPTER 35

Psychopharmacology

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MANY USEFUL THERAPEUTIC APPROACHES ARE available for those who have experienced brain injury. As has been found with the treatment of psychiatric disorders such as depression, panic disorder, and obsessive-compulsive disorder, a combination of therapeutic interventions administered simultaneously often provides more effective treatment than using a single modality. Individual, cognitive, behavioral, and family therapy, as well as environmental manipulation, all may affect symptoms and the patient's ability to cope with them and are essential elements of any treatment plan for persons with neuropsychiatric disturbances after traumatic brain injury (TBI) (see Chapters 31 and 36–39). For many patients, pharmacotherapy may be required to provide relief from such symptoms and to facilitate their ability to benefit maximally from nonpharmacological interventions. In this chapter, we first consider neurochemical disturbances produced by TBI in order to frame the review of pharmacological interventions for posttraumatic neuropsychiatric disturbances. Next, the general principles of psychopharmacological management are reviewed. Finally, we describe briefly the medication options for the treatment of the most common neuropsychiatric sequelae of TBI and offer practical guidance for their use in everyday clinical practice. A more detailed description of the role of pharmacotherapy in the treatment of specific neuropsychiatric symptoms or syndromes following TBI is presented in chapters on those subjects elsewhere in this volume.

Neurotransmitter Disturbances After TBI

Human and experimental injury studies suggest that the application of stretching and straining forces to the brain produces acute alterations of cerebral neurotransmitter levels (see Arciniegas and Silver 2006 for a detailed review). Mechanical stretching of axons alters their membrane potentials and incites a cascade of intra- and extracellular processes that increase the likelihood of action potential propagation along the axon and, subsequently, neurotransmitter release at their synaptic terminals (Lea et al. 2003). Cerebrospinal fluid sampling analyses of humans with TBI demonstrate acute excesses of glutamate (Alessandri et al. 1999a, 1999b; Kerr et al. 2003; Koura et al. 1998; Palmer et al. 1994; Wagner et al. 2005; Yamamoto et al. 1999), L-aspartate (Kerr et al. 2003; Koura et al. 1998; Palmer et al. 1994), γ-aminobutyric acid (GABA) (Palmer et al. 1994), dopamine (Markianos et al. 1992, 1996), norepinephrine (Markianos et al. 1992, 1996), serotonin (Markianos et al. 1992, 1996; Porta et al. 1975; van Woerkom et al. 1977), and acetylcholine (Bogdanovitch et al. 1975; Grossman et al. 1975; Sachs 1957; Tower and McEachern 1948, 1949). Although the relevance of each individual disturbance to immediate postinjury neurological and neuropsychiatric disturbances remains controversial (Obrenovitch and Urenjak 1997), there is general agreement that this "neurotransmitter storm" (McIntosh et al. 1999) contributes to the early neuropathophysiology of TBI. As this neurotransmitter storm waxes in the immediate postinjury period, excess neurotransmitter levels interact with other elements of the cytotoxic cascade (Lea et al. 2003; Meythaler et al. 2001; Povlishock and Katz 2005) as well as other cerebral neuropeptides to disrupt brain function and, via excitotoxicity, brain structure.

Neurotransmitter excesses in humans appear to abate over the course of the first several weeks following severe TBI (Markianos et al. 1992, 1996). There is specific evidence that levels of excitatory amino acids (e.g., glutamate, aspartate) (Kerr et al. 2003) and the monoamine neurotransmitters (i.e., dopamine, norepinephrine, serotonin) (Markianos et al. 1996) normalize among those who survive these injuries. The interval over which acute cholinergic excesses wane after TBI in humans has not been established, although there is at present no evidence to suggest that the time course of this process differs from that of other neurotransmitter excesses. Because these

neurotransmitter systems are the targets of pharmacotherapies for posttraumatic neuropsychiatric disturbances, the effects of TBI on each of these systems are considered here.

Glutamate

Cerebral glutamate levels are elevated within minutes following TBI, peak over the first 48 hours postinjury, and tend to remain elevated throughout the first week following TBI in humans (Baker et al. 1993; Stover et al. 1999; Yamamoto et al. 1999; Zhang et al. 2001). Although such elevations are greatest among persons with the most severe injuries, they have been observed among patients with mild TBI as well (Zhang et al. 2001). The principal neurotoxic effect of glutamate is attributable to its action at *N*-methyl-D-aspartate (NMDA) receptors, excess activation of which results in toxic intracellular levels of calcium, oxidation, and activation of proteolytic enzymes. Excess levels of glutamate and other excitatory amino acids also "drive" glucose utilization past the brain's capacity for oxidative metabolism, resulting in toxic accumulations of lactate and other problematic metabolic changes. Excessive glutamate levels appear to normalize after the first week following TBI but may be maintained or exacerbated by concurrent hypoxia (Sarrafzadeh et al. 2003).

In humans, the degree of elevation of these excitatory amino acid neurotransmitters appears to be associated with the severity of injury and postinjury survival (Gopinath et al. 2000; Hutchinson et al. 2000; Kerr et al. 2003). Despite considerable interest in neuroprotective strategies employing NMDA receptor antagonists, clinical trials using this class of medication or calcium channel blockers have not produced encouraging results (Maas et al. 2010). Similarly, memantine and amantadine, two moderate-affinity uncompetitive NMDA receptor antagonists, are of theoretical interest with respect to both the prevention of glutamate-mediated neurotoxicity in TBI and remediation of posttraumatic cognitive impairments. Although there is experimental evidence suggesting that memantine confers neuroprotection from glutamate-mediated excitotoxicity when administered shortly after TBI (Rao et al. 2001), there are at present no studies demonstrating a similar neuroprotective benefit of either amantadine or memantine following TBI in humans.

Catecholamines

Intracerebral catecholamine levels are elevated in the immediate postinjury period; persistent elevations of intracerebral dopamine and norepinephrine levels are inconsistently associated with poor outcome, including death, in the first weeks after TBI (Markianos et al. 1992, 1996). Inferential reasoning from the effects of pharmacotherapies suggests that catecholaminergic dysfunction may contribute to posttraumatic cognitive and other neuropsychiatric disturbances, but the extent of posttraumatic catecholaminergic dysfunction and its contribution to those disturbances remains uncertain. Tang et al. (1997a, 1997b) suggested that striatal hyperdopaminergia contributes to post-TBI memory deficits in recently injured animals, antagonism of which improved visual memory performance. This finding appears to contradict the inference of reduced dopamine function drawn from observations of cognitive benefits following augmentation of dopaminergic function (using methylphenidate, for example) among persons with TBI in the days to weeks following injury (Whyte et al. 1997, 2002, 2004) as well as other observations of the adverse effects of dopamine antagonism on memory function after experimental TBI (Hoffman et al. 2008; Kline et al. 2007, 2008). However, all of these observations are consistent with the inverted-U-shaped response of cerebral information processing systems to dopamine in that either hyper- or hypodopaminergia appears to interfere with cognition following TBI.

Direct evidence of primary, persistent, and clinically significant injury to catecholaminergic afferents following TBI in humans is at present lacking. However, the effects of any degree of neurotrauma-induced losses of dopaminergic or noradrenergic neurons could be magnified into clinical significance by virtue of the interaction between catecholaminergic and other traumatically injured neurotransmitter systems (e.g., glutamatergic, cholinergic) (Lester et al. 2010; Smiley et al. 1999). Additionally, genetically determined individual differences in cerebral catecholamine metabolism, including variations in catechol O-methyltransferase enzyme activity (Lipsky et al. 2005; Redell and Dash 2007) or dopamine receptor or transporter function (McAllister 2009), might interact with modest structural injury to catecholaminergic systems to produce disturbances in cognitive and neuropsychiatric functions dependent on these systems.

Serotonin

As with other ascending neurotransmitter projections, serotonergic efferents are vulnerable to biomechanical trauma but also appear to be particularly susceptible to secondary neurotoxicity from excitotoxins and lipid peroxidation (Karakucuk et al. 1997). In humans, ventricular, rather than lumbar, cerebrospinal fluid sampling in the immediate postinjury period consistently demonstrates increase serotonin (or serotonin metabolite) levels (Markianos et al. 1992, 1996; Porta et al. 1975). However, focal and diffuse lesions may result in differences with respect to monoaminergic alterations after TBI (van Woerkom et al. 1977), with decreased serotonin levels in the setting of focal frontotemporal contusions and increased levels accompanying diffuse injuries. Serotonergic excesses decrease cerebral glucose utilization (Pappius 1989; Tsuiki et al. 1995). In principle, this might have the effect of mitigating the adverse effects of elevated excitatory amino acid (e.g., glutamate) levels. On the other hand, excessive reductions of cerebral glucose utilization may reduce or injure nervous system tissues as well.

Although serotonergic excesses contribute to early postinjury alterations of cerebral function, there is no clear evidence of persistent posttraumatic serotonergic deficits; and, not unexpectedly, the reported benefits of serotonergic augmentation on cognitive and other neuropsychiatric functions in the late postinjury period are mixed (Ashman et al. 2009; Fann et al. 2000, 2001; Horsfield et al. 2002; Lee et al. 2005; Rapoport et al. 2008). Collectively, these studies suggest that while serotonergic augmentation may

improve depression following TBI, the effects of nonspecific serotonergic augmentation (such as is afforded by the selective serotonin reuptake inhibitors and related agents) on posttraumatic neuropsychiatric disturbances are modest, at best. It is possible that receptor-specific modulation of serotonergic function (antagonism of 5-HT_{1A}, 5-HT_{1B}, and 5-HT_3 receptors, or agonism of 5-HT_{2A}, 5-HT_{2C}, and 5-HT_4 receptors) may improve posttraumatic cognitive impairments (Buhot et al. 2000; Kline et al. 2001, 2004; Wilson and Hamm 2002). However, this approach to clinical neurobehavioral intervention in the early and late postinjury periods has not been adequately investigated.

Acetylcholine

Acute cholinergic excesses develop in the immediate postinjury period; these were among the first documented neurochemical effects of severe TBI (Bogdanovitch et al. 1975; Grossman et al. 1975; Sachs 1957; Tower and McEachern 1948, 1949). Acute cerebral cholinergic excesses contribute to acute alterations of arousal ("consciousness") (Hayes et al. 1984) and to the cataplexy associated with acute concussive injuries (Hayes et al. 1986; Katayama et al. 1984). Preinjury treatment or early postinjury administration of scopolamine (Lyeth et al. 1988a, 1988b, 1992; Saija et al. 1988), as well as scopolamine and phencyclidine (Jenkins et al. 1988), attenuates the neurodestructive effects of cholinergic excesses and also attenuates early and late spatial memory impairments. However, the therapeutic effects of administering anticholinergic agents in the immediate postinjury period in humans with TBI has not been investigated in randomized controlled trials.

In animals, elevated cerebral acetylcholine levels and related functional disturbances wane substantially over the first 2 weeks postinjury (Dixon et al. 1995). The interval over which acute cholinergic excesses wane after TBI in humans is uncertain; however, there is at present no evidence to suggest that the time course of this process differs from that of other neurotransmitter excesses. Early postinjury cholinergic excesses in humans are followed by the development of late cerebral cholinergic deficits. The University of Glasgow group (Dewar and Graham 1996; Murdoch et al. 1998, 2002) demonstrated reductions of choline acetyltransferase levels (by as much as 50%) and linked this finding to losses of neurons in the nucleus basalis and to losses of ventral forebrain cholinergic efferents. Longer survival periods, as well as presence of subdural hematoma, were associated with lower choline acetyltransferase levels, suggesting gradually worsening cortical cholinergic deficit in the immediate postinjury period. They also observed preservation of type 1 and type 2 muscarinic receptors as well as high-affinity nicotinic receptors, suggesting preserved cortical targets for acetylcholine despite losses of cholinergic projections to those targets.

Treatment Implications of Neurotransmitter Disturbances

Neurochemical disturbances interact with preinjury factors, injury-related neuroanatomic insults, and postinjury psychosocial and environmental factors to produce posttraumatic neuropsychiatric problems. The treatment of those problems necessitates a broad consideration of all of these factors but will be guided usefully by an understanding of neurotransmitter disturbances in the early and late periods after TBI. Immediately postinjury, elevated neurotransmitter levels contribute to elementary neurological impairments and alterations in cognition, emotion, and behavior; elevated glutamate and acetylcholine levels also appear to contribute directly to the neuropathology of TBI. Intervention directed at those disturbances has not yet led to clinically effective neuroprotection for persons with TBI. However, the use of agents that exacerbate or prolong these disturbances may complicate early recovery after TBI (Rao et al. 1985). In the late period after TBI, there is substantial evidence of primary cerebral cholinergic deficits and additional evidence suggesting, at a minimum, secondary catecholaminergic dysfunction. Thus, the selection of medication agents to control early posttraumatic neurobehavioral problems is best undertaken with an understanding of the possible interactions of those agents with the neurochemical state of the individual to whom medications are administered (Saniova et al. 2006; Wheaton et al. 2009). In the following sections of this chapter, we review such pretreatment considerations and medication selection in light of this review of posttraumatic neurotransmitter disturbances.

Pretreatment Evaluation

A thorough neuropsychiatric assessment of the patient is a prerequisite to the prescription of any intervention, particularly pharmacotherapy. For purposes of this discussion, we assume that a complete developmental, medical (including medication), neurological, psychiatric, substance use, social, and family history has been obtained and a thorough physical, neurological, and mental status (including cognitive) examination has been performed (see Chapter 4, Neuropsychiatric Assessment).

With respect to the subsequent initiation of pharmacotherapy for one or more posttraumatic neuropsychiatric symptoms, two issues require particular attention. First, the presenting complaints must be carefully assessed, defined, and operationalized, preferably through the use of objective rating scales such as the Overt Aggression Scale (Silver and Yudofsky 1991) (see Chapter 14, Aggressive Disorders), the Neurobehavioral Rating Scale—Revised (Levin et al. 1987; McCauley et al. 2001) (see Chapter 4, Neuropsychiatric Assessment), or the Neuropsychiatric Inventory (Cummings et al. 1994). In addition to clarifying the type, frequency, and severity of symptoms before treatment, repeated use of such scales during treatment improves the accuracy and objectivity of symptom monitoring.

Second, the use and effectiveness of all ongoing treatments must be reevaluated, including prescribed pharmacological and nonpharmacological therapies as well as self-administered agents. Of particular concern is the use of anticonvulsants among persons with TBI (see Chapter 16, Posttraumatic Epilepsy). It is important to ascertain whether such agents were prescribed for the treatment of recurrent seizures, for seizure prophylaxis (i.e., treatment

prior to the occurrence of any seizures), or for the treatment of another neuropsychiatric problem. As reviewed by Frey (2003), persons with TBI remain at risk for the development of posttraumatic seizures for years postinjury. The development of recurrent posttraumatic seizures requires treatment with anticonvulsants. The selection of agents for this problem must weigh the benefits of treatment against many risks and, in this population, the risk of treatment-related cognitive, behavioral, and motor impairments. Administration of anticonvulsant medications ("seizure prophylaxis") is commonly undertaken in the first week post-TBI; use of anticonvulsants in this manner is associated with a decreased incidence of seizures during that period (Schierhout and Roberts 2000), and their use in this manner is consistent with the "Evidence-Based Guidelines for Traumatic Brain Injuries" (Marion 2006). Prescribing "prophylactic" anticonvulsants to persons with TBI for months or years postinjury does not effectively mitigate the risk of developing late posttraumatic seizures and does not reduce mortality or long-term neurological disability after TBI (Schierhout and Roberts 2000). In fact, treatment with some of these medications—particularly phenytoin (Dikmen et al. 1991; Smith et al. 1994) and carbamazepine (Smith et al. 1994)—during the acute and subacute period after TBI is associated with treatment-related impairments in cognitive and motor function. Levetiracetam is gaining popularity as an agent for seizure prophylaxis in the early postinjury period (Ruegg et al. 2008; Szaflarski et al. 2007). This agent may be better tolerated among persons with TBI both in the short and long term when compared with phenytoin (Jones et al. 2008; Szaflarski et al. 2010). Unfortunately, levetiracetam is associated with treatment-related agitation, depression, and other neurobehavioral disturbances (Helmstaedter et al. 2008; Hirsch et al. 2007; Kanner 2009; Mula et al. 2003, 2004), particularly among the elderly and persons with a history of psychiatric problems or developmental disabilities. By contrast, valproate appears to be relatively benign with respect to its effects on cognition (Dikmen et al. 2000) and other neurobehavioral functions among persons with TBI but entails hepatic and hematological risks as well as risks for alopecia, weight gain, and polycystic ovarian syndrome. It is therefore important to discontinue "seizure prophylaxis" at the end of the first week post-TBI—regardless of the agent selected for that purpose—and to maintain clinical vigilance for the development of posttraumatic seizures thereafter. When an anticonvulsant is required for the treatment of recurrent posttraumatic seizures, when neurosurgical or neurological consultants insist on longer-term seizure prophylaxis, or when an anticonvulsant is used for the treatment of another neuropsychiatric problem, valproate is generally preferable to phenytoin, carbamazepine, and levetiracetam. When treatment with this agent is not feasible or effective, the selection of other agents is guided by consideration not only of their potential effects but also their cognitive, psychiatric, and behavioral side effects (for reviews of these issues, see Chapter 16, Posttraumatic Epilepsy, and Arif et al. 2009 and Weintraub et al. 2007).

Consultation with other specialists (e.g., internal medicine, neurology, physiatry) sometimes may be required to decide whether a current or new medication is necessary. Such consultations may identify problems in treatment that require resolution before initiating a new pharmacological intervention. For example, pharmacological treatments are sometimes implemented when in fact the best treatment recommendation is to prescribe no medication and instead to employ another therapeutic intervention. Evaluating first the target symptoms that current treatments were intended to address and also whether such medications are the best intervention for those symptoms is essential. In many cases, other treatment modalities (e.g., individual, group, and/or family psychotherapy, behavioral/environmental management, life skills training/community reintegration, and other nonpharmacological interventions) either were not considered or not properly applied. In other cases, medications are mistakenly deemed "ineffective" or "intolerable" as a result of inadequate or excessive dosing (including overly rapid dose escalation), inadequate or unnecessarily extended treatment periods, or drug-drug interactions resulting from concurrent use of multiple agents with similar mechanisms of action. Additionally, problems may arise as a result of misdiagnosis of the neuropsychiatric condition and may develop as a consequence of poor communication and coordination of care among health care providers. Consideration of these issues is an essential element of the pretreatment neuropsychiatric evaluation.

Common Patient Concerns Regarding Pharmacotherapy

Patients, families, and treatment centers commonly express reservations about the use of medications to treat neuropsychiatric symptoms experienced by persons with brain injuries. The causes of such reservations are many and varied but frequently involve reluctance to acknowledge the abnormal nature of such symptoms, concerns about stigmatizing the person with TBI as having a "mental illness," and misperceptions about and/or fears of psychiatric treatment. When these and related concerns are coupled with a patient's previous suboptimal experiences with psychotropic medications, reservations may evolve into frank resistance to pharmacotherapy for posttraumatic neuropsychiatric disturbances. We have suggested that the neuropsychiatric paradigm—one that rejects the misleading demarcation between "brain" and "mind" and emphasizes the neurobiological bases of all cognitive, emotional, and behavioral problems regardless of the relationship of such problems to brain injury—is the most useful approach to addressing such concerns and reducing the stigma associated with neuropsychiatric problems and their treatment (Arciniegas and Beresford 2001; Yudofsky and Hales 1989). Patients struggling to accept treatment in the face of old stigmas may benefit from an explanation of symptoms as the products of alterations in neurotransmitters, brain structures, brain networks, or some combination of these and by presenting treatments for them as interventions designed to alleviate or compensate for such brain dysfunctions.

Another commonly voiced concern is that the use of medication will interfere with the "natural healing pro-

cess" after TBI. This concern is not entirely unfounded, at least as it regards certain types of medications. For example, antagonists of dopamine type 2 (D_2) receptors and/or benzodiazepines are used commonly for the treatment of agitation, delirium (Francisco et al. 2007) and, in the critical care period, as an adjunctive agent to improve compliance with mechanical ventilation (Milbrandt et al. 2005). Agents with noradrenergic-attenuating effects (e.g., clonidine) are sometimes used for these and other purposes as well. However, animal models suggest that dopamine and norepinephrine antagonists delay neuronal recovery and impair neuronal plasticity (Goldstein 1993, 1999, 2003, 2006) as well as functional and behavioral recovery in experimental injury models (Hoffman et al. 2008; Kline et al. 2008). Among persons with TBI, treatment with typical antipsychotics exacerbates cognitive impairments (Stanislav 1997) and may prolong posttraumatic amnesia (Rao et al. 1985). Benzodiazepines impair memory and other aspects of cognition (Buffett-Jerrott and Stewart 2002) in healthy adults and persons with TBI (Bleiberg et al. 1993) as well. The neurochemical consequences of TBI create chronic vulnerability to adverse effects of agents with anticholinergic properties (Arciniegas 2003; Arciniegas and Silver 2006). Opiate analgesia produces impairments in memory among persons without TBI of severity comparable to those encountered among persons in posttraumatic amnesia (McCarter et al. 2007), and their use for the treatment of pain (from any cause) after TBI poses a risk of exacerbating posttraumatic cognitive impairments.

Many of these studies, as well as common clinical experience, suggest that medication-related interference with neurobehavioral and function status is reversible upon discontinuation of an offending agent. Nonetheless, both patient experiences and clinician observations of treatment-related delays in recovery contribute to bias against the use of psychotropic agents among persons with TBI and perhaps not entirely unreasonably so. Avoiding, eliminating, or using the minimum-necessary dose of any medication in the acute postinjury period and using it for as brief a time as is feasible clinically therefore is encouraged. When it is necessary to treat patients with agents that may interfere with neurobehavioral recovery, we recommend acknowledging that possibility openly during the treatment consent process and also proactively addressing any concerns about such possibilities held by patients, families, and other health care providers. At the same time, discussing clearly the risks attendant to withholding pharmacological intervention as well as the goal of discontinuing these medications when it is clear that they are no longer necessary may be highly productive. This approach often allows patients and/or those assisting with their medical decision making to have their reservations about the risks of pharmacotherapy understood and to become more open to considering an empirical trial of pharmacotherapy for problematic posttraumatic neuropsychiatric disturbances.

General Principles

When a pharmacological intervention is prescribed to treat one or more posttraumatic neuropsychiatric problems, clinicians are encouraged to remain mindful that there are few controlled clinical trials available to guide such treatments. No medication has received approval from the U.S. Food and Drug Administration for the treatment of any posttraumatic neuropsychiatric problem; therefore, all such treatments must be considered "off label." In light of the limited body of information with which to assess the benefits, risks, and side-effects of pharmacotherapies in this population, it is best to prescribe medications judiciously and only after making every effort to obtain informed consent from the patient or his legally authorized proxy medical decision makers. Toward that end, we offer here several general principles of pharmacotherapeutic treatment planning.

First, the target symptom for any medication prescribed needs to be identified explicitly and assiduously assessed, using valid and reliable measures appropriate for this population. Second, the clinician must determine whether currently prescribed medications are effective with respect to their intended target symptoms and therefore still necessary. Third, the patient's ability to tolerate the intrinsic side effects of a new medication as well as the potential interactions—both beneficial and detrimental—of any new medication with currently prescribed medications requires careful consideration. For example, synergy with respect to the development of treatment intolerance with multiple agents is not uncommon in this population, particularly when medications with similar mechanisms of action are employed (e.g., two agents that augment cerebral catecholamine levels or that both possess anticholinergic or antihistaminic effects or that both lower seizure threshold). Similarly, if a current treatment has been partially effective then it may be productive to employ a second intervention for the purpose of augmenting the effectiveness of the first treatment.

The decision regarding which medication (if any) to prescribe is based on 1) current knowledge of the efficacy of the medication among persons with TBI, 2) current knowledge of the efficacy of the medication among persons with other neurological conditions or psychiatric disorders, 3) the side-effect profile of the medication, 4) consideration of the possibility of increased sensitivity to medication side effects among persons with TBI, 5) development of analogies between the symptom observed in the person with TBI and those commonly observed in other neuropsychiatric syndromes, and 6) hypotheses regarding how the neurochemical changes after TBI align with the proposed mechanisms of action of psychotropic medications.

Several general guidelines for the pharmacological treatment of neuropsychiatric symptoms among persons with TBI (described more fully in Table 35–1) are suggested:

1. With respect to dosing, "start low and go slow."
2. Employ therapeutic trials of all medications.
3. Establish a schedule for the systematic reassessment of the clinical condition for which treatment is prescribed.
4. Monitor for the development of drug-drug interactions.
5. Consider augmentation of partial responses to medications.

TABLE 35–1. General principles of pharmacotherapy for patients with traumatic brain injuries

Start low, go slow	Initiate treatment at doses lower than those used in patients without brain injuries, and raise doses more slowly than in patients without brain injuries.
Adequate therapeutic trial	Although patients with brain injuries may be more sensitive to the side effects of many medications, standard doses of such medications may be needed to treat adequately the neuropsychiatric problems of these patients.
Continuous reassessment	The need for continued treatment should be reassessed in an ongoing fashion, and dose reduction or medication discontinuation should be attempted after achieving remission of target symptoms. Spontaneous recovery occurs, and in such circumstances continued pharmacotherapy is unnecessary.
Monitor drug-drug interactions	Because patients with brain injuries are often sensitive to medication side effects and because they may require treatment with several medications, it is essential to be aware of and to monitor these patients for possible drug-drug interactions.
Augmentation	A patient experiencing a partial response to treatment with a single agent may benefit from augmentation of that treatment with a second agent that has a different mechanism of action. Augmentation of partial responses is preferable to switching to an agent with the same pharmacological profile as that producing the partial response.
Symptom intensification	If targeted psychiatric symptoms worsen soon after initiation of pharmacotherapy, lower the dose of the medication; if symptom intensification persists, discontinue the medication entirely.

6. Discontinue or lower the dose of the most recently prescribed medication if there is a worsening of the treated symptom soon after the medication has been initiated (or increased).

Although individuals with TBI may experience multiple concurrent neuropsychiatric symptoms (e.g., depressed mood, irritability, poor attention, fatigue, and sleep disturbances) that suggest a single psychiatric diagnosis (e.g., major depression), it is common clinical experience that the neuropsychiatric symptoms of these patients are often less tightly coupled than are such symptoms among patients with idiopathic psychiatric syndromes. It therefore is important to help the patient (and/or his caregivers) identify the neuropsychiatric symptoms that are interfering most with everyday function and to target those symptoms first. Concurrently, clinicians may help patients to prioritize target symptoms for treatment by providing education regarding the interactions between neuropsychiatric symptoms. For example, depression after TBI exacerbates cognitive impairments and increases both the number and perceived severity of other postconcussive symptoms (Fann et al. 2000, 2001). Treatment of depression after TBI is associated with improvements in cognition, reductions in the total number of postconcussive symptoms, and decreases in the perceived severity of those symptoms (Fann et al. 2000, 2001). In general, then, when depression is present it is prudent to make it the primary target symptom of treatment. Similarly, cognitive impairment, anxiety, affective lability, and/or agitation commonly co-occur. In some patients, functional problems resulting from cognitive impairments generate anxiety, affective lability, and agitation; in others anxiety is a primary problem, and it produces affective lability, agitation, ineffective use of remaining cognitive abilities, and functional impairments. Helping the patient to evaluate the manner in which co-occurring symptoms interact and contribute to functional problems will facilitate selection of initial treatments (e.g., treating cognitive impairments first rather than anxiety symptoms or vice versa).

Where possible, monotherapy is preferable to polypharmacy as a treatment approach: because many medications may treat several posttraumatic neuropsychiatric symptoms effectively, it is prudent to meet an individual's treatment needs by employing the fewest number of agents with the broadest possible benefits and the most benign adverse effect profiles. Multiple medications can be used when a single agent will not suffice or proves ineffective for one or more target symptoms. When polypharmacy is required, initiating treatment with multiple medications sequentially, rather than concurrently, is preferable because it increases the likelihood that both the prescribing physician and the patient will make correct attributions of benefits and side effects to the agent or combination of agents responsible for them.

In our experience, patients with brain injuries of any type are more sensitive to the side effects of medications than are patients who do not have brain injury. Medications often should be initiated at dosages that are lower than those usually administered to patients without brain injury. Dose increments should be made gradually to minimize side effects and enable the clinician to observe both the beneficial and adverse consequences of such adjustments. It is important that such medications be given sufficient time to impart their full effects. Although it is prudent to employ a "start low and go slow" approach to treatment initiation and dosing titration, patients may require the same doses and serum levels that are therapeutically effective for patients without brain injury. Thus, when a decision is made to administer a medication, the patient must receive an adequate therapeutic trial of that medication in terms of dosage and duration of treatment.

Because of frequent changes in the clinical status of patients after TBI, particularly during the first year postinjury, systematic and frequent reassessment is necessary to determine whether treatment with a prescribed medication is still required. In general, establishing at the beginning of treatment a defined reassessment interval (i.e., daily, twice weekly, weekly, etc., depending on the treatment context) and adhering to that reassessment schedule

is recommended. Using standardized scales not only for diagnostic purposes (as described above) but also as an anchor for treatment reassessment is encouraged. In this context, it is important to recall that recurrence of an unwanted behavior—especially those that are intermittent at treatment outset—does not necessarily suggest that the treatment directed at that problem is ineffective. If the frequency and severity of the behavior have been improved by treatment, the recurrence of the problem for which treatment is prescribed may indicate the need for education and counseling of the patient, family, or other health care providers on treatment expectations as much as it does the possible need for a change in the dose of or the specific medication prescribed. It may also suggest the need to reevaluate the patient for other medical (e.g., urinary tract infection, metabolic disturbances) and neurological (e.g., seizure) problems. When problematic behaviors recur during treatment, it is prudent to consider this broad differential diagnosis for such recurrences prior to making substantive changes in treatment.

Although there is some evidence for the selection of medications for specific neuropsychiatric problems after TBI (Arciniegas and Silver 2006; Chew and Zafonte 2009; Warden et al. 2006), there is no literature describing optimal duration of treatment and/or clarifying the risks of treatment discontinuation and relapse/recurrence risk for posttraumatic neuropsychiatric problems. In the early period following TBI, recovery from injury may result in spontaneous remission of neuropsychiatric symptoms and thereby obviate the need for continued pharmacotherapy. Even after the period of spontaneous recovery from TBI, neuropsychiatric symptoms may in some cases remit spontaneously; reassessing the need for continued treatment necessitates consideration of this possibility. In the absence of formal guidelines regarding duration of maintenance pharmacotherapy, the American Psychiatric Association (2000) practice guidelines for the treatment of major depression offer a reasonable treatment planning framework for most neuropsychiatric symptoms following TBI: continue treatment with medication for a minimum of 16–20 weeks after complete remission of symptoms and then offer counseling on the possibility of medication discontinuation phenomena and symptom recurrence. These risk-benefit determinations require clinical judgment and must be tailored to the fit the symptoms and functional concerns of the patient (and/or caregiver) with whom they are discussed.

When a new medication is initiated in combination with medications previously prescribed, vigilance for the development of drug-drug interactions is particularly important. These interactions may include alteration of pharmacokinetics that result in increased half-lives and serum levels of medications, as can occur with the use of multiple anticonvulsants. Additionally, alterations of pharmacodynamics may develop as a result of TBI: a medication used to treat a preinjury disorder may become poorly tolerated after TBI as a result of a change in the neural substrate on which that drug acts.

If a patient does not respond favorably to the initial medication prescribed, it is generally the case that several alternatives to the treatment of that problem are available. When switching pharmacotherapies, we recommend selecting an agent with a substantially different mechanism of action than the first, and ineffective, agent. If there has been a partial response to the initial medication, augmentation with a second medication may be useful. As with treatment switching, selecting a supplementary/augmenting medication with a substantially different mechanism of action than the primary agent is encouraged. Additional considerations also must be given to possible contrary mechanisms of action of between agents, the individual and combined side-effect profiles of the initial and secondary agents, and their potential pharmacokinetic and pharmacodynamic interactions.

Pharmacological Treatment of Specific Neuropsychiatric Syndromes

Studies of the effects of psychotropic medications in patients with TBI are few, and rigorous double-blind, placebo-controlled studies are rare (see Arciniegas and Silver 2006; Chew and Zafonte 2009; Warden et al. 2006). Nonetheless, common clinical experience suggests that many persons with neuropsychiatric symptoms after TBI, regardless of whether those symptoms reflect new problems or recurrence/exacerbation of prior neuropsychiatric problems, will respond well to pharmacotherapy. Selection of medications is guided most usefully by developing, as completely as possible, an understanding of the relationship between the neuroanatomy and neurochemistry of TBI (i.e., is there an anatomic "target" for pharmacotherapy, or has that target been traumatically ablated?).

In this section, we review briefly the most common and practical pharmacotherapies for posttraumatic neuropsychiatric symptoms and syndromes; more detailed discussion of these problems and their treatments may be found in the chapters corresponding to each of these topics elsewhere in this volume. The recommendations contained in this chapter represent a synthesis of the available treatment literature in TBI, extensions of the known uses of these medications in phenotypically similar non-brain-injured psychiatric populations of patients with other types of brain injuries (e.g., stroke and multiple sclerosis), and the opinions of the authors of this chapter.

Cognitive Impairment

The treatment of posttraumatic cognitive impairments generally entails both pharmacological and nonpharmacological approaches. Cognitive rehabilitation, usually provided by an occupational therapist, speech therapist, or neuropsychologist, is most useful for the development of compensatory strategies to address difficulties with memory, attention, interpersonal communication skills, and executive function (see Chapter 37; see also Cicerone et al. 2000, 2005). Cognitive rehabilitation appears best suited to the treatment of patients with mild to moderate cognitive impairments, with relatively preserved functional independence, and who are motivated to engage in and rehearse these strategies. Pharmacotherapy may improve

posttraumatic cognitive impairments, but it is important for prescribing clinicians to remember to role of medication in the treatment of such problems: they are best used as adjuncts to or facilitators of cognitive rehabilitation.

The neuroanatomy and neurochemistry of TBI yield two general approaches to the treatment of posttraumatic cognitive impairments: catecholaminergic augmentation and cholinergic augmentation (Arciniegas and Silver 2006). Methylphenidate, a stimulant that augments cerebral dopaminergic and noradrenergic function, is regarded as the first-line treatment for impaired speed of processing and may also benefit arousal and, to a lesser extent, attention and memory (Warden et al. 2006). Pharmacologically similar agents such as dextroamphetamine may afford comparable benefits in clinical practice, although there are few studies published for any stimulant other than methylphenidate. Stimulants generally take effect quickly (within 0.5–1 hour following administration) and lose effect after a few hours. Therefore, the first issue in the administration of these agents is to determine optimal dose and dosing frequency. Initial dosing with either agent generally begins at 5 mg once daily and is gradually increased by increments of 5 mg until either there is beneficial effect or medication intolerance occurs. Most studies suggest that optimal doses of either methylphenidate or dextroamphetamine are in the range of 20–40 mg twice daily (i.e., 0.15–0.3 mg/kg twice daily). Individuals requiring relatively high and frequent doses of methylphenidate or dextroamphetamine may benefit from use of longer-acting preparations. In such cases, it also may be useful to obtain blood levels of methlyphenidate 90 minutes after ingestion to evaluate patient-specific pharmacokinetics and to use that information to guide considerations regarding the prescription of higher doses of this agent. Methylphenidate and dextroamphetamine may induce mild increases in heart rate and/or blood pressure, although such changes are relatively infrequent and rarely require treatment discontinuation. Nonetheless, baseline pulse and blood pressure should be obtained and monitored until a final dosage level is achieved.

Placebo-controlled studies suggest that donepezil (Kim et al. 2009; Zhang et al. 2004) and rivastigmine (Silver et al. 2006) may be useful for the treatment of posttraumatic cognitive impairments, particularly memory impairments. Cholinesterase inhibitor-related improvements in attention and executive functioning are also reported (see Arciniegas and Silver 2006 and Chew and Zafonte 2009 for review), and these agents are sometimes used for this purpose in clinical practice. Consistent with this suggestion, the Neurobehavioral Guidelines Working Group (Warden et al. 2006) recommended donepezil (5–10 mg daily) to enhance aspects of attention and memory for patients with moderate to severe TBI in subacute and chronic periods of recovery. Based on findings published subsequent to the Neurobehavioral Guidelines Working Group report (Silver et al. 2006, 2009; Tenovuo et al. 2009), rivastigmine (3–12 mg daily) is also suggested as an option for the treatment of chronic posttraumatic memory and attention problems, including those experienced by persons with mild TBI.

Some patients respond robustly to catecholaminergic agents, others to cholinesterase inhibitors; some require treatment with some combination of these agents, and others respond poorly to all presently available medications. Although a matter of empirical trial for each patient, these pharmacological interventions are useful in enough cases to suggest that they be regarded as an option for the treatment of cognitive problems caused by TBI.

Cytidine 5′-diphosphocholine (CDP-choline or citicoline) is an essential intermediate in the biosynthetic pathway of phospholipids incorporated into cell membranes that appears to activate the biosynthesis of structural phospholipids in neuronal membranes, increase cerebral metabolism, and enhance activity of dopamine, norepinephrine, and acetylcholine (Dixon et al. 1997; Secades and Frontera 1995). A single-blind, randomized study of 216 patients with severe or moderate TBI demonstrated improved motor, cognitive, and psychiatric function during treatment with CDP-choline, and this treatment decreased length of stay in the hospital (Calatayud-Maldonado et al. 1991). Levin (1991) performed a double-blind, placebo-controlled study of 14 patients to evaluate the efficacy of CDP-choline (1 g/day) for the treatment of postconcussional symptoms in the first month after mild to moderate TBI. This treatment reduced the severity of postconcussional symptoms and improved recognition memory for designs but did not influence other aspects of neuropsychological performance. CDP-choline is available only as an over-the-counter agent; because content, purity, and effective dose may be difficult to predict in present formulations, patients electing to undertake treatment with CDP-choline should be cautioned about these potential problems and monitored carefully for both benefit and adverse reactions during its use (see Chapter 39, Complementary and Integrative Treatments, on the use of alternative medications).

Emotional Disturbances

Depression

Depression is a common problem among persons with TBI and is amenable to pharmacological intervention (Alderfer et al. 2005; Chew and Zafonte 2009; Warden et al. 2006). Treatment of depression may alleviate not only the mood disturbance but also reduce other neurobehavioral disturbances such as impulsivity, aggression, and self-injurious behaviors (Janowsky and Davis 2005). Although many factors (e.g., sleep disturbance, fatigue [anergia], difficulty concentrating, anhedonia [apathy]) may produce or contribute to apparent depressive symptoms, when there are sufficient symptoms (or behavioral equivalents) to merit a diagnosis of depression, an antidepressant treatment should be initiated. Apathy can be misinterpreted as depression and should be considered in the case formulation (see below).

Somatic therapies for depression among persons with TBI include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic and tetracyclic antidepressants, novel antidepressants (e.g., trazodone, mirtazapine, venlafaxine, bupropion), monoamine oxidase inhibitors, and psychostimulants. Given the relatively favorable profile of the SSRIs, these agents are suggested as the first-line treatment for depression among persons with TBI.

Although there is no evidence to suggest that any SSRI is clearly superior to the others for the treatment of depression (with or without other behavioral disturbances) in these populations, we generally recommend using agents with relatively short half-lives, limited cytochrome P450 (CYP 450) inhibition, and no anticholinergic effects. With these considerations in mind, sertraline, citalopram, and escitalopram are considered first-line treatments. When cost considerations, treatment intolerance, or patient/caregiver preference precludes use of these agents, fluoxetine and paroxetine are reasonable to consider and would, in general, be expected to be similarly effective. However, their use may require more careful consideration of possible drug-drug interactions (mediated via their effects on CYP 450 drug metabolism) and, in the case of paroxetine, on cognition (via its anticholinergic effects).

The tricyclic and tetracyclic antidepressants are used less commonly for the treatment of depression in general as well as for depression among persons with TBI, and we regard them as second-line treatments for this purpose. The possibility of increased side effects associated with these agents, waning familiarity with the use of these agents on the part of recently trained clinicians, or some combination of these factors may explain the declining use of these agents. Nonetheless, these agents may be helpful for some patients and merit consideration among those unable to tolerate or unwilling to take SSRIs. When a tricyclic or tetracyclic antidepressant is used, nortriptyline and desipramine are recommended because of their more favorable side-effect profiles.

Common clinical experience (Patel et al. 2001) suggests that the novel antidepressants may be useful in the treatment of depression among persons with TBI, but their use must be undertaken cautiously given the very limited data describing the benefits and risks attendant to their use in these populations. Bupropion is of particular concern due to its dose-related incidence of seizures, which appear to be more common among persons with underlying neurological conditions (Davidson 1989; Johnston et al. 1991). However, this agent may be used judiciously in patients with TBI (see Chapter 16, Posttraumatic Epilepsy, for discussion).

Psychostimulants, particularly methylphenidate and dextroamphetamine, may improve depression and other behavioral disturbances among persons with TBI (Lee et al. 2005) and may be particularly useful when a rapid response to depression is required. In such circumstances we generally use these agents as an initial intervention, which is then followed by initiation of and attempted transition to with a standard antidepressant (usually an SSRI) for long-term treatment.

Mania

Optimal treatment strategies for posttraumatic mania remain underdeveloped; this, at least in part, reflects the relatively uncommon occurrence of this problem. In fact, the Neurobehavioral Guidelines Working Group (Warden et al. 2006) note that there is insufficient evidence to support the development of formal treatment standards, guidelines, or options for posttraumatic mania. Nonetheless, valproate, quetiapine, carbamazepine, lithium, haloperidol (with or without benzodiazepines), and combinations of these agents are sometimes used to treat posttraumatic mania (see Chapter 10, Mood Disorders, and Oster et al. 2007 for review).

In the absence of evidence demonstrating the clear superiority of one of these agents over the others, we generally recommend either valproate or quetiapine as a first-line treatment given their effectiveness for acute mania, rapid-cycling bipolar disorder, and antimanic prophylaxis as well as their reasonable tolerability in persons with TBI. Although valproate may exacerbate cognitive impairments in some patients, and particularly during the acute titration period, it is less likely to do so than either carbamazepine (Massagli 1991) or lithium (Hornstein and Seliger 1989). Nonetheless, its use should include careful and ongoing assessment for adverse cognitive effects as well as for typical treatment-related side effects such as tremor, weight gain, diarrhea, blood dyscrasias, hepatotoxicity, and hair loss. Manic episodes occurring after TBI also may respond to carbamazepine; however, monitoring carefully for adverse cognitive and motor effects is recommended when using this agent among patients with TBI. Lithium carbonate also may be useful for the treatment of mania in persons with TBI, although partial response, relapse of symptoms, or need for a second mood-stabilizing medication are common limitations of the use of this agent in this population. Both carbamazepine and lithium adversely affect cognitive and motor performance among persons with TBI, particularly in the early postinjury period. Among persons with TBI, adverse cognitive and motor effects may develop during treatment with doses of lithium that would be expected to be tolerable among persons without TBI. Lithium may also lower seizure threshold and is more likely to produce nausea, tremor, ataxia, and lethargy in persons with neurological disorders than in the general psychiatric population. Lithium is an important and often useful treatment for mania among persons with TBI, but these observations emphasize the need for vigilance for adverse effects (even at ostensibly "therapeutic" doses and serum levels) when using this agent in persons with TBI.

Several of the newer anticonvulsants (e.g., lamotrigine, oxcarbazepine) and the atypical antipsychotics (e.g., risperidone, olanzapine, ziprasidone, aripiprazole) may be useful in the treatment of posttraumatic mania, but there are few published reports of their use among persons with posttraumatic mania. Clinicians interested in using these agents for this purpose are advised to undertake such treatments cautiously and with careful monitoring for adverse cognitive, motor, cardiac, and metabolic side effects.

Pathological Laughing and/or Crying

In contrast to mood disorders, conditions in which the baseline emotional state is pervasively disturbed over a relatively long period (i.e., weeks), disorders of affect denote conditions in which the more moment-to-moment variation and regulation of emotion is disturbed. The classic disorder of affect dysregulation is pathological laughing and/or crying (PLC), also referred to *emotional incontinenc*e or *pseudobulbar affect.* Patients with this condition experience involuntary and uncontrollable episodes of involun-

tary crying and/or laughing that may occur many times per day, are provoked by trivial (i.e., often not sentimental) stimuli, are quite stereotyped in their presentation, may be of a valence contradictory to the context in which they occur (i.e., crying when laughing would be expected and vice versa), and do not produce a persistent change in the prevailing mood.

The prevalence of PLC among persons with TBI is not clear, but it may be as high as 5%–11% in the first year postinjury (Tateno et al. 2004; Zeilig et al. 1996). As a result of this condition's absence in the DSM-based diagnostic system, patients with TBI experiencing uncontrollable paroxysms of crying are often diagnosed as "depressed," and those with paroxysms of crying and laughing are often misdiagnosed as "bipolar," despite the absence of pervasive and sustained disturbances of mood, psychological, and neurovegetative symptoms required for these diagnoses. The misdiagnosis of PLC as bipolar disorder, and especially of the rapid-cycling or ultra-rapid-cycling types, is particularly concerning given the dissimilarity of treatments between these conditions.

The treatment literature overwhelmingly supports the use and effectiveness of relatively low doses of serotonergically and noradrenergically active antidepressants for PLC, regardless of whether this condition manifests predominantly as crying, laughing, or both (for review, see Wortzel et al. 2007, 2008). We recommend SSRIs as first-line agents for this purpose; they may improve PLC symptoms within a few days of treatment initiation. Given that a misdiagnosis of PLC as bipolar disorder would generally lead clinicians to avoid prescription of an unopposed SSRI and given the lack of benefit on PLC conferred by most "mood stabilizers," the importance of diagnostic accuracy in this context cannot be overstated. As with the treatment of depression, no SSRI is a clearly superior choice for treating PLC. However, using agents with relatively short half-lives, limited drug-drug and CYP 450 interactions, and favorable side-effect profiles is recommended.

Tricyclic and tetracyclic antidepressants may also be effective for PLC, with nortriptyline being the most favorable of these agents. Although psychostimulants and other medications that enhance dopamine and/or norepinephrine neurotransmission are used most often for the treatment of cognitive impairments and/or diminished motivation following TBI they may also concurrently afford relief from PLC. Among patients in whom PLC is accompanied by irritability/anger, aggressive, and/or self-destructive behaviors, treatment with anticonvulsants, especially as adjuncts to SSRIs, may be of some benefit. Finally, dextromethorphan/quinidine or amantadine—both of which are uncompetitive *N*-methyl-D-aspartic acid receptor antagonists—also may improve PLC (see Wortzel et al. 2008). The latency between dextromethorphan/quinidine treatment initiation and improvement in PLC is often longer than that of SSRIs (4–5 weeks), whereas the latency between treatment and response of PLC to amantadine is similar to that of the SSRIs (2–5 days). Although both of these agents may be effective treatments for PLC, tolerability and the potential for drug-drug interactions attendant to their use are concerning; they are therefore best reserved for use in the treatment of PLC when other agents have proved ineffective or intolerable.

Anxiety Disorders and Posttraumatic Stress Disorder

Anxiety disorders, including generalized anxiety disorder, panic disorder, phobias, obsessive-compulsive disorder, and/or posttraumatic stress disorder, may develop among persons with TBI and may be a source of substantial morbidity for persons with these problems and their families. When any of these conditions are present, clinicians should carefully assess patients for comorbid conditions (medical, psychiatric, substance-related, etc.) and environmental factors that may be driving the anxiety symptoms and, when possible, treat such conditions before specifically targeting anxiety symptoms.

We generally prefer to treat complaints of anxiety in these populations with supportive psychotherapy, cognitive-behavioral therapy, and social interventions most appropriate to the specific anxiety disorder with which the patient presents before adding an anxiolytic medication. However, when anxiety symptoms are so severe that they require pharmacological intervention, treatment with SSRIs, benzodiazepines, or buspirone may be needed. Among these medications, we prefer SSRIs for the treatment of anxiety disorders following TBI given their considerable benefits on a host of anxiety disorders in the general psychiatric population and also their relatively favorable side-effect profiles.

When SSRIs fail to produce adequate and sustained anxiolysis, it may be necessary to consider treatment with a benzodiazepine or buspirone. Although benzodiazepines offer the benefit of rapid anxiolysis, their use among persons with TBI is concerning given their tendency to produce a variety of potentially problematic side effects, including memory and motor impairments. The use of these agents as first-line treatments for anxiety is not encouraged. When benzodiazepines are used, agents with moderate half-lives (lorazepam, oxazepam) are preferable to those with very short half-lives (which are highly reinforcing and may produce rebound anxiety between doses) or very long half-lives (which may result in cumulative adverse effects with repeated administrations).

Buspirone appears to carry less risk of worsening cognitive functioning in patients with TBI than benzodiazepines, and use of buspirone is not associated with dependency. Unfortunately, buspirone's therapeutic effects appear to require several weeks to develop, and not all patients respond to this agent. The prolonged latency of action sometimes necessitates short-term treatment with another anxiolytic, usually one of the benzodiazepines, and/or more intensive psychotherapy to keep the patient engaged in the use of this medication.

Psychosis

Typical antipsychotic medications are used commonly to control agitation and psychosis after TBI but are not benign treatments in this population. Side effects such as hypotension, sedation, and confusion are common. Patients with brain injury are susceptible to dystonias, akathisias, and other extrapyramidal side effects—even when relatively low doses of these agents are prescribed. Stanislav

(1997) demonstrated improvement in cognitive performance in brain-injured patients after discontinuation of antipsychotic medications, the magnitude of which appeared to be greater after discontinuation of thioridazine than of haloperidol (an effect attributed to the more prominent anticholinergic properties of thioridazine). Similarly, Sandel et al. (1993) observed new-onset delusions in a TBI patient receiving chlorpromazine for the treatment of agitation after TBI, an effect attributed to the anticholinergic properties of this agent. Antipsychotic medications have also been reported to delay neuronal recovery after brain injury (Hoffman et al. 2008; Kline et al. 2008). Consistent with this observation, Rao et al. (1985) found that patients treated with haloperidol in the acute period after TBI experienced significantly longer periods of posttraumatic amnesia, although the acute rehabilitation outcome did not differ from those not treated with this medication.

Given this literature and the availability of several atypical antipsychotic medications, we discourage the use of the typical antipsychotics among persons with TBI. Unfortunately, there are few reports with which to guide selection among the atypical antipsychotic agents in this population. Michals et al. (1993) used clozapine to treat nine brain-injured patients with psychotic symptoms or outbursts of rage and aggression that had failed to respond to other medications. Three of these patients demonstrated marked improvements in aggression and/or psychosis, three demonstrated decreased agitation and auditory hallucinations, and an adequate duration of treatment was not achieved in three patients. Two of the nine patients experienced seizures during treatment. Burke et al. (1999) also reported improvement in refractory psychotic symptoms after TBI during treatment with clozapine. Schreiber et al. (1998) reported a case in which risperidone treated delusions and sleep disturbance after TBI effectively. Arciniegas et al. (2003) reported improvements in non-delirium-related psychotic symptoms (paranoid delusions, auditory hallucinations) in response to treatment with risperidone in two patients with TBI during the acute rehabilitation period. Guerreiro et al. (2009) reported improvements in posttraumatic psychosis in an individual treated with olanzapine. As this set of case reports suggests, treatment of psychosis following TBI is entirely a matter of empirical trial for each individual patient in which it is attempted. Although there is reason to believe that many patients will respond to such treatments, individually tailored treatment with careful monitoring for treatment-related symptomatic benefits as well as adverse effects is presently the standard of care for persons with psychosis after TBI.

Aggression and Agitation

Discussion of the pharmacotherapy of aggression and agitation is found in Chapter 14, Aggressive Disorders. After appropriate assessment of possible etiologies of these behaviors, treatment is focused on the occurrence of comorbid neuropsychiatric conditions (e.g., depression, psychosis, insomnia, anxiety, delirium), whether the treatment is being undertaken in the acute phase (hours to days) or the chronic phase (weeks to months), and the severity of the behavior (mild to severe). Suggested therapeutic strategy is summarized in Table 35–2.

TABLE 35–2. Pharmacotherapy of agitation/aggression

Presentation/drug	Primary indication
Acute agitation/severe aggression	
High-potency antipsychotic drugs (haloperidol, risperidone)	Acute agitation/severe aggression
Benzodiazepines (lorazepam)	
Chronic agitation	
Atypical antipsychotics (risperidone, olanzapine, quetiapine, clozapine)	Psychosis
Valproic acid, carbamazepine	Seizure disorder, severe aggression
Serotonergic antidepressants (selective serotonin reuptake inhibitors, trazodone)	Depression, mood lability
Amantadine	Under investigation
Buspirone	Anxiety
Beta-blockers	Aggression without concomitant neuropsychiatric sequelae

Apathy

States of diminished motivation, or apathy, are common consequences of TBI (see Chapter 18, Disorders of Diminished Motivation). Diminished motivation or apathy denotes a neuropsychiatric syndrome in which there is a clinically significant decrease in goal-directed cognition, emotion, and/or behavior. Apathetic states occur on a continuum of severity, with states of mildly diminished motivation at one end of that continuum and akinetic mutism at the other end. Determining whether an individual patient's apathy is a symptom of another neuropsychiatric condition such as depression or is instead an independent syndrome is imperative before undertaking treatment.

When apathy is a feature of depression, treatment of the underlying depression with agents such as SSRIs may relieve both mood and apathy symptoms. However, when apathy occurs independently of depression and a pharmacotherapy is required, common clinical experience suggests that psychostimulants and other dopaminergically active medications are the most useful treatments of this disorder. As opposed to their use in depression, the SSRIs are unlikely to improve apathy alone and may actually worsen this problem—highlighting the need to distinguish apathy from depression to the greatest extent possible.

Complicating the evaluation and treatment of apathy after TBI is its common co-occurrence with intermittent behavioral dyscontrol (i.e., disinhibition, impulsivity, and aggression). Family and caregivers sometimes describe patients with this combination of problems as doing very little in general but doing problematic and/or unwanted things when they do anything at all. This seemingly odd combination of behavioral problems may occur in the setting of injury to both the anterior cingulate-subcortical

circuits (resulting in apathy) and the lateral orbitofrontal-subcortical circuits (resulting in a behavioral dyscontrol syndrome). In such circumstances, patients appear apathetic at baseline and demonstrate episodic behavioral dyscontrol when an environmental or somatic stimulus provides enough of a stimulus to drive aggressive and/or appetitive (or other "limbic") behaviors. The combination of apathy and behavioral dyscontrol presents substantial challenges to clinicians attempting to treat such problems: therapies to improve apathy may worsen behavioral dyscontrol, and therapies for behavioral dyscontrol may worsen apathy. Selection of pharmacotherapies for this combination of problems is often guided by the caregivers' tolerance for them or the relative safety risks of each problem for the patient and others: caregivers and environments that are better able to tolerate and manage episodic dyscontrol, and/or those that require patients to be relatively independent in mobility and self-care, may elect to treat apathy despite the risks of increased dyscontrol; environments and caregivers better able to manage the functional consequences of apathy nonpharmacologically may elect to pharmacologically manage dyscontrol even when such treatment worsens apathy. Careful consideration of not only the problematic behaviors but also the caregivers and the environment in which those behaviors occur is essential in the development of an acceptable and effective treatment plan for this challenging behavioral comorbidity.

Sleep

Sleep patterns of patients with brain damage are often disordered (see Chapter 20, Sleep Disturbance and Fatigue). Nonpharmacological approaches are the primary treatments for posttraumatic sleep disturbances; initiating and evaluating the effectiveness of such interventions, including minimizing daytime naps, maintaining regular sleep onset times, and engaging in regular physical activity during the day, is a prerequisite to pharmacotherapy. When sleep disturbances occur, they frequently do so in the context of other posttraumatic neuropsychiatric problems. If a medication is used to treat those other problems, selecting one (or more, when necessary) that also may facilitate normalization of sleep is encouraged.

Among medications used specifically for the treatment of problems initiating or maintaining sleep, trazodone is preferred by many neurorehabilitation specialists: it is a sedating antidepressant medication that is devoid of anticholinergic side effects, does not produced medication dependence, and is generally well tolerated by persons with TBI. A dose of 50 mg should be administered initially; if ineffective, doses up to 150 mg may be prescribed. Short-acting sedative-hypnotics, including zolpidem, eszopiclone, ramelteon, lorazepam, oxazepam, and chloral hydrate, are sometimes used to treat early and middle insomnia as well. These agents are best used for relatively short treatment periods (e.g., several weeks); however, some patients may require and derive benefit from long-term treatment with them as well. When used for longer periods, maintaining vigilance for tachyphylaxis and dependence as well as the possibility of adverse effects on cognition (especially memory), behavior, and motor function is recommended.

Long-acting benzodiazepines should be avoided in this population; if prescribed at all, they should be used with great caution. These drugs interfere with rapid eye movement and stage 4 sleep patterns and may contribute to persistent insomnia. Clinicians also should warn patients of the dangers of using over-the-counter sleeping agents because many of these possess (somewhat or predominantly) anticholinergic properties that may adversely affect cognitive function.

Fatigue

The pharmacotherapy of fatigue is best deferred until treatments directed at improving sleep have been implemented and afforded an opportunity to secondarily improve daytime fatigue. When pharmacotherapy of fatigue and/or excessive daytime sleepiness is required, stimulants (methylphenidate and dextroamphetamine) and amantadine may be useful. Dosages used would be similar to those used for treatment of diminished arousal and concentration. These medications may be of particular benefit in patients with apparent depression after TBI in whom fatigue persists despite improvement in mood during treatment with antidepressants. Despite initial enthusiasm for the promise of modafinil for the treatment of fatigue and excessive daytime sleepiness after TBI (Elovic 2000; Teitelman 2001), a randomized trial of this agent for this purpose failed to demonstrate group-level differences between treatment with this agent and placebo (Jha et al. 2008). Common clinical experience suggests that individual patients may benefit from treatment of this agent; it therefore may be worthwhile to consider an empirical trial of modafinil for individual patients that are unable or unwilling to use stimulants or amantadine for the treatment of posttraumatic fatigue.

Coldness

Complaints of feeling cold, without actual alteration in body temperature, are occasionally seen in patients who have experienced brain injury. This feeling can be distressing to those who experience it. Patients may wear excessive amounts of clothing and adjust the thermostat so that other members of the family are uncomfortable. Although this is not a commonly reported symptom of TBI, Hibbard et al. (1998) have found that in a sample of 331 individuals with TBI, 27.9% complained of changes in body temperature, and 13% persistently felt cold. Eames (1997), while conducting a study of the cognitive effects of vasopressin (DDAVP) nasal spray in patients with TBI, reported incidentally that 13 patients had the persistent feeling of coldness, despite normal sublingual temperature. All were treated with nasal DDAVP spray for 1 month. Eleven of these patients stopped complaining of feeling cold after 1 month of treatment, and one other patient had improvement in the symptom, without complete relief.

Silver and Anderson (1999) performed a pilot study of the effects of intranasal DDAVP twice daily for 1 month among six patients who complained of persisting coldness after brain injury. Five of the six patients had a dramatic response to DDAVP—some as soon as 1 week after initiat-

ing treatment—and no longer complained of feeling cold. This response persisted even after discontinuation of treatment. Patients denied any side effects from treatment with this agent. The authors of this study suggested that DDAVP may reverse physiological effects of a relative deficit in DDAVP in the hypothalamus caused by injury to the DDAVP precursor, producing cells in the anterior hypothalamus, and may thereby correct an internal temperature set point disrupted by the brain injury.

Conclusion

It would be ideal if cognitive impairments, psychosis, depression, anxiety, aggression, and agitation after TBI could be controlled without medications. However, these neuropsychiatric problems are associated with significant distress and considerable functional disability; without treatment, some of these problems may also endanger the patient and others. In many cases, behavioral treatment and cognitive rehabilitation cannot be effective until psychopharmacological interventions are initiated. In other psychiatric conditions such as major depression, there is evidence that delay of effective treatment may result in refractoriness of the condition. Post (1992) reported that recurrent affective disorder becomes more difficult to treat the longer the condition persists. Thus there are theoretical reasons for prompt initiation of pharmacological treatment of psychiatric syndromes in patients with TBI.

In this chapter, we reviewed the role of medication in the treatment of the most frequently occurring neuropsychiatric symptomatologies that are associated with TBI. When appropriately administered, medications may significantly alleviate these symptoms and improve rehabilitation efforts.

KEY CLINICAL POINTS

- Pharmacotherapy of neuropsychiatric disturbances is a potentially effective element of a comprehensive treatment plan for persons with TBI.
- The literature describing the benefits, risks, and side effects of pharmacotherapies for most posttraumatic neuropsychiatric disturbances is underdeveloped. Treatment is therefore guided by application of the available literature, analogy to the management of such problems among persons with other neurological and psychiatric disorders, clinical judgment, and therapeutic collaboration with patients, their families, and other care providers.
- The principles of pharmacotherapy for posttraumatic neuropsychiatric problems include identification and prioritization of functionally relevant target symptoms; judicious dosing of medications ("start low, go slow"); development of all treatments using an empirical trial model; systematic and regular reassessment of treatment effects, both beneficial and adverse; vigilance for drug-drug interactions; and consideration of augmentation approaches to partial treatment responses.

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CHAPTER 36

Psychotherapy

George P. Prigatano, Ph.D.

The National Institutes of Health's 1999 Consensus Conference on the rehabilitation of persons with traumatic brain injury (TBI) concluded that psychotherapy is an important component of comprehensive rehabilitation. In their published consensus statement, the following observation was made: "although the use of psychotherapy has not been studied systematically in persons with TBI, support for its use comes from demonstrated efficacy for similar disorders in other populations" (National Institutes of Health 1999, p. 978).

Psychotherapy is defined as the process of teaching patients to learn to behave in their own best self-interest, not selfish interest (see Prigatano 1999 for a more detailed discussion of this definition and its implications). This process is achieved through establishing a working or therapeutic alliance with the patient and treating the patient in light of some basic facts about human nature before and after brain injury. It also requires that the psychotherapist have a good understanding of how various brain disorders at different stages of development influence cognitive capacities, as well as emotional and motivational responses.

"Psychotherapy can be one of the most practical types of assistance to offer another human being, or an incredible waste of time, energy, and money" (Prigatano 1999, p. 201). Much depends on the knowledge and clinical skill of the psychotherapist and the cognitive capacity and emotional and motivational characteristics of the patient. Effective psychotherapy requires that both parties have the willingness and commitment to face the truth in their lives. Once the patient obtains reasonable insight into the nature of his or her problems, practical efforts to change behavior are necessary in order for the patient to truly benefit from such a dialogue.

My goal of this chapter is a practical one. I will attempt to discuss and build upon Pollack's (2005) suggestions for conducting psychotherapy with persons who have suffered TBI. I will not review the various types of psychotherapies that can be found in the literature (e.g., psychoanalysis, psychoanalytic psychotherapy, brief psychotherapy, family therapy, cognitive-behavioral therapy). A description of these therapies can be found elsewhere (e.g., Sadock and Sadock 2003). To date, there have not been systematic studies comparing the efficacy of these treatments with the different subtypes identified within the TBI population. What follows is a summary of clinical observations that have emanated from conducting neuropsychological rehabilitation with persons with TBI (Prigatano 1986, 1999).

Psychotherapy With Persons Who Have Brain Injury: Lingering Doubts

Brain damage of various types can negatively influence a person's ability to abstract, self-monitor, tolerate frustrations and anxiety, and remember what was discussed during a previous psychotherapy session. Pollack (2005) noted that there have been lingering doubts about whether psychotherapy can be meaningfully applied to help people with moderate to severe TBI. Aware of these problems, the psychotherapist can use them to guide the dialogue with the patient. When developing a neuropsychological rehabilitation program (Prigatano 1986), I had brought to the patients' attention that some of my colleagues have questioned whether psychotherapy could be helpful to them (Prigatano 1986). Given the typical neuropsychological problems associated with various brain disorders, I told patients we needed to establish some guidelines on how we would proceed when attempting psychotherapy. We agreed that each psychotherapy session, be it individual or group psychotherapy, would begin with a review of the purpose of that session for the patient. This would be followed by prompts from myself (or other members in the group) to help remind a patient of what was said in a previous session. It was also a time to help clarify if there was a miscommunication during a previous session. After brain injury, individuals can get easily upset, and therefore I would go slowly, or change topics if need be, to avoid intense negative reactions that would disrupt the session. At the end of each session, the patients (often referring to

their notes) would begin by summarizing what was said during the session. Therefore, at the end of each session, patients would be assisted in writing one or two sentences in their memory books that summarized the essence of what was important to them in that session.

This approach to using memory compensation techniques in the therapy session served two purposes. First, it gave patients an opportunity to access (and therefore experience the benefits of) compensation techniques in their daily life. Second, it built a working or therapeutic alliance between (some) patients and their psychotherapist. It demonstrated that the psychotherapist was invested in promoting the effectiveness of psychotherapy for the patients. Also, the patients' responsibility to this process was made clear by their willingness to use compensatory techniques.

Starting Psychotherapy Sessions

Within the context of a day treatment neuropsychological rehabilitation program (Prigatano 1986), individual and group psychotherapy sessions would begin with the psychotherapist asking the patient or patients what they wished to discuss during that session, in light of what was previously reviewed. Many times, the review of previous material did lead into a continuation of a previous discussion, but in some instances it did not. The patient might become tangential or confused over what the next topic would be. During these times, the psychotherapist would take the lead in clarifying what was said, at times moving the discussion to the "next level." The psychotherapist might also shift topics that would be relevant to the patient's care at that point in the patient's rehabilitation. The failure of the patient to reconstruct in a clear way what was previously said, even with the presence of notes, does not necessarily represent resistance to the psychotherapeutic process. It frequently reflects the problems that patients have in abstract thinking, memory, and initiating a logical discussion. Patients were told that if it was difficult for them to bring up a topic on any given day, the psychotherapist would attempt to lead the discussion. A list of 26 topics was identified, and these were addressed in the context of group psychotherapy with TBI patients (Prigatano 1986).

It is the responsibility of the psychotherapist to help patients use appropriate compensations to review and discuss the content of therapy sessions. Taking these steps may circumvent many of the problems caused by brain injury that can negatively impact the psychotherapeutic process and serves to strengthen the psychotherapeutic alliance.

Finding Areas of Mutual Experience

Pollack (2005, p. 642) noted that the "starting point" of all psychotherapy is to "find areas of shared meaning" to help reduce the patient's loneliness and social isolation. Psychotherapy initiates the process of talking about (and experiencing) thoughts and feelings that influence a patient's behavior and sense of well-being in life after brain injury. Because many patients with moderate to severe TBI have difficulties with word retrieval and articulating their ideas in a clear and concise way (Prigatano 1986), verbal communication is only partially helpful in psychotherapy with brain-dysfunctional patients.

Other methods have been used to aid the psychotherapeutic process (Prigatano 1986). Having patients relate to symbols that reflect thoughts and feelings about their existential situation is important (Prigatano 1991). For example, some TBI patients may not know where to begin discussing the myriad fragmented and confusing thoughts and feelings they experience after their brain injury. Patients also come from different cultural backgrounds in which discussing feelings may be difficult. In therapeutic work in Oklahoma with a group of cowboys and oil-field workers who sustained TBI, the use of music within the context of group psychotherapy proved to be a powerful aid to the therapeutic process (Prigatano 1986). Patients were asked to bring in their favorite song. The psychotherapist did the same. The ground rule was that no one would discuss the psychological significance of a person producing a certain song, but rather group members would discuss the feelings that were generated in them by listening to the song that someone else picked. This was not a "technique" of psychotherapy. It was a method for facilitating entering each other's phenomenological field in a nonthreatening way. This approach has proved to be extremely helpful, and if introduced at the proper time can reduce social isolation and help patients begin to discuss important emotions that are stimulated by the lyrics and the tone of various songs.

Over the years, other methods of expressing thoughts and emotions have been shown to be helpful. Patients have written poems (Prigatano 1986), done drawings and paintings (Prigatano 1986, 1999), and told stories (Prigatano 1991) that reflect their culture, their personal background, and what they experience "right now" as it relates to the impact of their brain disorder on their life. These art forms have been helpful in conveying what the patient experiences and often provide a connection with the treating psychotherapist. Again, the use of these art forms is not something that is a technique. They become a natural form of human expression within the context of potentially psychotherapeutic dialogue.

Goldstein (1952) noted that many patients with brain dysfunction try to reduce disorder in their life and thereby avoid the catastrophic condition (Pollack 2005 discusses this point in some detail). These art forms use symbols to maintain order and meaning to the patient's life. Psychotherapeutic work with young adults who have suffered brain injury and have lost meaning in life has suggested that three symbols may be important for them. These are the symbols of work, love, and play (Prigatano 1989, 1999).

The Purpose of Psychotherapy

Traditionally, psychotherapy has focused on reducing symptoms of anxiety, depression, and interpersonal conflict between people. It is geared to helping people have an acceptable sense of self, meaning that they feel comfortable with who they are (Pollack 2005). Individuals with moderate to severe TBI are often psychologically lost, or at

a minimum, confused about their life. Their purpose and direction are unclear. They have lost the acceptable sense of self (Luria 1972; Pollack 2005). To help these individuals to reconstruct their lives, psychotherapy can assist them in relating to the symbols of work, love, and play, even though doing so is a highly individual process (Prigatano 1999).

These symbols are important in Western culture because a person's ability to work suggests that the person is able to be productive and potentially self-sustaining. Work, or the act of producing something, provides an important sense of accomplishment. It also provides an important social contact in that work puts a person in touch with other people and often is a way of shared meaning with others.

The ability to love is, of course, the most important symbol that has to be related to in adult living. It translates into our capacity to be empathetic to others' needs and situations, something frequently compromised after TBI (Prigatano and Maier 2009). It allows us to show joy and pleasure in others' accomplishments and sense of personal well-being. When we are able to work and to love, we are able to begin to function again in a normal fashion.

However, people who work and love may still have a sense of depression or emptiness about life. They may not be living the life they want to live. They can become depressed and angry. Dr. Yehuda Ben-Yishay years ago made the comment: "You cannot be a sourpuss and be rehabilitated" (cited in Prigatano 1999, p. 244). What he meant by this is that you have to get past the anger and the depression in order to be meaningfully rehabilitated. This means the capacity to relate to symbols that help you become the individual that you are within the context of a given culture and time. The symbol of play highlights this psychological goal (see Prigatano 1999 for further discussion of this point).

The purpose of psychotherapy after brain injury is, therefore, very clear: to help the individual to become productive, to establish mutually satisfying interpersonal relationships, and to do so in a way that is true to the person's individuality, and therefore his or her ability to have joy and maintain the playful attitude in life. Outcome measures on the effectiveness of neuropsychological rehabilitation (which include psychotherapeutic interventions) must find objective and subjective markers of whether these important goals have been met (Prigatano and Pliskin 2003).

The Patient's History Before the Brain Injury

Working with patients in the context of a day treatment, holistic neuropsychological rehabilitation program brings into clear focus the fact that their premorbid personality characteristics are interacting with the brain injury to produce the various symptoms that are observed after the brain injury. While the severity, location, and type of brain injury will produce predictable neuropsychological and psychiatric disturbances (see Prigatano 1999; Prigatano and Maier 2009), these disturbances are always interacting with the premorbid characteristics of the patient (Prigatano 1999). Therefore, one must know the patient reasonably well and how he or she functioned before the brain injury to conduct meaningful psychotherapy with the patient after the brain injury. It is for this reason that the patient's history, as told by the patient, must guide the psychotherapeutic process.

Taking Time to Listen to the Patient's Story

In his memoirs, Carl Jung (1965) had the following to say:

> Clinical diagnoses are important since they give the doctor a certain orientation; but they do not help the patient. The crucial thing is the story. For it alone shows the human background and the human suffering, and only at that point can the doctor's therapy begin to operate. (p. 124)

Every human being has an important story to tell about his or her life. The story or stories (as is commonly the case) reflect how the person responded to unexpected events in life and how the person viewed those experiences. These experiences often are crucial in how the person subsequently develops (before and after the brain injury). After any significant loss, a person often reflects on those stories and what they have told the person about life and how to deal with life in an adaptive fashion. At times old beliefs, values, and relationships are held in question when they no longer guide the individual in dealing with present life circumstances. Jung was especially aware of this and tried to have individuals deal with their life's problems in light of their cultural and religious backgrounds.

When a person seeks help with the effects of brain injury, the psychotherapist must be armed with a very good knowledge of human nature and behavior by understanding animal behavior, reinforcement or learning theory, and analytic psychology, as well as psychodynamic theories (Prigatano 1999). It is for this reason that the psychotherapist must be flexible in how he or she approaches persons with TBI at a given time in the rehabilitation process. As Pollack (2005) noted, "successful psychotherapeutic work with people who have experienced a brain injury usually requires that the therapist use several different approaches to treatment" (p. 643).

The Problem of Lost Normality After TBI and the Realities of Life

While persons with a history of TBI may face a variety of neurological and neuropsychological disturbances, a common experience is that they are not the way they used to be. They are changed, even though they may not be fully aware of how they have changed. A core issue in psychotherapy of persons with moderate to severe TBI is to address this issue of lost normality (Prigatano 1999). This requires a knowledge of the patient's neuropsychological deficits, which may include a disturbance in self-awareness. The psychotherapist must also have an informed understanding of the realities of a given patient's life. Is it probable that the patient will become independent with rehabilitation? Can the patient be

gainfully employed, and if so, in what work capacity? What types of emotional changes are necessary for the patient to accept a lower salary or less job responsibilities? Is the patient only capable of voluntary work, and at what level? How can the therapist help the patient see these realities and adjust to them in the most positive manner possible?

A strict behavioral or even cognitive-behavioral approach often fails to understand the patient's confusion and psychological suffering associated with dealing with these existential realities. Those approaches do not focus on the patient's shattered sense of self, loneliness, and loss of meaning in life, nor do they adequately consider the historical influences and the patient's subjective experience. Understanding these issues is necessary to reducing the patient's feelings of social isolation.

Practical Considerations and Tactics for the Psychotherapist

Pollack (2005) suggested that specific tactics be used in the psychotherapeutic process with persons with TBI. These suggestions are reproduced, with permission, in Table 36–1. In italics are additional comments made to further expand on this insightful table. Although the table will not be reviewed in its entirety in this section, many of the points made by Pollack are discussed elsewhere in this chapter. The reader is encouraged to review this table periodically as a helpful reminder of things to attend to in the process of doing psychotherapy with brain-dysfunctional patients.

Basic Facts About Human Nature With Which Psychotherapists Must Be Familiar

Behavior is a function of its consequences or lack thereof (Skinner 1938). It is driven by biological urges that are modified in their expression by culture and language (Luria 1979). Hebb (1974) noted that while human beings can be rational to their approach to problem solving, they are inherently irrational. Emotional attachments, or bonds, become crucial for survival and greatly influence interpersonal behavior throughout the life span.

In addition, people often trust their own subjective experience to be true as opposed to other people's opinion. Their subjective experience, therefore, guides their behavior. Psychotherapists must understand that the adaptive management of sex and aggression in a given society for a given individual at different stages of the life cycle is crucial for the individual's psychological sense of well-being. The psychotherapist should be mindful of the fact that all humans fight for some form of territoriality, and this is also a residual of their animal heritage (MacLean 1973).

Furthermore, symbols are powerful guides to behavior for the better or for the worse (Jung 1964). Understanding what symbols individuals relate to will provide useful insights as to their motivations and what they are willing to sacrifice for.

Psychotherapists must understand that human consciousness evolves to guide brain function and to expand the adaptive choices individuals face (Sperry 1969). In this context, human beings search for meaning in life to deal with suffering and losses. This brings the psychotherapist into close proximity with issues of philosophy and theology, and the psychotherapist must be comfortable in navigating through these issues with patients of different religious and philosophical backgrounds.

Finally, the psychotherapist has to face the fact that not all behavior is consciously motivated. There seem to be unconscious motivations that influence what people do and when they do it. Many behaviorists may disagree with such a statement, citing a lack of evidence. However, common experience in insight-oriented psychotherapy with individuals over a prolonged period of time reveals many instances in which the individual "discovers" motivations that he or she had not been previously aware of. The mechanisms of denial, repression, rationalization, and so on are real clinical phenomena and suggest that there is indeed an unconscious component to one's mental functioning that by nature is not easily accessed but clearly influences what one does. Understanding these "basic facts" about human beings can be helpful when working within the context of psychotherapeutic dialogue.

Special Problems Associated With Brain Injuries

Special therapeutic problems and management issues associated with psychotherapy for persons with TBI have been identified (Pollack 2005). The phenomena of transference and countertransference are extremely relevant and have to be carefully managed. The catastrophic reaction associated with various brain disorders is often not properly understood, and yet can have a great impact on the patient's overall adjustment (Goldstein 1952). Neuropsychological rehabilitation must begin with an effort to understand this reaction and to reduce the patient's emotional distress and confusion in order to engage the patient in psychotherapy as a part of the broader rehabilitation enterprise.

Pollack (2005) described the problem of denial after TBI, which deserves further discussion in light of recent theoretical and empirical advances. It has been long recognized that some people with severe TBI appear unaware of their neuropsychological problems, even after the period of posttraumatic amnesia resolves. A growing literature suggests that impaired self-awareness (ISA) after TBI relates negatively to both the process and outcome of rehabilitation (see Chapter 19, Awareness of Deficits). ISA is associated with treatment compliance and later employability (see Prigatano 2008). It is also associated with numerous behavioral problems (Bach and David 2006). Some have observed that patients with ISA may not change or may be very resistant to change during the course of rehabilitation (Ranseen et al. 1990; Schönberger et al. 2006). Strict behavioral approaches have not shown that an increase in error detection monitoring translates into improved self-awareness (Ownsworth et al. 2006).

I have suggested a model that equates a complete syndrome of ISA with traditional anosognosia (Prigatano 1999).

TABLE 36–1. Suggested tactics for the psychotherapeutic process

Tactic	Description
Gain a historical perspective	Obtain information from family, friends, employers, and teachers concerning preinjury growth and development, health, education, occupation, personality, interests, values, goals, and impediments. *Specifically, include a discussion of the patient's favorite fairy tales, stories, music, and topics that help mold the patient's personal life. Understand key and early memories that seem to influence how the patient approaches key relationships in life. Clearly understand the patient from a cultural and psychodynamic perspective.*
Find areas of shared meaning	Determine what having a brain injury means to the patient and how he or she perceives its effects. At first, the psychiatrist *(or psychotherapist)* may have to take the initiative, explaining the mechanism of traumatic brain injury in simple terms, relating the patient's difficulties to the injury, and describing the problems, events, and so on that can be expected in the future.
Encourage the patient to take the lead	Concentrate on the concrete real-life difficulties that the injury has caused the patient. Early in treatment, focus on the here and now, avoid discussing the past (it requires good memory, and it is over), avoid discussing the future (it requires the ability to abstract, and at this point it is beyond comprehension). *However, be prepared to discuss topics that you suspect are relevant to the patient's neuropsychological and psychosocial difficulties, even if the patient cannot articulate them on certain days.*
Help the patient develop simple coping strategies	For example, suggest that the patient keep a notebook, follow a sequence of predetermined steps, rest before becoming too fatigued, request that a confusing message be repeated slowly and in simpler terms, set up priorities for a series of necessary tasks. *Through cognitive rehabilitation exercises, demonstrate how compensations are helpful, but be mindful as to their cost in terms of time and energy.*
Manipulate aspects of the environment to enable the patient to function more effectively	For example, suggest organizing household equipment, utensils, dishes, and so on in a systematic fashion; labeling drawers and closets; using an alarm or calendar watch. *Teach the patient to use a memory compensation notebook during the process of psychotherapy.*
Mobilize assistance	Mobilize the assistance of family members, employers, teachers, and friends to help keep the social and work demands as noncomplex and as manageable as possible. *Work at developing a strong working alliance with key family members.*
Build on the patient's assets	Build on the patient's remaining assets and avoid focusing on the residual deficits. Do not make every task seem like a test. *But "keep in front of the patient" in a therapeutic way what, in fact, are the patient's neuropsychological deficits that he or she must deal with on a daily basis. This touches on the important issue of separating denial from unawareness after traumatic brain injury. Focusing on issues that the patient denies may only cause more irritation. Reducing unawareness, however, will greatly assist the patient.*
Engage the patient in meaningful goal-directed activities	Use members of professional groups that are action oriented, such as actors, dancers, and artists, in addition to the more traditional rehabilitation staff. *Include voluntary work trials if possible. Therapists working with the patient in various therapies should go to the work trial to determine how the patient actually performs, and to use this as important information in individual and group psychotherapy.*
The patient's world may differ from that of the psychiatrist	Interpret the meaning of behavior with caution. Provide guidance to improve inappropriate behavior with authority. *Again, the problem of impaired awareness vs. denial of disability must be kept in mind when working with these patients and their family members.*
Maintain flexibility	Many patients are adolescents or young adults in various stages of development; for most of these patients, some improvement in physical condition and cognitive function can be expected over time. Remember that a patient's abilities and emotional state can vary from moment to moment depending on preceding events, the character of the task, the degree of alertness and motivation, and the environmental conditions. *To help maintain flexibility, periodically obtain consultation from other psychotherapists to get their view on how to manage difficult problems with the patient.*
Recognize that the approach to therapy should change as the patient changes	This should happen both within and across treatment sessions. Ideally, the treatment approach should move gradually from one that is concerned primarily with the management of concrete, here-and-now, practical problems to one that places greater demands on the patient to consider psychodynamic issues. *This insightful point needs to be revisited repeatedly.*
Instill hope	Instill hope in the patient and family without expressing unwarranted optimism. *The hope must always be realistic in nature in order for it to be helpful to the patient and the family.*
Measure the outcome of your clinical interventions	*Measure outcome in both objective and subjective terms to determine the value of this service for patients. This becomes crucially important for future funding (see Prigatano and Pliskin 2003).*

Note. Present author's modifications to the original suggestions by Pollack (2005) are shown in *italics.*

Source. Adapted from Pollack IW: "Psychotherapy," in *Textbook of Traumatic Brain Injury*, 1st Edition. Edited by Silver JM, McAllister TW, Yudofsky SC. Washington, D.C., American Psychiatric Publishing, 2005, pp. 641–654. Used with permission.

Theoretically, for a patient to have an anosognostic condition, bilateral cerebral dysfunction needs to be present. When bilateral dysfunction reduces or never occurs in the first place, then partial symptoms of impaired awareness can be identified. With partial knowledge of one's neurological and neuropsychological limitations, one can use both defensive and nondefensive methods of coping.

Social Isolation and Loneliness After Moderate to Severe TBI

Some TBI patients experience a deep sense of loneliness (Pollack 2005). Understanding this phenomenon and its relationship to addiction is important for successful psychotherapeutic work. For example, MacLean (1985) noted that in mammals a "separation cry" occurs when the infant is removed from its mother. Cutting the cingulate-thalamic connections abolishes this reaction. MacLean (1985, 1987) argued that this connection is important for the expression of distress associated with forced isolation that threatens survival. He suggested that various illicit drugs used in Western culture directly act on the neurotransmitters in these regions. The basis of drug abuse in our society, therefore, may have something to do with the distress experienced by emotional isolation. People with brain injury may be prone to various addictive behaviors if the problem of social isolation is not effectively dealt with.

To help the patient reduce social isolation, the therapist may use a variety of methods tailored to the individual patient's interests and abilities. Involvement in group interaction, particularly within the context of group psychotherapy, may be an important first step to providing social feedback to the patient within a safe environment. Group psychotherapy may include specific training at reading social cues and learning appropriate social responses. Once psychotherapy is completed, support groups may be helpful in providing social interaction with others who understand the context for the individual's social behaviors. Before the patient resumes regular employment, voluntary work trials may assist the patient gain social experience within the context of the work environment. Clearly, a major goal of neuropsychological rehabilitation is to reduce psychosocial isolation in both adults (Kozloff 1987) and children who show a decrease in number of friendships associated with more severe injuries (Prigatano and Gupta 2005).

Perplexity: Living With Long-Term Cognitive Dysfunction

Perplexity is low-grade confusion. This ongoing confusion results in social withdrawal and inappropriate responses. Follow-up of patients for 10–15 years post-TBI suggests that many of them experience daily frustrations with memory difficulties, word retrieval problems, and inappropriate comments. They become progressively disillusioned and humiliated by their difficulties and consequently seek out a more isolated existence. Engaging patients in activities that they can manage becomes important in reducing the social isolation and perplexity they experience. Principles of neuropsychological rehabilitation that are applied in early stages after brain injury should also be kept in mind when managing these patients over their lifetime (Prigatano 1999).

Conclusion

In this chapter, I have attempted to revisit and modestly expand on some of the important observations made by Pollack (2005) in his chapter on psychotherapy in the first edition of this book. It is hoped the definition of psychotherapy offered in this chapter makes it clear that psychotherapy is not the purchase of friendship (Schofield 1964) or simply healing via persuasion (Frank and Frank 1991).

The approach to psychotherapy described in this chapter suggests that much more is needed than behavioral therapy. The goal is not simply behavioral change, but rather productively and creatively dealing with the complex emotions and motivations that a person experiences when adjusting to the effects of brain injury in his or her life. It is for this reason that both civilians and returning veterans from war need neuropsychological rehabilitation programs that incorporate psychotherapeutic interventions for them and their family members. Behavioral modification programs in and of themselves are not enough.

KEY CLINICAL POINTS

- The psychological suffering that many brain-dysfunctional patients experience cannot be adequately treated with purely behavioral or cognitive-behavioral techniques.
- Psychotherapy with brain-dysfunctional patients is possible if one understands their subjective experience and guides them through the rehabilitation process.
- Taking time to listen to patients' life stories and help them relate to symbols that have guided their lives prior to their injury (i.e., their behavior, values, cognitions) is crucial to the psychotherapeutic process.
- Managing the catastrophic reaction using various approaches ultimately helps the patient to learn greater self-control and reestablish a sense of well-being.

- Psychotherapy with brain-dysfunctional patients requires that the treating clinician have a very good knowledge of human nature and behavior, attained by understanding animal behavior, reinforcement or learning theory, and analytic psychology as well as psychodynamic theories.
- The central goal of psychotherapy with brain-dysfunctional patients is to help them to deal with the problem of lost normality after brain injury and avoid social isolation.
- Several specific tactics should be kept in mind when working with these individuals, but they are not a replacement for clinical judgment that only comes with experience and commitment to the process and outcome of psychotherapy.
- Psychotherapy will not become a fully funded service for brain-dysfunctional patients until there is adequate evidence that such interventions lead to better outcomes from both a personal and a societal perspective.

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CHAPTER 37

Cognitive Rehabilitation

Wayne A. Gordon, Ph.D.

THIS CHAPTER IS ADAPTED FROM THE LEONARD Diller Lecture that I was asked to give at the annual meeting of the Rehabilitation Psychology Division of the American Psychological Association in April 2008. In that talk, I drew on my long history of research collaboration with pioneers of cognitive rehabilitation research at New York University (NYU) Medical Center, particularly Leonard Diller, Yehuda Ben Yishay, and Joe Weinberg. In this critique of our current knowledge base with respect to cognitive rehabilitation, I begin with a brief look at the earliest studies conducted at NYU and then proceed to a summing up of where we are now, with an attempt to summarize what has been learned and what still needs to be accomplished.

Early Studies at NYU Medical Center

Cognitive rehabilitation research began to emerge in the late 1960s and early 1970s at NYU Medical Center in New York City. At that time a group of researchers and clinicians led by Leonard Diller tackled the prevailing nihilistic perspective on brain injury, which was that since neurons do not regenerate, people with brain injuries could not relearn cognitive skills that they had lost. (This view still exists today, but to a lesser extent.) In the minds of bench scientists and also within the treating professions, no distinction was made between such terms as *recovery, spontaneous recovery,* and *improvement,* on the one hand, and *learning,* on the other. Thus, studying whether brain-injured persons can learn to perform tasks that have been affected by their brain injury was a direct assault on the conventional wisdom.

In the early years, three types of studies predominated: 1) task and process analyses of cognitive tasks, 2) exploration of whether brain-injured individuals could learn to do cognitive tasks that challenged them, and 3) examination of the functional, diagnostic, and treatment implications of visual neglect. The first and second lines of inquiry were accomplished by using a phenomenological approach in performing task analyses, in which the task was subdivided hierarchically into its components. Then, to examine the process of performance, individuals were observed while they were performing visual motor tasks, such as block design. Every maneuver that the person made with each block that was touched was noted. In this way, it was possible to examine the differences in the way that left-brain-injured, right-brain-injured, and non-brain-injured individuals approached the task. It was found that competence fell along a continuum, in that failure in brain-injured individuals was not random but instead was a function of task difficulty. One difference that emerged in study participants was that failure occurred sooner and more frequently in brain-injured than in non-brain-injured individuals (Ben-Yishay et al. 1970).

It is interesting that the way in which brain-injured individuals went about completing cognitive tasks was not that different from that of non-brain-injured individuals. Specifically, the types of maneuvers they made both in tasks they failed and in tasks they completed were no different than those made by people without a brain injury. However, when they failed tasks, compared with those with left-brain injuries, right-brain-damaged people tended to take longer to complete the task and used fewer strategies; that is, they were more haphazard in their approach to the task. They also used fewer maneuvers than did left-brain-damaged or non-brain-injured individuals. They tended to explore less and were more disorganized in their approach to the task when they were failing than when they were succeeding (Ben-Yishay et al. 1971). These analyses of process suggested that there was no such thing as a "brain-damaged style," as extensive differences were *not* found in the way in which brain-injured and non-brain-injured individuals performed the task (Ben-Yishay et al. 1974).

In another set of studies, my colleagues and I explored approaches for facilitating competence in a variety of neuropsychological tasks. In the first, we sought to determine the degree to which brain-injured people could learn to respond correctly to neuropsychological test items to which

they previously had not given the correct response, by providing cues to facilitate competence on failed items. This cuing method was developed by, once again, performing a phenomenological analysis of the task. In other words, the task was broken down into its constituent components, and a hierarchy of cues was developed. On failed items, individuals were given cues to the point that they were able to pass these items. The process began by giving the person the cue that provided the most information, and, if the person passed, with each successive item, information was removed. At the end of the sequence, the person was able to pass the previously failed design without any cues. The process was then repeated, but rather than being given all the information needed to pass the design, the person was provided only that information that was sufficient for them to pass. More specifically, the same cues were provided in reverse order, so that information was added incrementally until the person was able to pass a previously failed item. This process was repeated several times. In essence, one part of the learning paradigm was a considerable dose of practice. We labeled this approach to cuing *saturation cuing* (Diller et al. 1974), which is similar to the more recently developed approaches of *vanishing cues* (Gilsky et al. 1986) and *errorless learning* (Clare and Jones 2008).

What was learned from this series of studies published by Diller, Ben-Yishay, Weinberg, and colleagues was that brain-injured individuals could learn tasks they initially failed and thereby significantly increase their level of competence. However, the researchers also found that right-brain-injured individuals, although more competent than they were before they were trained, remained more disorganized and less persistent in their approach to the task than non-brain-injured individuals. It was also found that learning generalized to similar tasks. For example, training to perform block design generalized to object assembly tasks and to other aspects of function, as evidenced in a statistically significant improvement in the scores on tests of related tasks. This was found to translate clinically. For example, descriptions of patient behaviors in the chart notes of occupational therapists contained more positive statements after training than they did before. In addition, in a small sample of patients who were videotaped while they were eating, Diller et al. (1974) found that their approach to the task was more organized following training.

This phenomenological approach to breaking down cognitive tasks into their components was applied to conceptual tasks such as similarities, to tests of psychomotor speed such as the Purdue Pegboard Test, and to attention tasks. Each task that was chosen for training was selected because it reflected a specific domain of cognitive function. This process raised many questions. For example: In treating patients to restore cognitive function, how many tasks or skill domains does one need to address? Does each domain need to be treated in each individual? If one were to conceptualize human skills as being organized like the periodic table, would one need to train a skill in each column? Does skill training generalize to tasks within a domain, across skill domains, and to day-to-day function? How do the many domains of skill training become integrated into a unified whole? Does skill training affect day-to-day function?

At the same time that this work was proceeding, Diller, Ben-Yishay, Weinberg, and colleagues were also intrigued by the phenomenon of visual neglect. They were interested in the person who, for example, was only able to read the right side of a page (not the left), the man who shaved only one side of his face, or the woman who put lipstick on only one side of her mouth. They found that making errors on a visual cancellation task was strongly correlated to functional activity, for example, transferring in and out of a wheelchair (Diller et al. 1972) and having inpatient accidents such as falls (Diller and Weinberg 1970). Subsequently, they found that systematic training in which people were taught to anchor their visual search on their impaired side resulted in improved scanning behavior on visual scanning tasks, and that this generalized to tasks like reading words, simple arithmetic, and reading comprehension (Weinberg et al. 1977, 1979). Additionally, people whose scanning behavior improved spent more time reading. In current terms drawn from the International Classification of Functioning, Disability and Health (World Health Organization 2001), treatment was found to have an impact on aspects of both activity and participation (Gordon et al. 1985).

Current Assessment of Cognitive Rehabilitation

Keith Cicerone and members of the American Congress of Rehabilitation Medicine's Brain Injury Special Interest Group have reviewed more than 270 manuscripts, evaluating the quality of each study and describing the level of evidence available in remediating the disorders of attention, memory, language and communication, visuospatial disorders, executive dysfunction, apraxia, multimodal programs, and comprehensive holistic programs (Cicerone et al. 2000, 2005). Specifically, they classified 18% of the studies reviewed as Class I (using American Association of Neurology criteria; Edlund et al. 2004), 17% as Class II, and 65% as Class III. Their grading of papers suggests the extent to which methodological flaws in the design and the implementation of studies over the past several years threaten the internal and external validity of study findings. However, although the classification or grading of research studies may serve as a guide to the confidence one can have in the findings, classification is not a guide as to what works. It does not shed light on what can easily be translated into clinical practice or whether a given methodology is one that can be applied across multiple studies.

How one views what has emerged from these extensive reviews depends on the eyes of the beholder. On the one hand, in some areas of cognitive function, sufficient information has been derived from current studies to provide a basis for the development of practice guidelines in some areas of cognitive function. For example, strong evidence suggests that cognitive remediation helps individuals improve their function across multiple domains of function (e.g., attention, memory, and language). On the other hand, the methods that have been developed are highly diverse and stem from multiple theoretical and nontheoretical approaches, which limits what specifically can be "sug-

gested." Thus, from both clinical and scientific perspectives, the field is limited by the current state of knowledge. Specifically, from a clinical perspective, no gold standard or approach that is tried and true has been established to treat any area of cognitive dysfunction. Consequently, treatment remains largely idiosyncratic to either the treater or the institutional setting delivering the treatment. The clinician seeking to treat a patient's memory or attention difficulties, for example, is left in a quandary as to what treatment approach to apply, because no standard of care has emerged.

From a scientific perspective, the scaffolding upon which to build an information base does not exist. Instead, too many studies go on their own, de novo, failing to build on what came before. The consequence is that among the many bases on which treatment development has relied, none has been shown to be better than any other. As a result, no approach to treatment has emerged triumphant.

Outcome Measurement in Cognitive Rehabilitation

What is just as disturbing as this disorganized, nonsystematic growth in our field is the limited development of outcome measures to examine changes in function that may occur secondary to cognitive interventions. More than 20 years ago, I wrote that the *sine qua non* for judging the effectiveness of any intervention is documentation that intervention-relevant changes at lower levels of functioning, such as in neuropsychological tests, generalize to "real life" (Gordon 1987). While a relatively nearsighted view of outcome, with a focus on change relatively proximal to the site of intervention, may be appropriate if one is examining a theory-based issue or studying the learning of a specific skill, it still remains that altered performance on tests is a long way from—and with an unknown relationship to—performance in the real world.

Thus, consideration must be given to the appropriate level of outcome analysis when examining specific questions with regard to the effectiveness of an intervention. For example, are neuropsychological tests useful as outcome measures in clinical trials? The answer to this question depends on the purpose of the trial. For example, if a drug is hypothesized to improve memory function, it may be appropriate to use a score on a neuropsychological test of memory to document outcome (Silver et al. 2006). The reason for this is, in part, because the U.S. Food and Drug Administration requires a single endpoint when reviewing a drug. However, this approach is limited because, as noted earlier, it is not known how improvement on a test score is related to improvement in function. Thus, it would be a misstatement to claim that memory had been improved as a function of the intervention. Instead, one can, rather trivially, claim that a test score measuring a specific aspect of memory function has changed.

As Alderman and colleagues have noted, it is unfortunate that the ecological validity of neuropsychological tests (referring to the relationship between performance on these tests and real life) has not been systematically examined (Alderman et al. 2003; Burgess et al. 2006). Several responses to this lack have emerged, the first from Alderman and coworkers themselves. They developed the Multiple Errands Test (MET) to describe the level of executive deficits of individuals with brain injury in the context of carrying out everyday tasks (Alderman et al. 2003). This test examines the performance of the individual in standardized situations (e.g., purchase of a specified item in a store or locating a business from the directory of a building). The test has been found to be sensitive in discriminating between different types of deficits in executive function. At present, the use of the MET is limited because scoring criteria have not been validated, and a format that can be used beyond the environment in which the MET was developed has not yet been created.

Another alternative to neuropsychological tests is the Assessment of Motor and Process Skills (AMPS) developed by Merritt and Fisher (2003). This measure consists of a set of daily life tasks of graded difficulty. Performance on the test has been found to be moderately correlated with cognitive function (Bouwens et al. 2007) and to be sensitive to the effects of rehabilitation (Waehrens and Fisher 2007). The test is somewhat limited in that it must be administered by an AMPS-certified occupational therapist, and it is relatively narrow in its focus, as most of the AMPS tasks involve some type of homemaking activity. Thus, while the AMPS has promise as an outcome measure, its widespread application is limited by restrictions placed on its use and by the limited domains of life being tapped.

Finally, the Canadian Occupational Performance Measure (Law et al. 2005) examines goal attainment in three areas of performance: self-care, productivity, and leisure. It is a standardized approach to goal attainment scaling that takes into account the participant's ratings of the importance of the areas in which goals are set. It has promise for use as an outcome measure that can be shaped to the goals of the person.

Although the above-mentioned three measures are responsive to the need for ecological validity and show promise to some extent, substantial developmental research is needed before they become widely available as outcome measures for use in clinical trials.

Beyond the problem of ecological validity, a clear view of what comprises a successful outcome is needed. In other words, of the many aspects of the person's life that are likely to change as a result of treatment, which should be the target of assessment? For example, measures of the constructs of participation and quality of life, such as the Mayo-Portland Adaptability Inventory (Lezak and Malec 2003), the Neurobehavioral Rating Scale (Levin et al. 1987), the Participation Objective, Participation Subjective (Brown et al. 2004), the Craig Handicap Assessment and Reporting Technique (Walker et al. 2003), the Community Integration Questionnaire (Willer et al. 1993), and the Satisfaction With Life Scale (Diener et al. 1985), may be useful when examining the impact of a cognitive intervention on activity and participation. However, the relationship has not been studied between, for example, participation and cognitive function—much less changes in cognitive function. Thus, it is not known at what point diminished or altered cognitive function limits participation, nor the degree to which cognitive function needs to

improve before such change becomes manifest in activity or participation.

Another set of problems is associated with the goals that are formulated with respect to cognitive interventions. Is the goal to become more active or to engage in activities more effectively? For example, do we want people to watch television or go to ball games more frequently? Or, do we want them to be able to sustain their attention for longer periods of time or recall what they watched the next day? Do we want people to cook more often, cook more efficiently, or cook more complex meals? One needs to be clear on the specific aspects of participation that are expected to change as a consequence of an intervention. Similarly, some outcomes take a considerable amount of time to achieve. For example, if the goal of a comprehensive day treatment program for individuals with traumatic brain injury is to return participants to work or to school, these goals are unlikely to be achieved on the day that the program ends. It might take some time for a person to find a job, or it may be months before a new semester begins or a person is accepted into a course of study. The real outcome of an intervention may not be measurable within the time frame of a study.

Thus, although considerable progress has been made in developing approaches to treat various aspects of cognitive dysfunction, we are still a long way from having adequate measures that can be used to describe the efficacy of these interventions. And we have not formulated a clear approach to goal setting, assessment of outcome at different levels of functioning, and documenting long-term impact.

Reconciliation and Cognitive Rehabilitation

Rehabilitation, like life itself, involves the process of reconciliation. For the person without a disability, this process typically involves reconciling "who I am" with "who I want to be." Because the process of each human's development means trying to merge these two lines so that they intersect, reconciliation is the pathway of successful adult development—when hopes and dreams become reconciled with the reality of the person's life.

For the person with a disability, the process of reconciliation is more difficult. For example, the person with a spinal cord injury comes to rehab wanting to walk again. People with traumatic brain injury come to rehab wanting to be as they were before injury. In any person with a disability, reconciliation involves altering hopes and dreams so that they are aligned with the person's new reality. Because there is a different "who I am," which typically also implies altering the "who I want to be," the reconciliation of these two images becomes an unwritten part of rehabilitation.

Certainly, it is an unwritten part of cognitive rehabilitation. How do we facilitate people becoming aware of the fact that they are not who they were, that there is a different "who I am" and that this makes becoming "who I want to be" a more difficult challenge than before injury? The person must recognize the "new me" as well as the new "person I want to be." The inability to develop a different self is made all the more difficult because the person may look the same, have the same belief systems and values, live in the same place, and have the same family and friends. Thus, while many aspects of the person and of his or her environment remain unchanged, everything is likely to be somewhat different in its fit with the person. The fact that in so many ways life is the same makes becoming aware of the ways in which the new self and life are different is all the more difficult.

How does this reconciliation happen? It does not happen through constantly creating venues for failure and harping on the ways the person is different. The postimpairment pattern of failure and unawareness needs to be replaced by experiences of success and expanded awareness. This can happen in multiple ways. For example, skill training provides a subtle reminder of the basic tasks that challenge the person. If people see that they are making errors on the simplest of tasks, and then learn not to make errors on these tasks as well as learn how to perform more complex tasks, two messages are communicated: "Something is wrong if you are not performing the tasks you should be able to perform" and, more importantly, "You can learn."

Integrating the old self with the new also happens through listening to others tell their stories of daily life, for example, the emotional ups and downs, the simple situations of life that are unsolved, the times when memory fails. These are today's repeated failures that were yesterday's it-goes-without-saying successes. The experiences of brain injury when shared with others help the person to adjust and begin to acknowledge the "new person" and let that person emerge. This shared experience, in combination with the structure provided by skill training, provides a way for the person to move on. Thus, change takes place in a therapeutic environment, created by a dedicated treatment team of neuropsychologists, populated with a community of other people with traumatic brain injury and supported by the involvement of the person's family.

A Summing Up: Progress and Challenges

What has been learned about cognitive rehabilitation since the early studies of 40 years ago, and what needs to be accomplished in the next 40 years?

First, we have learned that cognitive rehabilitation needs to be *contextualized*. In other words, rehabilitation techniques must be applied directly to real-life problems and to challenges that treatment participants actually encounter, if generalization across situations is to be effected. As Ylvisaker and colleagues (Ylvisaker 2004; Ylvisaker et al. 2002) argued, while contextualized treatment has the benefit of producing behavioral change in the context in which it occurs, generalization of learning across situations has been found to be limited (Ownsworth and McFarland 1999; Park and Ingles 2001; Ylvisaker et al. 2002) unless the person is given sufficient opportunity to practice assigned training tasks in multiple contexts.

Second, although contextualization is necessary, it is not sufficient, because the person must also be taught the

principles underlying behavioral change. As noted by Cicerone et al. (2000, 2005), to succeed, the person needs to be provided strategies and be taught to apply these strategies across multiple situations. To the degree that the use of these strategies becomes second nature to the person, their application in daily life becomes automatic. To effect this generalization, we must give patients abundant opportunities to both learn and practice the rules of what is to be learned. This fosters generalization across tasks and situations. This approach has been successfully applied to the treatment of executive dysfunction by diverse groups of researchers, including von Cramon et al. (1991), Levine et al. (2000, 2006, 2007), Malec (2001), Manly et al. (2002), Rath et al. (2003), Gordon et al. (2006), and Stuss et al. (2007).

Third, Ben-Yishay et al. (1987) recognized many years ago that attention training was an essential ingredient in any comprehensive cognitive rehabilitation program. The reason for this is simple: How can people be expected to learn if they are unable to pay attention for more than brief periods? In other words, the ability to sustain attention over time and to filter extraneous information is necessary if cognitive rehabilitation is to have any chance for success. In addition, as noted by Goldberg and Bilder (1986), attention and memory are often nested together. So, a memory disorder may actually be one of attention. Attention not only mediates learning but also serves as the foundation of learning.

Fourth, many years ago, Mary Hibbard and I pointed out that learning in a brain-injured person is a slow process (Gordon and Hibbard 1991). Because the brain mediates all learning and the brain is injured, how can we expect anything else? Thus, achieving the outcomes our patients seek necessarily will require a long and tedious process. As noted earlier, we work to achieve an intervention's becoming integrated into the person's repertoire of habits so that changed behavior becomes automatic. For those of us who have tried to learn a sport such as tennis or golf, we know that there is no shortcut to learning the skills involved, no way to avoid the extensive time commitment needed, no quick fix. The people we see clinically are being asked to learn a new set of habits in approaching the cognitive challenges of everyday life. Clearly, it will take them considerable time to learn such habits to the point of becoming integrated into their repertoire of automatic function.

Fifth, we know little about the dose response of cognitive rehabilitation and how this varies across people. We do not know the optimal time course of treatment and how a desired outcome is mediated by such factors as severity of injury, age, or time since injury. Thus, if an intervention fails, it could be because the intervention did not work or because it was not given enough time to show its effect. Similarly, if the intervention was found to be effective, we do not know whether it would have been more effective if additional treatment were provided or just as effective with less treatment. Consequently, current practice is often guided, not by guidelines based in research, but instead by insurance company reimbursement policies or by our "clinical sense" of how long we think a person will be willing to participate in treatment or needs to participate to reach his or her goals. At the Mount Sinai School of Medicine in New York, currently we are running two randomized clinical trials evaluating two innovative comprehensive day treatment programs. One program involves 6 months of treatment, in which participants are expected to attend daily for 5 hours a day. The second program is a truncated version of the first, containing what we think are the same key ingredients but less of them and less intensely (about 9 hours per week for 12 weeks). When these trials are completed in 2012, we will have some idea of the way in which treatment dose interacts with outcomes and the extent to which participant characteristics play a role in differential treatment outcomes.

Sixth, it is my view that while skill training is useful when examining theory, in and of itself it is not an effective approach to cognitive rehabilitation if one wants to improve day-to-day, real-life function. For example, when theory A dictates that a certain deficit be treated in a specific manner, but theory B begs to differ and insists on a different treatment, this disagreement encourages a comparison of these respective approaches to treatment. This type of research on skill training fosters the development of a toolbox of effective treatments for diverse cognitive impairments. Once shown to be effective, cognitive rehabilitation tools must be packaged into a comprehensive treatment program rather than a single skill-based treatment. Within any given program, bottom-up skill training of various types needs to be combined with top-down approaches that teach strategies.

For example, in both of the treatment programs at Mount Sinai, program participants receive 25 hours of attention training. In addition, they are taught how to use a memory book and to organize information. And they are involved in various types of group treatments in which problem-solving training and emotional regulation training are embedded into activities such as current events, planning a group activity, and the like. Participants receive individualized skill training that is combined with group approaches teaching compensatory strategies. The groups contextualize the strategies into the real-life experiences of the group members. This process also serves as an unobtrusive way of confronting each person's lack of awareness, as there is much commonality in the tales of everyday failures that participants describe. So, the everyday failure described by Tom leads to an "I do that too" response in John. The repetition of shared experiences normalizes behavior and provides a means of "owning" behaviors that would otherwise not have been acknowledged as occurring.

Seventh, treatments provided under the umbrella of cognitive rehabilitation must be manualized. Manualization is the only way to create a standard of care, so that we know that the treatment delivered in setting A is the same as the treatment being offered in setting B and that both correspond to the treatment as it was evaluated in a clinical trial. Clinicians often respond to this point by saying that manualization takes away from the "art" of treatment. I believe that this is far from the case, as a treatment manual is not a script. It does not put words in the mouth of a therapist. It provides a guide as to how the treatment is to be provided and how it is to progress. It provides a basic outline of the activities that are to occur in each session.

Eighth, more research is needed on the ways in which technology can enhance the delivery of cognitive rehabil-

itation. For example, there has been promising use of pagers as a means of providing the person with memory problems reminders of when things need to be done (Wilson et al. 2005). It is easy to envision the use of PDAs (personal digital assistants) as a way of enhancing mnemonic skills. In addition, it is not difficult to envision these devices as useful in improving organizational skills.

Finally, the time has come for us to examine the ways in which the ever-increasing varieties of neuroimaging techniques can provide us information about cognitive rehabilitation. This technology has the potential of linking performance on tests to specific, highly localized areas of the brain, helping to define the characteristics of those who do and do not profit from treatment, as well as examining the impact of the intervention on a specific area of the brain. Research linking performance on neuropsychological tests and specific areas of neuropathology is at its infancy but has begun to slowly emerge (Stuss and Alexander 2007). Increased exploration of the validity of diffusion tensor imaging and similar protocols should shed further light on these relationships (Inglese et al. 2006; Miles et al. 2008).

Another area of needed research is examination of the types of neuroimaging that will be sensitive to the effects of cognitive rehabilitation. Are we looking at increased blood flow as a sign of neural growth or as an indicator of the development of new pathways that facilitate the processing of information? However, if we find no change with neuroimaging, does this mean that the intervention has not improved any aspect of cortical function? Or, on the other hand, does this only mean that the tool is not sufficiently sensitive to measure a change that has occurred?

Cognitive rehabilitation has come a long way in forty years, but perhaps not as far as we all would have liked. Because we have the most valuable resource needed—committed researchers—the biggest barrier to future development of the area is inadequate funds to test the programs that we develop, programs based on theory, on our history of achievement, and on our belief in pathways to a better life for people with disabilities.

KEY CLINICAL POINTS

- Cognitive rehabilitation is a scientifically based intervention for the treatment of cognitive dysfunction in individuals with traumatic brain injury that has evidence to support its efficacy.
- Further study of this intervention is needed to determine the relationship between patient characteristics and outcomes, document its benefits, and tease apart the effective ingredients.

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CHAPTER 38

Positive Behavior Interventions

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THE FOCUS OF THIS CHAPTER IS ON POSITIVE behavioral intervention for individuals with traumatic brain injury (TBI). After summarizing the literature on behavioral outcome of TBI with and without co-occurring disabilities, we describe the principles and procedures of a positive, antecedent-focused, context-sensitive approach to behavior management. In support of this approach, we introduce three neuropsychological considerations and look at available evidence, including a statewide program of behavioral supports and indicators of that program's effectiveness. Although pharmacological management often is a component of behavior interventions, review of the efficacy of pharmacological approaches is beyond the scope of this chapter. For an overall review of psychopharmacology in the management of TBI, see Chapter 35 in this volume.

Behavior Disorders After Traumatic Brain Injury

Personality and behavioral changes, including increases in challenging behavior, are common after TBI in both children and adults. Among individuals with mild TBI, general irritability was found to persist up to 1 year postinjury in roughly one-third of cases (Deb et al. 1998, 1999) and was the most frequently cited symptom of the injury. In the case of severe TBI, Brooks et al. (1987) identified 64% with irritability at 5 years postinjury. Tateno and colleagues (2003) found that 33.7% of their cohort of 89 patients with mild, moderate, or severe TBI had aggressive behavior after the injury, with no significant difference between the aggressive and nonaggressive groups in severity of injury. Furthermore, behavioral excesses (e.g., aggression) and behavior deficits (e.g., reduced initiation) are often judged by family members, teachers, employers, friends, and others to be the most problematic consequence of the injury. Finally, poorly controlled behavior has been linked to difficulty in both family reintegration and educational, vocational, social, and avocational pursuits (Perlesz et al. 2000; Schwartz et al. 2003; Winkler et al. 2006).

Potential contributors to ineffective social and behavioral regulation include preinjury adjustment problems, impairments tied directly to the injury, postinjury evolution of symptoms and adjustment, and poorly conceived interventions (e.g., overly restrictive settings and procedures against which individuals may choose to react). Since the seminal work of Lishman (1973) it has been common to assert that both children (Cattelani et al. 1998) and adults (Greve et al. 2001; MacMillan et al. 2002) with TBI disproportionately represent populations with preinjury adjustment problems, possibly exacerbated by the injury and associated impairments. Although this finding has been disputed by Tate (1998), it is clear that behavioral difficulties represent a significant challenge to individuals with brain injury, their families, and professionals alike.

Behavioral disturbances linked directly to the injury include impairments of self-regulation (e.g., impaired inhibition or initiation) as well as consequences of impairments of cognitive functions (e.g., attention, memory, organization) that lead to failure in everyday tasks, frustration, and acting out. Among children and adolescents with severe TBI, estimates of new persisting behavior and psychosocial problems (i.e., those not predating the injury) range from approximately 35% (Max et al. 1997) to 70% (Costeff et al. 1985). Behavior and social-communication problems are also common among adults with TBI and remain at high levels at long-term follow-up (Baguley et al. 2006).

Irritability, aggression, disinhibition, reduced anger control, sexual acting out, perseveration, poor social judgment, and other externalizing symptoms have been associated with brain systems vulnerable to closed head injury: orbitofrontal cortex, anterior temporal lobe cortex, limbic structures (especially the amygdala), and their interconnections (Eames and Wood 1985; Gualtieri 1991; Tateno et

al. 2003). In particular, when frontal control mechanisms are unavailable to regulate limbic impulses, minor everyday provocation or enticement can cause aggression, sexual acting out, or other socially unacceptable responses (Grafman 1994).

Behavior Disorders and Co-Occurring Disabilities After TBI: Substance Abuse and Psychiatric Disorders

Behavioral disturbances in adults with TBI are commonly combined with pre- and/or postinjury substance abuse and psychiatric diagnoses such as depression and anxiety disorder. (The outcome literature on psychiatric problems after TBI is reviewed in other chapters of this volume.) Co-occurring psychiatric diagnoses are not only common in populations of adults with TBI but also contribute substantially to negative functional outcomes (Franulic et al. 2004; Winkler et al. 2006). With respect to alcohol and drug use, Corrigan (1995, 2005) found rates of intoxication at the time of injury ranging from 37% to 56%. Bogner et al. (2001) found that 54% of 351 consecutive admissions to acute rehabilitation had a preinjury history of alcohol abuse or dependency, 34% preinjury abuse of or dependency on other drugs, and 58% dependency on one or the other or both. Etiology of injury also influences rates of preinjury substance abuse. Bogner and colleagues found that 55% of those with non-violence-related TBI had a history of substance abuse compared with 79% of those with violence-related TBI.

In large numbers, individuals with a preinjury history of substance abuse return to their addiction after the injury. Silver et al. (2001) found that 25% of their sample with TBI had postinjury alcohol use disorders (vs. 10% without TBI), and 11% had drug use disorders (vs. 5% without TBI). Furthermore, return to substance abuse increases over time after the injury (Corrigan et al. 1998; Kreutzer et al. 1996), and many individuals with no preinjury history of abuse initiate high levels of alcohol or drug consumption after the injury (Bombardier et al. 2003), presumably to alleviate their depression or anxiety (Corrigan 2005). Individuals with co-occurring TBI and substance abuse are less likely to be working, have lower subjective well-being, have an increased likelihood of committing suicide, and are at greater risk for seizures (Bogner et al. 2001; Corrigan 2005). MacMillan and colleagues (2002) found that preinjury psychiatric conditions and substance abuse predicted employment outcomes at least two years postinjury, and preinjury substance abuse predicted independent living status. As a result of these and the other aforementioned issues, it is evident that a comprehensive program of long- and short-term support will most likely require some form of behavioral support.

Intervention and Support

In this section we highlight the theory and practice of positive behavior interventions and supports (PBIS), offer a neuropsychological rationale for this approach, and summarize the available evidence. PBIS has evolved within the practice of applied behavior analysis (ABA) over the past 20 years, largely in application to children and adults with developmental disabilities. As a general approach to serving individuals with behavior problems, ABA is characterized by the following seven themes (Baer et al. 1968; Ylvisaker et al. 2003). These themes apply equally to traditional applications of ABA (i.e., contingency management, the most commonly recognized approach to behavior management) and PBIS.

1. *Applied:* ABA interventions address real-world concerns important to individuals with disability and stakeholders in their lives.
2. *Behavioral:* ABA interventions focus on measurable real-world behaviors, their interrelationships within the individual's contexts of life, and specific outcomes of intervention.
3. *Analytic:* Functional assessment must include observation of behavior in specific circumstances and systematic manipulation of relevant variables in those situations to isolate the function(s) of the problematic behavior for that individual.
4. *Technological:* ABA interventions are clearly specified so that other parties can replicate the procedures.
5. *Conceptual:* ABA procedures must be classifiable within clear conceptual systems so that the theoretical orientation of the intervention is clear. It is in this domain that support-oriented PBIS interventions are clearly distinguishable from the consequence-based interventions of traditional contingency management.
6. *Effective:* Intervention is useful only to the extent that it provides something of practical value to the people involved in relevant situations and environments. For this reason, single-subject experimental procedures are routinely used in monitoring ABA interventions.
7. *Generalized:* ABA interventions are designed to have an enduring effect on important everyday activities in relevant real-world environments. Therefore their effects are monitored for three types of generalization: 1) *maintenance:* durability of behavior change or a newly acquired skill over time; 2) *stimulus generalization:* transfer of a newly acquired skill or behavior from the training setting to other relevant settings (e.g., using polite requests with many different people in varied settings beyond the training setting); and 3) *response generalization:* spread of trained behaviors to other associated behaviors (e.g., transfer from training in the use of polite requests for activities to polite requests for information).

Although these seven principles are neutral in relation to the decision to modify problematic behavior by manipulating its consequences or by manipulating its antecedents, the tradition of ABA, including its application to individuals with TBI (Alderman 2003; Corrigan and Bach 2005), has been to focus on contingency management. This approach is designed to increase or decrease specific behaviors by controlling their consequences. Contingency management procedures are well understood by practitioners of behavior management and are used in many set-

tings in which individuals with TBI are served. Contingency management procedures that have been used with individuals with TBI in published reports include differential reinforcement of positive behaviors, of behaviors incompatible with the negative behavior, or of low rates of negative behaviors; token economy procedures (awarding tokens for positive behaviors that can be cashed in for rewards); contingency contracts; extinction procedures (e.g., planned ignoring of negative behaviors, time-out from reinforcement, time out on the spot); and response-cost procedures (e.g., losing points for negative behavior). Some treatment programs have facility-wide token economy programs in place for all clients, with individualized behavioral programs designed in a way that is consistent with the facility-wide program (Eames and Wood 1985).

Clinicians who predominantly use contingency management procedures may also focus on the antecedents of the problematic behavior but generally only on immediate antecedents (e.g., specific provocation, environmental conditions at the time of the behavior, instructions/demands that preceded the behavior). Moreover, programs that highlight contingency management often employ clinician or staff-controlled reinforcers (e.g., food, favorite activities, tokens) that are not logically and naturally related to the targeted behavior and therefore may pose an obstacle to generalization to natural environments. Although there are positive aspects to contingency management, there is evidence that its focus on correction procedures for negative behavior may inadvertently increase the frequency of that behavior as a result of implicit learning, especially during the early stages of recovery (Baddeley and Wilson 1994). In addition, if proactive prevention procedures are inadequate at this stage, behaviors that begin as purely neurological may become learned behavioral habits (Slifer et al. 1996).

Central Themes: Positive Behavior Interventions and Supports

As a theory and set of procedures, PBIS has evolved within the tradition of ABA but with several distinguishing features that are critical for certain populations, including TBI (Carr 2007). From its roots in ABA, PBIS has maintained the framework of antecedent-behavior-consequence (ABC) analysis, procedures of functional behavior assessment (including ongoing direct observation of the target behavior's antecedents and consequences as well as experimental manipulation of these antecedents and consequences), specific teaching methods (e.g., prompting, shaping, chaining, fading, planned schedules of reinforcement), and procedures to facilitate generalization and maintenance. Moreover, the antecedent-management procedures that dominate PBIS behavior plans have their roots in traditional ABA concepts, including stimulus control, setting events, and establishing operations (Ylvisaker et al. 2003). Finally, in a series of intervention experiments, Feeney and Ylvisaker (1995, 2003, 2006, 2008), Feeney et al. (2001) and Arco and Bishop (2009) demonstrated the effectiveness of the PBIS framework with young children, adolescents, and young adults with significant behavioral challenges associated with self-regulatory impairments caused by frontal lobe injury. In each case, the intervention was delivered by staff in the context of the individuals' everyday routines. And in each case, results included substantial reduction to acceptable levels of both frequency and intensity of negative behaviors as well as an increase in the amount of participation in required activities. In addition to the aforementioned clinical results, the emphasis on cognitive and behavioral antecedent supports that we are recommending is based, in part, on the repeated finding that individuals with ventral prefrontal damage learn at best inefficiently from the consequences of their behavior (Damasio 1994; Rolls 2002). This finding is especially important in light of the fact that, historically, behavior management programs for individuals with brain injury are organized almost exclusively around the consequences of behavior (e.g., Eames and Wood 1985; Slifer et al. 1996). Similarly, TBI rehabilitation tends to be organized around demands for performance followed by feedback. Thus individuals with brain injury may routinely receive interventions that are incompatible with their primary neuropsychological impairment.

In summary, distinguishing features of PBIS include its general orientation. Practitioners of PBIS look beyond specific negative behaviors to be targeted for extinction and specific positive behaviors to be targeted for acquisition. Rather, the primary focus is on overall quality of life for the individual and significant others. A guiding assumption is that when individuals' needs are effectively met, when they are competently engaged in an array of meaningful activities over which they have adequate control, when they have meaningful social relationships, and quality of life is correspondingly enhanced, problem behaviors substantially decrease in the absence of targeted response-deceleration interventions. Associated with this quality-of-life perspective, PBIS interventions attempt to increase participation in meaningful activities in natural activity contexts using a variety of cognitive, behavioral, and social support procedures to ensure positive participation. Furthermore, the antecedents highlighted in intervention and support plans include remote antecedents or setting events (e.g., a conflict earlier in the day influences later behavior) and internal antecedents (e.g., a feeling of isolation and loneliness influences behavioral choices). Finally, approaches that follow PBIS principles have effective self-regulation of behavior as their ultimate goal, necessitating a planned and systematic reduction of supports as self-regulation improves.

Specific PBIS Procedures

In the early stages of cognitive and self-regulatory recovery after TBI, individuals tend to be confused, seriously disinhibited, and episodically agitated. Poorly controlled behavior (e.g., shouting, physical aggression, refusal) is a natural consequence of this neurological condition. Although pharmacological management is often utilized in hospital settings in which behavioral services are inadequate, this element of intervention should be used with caution because of the possibility of interfering with spontaneous neurological recovery, and if its use is necessary, it should be only as one component of a larger behavioral intervention plan.

The primary behavioral approach at this stage is prevention of negative behavior by appropriately modulating environmental stimuli, performance expectations, and supports. This requires systematic identification of conditions under which the individual is calm and alert versus confused and agitated. Redirection procedures are used at the onset of negative behavior. Care must be taken to avoid systematically rewarding negative behavior by, for example, routinely removing a person from unpleasant therapies or nursing procedures in response to such behavior. Nursing and other staff may require considerable education and training so that they know what supports are relevant, remain calm during behavioral outbursts, and do not take challenging behavior personally.

Some behavioral problems spontaneously remit or reduce in intensity over the early stages of cognitive recovery. In other cases, behavior problems increase in frequency and intensity over time as the individual faces the frustrations of life with impairments and possibly with restrictions on activities that are perceived as unreasonable. This increase is exaggerated in the presence of reduced self-regulation (e.g., inhibition impairment) associated with commonly occurring frontolimbic injury. Our focus in this chapter is on supports and interventions particularly relevant during postacute stages and in community settings. However, the procedures listed are also applicable in inpatient settings.

Table 38–1 lists key PBIS procedures commonly used during the chronic stages of recovery. In addition to the procedures listed, all rehabilitation activities designed to teach functional skills (e.g., independent living, vocational, and social skills) are behavior management procedures in the sense that they reduce the likelihood of negative behavior that is motivated by frustration caused by an inability to successfully complete important tasks of everyday life. In this sense, vocational and educational interventions, communication and social skills training, cognitive rehabilitation, and adjustment counseling are all components of an integrated approach to behavior management.

PBIS and Aggression

Clinicians and family members often report that acts of aggression, directed at objects or people, are the most troubling aspects of behavioral disturbances. Early in recovery, aggression is rarely a planned attempt to cause harm but nevertheless mandates thoughtful management. Later, aggression may have a variety of functions, identified by systematic functional assessment.

From a PBIS perspective, prevention is key, requiring organized management of environmental setting events (immediate and remote) and task requirements. That is, environmental stressors and task difficulty and duration should be adapted to the individual's abilities and tolerance. This includes flexibility in scheduling, staff understanding of the person's limits, and minimal physical interaction. In addition, attention to the early signs of an aggressive episode should trigger redirection and diffusion efforts from staff and family members. During an aggressive episode, the primary responsibility of staff is to keep others safe. There should be little talk, no threats, and physical intervention only if required by safety considerations. Following the episode, the individual should be allowed to "cool down" in a neutral setting before resuming normal activity. Physical restraints may only increase agitation and are subject to restrictions by regulatory authorities. Staff and family training should focus on understanding the causes of aggression, environmental management, and specific procedures for redirection and diffusion.

Role of Consequences Within Support-Oriented Intervention

In emphasizing antecedents in behavior management for people with TBI, we do not wish to recommend inattention to consequences. First, some people with TBI escape frontolimbic injury entirely and can therefore be expected to be as efficient at learning from consequences as their uninjured peers (Mesulam 2002). Second, the frontolimbic threats to efficiency of consequence-oriented behavior management come in degrees and may not be serious in individual cases (Rolls 2002). Third, the positive, everyday routines that antecedent supports are designed to facilitate are positive in part because they result in extrinsic or intrinsic rewards for the person (e.g., praise, friends, employment) (Ryan and Deci 2000). Fourth, the possibility of serious punishment (e.g., jail) may serve as motivation for participation in the development of antecedent-supported routines. Finally, even those who are inefficient at learning from consequences benefit from a positive culture in which there is ample noncontingent reinforcement, successful performance is greeted with encouragement and praise, and failure and negative behavior elicit efforts to help the person succeed rather than punishment that may breed anger and additional failure (Wilson et al. 1994).

In the use of consequences, some basic rules apply. First, individuals who are impulsive and concrete in their thinking need consequences that are immediate (versus delayed) and salient. As cognition improves, consequences can become progressively more delayed and less salient. Second, with the goal of helping people succeed in the real world, rewards and punishments should be as natural and logically related to the individual's behavior as possible. For example, an enjoyable social interaction is a natural and logical consequence of socially appropriate initiation. On the punishment side, cleaning one's room after a "cool-down" period is a natural and logical consequence of "trashing" the room during a tantrum.

Furthermore, liberal use of extrinsic rewards can create dependence on such rewards and interfere with internally driven motivation, a finding that has been replicated many times with many populations over the past four decades (Deci 1995; Ryan and Deci 2000). Token economies, which are popular components of consequence-oriented behavioral programs, often fail to promote understanding of natural and logical relationships in the world and result in learned helplessness and learned dependence. Finally, our experience suggests that many oppositional young people become increasingly oppositional in an environment that they perceive as dominated by arbitrary authority figures arbitrarily dispensing rewards and punishments that are neither personally meaningful nor logically related to their actions.

TABLE 38–1. Key procedural concepts in antecedent-focused management of challenging behavior

People are more likely to engage in difficult tasks and prosocial behavior and refrain from problem behavior if there is/are…

1. **Positive, negotiated, well-understood daily routines:** The individuals understand the routines and expectations of their everyday lives, have had a hand in shaping those routines and expectations, and know that they can be adequately successful within those routines.
2. **Prevention of undesirable behavior by eliminating provocation:** Known provocations for challenging behaviors are avoided. For people with neurologically reduced self-regulation, the threshold at which provocation overwhelms self-control is lowered. Intervention also includes teaching self-regulation strategies to use in response to provoking stimuli.
3. **Reasonable compensations for cognitive impairments:** Frequently used environmental compensations include reduced requirements for information processing; reduced environmental distractors; effectively organized work, study, and living environments; reminders and organizational supports from others; and collaborative support for difficult tasks. Frequently used personal compensations include memory aids (e.g., lists, posted reminders, written notes), organization aids (e.g., schedule organizer, graphic organizers), and self-regulation aids (e.g., posted reminders of useful self-regulation strategies).
4. **Positive communication from communication partners:** Communication partners use clear, dignified, and respectful communication that focuses on positive attributes (e.g., avoiding threats, nagging, power battles, and the like). Communication competencies are included in all staff job descriptions.
5. **Positive communication alternatives to problem behavior:** When negative behavior serves a specific purpose (e.g., communicates a desire to escape an activity or person or to gain access to an activity or person), the individual is taught a positive way to communicate the same message (e.g., "I need a break").
6. **Positive setting events:** Individuals with poorly regulated behavior have a background of success, generally positive experiences, and a positive state of mind before challenging tasks are introduced.
7. **Positive behavioral momentum:** They experience success in a series of tasks immediately preceding more difficult tasks.
8. **Choice and control:** They have reasonable control over the tasks, activities, and routines of their lives (i.e., self-determination). Clear reasons are given for "no-choice" situations.
9. **A focus on pivotal behaviors:** Certain behaviors are pivotal in the sense that they facilitate chains of positive behavior or prevent chains of negative behavior (e.g., scripts to request help, to initiate social engagement, or to diffuse provocation).
10. **Positive roles and scripts:** They have personally meaningful roles to play in their lives, positive behavior is associated with those roles (e.g., helper roles, meaningful job), and their work has meaningful products. Project-oriented rehabilitation, discussed elsewhere in this chapter, is consistent with this principle.
11. **Recreation, leisure, and community mobility:** They have a reasonable amount of satisfying and personally meaningful avocational and recreational activities in their lives and reasonably easy access to a range of community activities of personal value.
12. **Satisfying social relationships:** They have personally meaningful social relationships in their lives (e.g., friends, family). Daily routines include activities that increase the likelihood that meaningful social relationships will be developed.
13. **Positive sense of self:** They have a sense of personal identity that is acceptable to them, and desirable behavior is associated with that sense of self. Metaphoric identity mapping, discussed elsewhere in this chapter, is consistent with this principle.
14. **Self-control of antecedents:** They learn to organize the antecedents in their lives so that they avoid behaviorally difficult experiences (analogous to the substance abuse rehabilitation mantra: "There are people, places, and things that must be avoided at all costs!").
15. **Self-regulation as a goal of behavioral intervention:** The ultimate goal of behavioral intervention is self-regulation of behavior in a way that is consistent with relevant environmental, vocational, and social factors. Self-coaching intervention, discussed elsewhere in this chapter, is consistent with this principle.

Meaning, Self-Regulation, and Identity

As a general orientation to intervention and support, PBIS focuses broadly on meaningful, competent, self-regulated, and satisfying engagement in activities that are consistent with the individual's sense of personal identity and take place within settings that are as natural as possible. To the extent that this goal is achieved, many types of negative behavior are rendered irrelevant. This orientation toward behavior supports can begin during inpatient rehabilitation and should dominate planning in community support programs.

Engagement in Personally Meaningful Activities

Many individuals with TBI have lives filled with personally meaningful and engaging activities, possibly including activities related to work, school, family, friends, and recreation. However, it is common for those with significantly altered profiles of ability after the injury to lack meaningful and engaging activities in these domains. They may be unable to work or attend school; they may have lost most of their friends and possibly even family ties; they may be unable to engage in recreational activities favored before the injury. Social isolation and inactivity have been documented in many long-term outcome studies (Dikmen

et al. 2003; Tate et al. 2005; Wade et al. 1998), particularly for TBI co-occurring with substance abuse and/or psychiatric disorder.

Under these circumstances, negative behavior may be a consequence of boredom, frustration, or a pervasive sense of isolation and incompetence. Conversely, a sense of competence and adequate social relatedness have been repeatedly found to be central to intrinsic motivation (Ryan and Deci 2000). Reductions in important life activities are related to poor emotional adjustment (Douglas and Spellacy 2000) and general life satisfaction after TBI (Corrigan et al. 2001). Huebner et al. (2003) found meaningful participation was positively associated with quality of life.

Ylvisaker et al. (2007a) described a project-oriented approach to rehabilitation to be used in long-term rehabilitation and community support programs with the goal of creating meaningful engagement in productive activity and an associated sense of competence. As they use the term, a *project* is a personal activity that has the following components: It creates an expert and helper/producer role for the participant; it is judged to be personally meaningful; it requires planning, organizing, and other cognitive activities that may require attention after TBI; if completed in a group, it offers opportunities for social engagement and for practicing social and self-regulatory competencies; it results in a product that is considered useful for others. Ylvisaker et al. (2008) demonstrated that project-oriented rehabilitation can become part of the culture of community-based rehabilitation programs and can contribute to meaningfulness as judged by the participants in the program. Examples of successful projects include the following: With considerable staff support, a participant with serious organizational impairment spent several months creating a user-friendly manual and video demonstration on the use of a spectrum of organizational prostheses. During this time, he progressed through a series of organizational supports with heightened motivation because of his project. Another participant with considerable artistic talent and a severe anxiety disorder created a series of drawings depicting the feelings associated with anxiety along with strategies to deal with the anxiety. These drawings were organized as a pictorial manual on anxiety and used with other participants with anxiety problems. A participant with profoundly impulsive behavior created a manual on impulsive behavior versus thoughtful decision making, including a large number of researched strategies to overcome impulsive behavior.

Facilitation of Self-Regulation

In many cases, behavioral disorders after TBI are associated with executive function or self-regulatory impairments caused by frontal lobe injury. Effective self-regulation is the ultimate goal of behavioral interventions but may be difficult to achieve because of these impairments. The importance of self-regulation was underscored by Cicerone and Azulay's (2007) finding that self-efficacy, including control over cognitive compensations, was the primary predictor of positive quality of life in their cohort of individuals with chronic TBI. In addition, overly intensive control by others is often the trigger for negative behavior.

Self-coaching is an organized approach to facilitating improved self-regulation. In group or individual sessions, specific obstacles are identified followed by construction of a "play" to overcome the obstacle (i.e., strategy or tactic modeled on the concept of a play in organized sports). The sports metaphors implicit in the terms *self-coaching* and *plays,* along with specific sports metaphors associated with the specific plays, tend to be compelling for sports-minded adolescents and young adults. Many alternative metaphors for self-regulation are also available. The goal is to create a compelling self-coaching "voice in the head" that is triggered automatically by relevant environmental events. These internalized scripts are negotiated along with reminder scripts for everyday support people. With sufficient supported practice, these self-regulatory self-reminders become automatic, thus reducing the processing load at times of stress or decision making. Ylvisaker (2006) described the theoretical rationale and procedures for this self-coaching approach to self-regulation.

Construction of an Organized and Positive Sense of Personal Identity

Identity or sense of self is often shattered by the effects of TBI on the individual's abilities and roles. Therefore effective reconstruction of an organized, compelling, and reasonably realistic identity is central to the process of rehabilitation. This reconstruction process is complicated by possible unawareness of impairments, denial, or profound desire to return to preinjury status, combined with cognitive impairments that interfere with traditional counseling procedures. It may appear that this theme is relevant for a chapter on adjustment counseling, not behavior management. However, reduced awareness of self or resistance to a change in sense of self after the injury may block acceptance of needed supports, of cognitive and vocational compensatory strategies, and of self-regulation strategies. This resistance in turn easily causes frustration, conflicts between the individual and staff, and associated negative behaviors. For this reason, a focus on identity construction is a component of a comprehensive program of behavior management.

A variety of established counseling procedures have been used with individuals with TBI, including cognitive-behavioral therapy (e.g., Khan-Bourne and Brown 2003; Williams et al. 2003), motivational interviewing (e.g., Bombardier and Rimmele 1999), and narrative therapy (e.g., Hogan 1999). In each case, modifications are typically made to address the cognitive impairments (e.g., in memory, organization, idea generation, abstract thinking) and self-regulatory impairments common after TBI. Metaphoric identity mapping is an organized set of procedures designed to address TBI identity themes and common impairments (Ylvisaker and Feeney 2000; Ylvisaker et al. 2008). A graphic organizer is used to facilitate organized idea generation and memory. Collaborative identification of a metaphoric base for identity descriptions (e.g., a personal hero) contributes to the concreteness of the process and enables the resulting identity descriptions to be housed in the "implicational" domain of meaning (i.e., emotion- and behavior-related "gut-level" meanings [Teasdale and

Barnard 1993]). Concrete action strategies are associated with the values, goals, feelings, and other associations of a positive "hoped-for" identity and are then regularly reviewed with the goal of internalizing and automatizing the action strategies as an integral component of a desirable "me." In a preliminary investigation, Ylvisaker et al. (2008) showed that the procedures of metaphoric identity mapping could be effectively used by a variety of rehabilitation professionals and could assist individuals with chronic TBI in setting and achieving meaningful goals. In inpatient rehabilitation, adoption of a compelling temporary identity may contribute to active participation in rehabilitation activities. The following identity metaphor illustrates the effective use of this approach with individuals with brain injury: social skills as basketball plays. In this case, a former basketball player whose impulsiveness led to serious trouble in his life came to agree that he needed to "be like Michael Jordan" and use set plays, rather than "running around the court like a crazy kid." The intervention that followed this identity construction included assisting the individual to define successful plays and review his plays with others.

Rationale for a Context-Sensitive PBIS Approach: Neuropsychological Foundations

Commonly observed neuropsychological profiles following TBI, combined with leading neuroscience theories designed to explain these profiles, lend support to an antecedent-focused, context-sensitive, and routine-based approach to behavioral and cognitive intervention. Relevant neuroscience theories include Damasio's theory of somatic markers, Mesulam's default mode theory of frontal lobe impairment, and Grafman's theory of structured event complexes.

Frontal Lobe Injury and Inefficient Learning From Consequences

Consequence-oriented (i.e., contingency management) approaches to behavior change assume reasonable capacity to learn from consequences, which in turn presupposes reasonable intactness of prefrontal neural circuits. According to Damasio's famous somatic marker theory, learning from consequences occurs when the brain connects two types of memory: memory for the factual aspects of past behavior and memory for the "somatic markers" or feeling states associated with the consequences of those behaviors. Without such connections in memory (however unconscious they may be), past rewards and punishments lack the power to drive future decision making and behavior. Extensive investigations of adults with frontal lobe injury have convinced Damasio and his colleagues that ventromedial prefrontal lesions, which are very common in closed head injury, weaken the ability to connect these two types of memory, resulting in the common clinical profile of people who respond immediately to rewards and punishments but whose behavior in the long run is inefficiently shaped by the organized arrangement of such consequences (Damasio 1998).

Related to the somatic marker theory is Rolls's view, based on extensive research with primates and humans, that a key function of ventral prefrontal cortex, in particular the orbitofrontal cortex, is to distinguish consequences as rewarding and to modify behavior in relation to changing contingencies (Rolls 2002). This explains the observed phenomenon of individuals with frontal lobe injury failing to learn from the consequences of their behavior. Rolls (2002) also attempts to bring more general frontal lobe phenomena under this reinforcement-learning umbrella. Elements of this umbrella of frontal lobe dysfunction include difficulty sorting, shifting, and changing direction; perseveration; euphoria; irresponsibility; lack of affect; lack of concern/egocentrism; socially inappropriate and disinhibited behavior; and impaired perception/identification of facial and voice emotion. The general result of these multiple impairments is an alteration of emotional processing, increased disinhibition, and behavior problems. Rolls theory, like that of Damasio and his colleagues, provides a comfortable theoretical home for intervention based on the creation of antecedent-supported, context-sensitive routines of action and interaction.

Context Dependence and Frontal Lobe Injury

Mesulam's (2002) review of frontal lobe function and dysfunction highlights as its central theme the frontal lobes' roll in enabling humans to transcend "the default mode" of inflexible stimulus-response linkages to the immediate stimulus environment. From this central theme evolve the commonly observed deficits associated with frontal lobe injury: 1) poor working memory (i.e., difficulty expanding consciousness beyond the here and now); 2) distractibility, perseveration, and disinhibition; 3) difficulty with decision making in novel situations; 4) impaired integration of reason, experience, and emotion; 5) inflexibility, insensitivity to contextual subtleties, failure to appreciate ambiguity, and difficulty with abstract thinking; and 6) cognitive egocentrism or difficulty switching perspectives (otherwise known as impaired "theory of mind").

Mesulam's theory effectively explains the "stimulus-boundedness" and extreme difficulty with transfer of training (i.e., generalization) observed in many individuals with frontal lobe injury. Problems with transfer have been identified in many clinical populations, yielding the following heuristic principle: behaviors or skills acquired in a laboratory or training context are unlikely to transfer (i.e., generalize) to functional application contexts and be maintained over time without heroic efforts to facilitate that transfer and maintenance (Detterman and Sternberg 1993). Recognition of the impact of this principle has led to the development and validation of increasingly context-sensitive interventions in many clinical fields and has had increased impact on the delivery of brain injury rehabilitation programs. The core elements of these interventions include an intervention perspective that is context sensitive and attempts to build repertoires of successful behavior, thinking,

and self-regulation, triggered by environmental stimuli that are specifically relevant to the individual being served.

Executive Dysfunction as Impairment of Structured Event Complexes

Grafman's theory of prefrontal function proposes that executive processes are complex mental representations ("structured event complexes") at greater or lesser levels of generality (Grafman 2002). Thus "executive direction" of complex activities, understood neurologically, is activation of a complex knowledge structure that represents that activity. These representations or knowledge structures are strengthened by multiple experiences of the activities in the world. Like the previous theories, Grafman's view supports an approach to rehabilitation that attempts to strengthen these complex knowledge structures by supportively creating routines of action and interaction triggered by contextually appropriate environmental stimuli.

Rationale for a PBIS Approach: Evidence

In a systematic review of the evidence for behavioral interventions for individuals with behavior problems after TBI, Ylvisaker et al. (2007b) located 65 studies with a total of 172 participants, including children, adolescents, and adults. Two of the studies were small randomized controlled trials; two were group studies with inadequate controls; 36 were well-controlled, single-subject experiments; and 25 were uncontrolled case studies or poorly designed single-subject experiments. All of the studies showed positive effects of the intervention, supporting the conclusion that behavioral intervention in general (i.e., not a specific intervention protocol) for behavior problems after TBI in both children and adults can be considered an evidence-based practice guideline at both acute and postacute stages of recovery.

The interventions in the published reports were classified as traditional contingency management (CM), PBIS, or combination. Twenty-six of the studies were classified as CM, 17 as PBIS (including the two randomized controlled trials), and 22 as combined. Ylvisaker and colleagues concluded that individuals with challenging behavior after TBI should be provided with systematically organized behavioral interventions and supports consistent with the available evidence and based on individualized functional behavior assessments. Furthermore, specific behavioral interventions grouped under the headings CM and PBIS can be considered evidence-based treatment options. Because most of the experimental evidence is from single-subject experiments and intervention protocols vary from study to study to address unique behavior-environment interactions, stronger recommendations (i.e., practice standards or intervention guidelines) for specific behavioral intervention protocols could not be supported by the available evidence. However, both CM and PBIS approaches meet the standard for evidence-based practice using single-subject experiments, which is the usual research methodology in behavioral studies (Horner et al. 2005).

TABLE 38–2. Responses on the Community Integration section of the Participant Experience Survey (*n*=37 of 46 participants living in New York State)

Satisfaction with employment/daily activity: Percentage of participants with a formal daily activity who report that they do *not* like their job, day program, volunteer work, or other daily activity.	37% (11 of 30)
Choice in employment/daily activity: Percentage of participants with a formal daily activity who report they did *not* help choose their current job, day program, volunteer work, or other daily activity.	23% (7 of 30)
Demand for employment/daily activity: Percentage of participants *without* a current formal daily activity who report that they want one.	85% (6 of 7)
Transportation: Percentage of participants who report *not* always having transportation when needed.	38% (14 of 37)
Community involvement: Percentage of participants who report that they do *not* always have an opportunity for community involvement.	27% (10 of 37)
Improvement on the waiver: Percentage of participants who report that they can do "*no more*" for themselves than when they first started on the waiver.	14% (5 of 37)

Source. Reprinted from Ylvisaker M, Turkstra L, Coehlo C, et al: "Behavioral Interventions for Individuals With Behavior Disorders After TBI: A Systematic Review of the Evidence." *Brain Injury* 21:769–805, 2007. Used with permission.

Trends over the past 30 years showed a strong movement toward PBIS. The CM to PBIS combined ratios by decade were as follows: 1980–1989: 9:0:2; 1990–1999: 14:6:14; 2000–2005: 3:11:6. This strong trend toward PBIS interventions corresponds in part to the rise of PBIS in behavioral psychology generally and in part to growing recognition of the neuropsychological rationale for antecedent support-oriented interventions for individuals with TBI. It is also interesting to note that only PBIS and combined interventions were used in community settings (e.g., homes, community schools), as opposed to inpatient or residential facilities in which all three categories were used. With decreasing lengths of stay in inpatient and residential settings and corresponding increases in community-based services for individuals with TBI, it is likely that use of PBIS procedures will increase.

Illustration of a Statewide Community Support Program

The New York State Department of Health TBI Medicaid Waiver Program began serving individuals with chronic disabilities following TBI in 1995. Criteria for entrance to this community-based support program include a history of brain injury and residual medical or cognitive-behavioral impairments sufficiently severe to qualify for admission to a nursing facility. The Neurobehavioral Resource Project

within the waiver provides a variety of services and supports for waiver participants with problem behavior and their staff. Principles guiding this support project, many of which are implicit in this chapter, were articulated by Ylvisaker et al. (2007a). In particular, waiver providers throughout the state are required to develop behavior support plans consistent with the principles and procedures of PBIS, including person-centered planning, antecedent-focused cognitive and behavioral supports, engagement in personally meaningful activities, and facilitation of self-regulation.

Long-term outcomes of this community support program have been presented by Feeney et al. (2001), who demonstrated cost savings as well as elevated markers of community living for 80 individuals representing the 1996 and 1997 cohorts. In a subsequent report, Ylvisaker et al. (2007a) presented similar outcome data specifically for those participants with co-occurring disabilities: TBI plus either substance abuse, a psychiatric disorder, or both. Because of significant behavioral challenges, all of the participants were in a restrictive living setting (e.g., nursing or correctional facility) during the year before enrollment in the waiver program. At follow-up, most of the participants (41 of the 46 who were alive and still living in New York State) continued to live in the community 8–9 years after commencement of community support services.

In addition to the evidence that individuals remained in community settings, Table 38–2 shows that the participants' community integration responses were generally positive, a finding that is encouraging in light of the generally discouraging findings in most outcome studies. The Participant Experience Survey is a standardized tool used by the New York State Health Department to measure important aspects of participant outcome.

Summary

We have described principles and procedures associated with an antecedent-focused, support-oriented approach to managing problematic behavior after TBI. In addition to specific behavior management procedures, this approach emphasizes support for engagement in personally meaningful activities, facilitation of effective self-regulation, and construction of a compelling, organized, and adequately realistic sense of personal identity. We have summarized three neuropsychological rationales for this approach along with empirical evidence. Finally, we have described a successful statewide community support program within which PBIS procedures are highlighted.

KEY CLINICAL POINTS

- A growing literature backs the use of positive behavioral intervention and supports in the development of interventions for individuals who experience behavioral challenges following brain injury.
- Comprehensive behavioral supports include interventions that focus on helping the individual with brain injury to 1) sustain engagement in daily activities meaningful to the individual, 2) construct an organized sense of identity that is non–disability oriented, and 3) learn strategies to regulate his or her own behaviors.
- Traditional clinician-directed, consequence-based, and externally controlled behavior supports are often ineffective for individuals with brain injury and behavioral difficulties who live in the community. This results in the need to develop context-sensitive interventions that are inclusive of the input of the individuals for whom the supports are developed.

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CHAPTER 39

Complementary and Integrative Treatments

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PATIENTS WITH TRAUMATIC BRAIN INJURY (TBI) are often left with residual deficits, disabilities, and reduced quality of life despite having received conventional treatments. Integrative treatments combining medication, rehabilitation, and complementary approaches are being developed to optimize patient outcomes (Brown et al. 2009). Complementary and alternative medicine includes herbs, nutrients, nootropics, mind-body practices, neurotherapy, and lifestyle changes. Patients seek alternative approaches when standard treatments are insufficient or cause intolerable side effects. In general, complementary treatments have fewer side effects and may ameliorate fatigue, cognitive dysfunction (attention, concentration, and executive functions), memory impairment, and aphasias. Furthermore, in our experience, psychological sequelae, such as anxiety, depression, anger, and posttraumatic stress disorder (PTSD), may respond better to complementary treatments in TBI patients, who are prone to adverse effects from psychotropic medications. Indications for complementary treatments are proposed in Table 39–1.

The number of human studies using complementary treatments in TBI per se is limited. Therefore, our review includes overlaps in the pathophysiology of TBI with dementia, age-associated memory impairment, stroke, and animal models of trauma and ischemia. Because TBI is often complicated by secondary ischemia, patients may benefit from compounds used to reduce ischemic injury. Controlled clinical studies are available for many agents, but for some there are only animal studies, open trials, and clinical experience. In general, the dearth of controlled studies may not reflect the usefulness of these agents but rather the lack of financial incentive to invest in costly clinical trials for products that are inexpensive or not patentable.

In this chapter we discuss physiological mechanisms, suggested clinical guidelines, complex cases, and comorbid conditions. Clinicians can safely augment standard treatments with complementary regimens to enhance recovery. Although early treatment is preferable, in practice

TABLE 39–1. Indications for complementary treatments in traumatic brain injury

I. Acute injury
Provide neuroprotection, accelerate neuronal repair.
Ameliorate damage due to secondary cerebral edema.
Reduce length of coma and improve neural function.
Reduce inflammation.
II. Recovery phase
Increase cellular energy and support repair systems.
Protect membranes and other cellular components.
Enhance neural transmission, neuroplasticity, and long-term potentiation.
Stimulate ascending reticular activating system.
Improve cognitive function, memory, language, energy, alertness, attention, mood, sleep, and anxiety.
III. Long-term rehabilitation
Augment cognitive, motor, and language rehabilitation.
Improve emotion regulation. Ameliorate psychological sequelae: depression, anxiety, posttraumatic stress disorder, insomnia, anger outbursts, and mania.
Reduce reliance on medications with adverse side effects, including anxiolytics (benzodiazepines), antipsychotics, antidepressants, opioids, and anticonvulsants.
Counteract medication side effects (e.g., cognitive slowing, memory problems, depression, or fatigue).
Improve higher-level cognitive functions necessary for interpersonal relationships and work.

we find that even those with long-standing deficits can derive substantial benefits. Additional controlled studies are needed to confirm the efficacy and extend the evidence base for clinical applications of complementary and integrative treatments for TBI.

Framework of Physiological Mechanisms

The probable mechanisms by which complementary treatments improve brain function can be placed within known pathophysiological constructs: neurotransmitter hypotheses, biochemical and metabolic derangements, neuroanatomy, and brain wave activity. Neurotransmitter abnormalities after TBI occur in the cholinergic system (acetylcholine), catecholamines (dopamine [DA] and norepinephrine [NE]), indoleamine (serotonin [5-HT]), and *N*-methyl-D-aspartate (NMDA)–glutamate receptor systems (Arciniegas and Silver 2006). Biochemical and metabolic derangements thought to be involved in brain injury include impairments in cellular (mitochondrial) energy production (Verweij et al. 2000, 2007), presence of free radicals, hypoxia, secondary ischemia, nerve membrane alterations, decreased calcium channel conductance, nitric oxide, and blood-brain barrier damage. Pericontusional edematous areas in patients with mild TBI show cell loss and ischemic changes (Son et al. 2000). After TBI in rats, there is an increase in neurotrophic factors such as nerve growth factor, which attenuates cholinergic deficits (Dixon et al. 1997).

Complementary treatments presumably enhance neuronal repair by neutralizing free radicals, increasing mitochondrial energy production and transport, reducing inflammation, improving cholinergic and dopaminergic function, and inducing neuroplasticity; they also work through stimulative effects. Mitochondrial energy production is critical to fuel both cellular activity and cellular repair mechanisms. Nootropics are synthetic cognitive-enhancing and neuroprotective agents widely studied and used in Europe. Evidence suggests that nootropics improve antioxidant status, membrane fluidity, mitochondrial function, neurotransmitter levels, mRNA protein synthesis, cerebral blood flow, neuroplasticity, transcallosal communication, and long-term potentiation (neuroplasticity based on increased neuronal connectivity) (Gouliaev and Senning 1994; Kessler et al. 2000; Kitani et al. 2000; Knoll 2000; Maruyama et al. 1999; Vernon et al. 1991; Zhu et al. 2000). Electroencephalographic (EEG) maps of TBI show excess slow wave activity and/or decreased beta or alpha, similar to poststroke. Cognitive activating agents decrease slow wave activity and increase alpha and beta. Neurotherapy protocols are being developed to improve brain wave activity, cognitive function, memory, and emotional stability (Duff 2004; Ochs 2006; Thornton and Carmody 2005, 2008). See Table 39–2 for putative mechanisms of action for alternative compounds. Space limitations preclude a detailed review of the evidence for probable mechanisms of action for each treatment (see Brown and Gerbarg 2005; Brown et al. 2009).

General Principles for Integrative Treatments in TBI

The psychopharmacological principles for using complementary treatments are essentially the same as those for conventional drugs, with some qualifications. As with prescription medications, in fragile patients, one begins with low doses and increases slowly. Doses are titrated while balancing benefits and side effects. Raw natural compounds often contain multiple bioactive constituents, and these may have therapeutic, antagonistic, synergistic, or toxic properties. Progress in biochemistry (e.g., high-pressure liquid chromatography) has improved identification of active therapeutic components, removal of toxic compounds, and standardization of products. Although there are few studies of combination treatments, understanding the probable underlying mechanisms informs clinicians of the need for caution with certain combinations (e.g., two agents that both have cholinergic effects) and, conversely, the safety and synergistic benefits of other combinations. Some agents have dramatic effects, but most are mild and gradual. Nevertheless, even modest effects may result in significant gains in quality of life. Combining agents is discussed for treatments that, in our experience, have been effective without serious adverse reactions. Patients with TBI are often too ill or inattentive to maintain adequate nutrition. Therefore, particular attention must be given to vitamins and nutrients that sustain and enhance neuronal functions. Mind-body practices are being used in rehabilitation of patients with brain injury (Leskowitz 2003). Benefits may include normalization of brain wave activity, balancing of stress response systems, pain reduction, as well as enhancement of body awareness, balance, cognitive function, and mental focus. In clinical practice, we also find improvements in emotion regulation (less anxiety and overreactivity). Table 39–3 presents suggested treatment guidelines, clinical indications, doses, and side effects. Figure 39–1 is a clinical decision-making flow sheet for target symptoms. For more information on how to combine standard care with complementary treatments, see Brown et al. (2009).

Doctors and consumers are concerned about the quality of herbs and nutrients. Advances in biochemistry have improved the purity and stability of many products (Wagner 1999). Although the publication of specific brands is not the norm in a text of this kind, in the field of alternative medicine it is particularly important to choose products that have proved to be of good quality (see Table 39–4 for product lists). The following compounds in the brands we have listed are available in pharmaceutical grade: centrophenoxine, acetyl-L-carnitine, citicoline, *S*-adenosylmethionine (SAMe), picamilon, idebenone, vinpocetine, racetams, and L-deprenyl. Brands of the herbs ginkgo and ginseng have been assessed and reported by ConsumerLab.com. We have contacted the manufacturers of *Rhodiola rosea,* galantamine, and SAMe for information regarding standardization, content, purity, and batch testing (including shelf life). Invariably, some products and companies will change over time. Appendix 39–1 provides resources for updated product information. Clinicians may

contact manufacturers and request information about content, purity, testing, and quality control.

Cholinergic Enhancing Agents

Citicoline

Citicoline (CDP-choline), or cytidine 5-diphosphocholine (CDPc), readily crosses the blood-brain barrier and dissociates into choline, an acetylcholine precursor, and cytidine, a ribonucleoside. Dempsey and Raghavendra Rao (2003) showed that in animals, CDPc prevented TBI-induced neuronal loss in the hippocampus, decreased cortical contusion volume, and improved neurological recovery. CDPc also enhances incorporation of the choline moiety into phospholipids, synthesis of phospholipids, and cerebral mitochondrial lipid metabolism (Petkov et al. 1992). In addition to increasing phospholipid synthesis, CDPc improves the regulation of cellular energy charge and the functioning of neurotransmitters and receptors by increasing the ability of adenosine triphosphatase to break down adenosine triphosphate (ATP) (to generate energy in mitochondria) and by improving the function of Na^+/K^+-adenosine triphosphatase (to maintain cellular membrane potential), which is crucial for cell membrane integrity and electrical transmission. The choline moiety is partially converted into betaine, a methyl donor to homocysteine, yielding methionine, which is incorporated into proteins. CDPc has been used in Europe and Japan to treat stroke, dementia, and TBI. A review of studies is presented in Table 39–5 (also see Poole and Agrawal 2008; Spiers and Hochanadel 1999). Animal studies have shown that CDPc protected cerebral cortex and hippocampus by decreasing edema and blood-brain barrier breakdown. Human studies indicate increased cerebral blood flow, reduced infarct volume, accelerated recovery of consciousness, and improved recovery of cognitive, memory, verbal, and motor deficits (see Table 39–5) (Fioravanti and Yanagi 2005; Mitka 2002; Secades and Lorenzo 2006). Human studies have been variable in quality (Poole and Agrawal 2008). Clinically, we find CDPc beneficial in mild, moderate, or severe TBI, immediately after injury or years later, for cognitive function, memory, mental clarity, and state of consciousness. CDPc is well tolerated with minimal side effects.

Galantamine

Galantamine, a tertiary alkaloid extracted from snowdrop (*Galanthus nivalis*), was used by the long-lived people of the Province of Georgia for centuries to enhance memory in old age. It was available in Eastern Europe and Russia for 40 years before being released in the United States as a prescription drug for Alzheimer's disease. Galantamine is a nicotinic allosteric modulator and a weak inhibitor of acetylcholinesterase (the enzyme that degrades acetylcholine at cholinergic synapses). For treatment of Alzheimer's disease, it is comparable to other cholinesterase inhibitors in short-term trials (5–6 months), and improvement continues beyond 6 months—that is, better than the delayed rate of deterioration seen with other cholinesterase inhibitors such as donepezil (Tariot et al. 2000; Wilcock et al. 2000). In our clinical practice, an herbal extract of *Galanthus nivalis* combined with *Rhodiola rosea* (see below) has been more tolerable and sometimes more effective than galantamine or donepezil.

Huperzine A

For patients who cannot tolerate cholinergic drugs, huperzine A has fewer side effects. This alkaloid extract of Chinese club moss (*Huperzia serrata*) is a potent selective reversible acetylcholinesterase inhibitor (Liang and Tang 2004; Little et al. 2008) with neuroprotective properties (see Table 39–2). Huperzine is rapidly absorbed, penetrates the blood-brain barrier, and has a long duration of acetylcholinesterase (AChE) inhibition. Positive outcomes have been reported in vascular dementia and age-related memory decline (Akhondzadeh and Abbasi 2006; Wang et al. 2006). A review of huperzine A for dementia included double-blind, randomized, placebo-controlled (DBRPC) studies from China showing significant improvements in the Alzheimer's Disease Assessment Scale (ADAS) cognitive subtest, Mini-Mental State Examination, behavior, mood, and activities of daily living (Little et al. 2008). The reviewers also described a Phase Ib study of 15 cognitively normal subjects (age 65–70) showing that huperzine A inhibited AChE more than 50% in all subjects but had no significant inhibition of butyrylcholinesterase (this may account for the mildness of peripheral cholinergic symptoms) (Haigh et al. 2008). A 24-week Phase II multicenter trial of huperzine A for mild to moderate Alzheimer's disease is being conducted under the direction of Paul Aisen at Georgetown University. Patients will be given huperzine A 200 μg bid, 400 μg bid, or placebo. Huperzine is generally well tolerated. Patients who are sensitive to side effects should be started on lower doses.

Centrophenoxine (Meclofenoxate)

Centrophenoxine (CPH), or meclofenoxate, widely used in Europe (brand name Lucidril), is a composite of parachlorophenoxyacetic acid (a synthetic version of plant growth hormone) and dimethyl-aminoethanol (DMAE, a by-product of choline metabolism). CPH supplementation elevates brain choline levels (Wood and Péloquin 1982). Based on the membrane hypothesis of aging, Zs-Nagy (1994) attributed the effects of CPH to the rapid delivery of DMAE to the brain for incorporation into nerve cell membranes as phosphatidyl-DMAE, an avid scavenger of rapidly acting OH-radicals (see Table 39–2). For a review of research, see Table 39–5 and Zs-Nagy (1994). In a DBRPC study of 50 patients with medium-level dementia, CPH alone significantly improved memory, cognitive function, and behavior compared with placebo (Pék et al. 1989). In our experience, CPH is useful in TBI treatment for memory, mental focus, and alertness. For improving memory and cognitive function, it is synergistic with racetams, ginkgo, and selegiline.

TABLE 39–2. Putative mechanisms of action for alternative compounds

Compound	Cholinergic	Neurotransmitters NE, DA, 5-HT	Receptors	Mitochondrial energy	Antioxidant	Hypoxia	Secondary ischemia
CDP-choline	+	+++		++	++	+	++
Galantamine	+		Nicotinic-Chol				
Huperzine A	+		NMDA				
Centrophenoxine	+			+	+	+	+
Acetyl-L-carnitine	+	+	NMDA	+++	+++	++	++
S-adenosylmethionine	+	+++	β-NE GABA (muscarinic-Chol)	++	+++		++
Picamilon							++
Creatine				++			
Idebenone	½+	++	+	++	++	+	+
Rhodiola rosea	+	+++		+++	++	+	
Withania somnifera		GABA	↓ DA		++		
Vinpocetine			Glutamate				+
Ginkgo biloba		++			+	+	+
Panax ginseng		++	GABA			+	+
Racetams	+	+++	NMDA-glutamate (muscarinic-Chol)	++		+	+
L-Deprenyl		+++	Protects		++		
Bio-Strath				+	++		
Omega-3 fatty acid			+		+		
Inositol	+		5-HT NE Chol				
N-acetylcysteine			NMDA?		++		
Choline	+						
Melatonin		DA			+++		

(Each row continues with additional columns on next page)

TABLE 39–2. Putative mechanisms of action for alternative compounds *(continued)*

Compound	Blood flow	Cell membrane	BBB	NGF	Lipofuscin	LTP	TC	Stimulant
CDP-choline		++	++					+
Galantamine								++
Huperzine A								++
Centrophenoxine		+	+		↓		+	++
Acetyl-L-carnitine	+	++	+		↓			++
S-adenosylmethionine		+++						+
Picamilon	+++							+
Creatine								
Idebenone	?			+		+	+	+
Rhodiola rosea								+++
Withania somnifera								
Vinpocetine	+++	+				+		+
Ginkgo biloba								+
Panax ginseng								+
Racetams	?	+				+	++	+
L-Deprenyl		++		+++				+
Bio-Strath		+						+
Omega-3 fatty acid		++						
Inositol		++						
N-acetylcysteine								
Choline								
Melatonin								

Note. β-NE=β-adrenergic; BBB=blood-brain barrier; Chol=cholinergic; DA=dopamine; 5-HT=5-hydroxytryptamine; GABA=γ-aminobutryic acid; LTP=long-term potentiation; NE=norepinephrine; NGF=nerve growth factor; NMDA=*N*-methyl-D-aspartate; TC=transcallosal transmission; +=some effect; ++=moderate effect; +++=strong effect; ?=possible effect; blank=no information available; ↓=decreased

TABLE 39–3. Treatment guidelines

Complementary treatment	Suggested clinical use	Recommended doses for TBI	Side effects and drug interactions[a]
CDP-choline	Cognition, memory, state of consciousness	Start 1,000 mg bid Max ≥1,500 mg bid	None significant, occasional agitation.
Galantamine	Memory	8–32 mg/day	Minor GI upset, nausea.
Huperzine A	Memory	Start 50 µg bid ↑ by 50 µg 3–7 days Max 100–200 µg bid	Rare, mild nausea.
Centrophenoxine	Memory, alertness, mental focus	Start 250 mg bid Max 1,000 mg bid	Take with breakfast and lunch. Minimal; combined with cholinergic agents: headache, muscle tension, insomnia, irritability, agitation, facial tics.
Acetyl-L-carnitine	Alertness, focus	500 mg bid ↑ every 3–7 days Max 1,500 mg bid	Take with food to prevent gastric upset, heartburn.
S-adenosylmethionine	Focus, vigilance, mood, energy	Start 400 mg bid ↑ by 400 mg every 3–7 days Max 1,500 mg bid	Mild occasional GI, agitation, anxiety, insomnia; rare palpitations. Mania in bipolar patients. Take 20 minutes before breakfast and lunch. Increase as tolerated (nausea and loose stools may occur).
Picamilon	Cerebral circulation, alertness, focus, anxiety, depression	50 mg bid Up to max 100 mg tid	High dose: hypotension. No allergenic, carcinogenic, or teratogenic effects in 6-month test.
Creatine	Memory, cognition, energy	Loading dose 5,000 mg qid (with juice) 5 days Maintain at 5,000 mg bid	Adequate hydration is necessary to minimize side effects. May cause renal problems if very dehydrated/overheated.
Idebenone	Focus, alertness, energy	270–900 mg/day	GI, anxiety, insomnia, headache, tachycardia, decreased platelet aggregation.
Rhodiola rosea	Fatigue, energy, cognition, attention, memory, mood	Start 75–150 mg qd Max 150–300 mg bid	Activation, agitation, insomnia, jitteriness. Rare: increased blood pressure, angina, bruising. Avoid in bipolar I mania. Take 20 minutes before breakfast and lunch.
EZ-Energy *R. rosea* 70 mg, *E. senticosus,* *S. chinensis*, *A. Mandshurica,* *R. carthamoides*	Fatigue, cognition, attention, memory, physical strength; calms patients who get agitated on activating herbs	1–2 tabs/day	Minimal side effects of component herbs. Caution in bipolar patients.
Energy Reserves *R. rosea*, *E. senticosus*, *S. chinensis*, *B. monnier*	Fatigue, cognition, attention, memory	1–3 tabs/day before 2 P.M.	Minimal side effects of component herbs. Caution in bipolar patients.
ADAPT232 *R. rosea*, *E. senticosus*, *S. chinensis*	Fatigue, cognition, attention, memory	1–3 tabs/day before 2:00 P.M.	Minimal side effects of component herbs. Caution in bipolar patients.
Withania somnifera	Augment energy	200 mg 1 or 2 bid 1.5% with anolides	Stomach upset, skin rashes.
Vinpocetine	Cerebral circulation, cognition, memory	5–10 mg tid	Rare: nausea, low blood pressure. Avoid with NSAIDs.
Ginkgo biloba	Alertness, energy, cognition, memory	120–240 mg/day	Minimal, headache, decreased platelet aggregation.
Panax ginseng	Energy, cognition, focus	400–800 mg/day	Activation. Excess doses: agitation, hormonal effects, insomnia.
Maca *Lepidium myenii*	Energy, cognition, focus	750 mg 2–6 tabs/day	Activation, jitteriness. Contraindications: estrogen sensitive tumors, prostate cancer, endometriosis.

TABLE 39–3. Treatment guidelines *(continued)*

Complementary treatment	Suggested clinical use	Recommended doses for TBI	Side effects and drug interactions[a]
Racetams Aniracetam Pramiracetam	Aphasia, dyslexia	750 mg bid ≥ 600 mg bid	Minimal. Rarely: anxiety, insomnia, agitation, irritability, headache.
L-Deprenyl	Cognition, memory	10–15 mg/week	Take 2.5 mg 5 days/week. More than 10 mg/day may lead to MAOI effects (e.g., hypertension).
B vitamins Bio-Strath B_{12} B complex	Cognition, memory, energy, mood	 1 tbsp bid or 3 tabs bid 1,000 µg/day 1 tab qd	Rare: agitation. May increase restenosis in men with cardiac stents with baseline homocysteine <15 mmol/L.
Omega-3 fatty acids	Depression or bipolar depression	8,000–10,000 mg/day EPA+DHA ~ ratio 2:1	GI distress, belching; gas can be minimized using highly refined fish oils.
Inositol	Depression or bipolar depression	12–20 g/day	Gas, loose bowels, mania in excess doses.
N-acetylcysteine	Depression or bipolar depression	1,200–2,400 mg bid	None reported in appropriate doses.
Choline	Mania or bipolar mania	2,000–7,200 mg	Excess doses: depression.
Melatonin	Insomnia	3–9 mg hs	Sedation. Rare: activation.

Note. DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; GI=gastrointestinal side effects; MAOI=monoamine oxidase inhibitor; mmol=micromoles; NSAID=nonsteroidal anti-inflammatory drug; TBI=traumatic brain injury; ↑=increase.

[a]Common side effects are listed. There may be additional rare side effects. The presence of high blood pressure, diabetes, or any chronic or serious medical condition should be considered in prescribing complementary treatments. The concomitant use of certain medications, such as anticoagulants, with supplements may cause adverse reactions. The safety of supplements, other than omega-3 fatty acids and vitamins during pregnancy or breast feeding, has not been established.

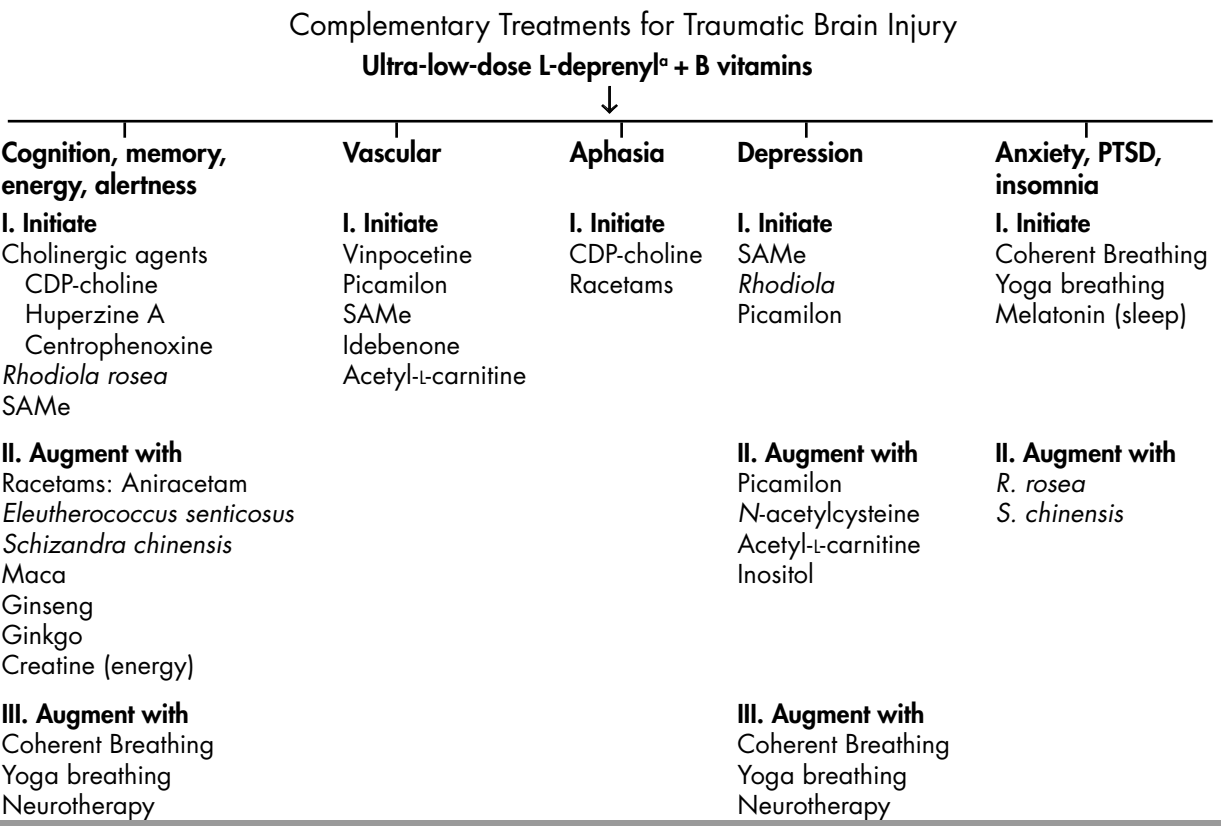


FIGURE 39–1. Clinical decision making for target symptoms.

[a]Ultra-low-dose L-deprenyl=10–15 mg/week.
CDP-choline=citicoline; PTSD=posttraumatic stress disorder; SAMe=*S*-adenosylmethionine.

TABLE 39–4. How to obtain quality complementary compounds

Compound	Brand/Company	Source
CDP-choline	Smart Nutrition (SN)	800-479-2107; www.smart-nutrition.net
	Life Extension (LEF)	800-544-4440; www.lef.org
Galantamine	Reminyl//IAS	866-800-4677; www.antiaging-systems.com
Huperzine A	GNC (General Nutrition Centers)	877-GNC-4700; www.gnc.com
	SN, Swanson Health Products	800-824-4491; www.SwansonVitamins.com
	Puritan's Pride	800-749-6172; www.Puritansale.com
Centrophenoxine	Lucidril/International	866-800-4677; www.antiaging-systems.com
	International Antiaging Systems (IAS)	Fax: 011-44-870-151-4145
Acetyl-L-carnitine	LEF	800-544-4440; www.lef.org
	Puritan's Pride	800-749-6172; www.Puritansale.com
S-Adenosylmethionine (SAMe)	SAMe/NatureMade	www.naturemade.com, pharmacies, buyer's clubs (Sam's, Costco, BJs)
	Donamet or Samyr/IAS	www.antiaging-systems.com
	Jarrow	www.jarrow.com
	Puritan's Pride	www.Puritansale.com
Picamilon	IAS	www.antiaging-systems.com
	Smart Nutrition	800-479-2107; www.smart-nutrition.net
Creatine	Major brands, GNC	Health food stores
	Now Foods	888-669-3663; www.Nowfoods.com
	Schiff	www.SchiffVitamins.com
	Solgar	800-645-2246; www.Solgar.com
	TwinLab	800-723-5837; www.Twinlab.com
Idebenone	Thorne Research	800-932-2953; www.thorne.com
	Smart Nutrition	800-479-2107; www.smart-nutrition.net
Rhodiola rosea	Rosavin Plus/Ameriden	888-405-3336; www.ameriden.com
	Arctic Root SHR-5/Swedish	+46-31-339-6680; www.shi.se
	Mind Body & Spirit/Verde Botanica	877-282-5366; www.proactivebio.com
	EnergyKare/Kare-N-Herbs	800-774-9444; www.Kare-N-herbs.com
	Rosavin100/Medicine-Plants	800-584-0228; www.Medicine-plants.com
EZ-Energy *R. rosea* 70 mg, *E. senticosus*, *S. chinensis*, *A. Mandshurica,* *R. carthamoides*	Ameriden	888-405-3336; www.Ameriden.com
Energy Reserves *R. rosea*, *E. senticosus*, *S. chinensis,* *B. monnieri*	Verde Botanica	877-282-5366; www.proactivebio.com
ADAPT232 *R. rosea*, *E. senticosus*, *S. chinensis*	Swedish Herbal Institute	+46-31-339-6680; www.shi.se
Withania somnifera	TranquilityKare/Kare-N-Herbs	800-774-9444; www.Kare-N-Herbs.com
Vinpocetine	LEF, SN, Intensive Nutrition	800-333-7414; www.intensivenutrition.com
Ginkgo biloba	Ginkgold/Nature's Way	Health food stores, pharmacies
	Ginkoba/Pharmaton	
Panax ginseng (Korean)	Hsu's Ginseng	800-388-3818; www.hsuginseng.com
	Power Max 4x/Action Labs	800-932-2953; www.action-labs.herbsmd.com
Maca	Medicine-Plants	800-584-0228; www.Medicine-plants.com
Racetams	IAS	www.antiaging-systems.com

TABLE 39–4. How to obtain quality complementary compounds *(continued)*

Compound	Brand/Company	Source
L-Deprenyl	Jumex, Cyprenil (liquid)/IAS	www.antiaging-systems.com
	Deprenyl, Selegiline, Eldepryl	By prescription from pharmacies
B vitamins	Bio-Strath/Nature's Answer	800-681-7099 or health food stores
B complex	Major brands	Health food stores
B_{12} (sublingual)	B12 Dots/Solgar	800-645-2246; www.Solgar.com
	TwinLab	800-723-5837; www.Twinlab.com
Omega-3 fatty acids	Major brands	
	Ultra Pure Fish Oil/Vital Nutrients	888.328.9992; www.Vitalnutrients.net
	Nordic Naturals	800.662.2544 x3; www.Nordicnaturals.com
Inositol	Major brands	Health food stores
N-acetylcysteine	NAC/Swanson	800-824-4491; www.SwansonVitamins.com
	Puritan's Pride	800-749-6172; www.Puritansale.com
Choline	Solgar	800-645-2246; www.Solgar.com
		Health food stores
Melatonin	LEF	800-544-4440; www.lef.com
	Major brands	Health food stores

Note. This list of specific brands is not comprehensive. It simply represents easily available brands that we have used and found to be consistently of good quality. Because brands and companies may change, the physician should reevaluate each product over time. For independent evaluations of many brands, see Appendix 39–1, www.consumerlab.com, or www.supplementwatch.com. Major brands include Now, Schiff, Solgar, TwinLab, and New Chapter.

Acetyl-L-Carnitine

L-Carnitine and acetyl-L-carnitine (ALCAR) protect against neurotoxicity (as do creatine, coenzyme Q10, lipoic acid, vitamins C and E, melatonin, and resveratrol) (Virmani et al. 2005). ALCAR and lipoic acid are synergistic. ALCAR, an ester of L-carnitine (a trimethylated amino acid), enhances the cholinergic system (Pettegrew et al. 2000) and facilitates uptake of acetylcoenzyme A into mitochondria during fatty acid oxidation. (For research on ALCAR, see Table 39–5.) In our experience, TBI patients often improve in energy, neural stamina, and cognitive function within weeks of starting ALCAR. Patients with TBI often experience mental and physical fatigue, sometimes lasting for years after their injury. The term *neural fatigue* is used to indicate mental fatigue or the fatigue that occurs with mental (as opposed to physical) activity.

Nutrients and Vitamins

S-Adenosylmethionine

SAMe, a naturally occurring condensation of the amino acid methionine and ATP, is crucial for methylation in the body. As a methyl donor, SAMe helps maintain cellular membrane integrity (repairing damaged proteins) and the fluidity of the lipid bilayer in nerve cell membranes (via formation of phosphatidyl choline) and generates glutathione, the body's major antioxidant. (For research reviews, see Brown et al. 2000, 2009.) Although SAMe has the EEG signature of a tricyclic antidepressant, it also enhances the function of the dopamine system (beneficial in treatment of TBI, attention-deficit/hyperactivity disorder [ADHD], and Parkinson's disease) (Brown et al. 2009). In primates, SAMe reduced impairments and facilitated recovery from lesions in motor and dorsolateral prefrontal cortex. In a pilot DBRPC study of 44 patients, SAMe significantly improved survival when given within 24 hours of ischemia or hemorrhagic stroke (Monaco et al. 1996) (Table 39–6). In a DBRPC study of 30 patients with TBI, 1 month of SAMe decreased mean postconcussion symptom scores by 77% compared with 49% in the placebo group. Statistically significant improvements in headache and vertigo were documented (Bacci-Ballerini et al. 1983). The fact that methylene tetrahydrofolate reductase and B_{12} cofactor regenerate methionine may explain why Vitamin B_{12} (1,000 μg/day) and folate (800 μg/day) can enhance response to SAMe (Brown et al. 2009). Because SAMe rapidly oxidizes when it is exposed to oxygen, the method of manufacturing and sealing tablets in individual blister packs is important for full potency. Also, some brands contain higher proportions of inactive isomers. Therefore, it is essential to use only brands that have demonstrated consistent efficacy in clinical trials and clinical practice.

Case 1. Combined treatments for postconcussion symptoms: CDPc, SAMe, selegiline, EZ-Energy (*R. rosea* and other herbs), T_3, phenylalanine

Angelina, a 50-year-old secretary, had a history of anxiety but was generally well until a large unit of office equipment fell on the left top of her head. Although she did not lose consciousness, she felt "dazed" and developed headaches, nausea, anxiety, fatigue, and had difficulty functioning. After 4 weeks without improvement, she sought

TABLE 39–5. Evidence for cholinergic enhancing agents

Authors	Study	Comments
CDP-choline (CDPc)		
Carcassonne and LeTourneau 1979	Double-blind controlled study of 43 children with "altered levels of consciousness" from mild-moderate TBI. CDPc accelerated recovery of normal consciousness, neuropsychiatric disorders, and electroencephalogram vs. standard-treatment control subjects.	Nonrandomized
Cohadon and Richer 1985	Placebo-controlled study of 60 comatose TBI patients 90 days. CDPc → shorter coma, improved motor deficits, and ability to walk vs. placebo.	Nonrandomized
Levin 1991	DBRPC study of 14 consecutive admissions mild-moderate brain injury (GCS 13–15): 1,000 mg/day of CDPc or placebo started after coming out of coma (≥1 month postinjury). CDPc → significantly more improvement (especially dizziness and recognition memory) vs. placebo.	Better results possible with earlier treatment
Calatayud Maldonado et al. 1991	SBRC study of 216 patients with moderate-severe brain injury (GCS 5–10). Immediate treatment with CDPc → ↑cognitive, motor, and psychic improvements and ↓ length of intensive care stays vs. standard treatment.	
Lozano 1991	39 TBI nonsurgical patients (GCS 5–7). Continuous infusion CDPc 3–6 g/day the first 2 weeks ↓ length of stay ($P<0.001$) vs. similar group given standard treatment. Control group computed tomography scans: more cerebral edema ($P<0.005$). Differences in GCS did not reach significance.	Nonrandomized
Clark et al. 1999, 2001	DBRPCMC 6-week study of 899 patients given 1,000 mg bid CDPc or placebo within 24 hours of stroke. Patients with baseline National Institutes of Health Stroke Scale scores ≥ 8 had higher rate of full recovery with CDPc (33%) vs. placebo (21%).	
Leon-Carrion et al. 2000	7 patients hypoperfusion of inferoposterior temporal lobe. Infusion 1 g CDPc 1 hour before inhalation of xenon-133 → ↑ average blood flow from 88.5% to 96.15% in area T3L.	Small number of subjects
Leon-Carrion et al. 2000	Randomized controlled trial of 10 patients with TBI and severe memory impairments given 3 months of neuropsychological memory rehabilitation randomly assigned to CDPc 1 g/day or placebo. CDPc improved attention, vigilance, visual retention; improvements statistically significant for verbal fluency and Luria's Memory Words—Revised ($P<0.05$) vs. placebo.	Small number of subjects
Warach, in Mitka 2002	DBPC 6-week study of 214 patients with middle cerebral artery strokes. CDPc → dose-related reduction in average increase in infarct volume (magnetic resonance imaging).	Nonrandomized
Huperzine A		
Zhang et al. 2002 (cited in Wang et al. 2006)	60 patients with mild and moderate TBI, 30 given 0.8 g piracetam and 20 mg nimodipine bid. A comparable group of 30 received the same interventions plus 0.1 mg huperzine A bid. Both groups improved in memory and cognitive function; those given huperzine-A showed more dramatic improvements.	Nonrandomized
Centrophenoxine (CPH)		
Pék et al. 1989	DBRPC study of 50 patients older than age 60, medium-level dementia (DSM-III, Category 1) residents in nursing home over 3 months. Those given CPH alone (1 g bid) for 8 weeks → 47.6% significantly improved memory, cognitive function, behavior vs. 28.0% given placebo. Ratings: Nuremberg Gerontopsychological Inventory, psychologist rating, staff rating of activities, and self-rating.	Overall rating was more qualitative than quantitative
Acetyl-L-carnitine (ALCAR)		
Thal et al. 2000	1-year study of 431 patients with probable Alzheimer's disease. Those under age 65 years given ALCAR 3 g/day deteriorated less than those given placebo.	Apolipoprotein E status not reported
Arrigo et al. 1990	DBPC crossover study of 12 elderly subjects with cerebral vascular disease. ALCAR improved reaction time, memory, and cognitive performance vs. placebo. ALCAR caused no side effects.	
Rosadini et al. 1990	8 out of 10 men with brain ischemia had increased regional cerebral blood flow 1 hour after a dose of ALCAR, 1,500 mg intravenously.	

Note. DBPC=double-blind placebo-controlled; DBRPC=double-blind, randomized, placebo-controlled; DBRPCMC=double-blind, randomized, placebo-controlled multicenter; GCS=Glasgow Coma Scale; SBRC=single-blind, randomized, controlled; TBI=traumatic brain injury. →=resulted in; ↑=increased.

treatment and responded to CDPc 1,000 mg bid and selegiline 10 mg/day with some increase in mental clarity. The addition of *R. rosea* 150 mg caused overstimulation, but she responded well to EZ-Energy (*R. rosea, P. ginseng, S. chinensis, A. mandshurica*), with improvements in energy and mood (see Table 39–3). Supplementation for 1 month with SAMe 600 mg/day led to significant increases in alertness, mental clarity, mental focus, and energy. When she later discontinued SAMe, the symptoms of mental fogginess, fatigue, and difficulty functioning rapidly returned. Two weeks after resuming SAMe, she regained the previous improvements and functioned well at work. She was subsequently diagnosed with subclinical hypothyroidism (slightly elevated TSH) and responded to 25 μg/day T_3 with further gains in energy and cognitive functions. On one occasion, she stopped taking T_3 only to relapse with fatigue. On a separate occasion, when Angelina tried to discontinue selegiline, the fatigue and loss of mental focus reoccurred. She restarted selegiline 10 mg/day augmented with phenylalanine 500 mg bid (selegiline uses phenylalanine as a substrate to form phenylethylamine, an excitatory neurotransmitter with mood-enhancing effects). Within 1 week, she felt much better with increased energy, alertness, and mental clarity.

Picamilon

Picamilon, a synthetic combination of two natural compounds, γ-aminobutyric acid and the B vitamin niacin, decreases cerebral blood vessel tone and increases cerebral blood flow in animal studies (Mirzoian and Gan'shina 1989). Despite its mild tranquilizing action (decreases motivated aggression in animals), it has mild stimulative properties and improves cognition. Although clinical trials in Russia using picamilon for stroke, dementia, and TBI report positive results, those studies were not available in English for our evaluation. In our experience, picamilon may improve alertness, mental focus, anxiety, and depression in patients with cerebral vascular impairment, TBI, and ADHD.

Creatine

Animal models show that creatine enhances cellular energy in brain injury (as well as in muscular dystrophy and other mitochondrial cytopathies). In a randomized pilot study of children (1–18 years of age) with TBI, 19 children were given standard treatment alone and 20 children were given standard treatment plus creatine (0.4 g/kg/day oral suspension) for 6 months. Children treated with creatine had shorter durations of posttraumatic amnesia, intubation, and intensive care unit stay. The proportion of children having headache, dizziness, and fatigue was significantly greater in controls than in those receiving creatine. No side effects were associated with creatine (Sakellaris et al. 2008) (see Table 39–6). The authors note that creatine ameliorates headaches, dizziness, and fatigue in children and adult TBI patients.

Idebenone

The extensive literature on idebenone, a variant of coenzyme Q10, has been reviewed (Brown et al. 2009; Gillis et al. 1994) (see Table 39–6). Idebenone serves as an electron carrier in the ATP-producing mitochondrial electron transport chain (Ikejiri et al. 1996), exerts antioxidant effects, protects astrocytes against reperfusion injury, and improves transcallosal response (transfer of information between hemispheres). Mitochondrial impairment has been demonstrated in TBI in humans (Signoretti et al. 2008). Idebenone improves mitochondrial oxidative metabolism in the human brain (see Table 39–6). A double-blind, randomized, placebo-controlled multicenter (DBRPCMC) study of 97 patients with mild to moderate multi-infarct dementia found that those given idebenone 90 mg/day showed greater improvements in memory, attention, orientation, vigilance, and verbal comprehension (Bergamasco et al. 1992). In two double-blind, randomized multicenter studies of patients with mild to moderate Alzheimer's disease, idebenone significantly improved Alzheimer Disease Assessment Scale (ADAS; Rosen et al. 1984) scores compared with placebo and tacrine (Gutzmann and Hadler 1998; Gutzmann et al. 2002). However, another DBRPCMC study failed to show significant slowing of cognitive decline (Thal et al. 2003). Apolipoprotein E status (associated with increased susceptibility to Alzheimer's disease) was not documented in these studies. We find that sluggish, psychomotor-retarded patients benefit most. The cost of idebenone is prohibitive for many patients.

B Vitamins and Bio-Strath

The methylation pathways that maintain cellular proteins, membranes, and antioxidants depend on B vitamins and folate as cofactors. B vitamin and folate deficiencies are associated with abnormalities of mood, memory, and cognition (Bottiglieri 1996). Supplementation with B vitamins improves mood and cognitive function in healthy subjects. Bio-Strath (B vitamin plus antioxidants) given to 75 patients ages 55–85 years with mild dementia for 3 months in a DBRPC trial led to improvement in short-term memory with physical and emotional benefits compared with placebo (Pelka and Leuchtgens 1995). The relationship between B vitamins and cognitive function persuades us to treat brain-injured patients with B vitamins. In men with baseline homocysteine levels of less than 15 μM/L, folate with B_{12} and B_6 supplementation may accelerate restenosis of cardiac stents (Lange et al. 2004).

Herbal Treatments

Rhodiola rosea (Golden Root, Arctic Root, or Roseroot)

Of the 30 species in the Rhodiola genus, *R. rosea* has been the most extensively studied. The following discussion draws on decades of Soviet research (Saratikov and Krasnov 1987), based on translations by Zakir Ramazanov (personal written communication, July 2001). (For reviews, see Brown and Gerbarg 2002; Brown et al. 2004, 2009; Petkov et al. 1986.) Root extracts of *R. rosea* have been approved for medicinal uses in the Russian pharmacopoeia

TABLE 39–6. Evidence for nutrients and vitamins

Authors	Study	Comments
***S*-Adenosylmethionine (SAMe)**		
Bacci-Ballerini et al. 1983	DBRPC study of 30 TBI patients given SAMe: 28 during acute phase and 2 at 1 month post-TBI. SAMe 100 mg iv plus 50 mg im daily for 30 days reduced mean postconcussion symptom scores by 77% vs. 49% on placebo. SAMe improved headache ($P<0.05$) and vertigo ($P<0.05$) vs. placebo. Two subjects had allergic reaction to iv SAMe.	Small number of subjects. Low dose of SAMe used. Nonstandard 4-point rating scale.
Monaco et al. 1996	DBRPC study of 41 patients within 24 hours of ischemic or hemorrhagic stroke given standard therapy with SAMe 2,400 mg/day iv, SAMe 3,200 mg/day iv, or placebo for 14 days. SAMe significantly improved survival ($P=0.017$).	
Creatine		
Sakellaris et al. 2008	6-month randomized controlled trial of 39 children (ages 1–18 years) with TBI (Glasgow Coma Scale 3–9 and Pediatric Trauma Score 4–12): 19 given standard treatment alone vs. 20 given standard treatment plus creatine (0.4 g/kg/day oral suspension) initiated within 4 hours of injury. Children given creatine had better short-term outcomes than control group: duration posttraumatic amnesia (21.40 vs. 81.50 days, $P<0.019$), intubation (4.10 vs. 8.89 days, $P<0.051$), intensive care stay (7.08 vs. 32.84 days, $P<0.056$). Proportion of children having symptoms was significantly greater in controls than in those given creatine: headache (93.8% vs. 11.1%, $P<0.001$), dizziness (56.3% vs. 11.1%, $P<0.005$), and fatigue (88.9% vs. 17.6%, $P<0.001$). No side effects with creatine.	
Idebenone		
Ihara et al. 1989	Two patients with MELAS: addition of idebenone to CoQ10 improved EEG, Wechsler Adult Intelligence Scale score, muscular weakness, peripheral nerve damage, and (cerebrospinal fluid) monoamines.	
Ikejiri et al. 1996	36-year-old man with MELAS: 5-month high-dose idebenone increased markedly cerebral metabolic ratio of oxygen and oxygen extraction fraction without increased cerebral blood flow on positron emission tomography, indicating idebenone improves mitochondrial oxidative metabolism in the brain.	
Seki et al. 1997	16-year-old boy with MELAS: EEG markedly improved after addition of idebenone to CoQ10. No progression of clinical abnormalities for 16 months.	
Napolitano et al. 2000	One patient with MELAS treated 24 months with idebenone and riboflavin, during which no strokelike episodes occurred. Neurological symptoms improved with recovery of brain magnetic resonance imaging and EEG abnormalities.	
Nakano et al. 1989	Nine patients with cerebrovascular disorders (arteriosclerosis or infarction) given idebenone 30 mg tid. Five patients showed improvements in EEG related to improvements in anxiety, irritation, restlessness, sleep, depression, and volition.	Open trial. Small number of subjects.
Bergamasco et al. 1992	DBRPCMC study of 97 patients with mild to moderate multi-infarct dementia. Those given idebenone 90 mg/day for 90 days showed greater improvements in memory, attention, orientation, vigilance, and verbal comprehension vs. placebo.	
Gutzmann and Hadler 1998	DBRPCMC 2-year study of 450 patients with mild to moderate Alzheimer's disease. Idebenone 270–360 mg/day statistically significant dose-dependent improvement on ADAS total score and all secondary measures vs. placebo. During the second year, further improvements occurred. Safety and tolerability comparable with placebo.	ApoE status not reported.
Gutzmann et al. 2002	DBRPCMC 60-week study of 203 patients with mild to moderate Alzheimer's disease. Intent-to-treat analysis: Idebenone (260 mg/day) performed better than tacrine (up to 160 mg/day). At 60 weeks, dropouts: 71.2% on idebenone and 90.9% on tacrine.	Large dropout rate. ApoE status not reported.
Thal et al. 2003	DBRPCMC 1-year study of 536 patients with mild to moderate Alzheimer's disease. Three different doses of idebenone failed to significantly slow cognitive decline (ADAS) compared with placebo.	ApoE status not reported.
B vitamin plus antioxidants		
Pelka and Leuchtgens 1995	DBRPC 3-month study of 75 patients with mild dementia ages 55–85 years. Bio-Strath (B vitamins, antioxidants) double usual adult dose. Placebo group deteriorated. Bio-Strath group improved short-term memory, physical and emotional benefits.	

Note. ADAS=Alzheimer's Disease Assessment Scale; ApoE=Apolipoprotein E; DBRPC=double-blind randomized, placebo-controlled; DBRCMC=double-blind randomized-controlled multicenter; DBRPCMC=double-blind randomized, placebo-controlled multicenter; EEG=electroencephalogram; MELAS=mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes; TBI=traumatic brain injury.

since the 1960s. Soviet investigators observed therapeutic effects (improvements in energy, alertness, cognitive function, and memory) in posttraumatic and vascular brain lesions, especially in early postinjury stages (Saratikov and Krasnov 1987). Rhodiola species contain many compounds that scavenge superoxide and hydroxyl radicals (Furmanowa et al. 1998). In animal studies, *R. rosea* increased and maintained higher levels of ATP and creatine in brain, muscle, liver, and blood (Kurkin and Zapesochnaya 1986; Saratikov and Krasnov 1987). It also increased brain norepinephrine, DA, and 5-HT and stimulated nicotine cholinergic systems (Petkov et al. 1986). In healthy individuals, *R. rosea* enhanced intellectual work capacity, abstract thinking, accuracy on tedious tasks, and reaction time (see Table 39–7). In a double-blind, placebo-controlled study of 60 first-year college students under stress, those given low-dose *R. rosea* (100 mg/day) showed significant improvement in mental fatigue, psychomotor function, and overall well-being (self-evaluation) (Spasov et al. 2000). We have observed that in patients with brain injury, *R. rosea* has a mild cognitive stimulant effect while it is also emotionally calming. No significant drug interactions have been reported. In our experience, *R. rosea,* particularly when combined with *Eleutherococcus senticosus, Schizandra chinensis, Panax ginseng, Ginkgo biloba, Withania somnifera* (Ashwaganda), and/or piracetam, can be beneficial for memory and cognition in TBI, age-associated memory impairment, stroke, and dementia patients. Patients often report improved energy, mental clarity, and memory. Response takes 1–12 weeks. Highly anxious patients may not tolerate higher doses because the activating effects sometimes exacerbate anxiety. *R. rosea* should be given 20 minutes before breakfast and lunch, starting with 150 mg/day and increasing by 150 mg every 3–7 days up to a maximum of 300 mg bid. Elderly, medically ill, or anxious patients should start by taking one-fourth to one-half of a capsule (37–75 mg) per day dissolved in tea or juice and increased slowly. We use *R. rosea* in a wide range of disorders of memory, cognition, and fatigue with generally good results. Combining treatments that target multiple aspects of neuronal repair can significantly improve recovery.

Case 2. Integrative treatments for TBI with mixed dysphoric mania: *R. rosea,* CDPc, SAMe, and huperzine A

Andrea was a successful corporate executive until she was hit by a car while bicycling and was found unconscious. She suffered loss of consciousness for over 3 hours and was treated for 1 month in the hospital for multiple injuries. Her symptoms included cognitive impairments with clouded thinking, memory problems, labile mood, lack of concern or awareness of her difficulties, and inability to function at work. Andrea's sister brought her to a psychiatrist who first treated her with sertraline, which triggered a manic episode with pressured speech, euphoria, and insomnia. Severe cognitive and memory deficits noted on neuropsychological testing were consistent with a clinical diagnosis of TBI with mixed dysphoric mania. After consulting Dr. R.P. Brown, Andrea was treated with 300 mg bid *Rhodiola rosea* (brand Rosavin Plus by Ameriden). Over the ensuing 3 months her memory, cognitive functions, and awareness improved. Addition of CDP-choline 1,000 mg bid led to further progress in memory, mental clarity, writing abilities, appropriate socialization, and resumption of work. SAMe 600 mg bid was added to alleviate depression. Note that SAMe was not used initially because it might have triggered mania in the earlier stages of recovery. SAMe was added safely only after there was improvement in mood lability from the *R. rosea* and CDP-choline. Although Andrea felt subjectively that she had recovered 60% of her cognitive function, she continued to experience difficulty focusing and concentrating. Donepezil (Aricept) 2.5 mg yielded a small benefit, but Andrea could not tolerate the side effects (nausea and diarrhea). She subsequently responded to huperzine A starting with 50 mg bid and slowly increasing to 100 mg bid with marked improvements in memory, concentration, and the ability to function at her previous level at work. There were no side effects. Although it could be argued that the patient might have recovered spontaneously, the clinical course had shown no progress for 8 months. Treatment with *R. rosea*, CDP-choline, and SAMe was followed by significant and rapid improvements with each complementary agent.

Vinpocetine

Vinpocetine, a semisynthetic alkaloid derivative of periwinkle (*Vinca minor*), has been used in Eastern Europe for cerebral vascular disorders. Studies show neuroprotection by inhibiting calcium/calmodulin-dependent cyclic guanosine monophosphate-phosphodiesterase 1, enhancing intracellular cyclic guanosine monophosphate levels in vascular smooth muscle, reducing resistance of cerebral blood vessels, and increasing blood flow (Bönöczk et al. 2000; van Staveren et al. 2001). Vinpocetine inhibits the molecular cascade caused by the rise of intracellular calcium. In a DBRPC study of 43 stroke patients, transcranial Doppler and near infrared spectroscopy found that vinpocetine improved cerebral perfusion and parenchymal oxygen extraction in the peristroke area (Bönöczk et al. 2002). (See Table 39–7 for review of studies.) We find that vinpocetine helps patients with positron emission tomography (PET) scan evidence of blood flow abnormalities.

Ginkgo biloba

As a neuroprotectant, *Ginkgo biloba* improves membrane fluidity and resistance to oxidative damage. Its EEG profile indicates cognitive activation, increasing alpha and low-beta frequencies as well as decreasing slow theta and delta. This pattern is typical of other cognitive activators such as donepezil, stimulants, monoamine oxidase inhibitors, and aniracetam. Diamond et al. (2000) reviewed 22 controlled ginkgo studies in cerebrovascular disease, memory impairment, cognitive impairment, dementia (Alzheimer's and multi-infarct), subarachnoid hemorrhage, aging, hypoxia, and vestibular disorder and in healthy volunteers. They found evidence for clinically meaningful (though subtle) improvements. (For review of studies, see Table 39–7 and Brown et al. 2009.) In a 52-week DBRPCMC study of 236 Alzheimer's patients, *G. biloba* (EGB 761) 120 mg/day improved cognitive performance in patients with mild to moderate cognitive impairment. A 22-week DBRPC trial of 400 patients with mild to moderate dementia found that patients given

TABLE 39–7. Evidence for herbs

Authors	Study	Comment
Rhodiola rosea		
Spasov et al. 2000	DBPC study of 60 first-year college students under stress. Those given low-dose *R. rosea* (100 mg/day) showed significant improvement in mental fatigue, psychomotor function, overall well-being (self-evaluation), physical work capacity, and heart rate.	
Vinpocetine		
Balestreri et al. 1987	DBPC study of 84 patients with chronic cerebral dysfunction and cognitive impairment. Those given vinpocetine 60 days had significantly higher scores on CGI, Mini-Mental State Examination, and Sandoz Clinical Assessment Geriatric Scale vs. placebo.	Subjects not well characterized.
Hindmarch et al. 1991	DBRPCMC study of 203 patients with mild to moderate organic brain syndromes. Those on vinpocetine for 16 weeks had significant improvements on CGI, severity of illness, and quality of life.	Limited information on diagnoses.
Feigin et al. 2001	DBPC study of 30 consecutive patients with computed tomography–verified acute ischemic stroke. Within 72 hours of stroke onset, 15 received low-molecular-weight dextran and 15 received low-molecular-weight dextran plus vinpocetine. At 3 months, vinpocetine group had 30% risk reduction of poor outcome and marginally better scores on the National Institutes of Health Neurological Disorders and Stroke Scale.	
Bönöczk et al. 2000	12 patients. Review of positron emission tomography scans. Vinpocetine improved cerebral glucose kinetics and blood flow in peristroke area.	
Bönöczk et al. 2002	DBRPC study of 43 stroke patients. Transcranial Doppler and near infrared spectroscopy: vinpocetine improved cerebral perfusion and parenchymal oxygen extraction in the peristroke area.	
Ginkgo biloba		
Le Bars et al. 2002	DBRPCMC 52-week study of 236 Alzheimer's disease patients. *G. biloba* (EGB 761) 120 mg/day ↑ cognitive performance (P=0.02) on ADAS-Cog and social functioning (P=0.001) while it slowed deterioration in patients with severe impairment.	
Scripnikov et al. 2007	DBRPC 22-week trial of 400 patients with mild to moderate dementia; 240 mg/day EGB 761 → better outcome Short Cognitive Performance Test and Neuropsychiatric Inventory vs. placebo. Mean composite score and the mean caregiver distress score on NPI dropped from 21.3 to 14.7 and 13.5 to 8.7, respectively, in the EGB 761 treated patients but increased from 21.6 to 24.1 and 13.4 to 13.9 on placebo (P<0.001). The largest differences favoring EGB 761: apathy/indifference, anxiety, irritability/lability, depression/dysphoria, sleep/nighttime behavior.	
DeKosky et al. 2008	DBRPCMC study of people with normal cognition (n=2,587) or mild cognitive impairment (n=482). *G. biloba* 120 mg bid did not affect incidence rate of dementia or Alzheimer's disease.	
Panax ginseng		
Sorensen and Sonne 1996	DBRPC 8-week study of healthy volunteers (≥ 40 years old); 400 mg/day ginseng → significantly better abstract thinking and reaction time vs. placebo. No significant differences in memory or concentration.	

Note. ADAS-Cog=Alzheimer's Disease Assessment Scale cognitive subtest; CGI=Clinical Global Impression Scale; DBPC=double-blind, placebo-controlled; DBRPC=double-blind, randomized, placebo-controlled; DBRPCMC=double-blind, randomized, placebo-controlled multicenter; →=resulted in; ↑=increased.

240 mg/day EGB 761 had better cognitive outcomes compared with placebo (Napryeyenko and Borzenko 2007). In a DBRPCMC study of volunteers over age 75 with normal cognition (n=2,587) or mild cognitive impairment (n=482), *G. biloba* 120 mg bid did not affect the incidence rate of dementia or Alzheimer's disease (DeKosky et al. 2008). A review of double-blind randomized, controlled trials found evidence of benefits for cognitive impairment and dementia but concluded that it was inconsistent and unconvincing (Birks and Grimley Evans 2007). The mixed results may be due to use of inadequate doses, choice of outcome measures, differences in patient populations, or the likelihood that *G. biloba* works best in combination with other cognitive enhancers rather than as a solo agent. Our clinical experience is that ginkgo is best used to augment CPH and racetams in patients with TBI because its effects alone are mild. Side effects are rare, with occasional nausea, headache, or rash. Although ginkgo can somewhat reduce platelet aggregation, it does not affect coagulation or bleeding time, fibrinogen, prothrombin time, or partial thromboplastin time. Nevertheless, ginkgo should not be given with Coumadin, and it should be discontinued 2 weeks before surgery.

Ginseng (Panax, Korean)

Ginseng contains many compounds that exert complex effects in animal and human studies (Brown et al. 2009). *Panax ginseng* increased production of nitric oxide by endothelial cells (crucial for blood flow and oxygen delivery)

in the rabbit. In an 8-week DBRPC study of healthy volunteers, 400 mg/day ginseng led to significantly better abstract thinking and reaction time compared with placebo (Sorensen and Sonne 1996). In practice, ginseng may augment activating effects of other agents to improve alertness, energy, and cognitive function.

Maca (*Lepidium peruvianum myenii*)

Maca is an adaptogenic herb (increases the ability of organisms to resist numerous forms of stress) from the Peruvian Andes. Mainly studied for its sexual stimulative and fertility-enhancing properties, rodent studies also show neuroprotection, cognitive activation, and antistress effects. We have found that as an adjunctive treatment for fatigue, Maca improves alertness, mental focus, and physical resilience (Brown et al. 2009).

Nootropics

Pyrrolidinones (Racetams)

While piracetam increases nerve cell membrane fluidity and normalizes hyperactive platelet aggregation, its effects are considerably potentiated by CDP-choline, idebenone, vinpocetine, and selegiline. Piracetam enhances the antihypoxic effect of CPH by protecting cell membranes from phospholipid peroxidation. Oxiracetam, aniracetam, and pramiracetam have shown greater benefits than piracetam. Human studies using racetams to augment the effects of CDP-choline and other cholinesterase inhibitors are needed. Large double-blind, placebo-controlled studies support racetam benefits in poststroke aphasia and dyslexia. (For reviews, see Table 39–8 and Brown et al. 2009.) Piracetam given within 7 hours of stroke, combined with speech therapy, enhanced language recovery (De Deyn et al. 1997). In postconcussion syndrome, piracetam reduced symptoms (especially vertigo and headache) and accelerated recovery (Hakkarainen and Hakamies 1978). PET scans demonstrated improved task-related blood flow in the left hemisphere speech area in poststroke patients given piracetam (Kessler et al. 2000). In practice, ginkgo and piracetam can synergistically augment language retraining for dyslexia and aphasia: gingko improves attention and perception; piracetam improves learning. In a DBRPC of 98 patients with ischemic stroke following coronary artery bypass surgery, those treated with piracetam had significant improvement in cognitive function versus placebo (Szalma et al. 2006).

Rehabilitation from TBI is often impeded by neural fatigue and neural apathy. We use the term *neural fatigue* for the kind of mental fatigue described by TBI patients; that is, after restful sleep they may be better able to perform mental tasks for a few hours, but they then become fatigued, with deterioration of cognitive function, beyond what is experienced by non-TBI patients when they are tired. Neural apathy refers to the kind of apathy that occurs after TBI as distinguished from apathy due to depression or schizophrenia. Fezam, which contains piracetam 400 mg and cinnarizine 25 mg (a piperazine derivative with antihistaminic, sedative, and calcium channel blocking properties), improved neural fatigue, neural apathy, anxiety, and depression in two-thirds of 21 patients with posttraumatic encephalopathy, transient ischemic attacks (vascular encephalopathy), and other postencephalitic syndromes (Boiko et al. 2007). Further trials with better design and characterization of subjects are needed. Cinnarizine may be a beneficial adjunctive treatment in vascular dementia (particularly for aphasia, apraxia, and acalculia).

L-Deprenyl (Eldepryl, Selegiline)

Although L-deprenyl is a prescription drug in the United States, we include it because many physicians are not familiar with its complementary use in brain injury. In very low doses (5–10 mg/day), it does not act as a monoamine oxidase A inhibitor. Joseph Knoll (2000), the discoverer of L-deprenyl, described a novel mechanism of action at a receptor site for an endogenous enhancer, which selectively improves impulse propagation–mediated release of central nervous system catecholamines and 5-HT, most markedly in the hippocampus. In response to stimulation of this receptor, glial cells and astrocytes secrete higher amounts of nerve growth factors (J. Knoll, personal verbal communication, July 2001). Knoll (2003) reviewed evidence that selegiline enhances mesencephalic drive regulation and resilience under extreme stress as well as age-related damage. Ebadi et al. (2006) reviewed data showing that selegiline enhances dopamine function, improves cognitive function, and has neuroprotective actions (particularly in catecholaminergic and cholinergic neurons), including release of brain-derived neurotrophic factor and protection against glutamate excitotoxicity. In a 2-year DBRPC trial, 340 patients with moderately severe Alzheimer's disease given selegiline (10 mg/day), alpha-tocopherol, or the combination of both had slower progression of Alzheimer's disease compared with placebo (Sano et al. 1997). Four patients with post-TBI apathy without depression responded to selegiline (<20 mg/day) with significant improvements in Apathy Evaluation Scale (AES) scores (Newburn and Newburn 2005). Our clinical experience is that L-deprenyl has a modest place in treatment of TBI in ultra low doses of half of a 5-mg tablet 5 days a week. Liquid L-deprenyl citrate may be more effective and tolerable, but no comparative studies have been done.

Neurotherapy

Traditional neurotherapy (neurofeedback or EEG biofeedback) trains patients to suppress certain EEG frequencies (usually 4–8 Hz) and increase amplitudes of other frequencies (usually 12–18 Hz), based on electroencephalography-driven feedback. The patient must actively cooperate during treatments over a period of months. Patients with TBI often develop higher amplitudes in low frequency bands (1–8 Hz). In such cases, neurotherapy attempts to balance activity across the EEG spectrum. Protocols have used sensorimotor rhythm (12–15 Hz) ("low-beta") for seizure disorders (Sterman and Macdonald 1978), ADHD (Lubar and Lubar 1984),

TABLE 39–8. Evidence for nootropics

Authors	Study	Comments
Racetams (Pyrrolidinones)		
Hakkarainen and Hakamies 1978	DBRPC 8-week study of 60 patients with postconcussion syndrome of 2–12 months; 4,800 mg/day piracetam reduced symptoms (especially vertigo and headache) and accelerated electroencephalogram normalization and hospital discharge.	
Deberdt 1994	In dyslexia, AAMI, and aphasia, significant augmentation of cognitive retraining: gingko improved attention and perception; piracetam improved learning.	Review.
Enderby et al. 1994	DBRPCMC study of 158 poststroke patients, 137 studied after 12-week treatment and 88 at 24-week follow-up; 31 patients on piracetam (45%) and 37 on placebo (53%) were aphasic on entry. Groups matched at baseline for demographic data, stroke sequelae, type and severity of aphasia, and prognostic parameters. Multivariate analysis of Aachen Aphasia subtest showed significant overall improvement relative to baseline in favor of piracetam (P=0.02) at 12 weeks.	Piracetam did not show advantage at 24 weeks, but 43% of subjects were not retested.
Israel et al. 1994	DBRC trial of 162 AAMI patients, age >55 years, 3-month memory training program (MTP), MTP + piracetam. Best results: MTP after 45 days of piracetam 4.8 mg/day. Piracetam 2.4 mg/day →↑ immediate recall; piracetam 4.8 mg/day →↑ immediate, delayed, and global recall.	
Boiko et al. 2007	Open series study of 50 patients with focal brain lesions and chronic fatigue syndrome: 29 patients with multiple sclerosis; 21 patients with posttraumatic encephalopathy, transient ischemic attacks (vascular encephalopathy), and other postencephalitic syndromes. Fezam (400 mg piracetam and cinnarizine 25 mg) improved fatigue, anxiety, and depression in two-thirds of the 21 patients without multiple sclerosis.	Open series.
De Deyn et al. 1997	DBRPC study of 452 patients given piracetam within 7 hours of ischemic stroke, 12 g daily for 4 weeks and 4.8 g/day for 8 weeks. Neurological outcome Orgogozo scale scores at 4 weeks (piracetam 60.4, placebo 54.9; P=0.07) and functional status Barthel Index scores at 12 weeks (piracetam 58.6, placebo 49.4; P=0.02).	
Kessler et al. 2000	DBRPC study of 24 poststroke aphasia patients, 6 weeks intensive speech therapy; 12 given piracetam 2,400 mg/day → improved 6 language functions; 12 given placebo → improved 3 language functions. Piracetam significant ↑ task-related flow activation in left hemisphere speech areas vs. placebo.	
Szalma et al. 2006	6-week DBRPC study of 98 patients with ischemic stroke following coronary artery bypass surgery. Patients given piracetam (150 mg/kg/day iv the day before and 6 days after surgery; 300 mg/kg iv day of surgery; and 12 g/day po up to 6 weeks) → significant improvement in cognitive function (P=0.041) vs. no treatment effect with placebo.	
Szaflarski et al. 2007	Retrospective review of 379 charts of TBI patients treated with antiepileptic drugs in neuroscience ICU. Diagnoses: trauma (29.1%), subarachnoid hemorrhage (26.3%), brain tumor (20.4%), subdural hemorrhage (18.4%). Leviracetam (Keppra) monotherapy → shorter ICU stays and fewer complications than phenytoin monotherapy or other anticonvulsants.	
Selegiline (L-deprenyl)		
Sano et al. 1997	DBRPC trial of 340 patients with moderately severe Alzheimer's disease given selegiline 10 mg/day, alpha-tocopherol (vitamin E 2,000 IU/day), a combination of both, or placebo for 2 years. Selegiline, alpha-tocopherol, and the combination slowed progression as indicated by time to institutionalization, death, loss of ability to perform activities of daily living, or severe dementia vs. placebo.	
Newburn and Newburn 2005	Four cases post-TBI apathy without depression. Each patient responded to selegiline (less than 20 mg/day) with significant improvements in Apathy Evaluation Scale scores: declines of 23, 46, 20, and 41 points. Patients had many other problems (e.g., memory, attention, information processing, balance, communication, and impulse control); they also showed improvements in ability to function at work and at home.	

Note. AAMI=age-associated memory impairment; DBRC=double-blind, randomized controlled; DBRPC= double-blind, randomized, placebo-controlled; DBRPCMC=double-blind, randomized, placebo-controlled multicenter; ICU=intensive care unit; TBI=traumatic brain injury; →=resulted in; ↑=increased.

PTSD (Ochs 1994), and TBI (Ayers 1987). Inhibition of theta and reinforcement of sensorimotor rhythm have been postulated to explain the beneficial effects of biofeedback on attention, mood, sleep, digestion, and anxiety. Quantitative electroencephalography measures frequencies and amplitudes at specific sites. Newer techniques modify the frequency or amplitude of brain waves at specific sites, using the patient's electroencephalogram to provide feedback via light-emitting diodes, a procedure that requires no specific activity from the patient other than briefly looking at a light source. Although machines using light or sound as feedback have been used, light flashing at the brain's own frequency can amplify instabilities, causing adverse reactions (e.g., seizures). The Flexyx Neurotherapy System (FNS), now called the Low Energy Neurofeedback System (LENS), uses "offsets" to decrease rather than increase such amplitudes (Ochs 2006). Weak signals derived from the patient's EEG tracing are modified with an offset and then delivered back to the patient on a low-energy radio carrier. This short, painless procedure requires minimal cooperation and can be readily tolerated by children. Case series report that LENS neurotherapy significantly reduces symptoms of TBI, seizures, ADHD, PTSD, affective disorders, pain syndromes, chronic fatigue, and fibromyalgia (Larsen 2006; Ochs 2006). A preliminary study of 12 mild to moderately severe TBI patients (ages 21–53) with substantial cognitive impairment, whose time since injury ranged from 36 months to 21 years, randomly assigned subjects to immediate intervention or intervention after a 6- to 8-week waiting period. Subjects were given 25 FNS treatments over 5–8 weeks. The duration of treatment sessions depended on the tolerance of each subject. Significant improvements were found in the Beck Depression Inventory ($F=10.01$, $P<0.02$), Multidimensional Fatigue Index subscales for general fatigue ($F=8.4$, $P<0.02$) and mental fatigue ($F=9.10$, $P<0.02$), digit span backward ($F=5.371$, $P<0.05$), delayed recall ($F=7.47$, $P<0.03$) on the auditory verbal learning test, ability to function (at work, at school, and socially), and other measures when compared with a wait-list control group (Schoenberger et al. 2001). LENS neurotherapy is a promising treatment with few serious adverse effects when administered by an experienced clinician. Side effects include transient fatigue, headaches, nausea, restlessness, and reexperiencing of symptoms related to trauma. In our clinical practices, many patients with complex treatment-resistant disorders report synergistic benefits when given a LENS neurotherapy (minimum of 10 sessions) followed by training in yoga breathing. Among responders are patients with anxiety, depression, PTSD, ADHD, substance abuse, neurodegenerative diseases, and TBI. Medications may be reduced in tandem with clinical improvements. Emerging technologies that provide real-time neurofeedback training, based on instantaneous measures of the patient's EEG frequency band power, power ratios, amplitude asymmetries, coherence, and phase differences, are being developed to normalize connectivity (how different parts of the brain communicate) (Collura 2007).

Mind-Body Practices

Mind-body medicine is a holistic approach that takes into account the effect of the mind (including thoughts, emotions, and the effects of psychosocial stressors and conditioning) on physical processes and the effect of physical practices on the mind and body. The integration of mind-body practices with other complementary and standard treatments for patients recovering from TBI is an emerging field (Leskowitz 2003). Preliminary studies show that yoga, tai chi, qigong, and meditation can enhance parasympathetic tone, heart rate variability, neuroplasticity, EEG coherence and synchrony, long-term potentiation, and oxygenation (Brown et al. 2009). Yoga stretches, which increase joint mobility, flexibility, and strength, are beneficial for muscle contractures, muscle tone, postural abnormalities, and balance. By teaching concentrated focus on subtle sensations in parts of the body, yoga can improve body awareness and control. The use of yoga breathing, particularly, Ujjayi (Ocean Breath), relaxes not only the mind but also the body while increasing the length of muscle stretches during inhalation and exhalation. A small case study of four subjects with greater than 9 months post-stroke hemiparesis found that two yoga sessions (1.5 hours each) for 8 weeks improved scores on the Timed Movement Battery and the Berg Balance Scale (Bastille and Gill-Body 2004).

Emotion dysregulation following TBI can be debilitating, particularly if there are mood swings, anxiety, or anger outbursts. Yoga can improve emotion regulation (Brown et al. 2009; Gerbarg 2008). Anxiety is a major factor in the subjective experience of pain. Mind-body techniques such as hypnosis, relaxation, yoga breathing, and guided meditation that alleviate anxiety have been used to reduce pain. An additional mechanism by which yoga breathing may reduce or block pain perception is through stimulation of the vagus nerve, which is involved in nociception (discrimination of painful stimuli). Slow yoga breath practices such as Coherent Breathing (5 breaths per minute), Ujjayi (4–6 breaths per minute), and Alternate Nostril Breathing reduce anxiety and induce a state of calm alertness (Brown et al. 2009). Preliminary neurophysiological data are consistent with improvements in attention, cognitive integration, and learning (see Case 3 below).

Mood Disorders, Anxiety, PTSD, Insomnia, Apathy, Fatigue, Anger

Mood disorders in TBI may be due to the stress of trauma, illness, and loss of function as well as damage to brain structures involved in mood regulation. SAMe is as effective as prescription antidepressants but has far fewer side effects (Alpert et al. 2004; Brown et al. 2009; Bottiglieri 2002). Beginning with 400 mg SAMe 30 minutes before breakfast, one can increase the dose every 5–7 days as tolerated to a maximum of 2,000 mg/day. As mentioned, obtaining a high-quality brand with tablets in individual blister packs is critical because SAMe oxidizes rapidly when exposed to air. SAMe should rarely be used in patients with bipolar disorder because it can trigger mania, as do other antidepressants. Omega-3 fatty acids (containing a 2:1 ratio of eicosapentaenoic acid and docosahexaenoic acid) can be beneficial for depression and, in high doses (8,000–10,000 mg/day), for bipolar disorder (Stoll

et al. 1999). B vitamins (1,000 µg/day B_{12} and 800 µg/day folate) may enhance response to antidepressants. Inositol (12–20 g/day) and *N*-acetylcysteine (1,200 mg bid) may reduce depression and bipolar disorder, and choline (2,000–7,200 mg/day) may reduce mania (Brown et al. 2009).

TBI patients tend to experience excess cognitive impairment and fatigue when given prescription anxiolytics. For anxiety and insomnia, they often benefit from calming breath practices that activate the vagus nerve (parasympathetic system), reduce overactivity of the sympathetic system, and enhance emotion regulatory systems. Coherent Breathing (5 breaths per minute) increases vagal tone and reduces anxiety. Using a CD to time the breaths, patients can learn this technique easily, practice it 20 minutes every morning, use it throughout the day for relief of stress and anxiety, and do it at night to facilitate sleep. For optimal results, the therapist teaches the patient Coherent Breathing and instructs the patient with the CD "Respire-1" (www.coherence.com) to ensure relaxation during practice. Yoga breath techniques such as Ujjayi enhance relaxation, alertness, and mental clarity (Brown et al. 2009). *R. rosea* can reduce symptoms of PTSD and enhance stress resilience. Patients who become overstimulated must begin with a low dose (fraction of a capsule) and gradually increase. Melatonin helps induce and maintain sleep and may reduce nocturnal agitation.

Apathy, depression, and fatigue often overlap. It is important to rule out obstructive sleep apnea after TBI. Modafinil can increase daytime energy and alertness. *R. rosea* may enhance physical and mental energy, mood, and motivation (Brown et al. 2009). Pyrrolidinones (racetams) with cinnarizine may alleviate fatigue, apathy, anxiety, and depression in TBI (as discussed in the earlier section Pyrrolidinones). Centrophenoxine, ginseng, and *R. rosea* may improve alertness, attention, and fatigue.

Disinhibition and overreactivity in TBI patients who are confronted with frustrations and disappointments can lead to outbursts of anger or aggression. Mind-body practices such as yoga breathing followed by guided meditation can reduce overreactivity and provide a tool for self-management of anger (Brown et al. 2009), as the following case illustrates.

Case 3. Coherent Breathing for TBI

Eric, a 40-year-old lawyer, developed TBI with loss of consciousness for 30 minutes after a head injury during a sports event. He was unable to return to work for 6 weeks because of poor judgment, severe headaches, and feelings of being overwhelmed by his high-paced work schedule. Eric developed episodes of rage alternating with tearfulness that felt out of control. He also had difficulties with memory, organization, and word finding. His friends consulted his neurologist, who encouraged him to take an extended medical leave from work and to engage in rehabilitative therapy. Eric's rage attacks and headaches gradually lessened, but as he realized that the cognitive impairment would delay return to work, he became severely depressed. A trial of 5 mg escitalopram (Lexapro) caused nausea and more cognitive clouding. Low-dose Amitriptyline helped control headaches but not the depression. He was then referred to a colleague trained by Dr. R.P. Brown. Because Eric had already begun an active yoga practice, he was prescribed Coherent Breathing. Eric practiced the breathing 20 minutes twice daily and attended regular yoga classes three times a week. After 2 weeks, the depression improved dramatically. His cognitive functions and judgment began to improve, enabling him to return to work part time, but he began to experience panicky anxiety at the beginning and end of the workday. These residual symptoms resolved completely when he learned to do Coherent Breathing at the first sign of anxiety or anger.

Slow, gentle yoga breath practices are safe for patients in all stages of recovery from brain injury. Rapid or intense breath practices are not advisable during recovery as they may trigger anxiety, emotional instability, or seizure in epileptics. Most patients must be started on 5 minutes of practice twice a day and increased over a period of about 2 weeks. On average, 20 minutes of practice twice daily is necessary with additional practice as needed. After solid improvement (1–3 months), practice can often be reduced to 20 minutes/day. In clinical work, we find that most patients respond with a sense of relaxation and reduction in worry and anxiety. In addition, many experience improvements in emotion regulation, mood, energy, and concentration over a period ranging from 1 to 12 months. These changes complement their response to other rehabilitation modalities and enhance their ability to cope with the stresses of everyday life. The use of a CD (with voice cues to time breath cycles) and reinforcement of practices by health care providers and yoga instructors improve compliance (Brown et al. 2009).

Conclusion

Complementary treatments offer significant benefits with few side effects in patients with TBI. Certain agents may help repair the nervous system and enhance neuroplasticity. In practice, often persistence over time is required to craft an effective combination of treatments. Patients and families can participate in the development of an integrative treatment regimen.

KEY CLINICAL POINTS

- Integrative treatment, combining complementary and standard approaches, optimizes recovery from traumatic brain injury (TBI).
- Patients with TBI are prone to medication side effects and usually find complementary treatments more tolerable.

- Mechanisms underlying therapeutic effects of complementary treatments include improvement of neurotransmitter and receptor function, mitochondrial energy production, cellular repair, neuroprotection, antioxidant defense, membrane fluidity, cerebral blood flow, long-term potentiation, and neuroplasticity.
- Combining treatments that target multiple aspects of neuronal protection and repair can significantly improve recovery.
- TBI patients may be inattentive to their nutritional needs. Supplementation with vitamins and nutrients is important for neuronal repair.
- For TBI impairment of cognition and memory, the most useful agents are CDP-choline, huperzine, picamilon, aniracetam, and *Rhodiola rosea.*
- Racetams can augment response to speech therapy.
- Neural fatigue often responds to activating agents, including modafinil, *R. rosea,* Maca, and *Panax ginseng.*
- In TBI with anxiety, posttraumatic stress disorder, or depression, yoga breathing, SAMe, and *R. rosea* are particularly useful.
- Neurotherapy can improve cognitive and executive function, memory, motor recovery, attention, and seizures following TBI.

Recommended Readings

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Appendix 39–1

Resources and Information on Complementary Medicine

http://www.coherence.com: Information and CDs for Coherent Breathing

http://www.ConsumerLab.com: Objective updates on quality testing on supplement brands

http://www.fda.gov/medwatch: Warnings about product safety

http://www.haveahealthymind.com: Updates on integrative psychiatry by Richard P. Brown and Patricia L. Gerbarg

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