Neuropsychiatric Assessment of Traumatic Brain Injury During Acute Neurorehabilitation*

David B. Arciniegas

Abstract Traumatic brain injury (TBI) is a common and costly problem worldwide. In the United States, 1.5 million people sustain TBI each year, and approximately 230,000 of these require hospitalization for management of their injury. The majority of TBI resulting in hospitalization are moderate to severe in nature and produce significant mortality and morbidity. Among those surviving their injuries, most will develop cognitive, emotional, and behavioral (collectively referred to here as neuropsychiatric) disturbances in the acute postinjury period and will require acute rehabilitation management. These posttraumatic neuropsychiatric sequelae present substantial clinical management challenges that the consulting neuropsychiatrist is well suited to evaluate and manage. In the service of offering the consulting neuropsychiatrist with information that may be of use in the care of persons with TBI receiving care in the acute neurorehabilitation setting, this chapter first defines and describes TBI and reviews the neuroanatomical and neurobehavioral consequences of TBI relevant to understanding posttraumatic neuropsychiatric disturbances. These disturbances are organized under the framework of posttraumatic encephalopathy, and the characteristic forms and stages of recovery of this condition are discussed. Finally, a neuropsychiatric approach to the evaluation of persons with TBI in the acute inpatient neurorehabilitation setting is described.

Keywords Cognitive impairment • Encephalophathy • Frontal assessment battery (FAB) • Mini-mental state exam (MMSE) • Traumatic brain injury (TBI)

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Introduction

Neuropsychiatrists and behavioral neurologists are increasingly involved in the early postinjury and neurorehabilitation management of persons hospitalized after traumatic brain injury (TBI). In the United States, approximately 230,000 persons annually are hospitalized in the acute injury period [1, 2]. Most of these individuals sustain TBI as a result of road traffic accidents, transportation, falls, or assaults, including incidents involving firearms. Among those whose injuries require hospitalization, adolescents, young adults, and older persons are overrepresented, and most of these sustained TBI of moderate or greater severity [1, 2]. Between the early 1980s and late 1990s, the overall annual rate of hospitalization following TBI declined by 51% [1, 2]. This decline is generally attributed to 61% and 19% reduction in hospital-based care of persons with mild and moderate TBI, respectively. At the same time, annual hospitalization rates following severe TBI increased 90%, from 10 to 19 per 100,000 persons. Additionally, in-hospital mortality following TBI declined by 17% as a result of advances in pre-hospital and in-hospital trauma care [1, 2]. As a result of these changes in the epidemiology of TBI, individuals admitted to hospital following TBI are more likely than in past decades to have sustained a relatively severe injury and to survive it.

More than 40% of persons hospitalized following moderate-to-severe TBI (or about 125,000 persons in the United States annually) are expected to develop permanent disability as a result of that injury [3]. Posttraumatic neuropsychiatric disturbances – a term used here to denote the broad spectrum of impairments in cognition, emotional regulation, behavior, and elementary neurological function produced by mechanical trauma to the brain – are particularly common among persons with moderate or severe TBI [4–8]. Neuropsychiatric disturbances are substantial contributors to postinjury disability [9–11] and reduced quality of life for patients and their families during and after the early postinjury period [10, 12–14].

The care provided to persons with TBI in acute inpatient rehabilitation settings is intrinsically neuropsychiatric. The neurorehabilitation of persons with moderate-to-severe TBI requires identification and management of cognitive impairments (e.g., disturbances of arousal, attention, processing speed, memory, and executive function, among others), emotional disturbances (e.g., irritability, liability, depression, anxiety), behavior (e.g., restlessness, agitation, disinhibition, aggression, apathy), and elementary neurological functions (e.g., sleep–wake cycle disturbances, seizures, motor impairments, sensory impairments). Identifying and treating neuropsychiatric disturbances as early as possible during the course of postinjury care as well as avoiding interventions with the potential for acute and/or long-term neuropsychiatric complications will reduce long-term posttraumatic neuropsychiatric morbidity. Accordingly, developing further the consulting neuropsychiatrists' expertise in the neuropsychiatric assessment and management of persons with TBI is an important objective.

With these goals in mind, this chapter begins by defining TBI and reviewing the commonly used methods of identifying TBI and characterizing its severity. The neurobiology of TBI is reviewed briefly, including the neuroanatomy, neurochemistry, and brain–behavior relationships relevant to the management of acute and

subacute posttraumatic neuropsychiatric disturbances. Finally, a neuropsychiatric approach to the evaluation of persons with TBI in the acute neurorehabilitation setting is described.

Defining TBI

TBI is defined as a functionally significant disruption of brain function produced by blunt or penetrating trauma or rapid acceleration/deceleration forces that results in immediately apparent cognitive or physical impairments [15]. Although the CDC clinical case definition permits skull fracture to serve as a proxy marker for TBI, in this chapter we exclude from consideration those injuries that produce only skull fracture: although the association between skull fracture and TBI is well described [16–18], this association is neither invariate nor a sufficiently reliable predictor of TBI to permit skull fracture to serve as the sole clinical finding upon which to predicate a TBI diagnosis [19]. Additionally, brain injuries from other causes such as birth trauma, hypoxic-ischemic (anoxic), inflammatory, toxic, or metabolic encephalopathies, primary ischemic or hemorrhagic strokes, seizure disorders, intracranial surgery, and cerebral neoplasms, although these are all causes of acquired brain injury, are excluded from this definition of TBI (Table 1).

Table 1 Clinical case definition of traumatic brain injury (adapted from the Center for Disease Control *Guidelines for the Surveillance of Central Nervous System Injury*, 2002)

Clinical phenomena	Description
Objective neurological abnormality	Focal motor, sensory, or reflex abnormalities
	Seizures (focal or generalized)
Alteration of consciousness	Loss of consciousness (LOC)
	Impairment of wakefulness (arousal) and/or awareness
Amnesia	Loss or impairment of peri-event memory
	Retrograde amnesia (RGA): impaired memory for events immediately preceding the injury
	Anterograde amnesia (AGA): impaired memory for the injury or the events that follow it
	Posttraumatic amnesia (PTA): the period of dense impairment in new learning following TBI; inclusive of both AGA and RGA
Objective neuropsychological abnormality	Standardized neuropsychological examination (in the immediate postinjury period) reveals impairment of cognition (e.g., disorientation, confusion), disturbances of behavior (e.g., agitation), or other abnormalities in neuropsychiatric status (e.g., personality change)
Diagnosed intracranial lesion	On computed tomography (CT), magnetic resonance imaging (MRI), or another neurodiagnostic (i.e., neuroimaging) study, there is evidence of diffuse axonal injury, and/or epidural, subdural, subarachnoid, or intracerebral hematoma, and/or cerebral contusion or laceration, and/or penetration of brain by foreign body (e.g., gunshot wound)

With respect to the cognitive manifestations of brain dysfunction at the time of injury, no single symptom or sign is pathognomic of TBI. Instead, any one (or more) of several features, including loss of consciousness (LOC), dense impairment in declarative new learning (posttraumatic amnesia, PTA), and alteration in higher cognitive functions (e.g., feeling "dazed and confused" without LOC or PTA), is sufficient evidence of brain dysfunction to merit assignment of this diagnosis, regardless of the duration of these disturbances. With regard to elementary neurological impairments, the intended referents of this term are focal neurological signs (e.g., hemiparesis, hemianopia), focal neurological symptoms (e.g., hemisensory loss), or seizure. Nonlocalizing or generalized neurological symptoms such as headache, fatigue, dizziness, blurred vision, and so forth, although common postconcussive symptoms, are frequently produced by peripheral nervous system injury, musculoskeletal (i.e., cervicospinal) injury, and facial/head (without brain) trauma. Accordingly, these are less useful as indicators of brain injury and therefore not used as evidence of TBI in the standard definition of this condition [15].

Characterizing TBI Severity

TBI severity is generally divided into three categories: mild, moderate, and severe. Among hospitalized patients, the Glasgow Coma Scale (GCS) [20] is the most commonly used metric for determining TBI severity. Mild, moderate, and severe TBI are defined by GCS scores of 13–15, 9–12, and 3–8, respectively, reflecting performance on three relatively elementary assessments of verbal, eye opening, and motor responses. While the GCS is an excellent research and clinical measure when administered in a consistent and timely manner [6, 21, 22], its use in many hospitals is inconsistent, at best, and the data it yields are frequently confounded by other non-TBI factors [23].

In the absence of GCS scores, or as a supplement or complement to them, determination of the duration of PTA is also a useful gauge of TBI severity [24]. PTA describes the period of dense impairment in the ability to learn new information (with or without some degree of retrograde amnesia). Although PTA is most accurately understood as one of the later stages within the larger condition of posttraumatic encephalopathy (PTE; discussed later in this chapter) [25], the conventional assessment of PTA duration encompasses the entire period between injury and the recovery of reasonably continuous and accurate memory for daily events. There are several measures with which to formally assess PTA severity and duration, the most commonly used of which are the Galveston Orientation and Amnesia Test (GOAT) [26] and the Orientation Log (O-Log) [27, 28]; among these, we prefer the O-Log given its ease of administration and interpretation and its excellent statistical comparison to the GOAT [29].

When neither GCS nor prospective PTA data are available, TBI severity may be characterized retrospectively using the American Congress of Rehabilitation Medicine (ACRM) definition of mild TBI [30, 31]. These criteria define TBI as a physiological disruption in brain function resulting from the application of an external physical (including acceleration/deceleration) force, as evidenced by any one (or more) of the following: LOC, PTA, altered mental state ("dazed and confused"),

and/or a focal neurological deficit that may or may not be transient. To remain in the mild category, LOC must be less than 30 min, after which GCS scores are in the 13–15 range, and/or PTA duration is no longer than 24 h. Injuries that produce LOC of 30 or more min, GCS scores less than 13 at 30 min (or later) post injury, and/or PTA longer than 24 h are classified as moderate to severe. McMillan and colleagues in 1996 [31] demonstrated that retrospective interview-based estimates PTA of duration among hospitalized individuals with TBI correlate highly with prospective, GOAT-determined duration of PTA. Among patients whose PTA duration is longer than 24 h, practical classification of injuries as moderate or severe may be made according to PTA duration (whether prospectively or retrospectively determined) of 1–7 days and more than 7 days, respectively.

For the consulting neuropsychiatrist, the usefulness of measured or estimated PTA duration and PTA-based severity classifications lies in the prognostic utility of this value: PTA duration (as a continuous variable) is a robust predictor of functional independence [29, 34] and disability [34] at the end of acute inpatient rehabilitation, Glasgow Outcome Scale [35] scores at 6 and 12 months post injury [36, 37], long-term cognitive recovery [38–40], productivity [41], employment [42], and community reintegration [43]. As with the GCS, noninjury factors (e.g., sedating medications, severe communication impairments) must be considered when estimating PTA duration, particularly among subjects with more severe general physical injuries and complications. Nonetheless, in our clinical experience time between injury and emergence from PTA – regardless of the TBI and concurrent factors contributing to the duration of that period – define usefully the severity of injury and offer valuable prognostic information that the consulting neuropsychiatrist can use when communicating with patients and their families as well as other healthcare providers about the patient's prognosis and likely posthospital treatment and resource needs.

An important qualifier on ACRM-based TBI severity classification of which the consulting neuropsychiatrist should be aware is "complicated mild TBI" [32, 33]. This subtype of mild TBI is used to denote individuals who meet ACRM criteria for mild TBI but whose computed tomography (CT) or magnetic resonance imaging (MRI) of the brain demonstrates abnormalities consistent with TBI. The importance of noting this subtype is that the outcome of subjects with complicated mild TBI more closely resembles that of persons with moderate TBI than those with uncomplicated (i.e., "simple") mild TBI; awareness of this issue will allow the consulting neuropsychiatrist to interpret the patient's clinical presentation more accurately and to offer more fully informed education, counseling, and prognostic information to patients and their families.

Neurobiology of TBI

In addition to understanding the diagnosis and implications of TBI severity, the consulting neuropsychiatrist needs also to be familiar with the neuroanatomy, neurochemistry, and typical brain–behavior relationships that inform on neuropsychiatric outcome following TBI.

The injurious biomechanical effects of TBI consist primarily of two general types: contact and inertial. Contact injuries refer to those resulting from the penetration of the brain by material (e.g., projectiles, bone fragments) entering the intracranial space, as well as those injuries produced by movement of the brain within the intracranial space that results in the brain striking or being abraded by the inner surface of skull. The movement of the brain against the various ridges and bony protuberances of the anterior (frontal) and middle (temporal) fossae is especially injurious to the temporal and frontal poles as well as the ventral anterior, medial, and lateral temporal and frontal cortices (see Bigler [44] for a review of this subject). In case of penetrating injuries, tissue displacement/destruction by a projectile, fragmentation and deposition of bone or a projectile within brain tissue, and contamination of the intracranial space by potential infectious material on a projectile or the tissues through which it passes may all contribute to brain injury. The damage sustained in penetrating injuries is relatively focal, involving most brain tissue in the linear path of the material penetrating the intracranial space. In non-penetrating and penetrating contact injuries types of injuries, subarachnoid, subdural, and/or epidural hematomas may complicate this type of injury.

Inertial forces include linear translation and rotation, which in combination produce angular acceleration/deceleration forces. These forces strain, shear, and/or compress brain tissue [45–50]. Although all these forces are potentially injurious, strain and shear forces are tolerated particularly poorly by brain tissue and are major contributors to TBI at all levels of severity. These forces are maximal in brain areas experiencing high angular acceleration/deceleration forces (superficial > deep tissues, anterior > posterior regions of the brain); at the junctions between tissues of different densities and elasticities (i.e., gray–white junctions); and at the intracranial rotational center of mass (i.e., rostral brainstem). High-speed, long-duration acceleration/deceleration injuries exert their greatest effect on axonal projections and small blood vessels within and projecting from the brainstem, on parasagittal cerebral white matter, on the corpus callosum, and at the superficial cortical gray–white junctions [51], particularly in the ventral and anterior frontal and temporal lobes (see Bigler [44] for review). In light of these patterns of neuropathology, "diffuse axonal injury" (DAI) is probably a misnomer and is more accurately understood as "multifocal," rather than diffuse, axonal injury [51]. Although inertial forces may play a role in the pathophysiology of penetrating TBI [52], this type of TBI tends to be relatively stroke-like with respect to the pattern of tissue involvement (focal vs. multifocal/diffuse), the neuropsychiatric problems it produces, and long-term functional outcomes.

As reviewed in Povlishock and Katz [53], Bigler [54], and Meythaler et al. [51], injurious cytotoxic processes are initiated by biomechanical injury; these processes both add to and also complicate biomechanical injury in TBI. Injury-induced calcium and magnesium dysregulation, free radical formation, and excitatory amino acid and neurotransmitter disturbances are the principal contributors from this cytotoxic cascade to neuronal injury and cell death. Excitatory amino acid excesses facilitate calcium influx into neurons, resulting in neuronal depolarization, initiation of oxidative processes, activation of proteolytic enzymes, and eventually injury to or

destruction of neurons and/or their axonal termini. Excitatory amino acid excesses also overdrive glucose utilization, and oxidative metabolism, and produce potentially toxic accumulations of lactate. Concurrent excess of acetylcholine also appear to be excitotoxic and may amplify the destructive effects of excitatory amino acid excesses and be particularly injurious to brain areas where these neurotransmitters are densely colocated (i.e., hippocampus, frontal cortices; see Phillips and Reeves [55], Arciniegas [56], and Arciniegas and Silver [57] for review). The effects, benign or malignant, of acute cerebral monoaminergic (i.e., dopamine, norepinephrine, and serotonin) excesses that are part of the cytotoxic cascade remain uncertain. All these neurotransmitter excesses appear to wane over the first several weeks following TBI [58, 59], although the exact time course over which these excesses abate is not characterized fully. It is clear, however, that by several weeks post-TBI there is a relative cholinergic deficit resulting from injury to ventral forebrain cholinergic nuclei and their cortical projections [56, 57]. It is possible that TBI also results in primary or secondary disturbances in cerebral monoaminergic, and particularly noradrenergic and dopaminergic, systems [60], the effects of which may be modified by genetically mediated variations in catecholamine metabolism. These issues are particularly important for the consulting neuropsychiatrist, as the types and timings of posttraumatic neurotransmitter disturbances carry implications for pharmacotherapies directed at cognitive, emotional, and behavioral problems during the acute rehabilitation period and thereafter.

In addition to biomechanical and cytotoxic injury processes, persons with TBI who require hospitalization often experience other secondary neurological and systemic problems, whether as a consequence of TBI or as a comorbid process, that may complicate or exacerbate TBI. Such problems include traumatic intracerebral hematomas, focal or diffuse cerebral edema, elevated intracranial pressure (ICP), obstructive hydrocephalus, hypoxic-ischemic injury, intracranial/intracerebral infection, and subfalcine or transtentorial herniation. These latter problems may be fatal or, if not fatal, may compromise vascular supply in the areas of brain compression and thereby superimpose acute ischemic stroke on TBI. Additionally, systemic medical complications such as volume depletion/blood loss, hypoperfusion, hypothermia or hyperthermia, hypoxia, infection, and related problems may further complicate TBI. Aggressive treatment directed at these problems during acute care and, when necessary, in the acute rehabilitation period, therefore is essential.

Brain–Behavior Relationships and TBI

As noted in the prior section of this chapter, TBI disproportionately affects the anterior and ventral aspects of the frontal and temporal lobes, medial frontal and temporal areas, ventral forebrain, the diencephalon (thalamus, hypothalamus), the rostral and ventral areas of the upper brainstem, and the white matter within and between these areas [44, 53, 54, 61, 62]. Injury to these neuropsychiatrically salient areas produces typical, but not invariate, patterns of posttraumatic neuropsychiatric

Table 2 Brain–behavior relationships relevant to understanding the neurobehavioral sequelae of TBI commonly encountered in the acute rehabilitation setting

Structure injured	Neuropsychiatric consequence
Upper brainstem	
Reticulothalamic systems	Loss or impairment of consciousness caused by rotational strain/shear on ascending reticular activating system (ARAS) and ↑ ACh
Reticulocortical system	Acute and functionally disruptive ↑ GLU, ACh, DA, NE, 5HT
Ventral forebrain (cholinergic nuclei 1–4)	Acute and functionally disruptive ↑ AChChronic and functionally impairing ↓ ACh
Cerebral white matter	Slowed and inefficient information processing
Medial temporal areas	
Entrorhinal-hippocampal complex	Impaired sensory gating, attention, working memory, and declarative memory
Amygdala	Affective placidity, Klüver–Bucy-like syndromes
Anterior temporal cortices	Impaired sensory-limbic integration (cortical), declarative memory (uncinate fasciculus)
Ventral (orbital) prefrontal cortices	Behavioral dyscontrol (e.g., impulsivity, disinhibition, irritability, agitation, aggression)
Medial prefrontal (cingulate) cortex	Decreased goal-directed cognition, emotion, and behavior (apathy)
Inferior (inferolateral) prefrontal cortex	Impaired working memory
Dorsolateral prefrontal cortex	Impaired executive function, including executive control of other basic cognitive functions

disturbances in the acute and subacute postinjury periods (Table 2). These patterns of neuropsychiatric disturbances evolve in the days to weeks following TBI and are subsumed under the heading of PTE [25].

Posttraumatic Encephalopathy

Posttraumatic encephalopathy (PTE) is characterized by five stages: posttraumatic coma, posttraumatic delirium, PTA, posttraumatic dysexecutive syndrome, and recovery (Fig. 1). These stages are named according to the most salient (although clearly not the only) neurobehavioral feature of the clinical presentation. During posttraumatic coma, the most salient feature of the patient's presentation is complete impairment of arousal. The transition from posttraumatic coma to posttraumatic delirium is marked by the return of wakefulness (arousal), albeit sometimes in a fluctuating manner, and marked impairments in selective, sustained, and other aspects of attention; in the parlance of the American Psychiatric Association's Diagnostic and Statistic Manual, Fourth Edition, Text Revised [63], "reduced clarity of awareness of the environment." Although posttraumatic delirium also entails other disturbances in cognition, emotion, and behavior, profound inattention is the most salient and characteristic feature of this stage of PTE.

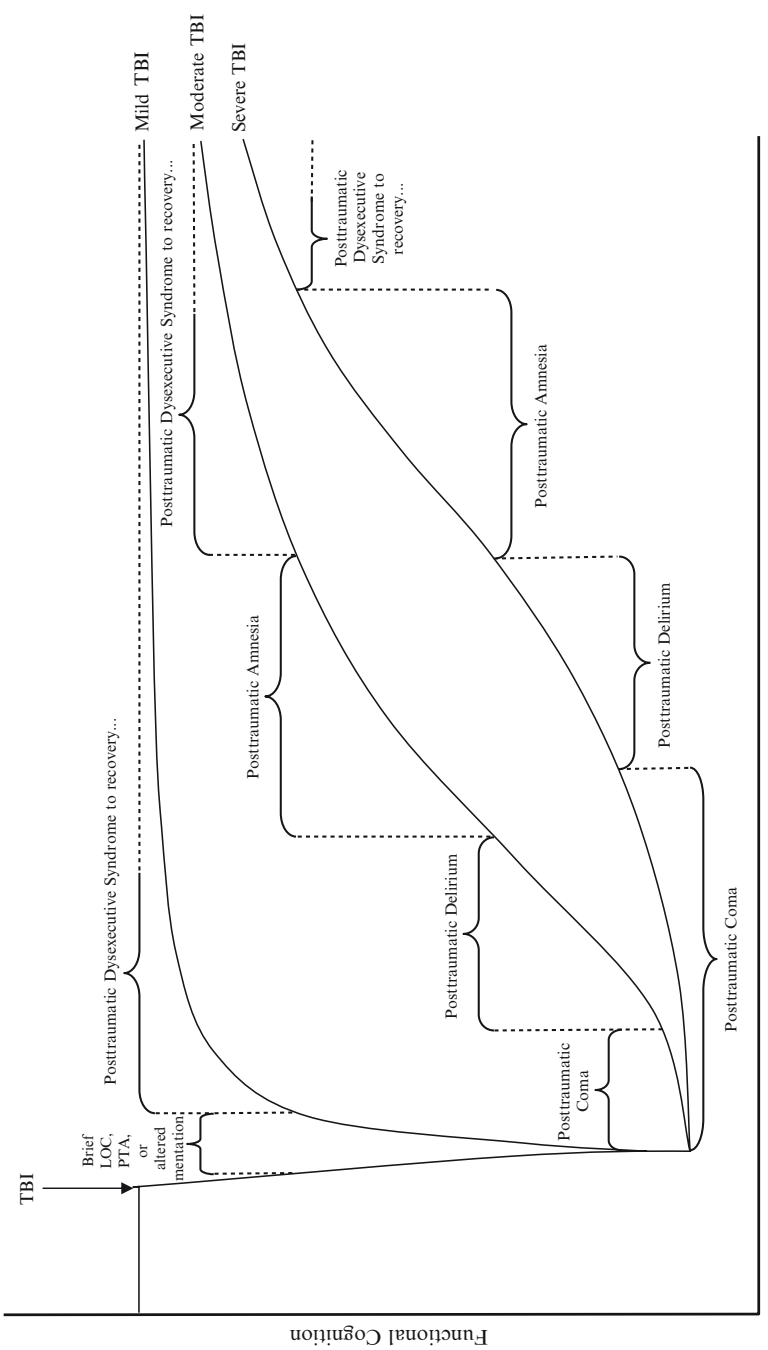

Fig. 1 Typical course of recovery through the stages of posttraumatic encephalopathy (PTE) following mild, moderate, and severe traumatic brain injury. *TBI* traumatic brain injury; *LOC* loss of consciousness; *PTA* posttraumatic amnesia

As the patient emerges from this stage, basic selective and sustained attention improve markedly; as a consequence, the patient's striking and dense impairment in declarative new learning becomes the most salient feature of the clinical presentation, and marks the patient's transition into PTA. As with posttraumatic delirium, the period of PTA also entails impairments in other aspects of cognition, especially executive function and executive control of attention, language, memory, and praxis. The patient is regarded as "in PTA" until his or her declarative new learning improves to the point that he or she is able to construct a reasonably continuous narrative of daily events from that point forward (formal criteria for emergence from PTA using the GOAT or O-Log are described in the next section of this chapter). The interval between onset of injury and subsequent recovery of declarative new learning defines the duration of PTA.

Unfortunately, the measured period of PTA duration is sometimes misunderstood as suggesting that the entire period measured is first and foremost characterized by impaired declarative new learning (i.e., amnesia); this clearly is not the case. It is important to be clear that although the formally measured duration of PTA necessarily encompasses posttraumatic coma, posttraumatic delirium, and (by some accounts) any preinjury period of retrograde amnesia, neither the concept of PTA nor its clinical manifestations are synonymous with posttraumatic delirium or, more obviously, posttraumatic coma. It is true that declarative new learning is impaired in these earlier stages of PTE; however, each of these entails other, and more salient, cognitive impairments. Nonetheless, duration of PTA as defined and used in the TBI literature is useful for both TBI severity characterization as well as a predictor of TBI outcomes and is, in this author's view, the most useful of the early stages of PTE to measure assiduously when offering prognoses to patients, their families, and other rehabilitation clinicians.

Upon emergence from PTA, impairments of executive function are the most salient feature of the clinical presentation; accordingly, this stage of PTE is referred to as the posttraumatic dysexecutive syndrome. Common clinical features of this syndrome include impairments of intrinsic executive function (e.g., abstraction, problem solving, the ability to generate, shift, and alter cognitive sets independent of environmental contingencies, judgment, and insight) as well as impaired executive control of other, more basic, cognitive functions. As illustrated in Fig. 1, some patients emerge from this stage of PTE into complete cognitive recovery whereas for others this becomes a chronic posttraumatic neurocognitive disorder.

The impairments that comprise each stage of PTE occur on a continuum clinically and temporally: patients at the transition between stages of PTE may vacillate for days (or longer) between those stages. Nonetheless, identifying the stage of PTE that best describes that patient is useful in that it facilitates the development of a treatment plan which is appropriate to the patient's current clinical status and also allows clinicians and the patient's family members to anticipate the course of continued recovery. By extension, this approach to PTE also helps clinicians to identify deviations from the expected course of recovery after TBI and therefore the need to evaluate the patient for conditions that explain such deviations.

Neuropsychiatric Evaluation of TBI in the Acute Rehabilitation Setting

The neuropsychiatric assessment of patients with TBI begins with corroboration of the diagnosis of TBI and entails characterization of its type and severity in the manner described in the preceding sections of this chapter. Next, identifying the stage of PTE using the framework described above is essential. It then is important to contextualize TBI and PTE by comprehensively assessing the patient's preinjury medical, neurological, psychiatric, and substance histories. It is particularly important to obtain collateral history on these issues from reliable informants (family, close friends, employers, etc.) because patients in the midst of PTE are frequently unable to provide this information themselves. Concurrently, assessment of the patient's social history (e.g., level of education, developmental history, legal history, military experience) and social supports should be obtained. This information often identifies strengths and limitations in the patient's personal and social contexts that may influence long-term outcomes and community reintegration, as well as the financial resources (or lack thereof) available to support the rehabilitation process. The assessment then moves from history-taking to examinations, including general physical, neurological, and neurobehavioral status examinations, as well as review of neuroimaging and other neurodiagnostic studies.

Bedside Assessment Methods

Standardized assessments appropriate to the phase of PTE in which the patient presents facilitate accurate diagnosis and guide prognostic and therapeutic formulations. Data derived from these measures may be used to gauge not only the extent and rate of recovery but also responses to treatment.

Although it is uncommon in the United States for patients to present to rehabilitation settings in posttraumatic coma, presentation of patients in this and other states of impaired arousal and awareness (i.e., with disorders of consciousness) is not uncommon in other parts of the world. The Coma/Near-Coma Scale [64] is particularly useful as an assessment of coma severity and recovery.

Upon emergence from posttraumatic coma, patients enter the period of posttraumatic delirium; at this point, it is very common for patients to be admitted to an acute inpatient rehabilitation hospital. The Delirium Rating Scale-Revised-98 (DRS-R-98) [65] or the Confusion Assessment Protocol (CAP) [66] are appropriate and useful measures for the consulting neuropsychiatrist to apply to the evaluation and monitoring of patients in posttraumatic delirium. The period of posttraumatic delirium corresponds to levels II–V of the Rancho Los Amigos Scale (RLAS) [67]. This scale and the descriptors of these lower levels of recovery after TBI are used frequently by rehabilitation physicians and therapists; the consulting neuropsychiatrist

will be well served to be familiar with this scale to ensure proper interdisciplinary communication when discussing patients in posttraumatic delirium.

Consistent with the description of RLAS levels II–V, posttraumatic delirium generally begins as a state of impaired arousal and profound inattention (RLAS level II). As arousal improves, inattention and behavioral disturbances (agitation) become prominent features of the clinical presentation (RLAS levels III–IV). As agitation remits and attentional disturbances become less problematic (RLAS level V), patients transition into a state in which impaired declarative new learning is the most salient clinical problem, or PTA. Identifying the point of transition between these states may be facilitated by the use of appropriate cutoff scores from delirium on the DRS-R-98 or the CAP and continued impairment on measures of PTA such as the O-Log or the GOAT [26].

With this in mind, it is useful to begin the assessment of PTA using the O-Log or the GOAT early during the course of posttraumatic delirium. Assessment using the O-Log of the GOAT continues until the patient meets criteria for emergence from PTA (on two consecutive days, O-Log scores ≥25 or GOAT scores ≥76). Although the validity of assessing orientation and memory function in the severely delirious patient is dubious, early and daily assessment with these measures ensures that the end of PTA will be captured accurately; as noted earlier, and as demonstrated by our own work [29], duration of PTA offers short- and long-term prognostic information that is useful to clinicians and also to patients and their families.

Neuropsychiatric assessment is most often undertaken when patients are in posttraumatic delirium or PTA. Our service, which provides Behavioral Neurology and Neuropsychiatry consultations on an acute inpatient neurorehabilitation unit, integrates neurological and neuropsychiatric assessments to offer diagnostic and treatment recommendations as well as guidance on rehabilitation prognosis and the types of support and caregiving resources that are likely to be needed during these periods of PTE as well as during and after subsequent rehabilitation care. In addition to elementary neurological and general mental status examinations, our consultations include detailed examination for subtle neurological signs (SNS) and a thorough bedside cognitive examination.

The assessment for SNS focuses on paratonia (*mitgehen* and/or *gegenhalten*) and also several primitive reflexes (also known as “frontal release signs”): glabellar response, snout response, suck reflex, palmomental response (left and right), grasp response (left and right), and rooting response. These simple additions to the neurological examination, from which we have developed a preliminary metric referred to as the SNS score [68], yield important information regarding neurobehavioral status and rehabilitation outcome: SNS score predicts raw and Z-transformed mini-mental state examination (MMSE) and frontal assessment battery (FAB) scores (all $P<0.003$), FIM scores at consultation (all $P<0.04$), and rehabilitation discharge (all $P<0.03$), and RLOS ($P<0.0002$). Accordingly, inclusion of these items in the neuropsychiatric assessment of persons with TBI during the acute rehabilitation period is recommended.

The bedside cognitive examination used on our service includes, among other items, the MMSE [69] and FAB [70]. Because performance on these measures is

influenced strongly by the effects of age and education, our interpretation of a patient's performance on them is normatively adjusted (for the MMSE, we use norms developed by Crum et al. [71], and for the FAB we use norms developed by Appollonio et al. [72]). After Z-transforming these data, the MMSE and, particularly, the FAB predict functional status and rehabilitation length of stay [73]. While other measures such as the Neurobehavioural Rating Scale – Revised [74, 75] may also be useful, the combination of the MMSE and FAB is time efficient and unlikely to overlap substantially with the assessments performed by neuropsychologists and rehabilitation therapists concurrently assessing these patients. For these reasons, this brief bedside battery of cognitive assessments is used in our clinical practice.

After patients emerge from PTA, neuropsychiatric assessment is most usefully directed toward disturbances in frontally mediated cognition, emotion, and behavior; in other words, at the posttraumatic dysexecutive syndrome. As noted previously, we have found the FAB particularly valuable for the evaluation of the cognitive components of this syndrome [73] but have employed other measures such as the Executive Interview (EXIT) [76] and the Behavioral Dyscontrol Scale (BDS) [77, 78] as well.

Assessment of other neuropsychiatric disturbances such as depression, mania, pathological laughing and crying, anxiety disorders, psychosis, and nondelirium-related impulse control problems and aggression also require neuropsychiatric assessment and treatment during PTE – and may require more specific assessment during PTA and posttraumatic dysexecutive syndrome in light of the fact that emotional and behavioral disturbances that occur during these stages of PTE cannot be dismissed as features of posttraumatic delirium. The Neurobehavioural Rating Scale – Revised [74, 75] is particularly well suited to the identification of such problems among patients able to participate in direct interview and examination. Among patients too impaired (neurologically or neuropsychiatrically) to engage effectively in interview and examination, assessment of posttraumatic emotional and behavioral disturbances may be performed productively by using the Neuropsychiatric Inventory (NPI) [79] as a guide to interviews of nursing and rehabilitation staff familiar with the patient. Our group at HealthONE Spalding Rehabilitation Hospital in Aurora, Colorado, is presently engaged in the development of an assessment instrument modeled after the NPI and adapted specifically for the assessment of persons with TBI in the acute neurorehabilitation setting; we expect to publish findings pertaining to this project in the near future.

Neurodiagnostic Methods

There is considerable debate regarding the timing of formal neuropsychological testing after TBI [80]. This debate generally centers around the validity of testing before the resolution of PTA and the potential bias of premature testing (due to test exposure) on later assessments. Recent studies [80, 81] suggest that a brief battery composed of the GOAT, California Verbal Learning Test-II, Trail Making Test,

Symbol Digit Modalities Test, grooved pegboard, phonemic and categorical word generation tasks, Wechsler Test of Adult Reading, and Wisconsin Card Sorting Test-64 may be a useful and practical brief neuropsychological assessment battery in the inpatient neurorehabilitation setting. Additionally, this battery – and, more specifically, its Weschler Test of Adult Reading and Trail Making Test-Part B components – are significant predictors of 1-year outcome after TBI as measured by the Disability Rating Scale, Supervision Rating Scale, and Glasgow Outcome Scale-Extended [81]. When it is feasible to obtain neuropsychological testing of this type in the acute neurorehabilitation setting, it is advisable to do so as a complement to other data obtained during the neuropsychiatric assessment.

Structural neuroimaging is an integral component of the neuropsychiatric assessment of patients receiving acute neurorehabilitation after TBI. In many (perhaps most) cases, CT of the brain will be performed in the acute care setting; unfortunately, CT is sensitive to gross abnormalities (i.e., skull fracture, acute hemorrhage or hemorrhagic contusion, severe DAI) but its value is generally limited to cases in which very severe injuries were sustained. MRI of the brain is frequently more useful as a neuroimaging guide to the severity of TBI; as a tool with which to determine the correspondence between bedside examination-identified neurological/neuropsychiatric problems and neuroimaging abnormalities; and as a guide to prognosis and treatment planning. For example, ventral prefrontal cortical and white matter injury is a relatively common consequence of severe TBI (see Table 2) and frequently is associated with impulsive, disinhibited, and/or aggressive behavior. MR evidence of overtly destructive damage (i.e., traumatic ablation) to these structures influences the selection of pharmacologic agents directed at these behaviors: selective serotonin reuptake inhibitors, anticonvulsants, or atypical antipsychotics suppressing brain (limbic) areas driving these behaviors is likely to be more useful than are agents (e.g., stimulants or cholinesterase inhibitors) intended to augment the function of the ventral prefrontal-subcortical circuit. Accordingly, we recommend obtaining (or reviewing one previously obtained) an MRI of the brain in all neurorehabilitation inpatients receiving neuropsychiatric assessment after TBI. When MRI is performed, T_1, fluid-attenuated inversion recovery (FLAIR), T_2* gradient echo, susceptibility-weighted, and diffusion-weighted sequences are the most useful sequences to obtain [82].

Electroencephalography (EEG), including evoked potentials, event-related potentials, and quantitative EEG (qEEG), does not usually contribute usefully to the neuropsychiatric assessment of patients undergoing acute neurorehabilitation after TBI [83]. When clinical history suggests the possibility of seizures (particularly complex partial seizures with post-ictal confusion or behavioral disturbances), then it is appropriate to obtain EEG to identify potentially epileptiform abnormalities. However, it is important to remain mindful that interictal EEG is relatively insensitive to epileptiform abnormalities and that the decision to treat patients for post-traumatic seizures rests on the event semiology and not on the presence or absence of electroencephalographic abnormalities.

The literature guiding the selection of laboratory assessments relevant to the neuropsychiatric assessment in the acute neurorehabilitation setting is underdeveloped. It is reasonable and appropriate to review and/or obtain laboratory data (including

serum and urine studies) that may inform on contributors to, or alternate explanations for, delirium and cognitive impairments experienced by persons with TBI. Recent reviews suggest that neuroendocrine disturbances are common and underdiagnosed in this population [84]; other than assessment of thyroid-stimulating hormone and thyroid hormone levels, however, the optimal methods for assessing and treating other posttraumatic neuroendocrine disturbances remains uncertain.

Review of Concurrently Prescribed Treatments

An essential component of the neuropsychiatric assessment of persons with TBI receiving acute neurorehabilitation services is a review of pharmacologic treatments that may be causing or contributing to neurological and neuropsychiatric problems identified during that assessment.

Treatment with anticonvulsant medications is common in this population, but this requires careful consideration with respect to both benefits and adverse effects on posttraumatic neurological and neuropsychiatric status. Persons with TBI are at risk for the development of posttraumatic seizures [85], and these are generally divided into two types according to the timing of their onset post injury: early (within 1 week of injury) and late (after the first week post injury). Administration of anticonvulsant medications (so-called seizure prophylaxis) during the first week after TBI decreases the incidence of early posttraumatic seizures [86], although this does not appear to reduce mortality, long-term neurological disability, or the risk of late posttraumatic seizures [86]. More important in the acute rehabilitation setting is the now well-established finding that prophylactic administration of anticonvulsants after the first week post-TBI does not prevent the development of late posttraumatic seizures, reduce short- or long-term neurological disability, or influence post-TBI mortality [86]. Additionally, many of these agents – particularly phenytoin [87, 88] and carbamazepine [88] – worsen cognitive and motor function in this population. Despite its increasingly common use as an alternate "seizure prophylactic" in this setting [89, 90], levetiracetam has not been shown to be effective for the prophylaxis of either early or late posttraumatic seizures and is known to produce agitation and other neurobehavioral disturbances ("psychiatric adverse events") [91, 92]. Valproate is less problematic with respect to its effects on cognition after TBI [93]; accordingly, when prophylaxis against early posttraumatic seizures is undertaken or if an anticonvulsant is used for behavior- or mood-stabilizing purposes, valproate is preferable to phenytoin, carbamazepine, and levetiracetam for this purpose. However, continued use of any of these or other anticonvulsants as prophylaxis against new-onset seizures after the first week post injury (i.e., late posttraumatic seizures) is discouraged [94].

A variety of similarly problematic medications are administered commonly to persons with TBI during the acute hospital and inpatient neurorehabilitation phases of care. Antagonists of type-2 dopamine (D2) receptors and/or benzodiazepines are used in many settings as treatments for posttraumatic delirium (particularly agitation

and aggression) [95] and as agents with which to improve compliance with mechanical ventilation [96]. Agents that attenuate noradrenergic function, including clonidine, propranolol, and other antihypertensives, are commonly used for medical and/or behavioral purposes as well. However, dopaminergic and noradrenergic antagonists delay neuronal recovery and impair neuronal plasticity [97–103]. Among persons with TBI, typical antipsychotics exacerbate cognitive impairments [104] and prolong the period of PTA [105]. Benzodiazepines are well known to impair memory and other aspects of cognition [106] in healthy adults and among persons with TBI [107]. In light of these findings, use of agents with potent antidopaminergic, antinoradrenergic, and/or GABA-ergic properties is best avoided during the neurorehabilitative care of persons with TBI. When evaluating neuropsychiatrically patients receiving these agents, considering their potential effects on neurological and cognitive function before making definitive diagnostic or prognostic statements is prudent.

With respect to the effects of other agents on posttraumatic neuropsychiatric function, medications possessing potent in vivo anticholinergic properties are of concern as well. These medications are commonly prescribed for posttraumatic dizziness and urinary incontinence. Antidepressants with potent anticholinergic properties (e.g., tricyclic and tetracyclic antidepressants and also paroxetine [108]) are often prescribed by rehabilitation physicians for pain, headaches, and emotional disturbances. However, TBI produces acute and chronic disturbances of cerebral cholinergic function [56], and cholinergic deficits become prominent and functionally significant in many patients over the first several weeks after TBI. As a result of these deficits, patients with TBI are vulnerable to the adverse cognitive and behavioral effects of agents with anticholinergic properties. In general, prescription of agents with potent anticholinergic properties for persons with TBI should be avoided whenever possible.

Finally, pain and spasticity are common problems among persons with TBI, most often as a result of injury to the head or other orthopedic or soft tissue injuries that are sustained concurrently with TBI. Among the agents used for these problems, opiate analgesics are particularly likely to adversely affect cognitive and neuropsychiatric function. At typical analgesic doses, these agents produce impairments in memory among persons without TBI of severities comparable to those encountered among persons in PTA [109]. These agents may exacerbate, prolong, or mimic posttraumatic coma, posttraumatic delirium, PTA, and the posttraumatic dysexecutive syndrome. Using the minimum necessary dose of any of these agents for as brief a time as is feasible clinically, or, better, avoiding or eliminating these whenever possible, is recommended.

Conclusion

TBI is a significant public health problem that produces substantial neurological and neuropsychiatric morbidity. The biomechanical and cytotoxic processes incited by TBI produce a predictable injury profile that involves anterior, and predominantly ventral, frontal, and temporal cortex, frontal subcortical white matter, and midbrain

areas. Damage to these structures explains, in large part, the anatomic contributions to the neurobehavioral sequelae of TBI, including alterations of arousal, attention, processing speed, memory, functional communication, executive function, emotional regulation, and behavior.

As discussed in this chapter, the period of neuropsychiatric disturbance that immediately follows TBI is understood usefully as posttraumatic encephalopathy (PTE), a condition with several stages through which patients proceed during recovery from TBI. These stages include, in typical sequence, posttraumatic coma, posttraumatic delirium, posttraumatic amnesia (PTA), posttraumatic dysexecutive syndrome, and full recovery. Among these, duration of PTA is particularly useful to measure accurately: duration of PTA is strongly predictive of short- and long-term neurorehabilitation outcomes. Additionally, data developed on our neuropsychiatric consultation service suggest that several elements of the neuropsychiatric assessment, including the number of SNS (paratonia, primitive reflexes) and also a brief bedside neurobehavioral status examination (normatively interpreted MMSE and FAB), yield data that allow neuropsychiatrists to assess functional status, functional prognosis, and rehabilitation lengths of stay among persons with TBI receiving inpatient neurorehabilitative care.

Treatment approaches based on data yielded by the neuropsychiatric assessment vary widely among institutions, both nationally and internationally. These treatment issues are beyond the scope of this chapter but are well described elsewhere [57, 110–117]. Independent of specific treatment recommendations, the principles of neuropsychiatric assessment of TBI in the neurorehabilitation setting described in this chapter apply broadly. Well informed and equipped with this information, neuropsychiatrists will contribute importantly and effectively to multidisciplinary teams working to improve the neuropsychiatric and functional outcomes of persons with TBI.

References

1. Thurman D, Guerrero J (1999) Trends in hospitalization associated with traumatic brain injury. JAMA 282:954–957
2. Thurman DJ, Alverson C, Dunn KA et al (1999) Traumatic brain injury in the United States: a public health perspective. J Head Trauma Rehabil 14:602–615
3. Selassie AW, Zaloshnja E, Langlois JA et al (2008) Incidence of long-term disability following traumatic brain injury hospitalization, United States, 2003. J Head Trauma Rehabil 23:123–131
4. Levin HS (1995) Neurobehavioral outcome of closed head injury: implications for clinical trials. J Neurotrauma 12:601–610
5. severe head injury. Experience of the Traumatic Coma Data Bank. J Neurosurg 73:699–709
6. Rapoport M, McCauley S, Levin H et al (2002) The role of injury severity in neurobehavioral outcome 3 months after traumatic brain injury. Neuropsychiatry Neuropsychol Behav Neurol 15:123–132
7. Hart T, Whyte J, Polansky M et al (2003) Concordance of patient and family report of neurobehavioral symptoms at 1 year after traumatic brain injury. Arch Phys Med Rehabil 84:204–213
8. Kaufman HH, Levin HS, High WM Jr et al (1985) Neurobehavioral outcome after gunshot wounds to the head in adult civilians and children. Neurosurgery (Baltim) 16:754–758
9. Dikmen S, Machamer J, Miller B et al (2001) Functional status examination: a new instrument for assessing outcome in traumatic brain injury. J Neurotrauma 18:127–140

10. Dikmen SS, Machamer JE, Powell JM et al (2003) Outcome 3 to 5 years after moderate to severe traumatic brain injury. Arch Phys Med Rehabil 84:1449–1457
11. Hall KM, Bushnik T, Lakisic-Kazazic B et al (2001) Assessing traumatic brain injury outcome measures for long-term follow-up of community-based individuals. Arch Phys Med Rehabil 82:367–374
12. Doctor JN, Castro J, Temkin NR et al (2005) Workers' risk of unemployment after traumatic brain injury: a normed comparison. J Int Neuropsychol Soc 11:747–752
13. Guilmette TJ, Paglia MF (2004) The public's misconception about traumatic brain injury: a follow up survey. Arch Clin Neuropsychol 19:183–189
14. Swift TL, Wilson SL (2001) Misconceptions about brain injury among the general public and non-expert health professionals: an exploratory study. Brain Inj 15:149–165
15. Marr AL, Coronado VG (2002) Central Nervous System Injury Surveillance Data Submission Standards – 2002
16. Kraus JF, Rice TM, Peek-Asa C et al (2003) Facial trauma and the risk of intracranial injury in motorcycle riders. Ann Emerg Med 41:18–26
17. Johnston JJ (2007) The Galasko report implemented: the role of emergency medicine in the management of head injuries. Eur J Emerg Med 14:130–133
18. Palchak MJ, Holmes JF, Vance CW et al (2003) A decision rule for identifying children at low risk for brain injuries after blunt head trauma. Ann Emerg Med 42:492–506
19. Borg J, Holm L, Cassidy JD et al (2004) Diagnostic procedures in mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med (Suppl 43):61–75
20. Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness. a practical scale. Lancet 2:81–84
21. Clifton GL, Hayes RL, Levin HS et al (1992) Outcome measures for clinical trials involving traumatically brain-injured patients: report of a conference. Neurosurgery (Baltim) 31:975–978
22. Cowen TD, Meythaler JM, Devivo MJ et al (1995) Influence of early variables in traumatic brain injury on functional independence measure scores and rehabilitation length of stay and charges. Arch Phys Med Rehabil 76:797–803
23. Gabbe BJ, Cameron PA, Finch CF (2003) The status of the Glasgow Coma Scale. Emerg Med (Fremantle) 15:353–360
24. Russell WR, Smith A (1961) Post-traumatic amnesia in closed head injury. Arch Neurol 5:4–17
25. Arciniegas DB, McAllister TW (2008) Neurobehavioral management of traumatic brain injury in the critical care setting. Crit Care Clin 24:viii, 737–viii, 765
26. Levin HS, O'Donnell VM, Grossman RG (1979) The Galveston Orientation and Amnesia Test. A practical scale to assess cognition after head injury. J Nerv Ment Dis 167:675–684
27. Jackson WT, Novack TA, Dowler RN (1998) Effective serial measurement of cognitive orientation in rehabilitation: the Orientation Log. Arch Phys Med Rehabil 79:718–720
28. Novack TA, Dowler RN, Bush BA et al (2000) Validity of the Orientation Log, relative to the Galveston Orientation and Amnesia Test. J Head Trauma Rehabil 15:957–961
29. Frey KL, Rojas DC, Anderson CA et al (2007) Comparison of the O-Log and GOAT as measures of posttraumatic amnesia. Brain Inj 21:513–520
30. Kay T, Harrington DE, Adams RE et al (1993) Definition of mild traumatic brain injury: Report from the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine. J Head Trauma Rehabil 8:86–87
31. McMillan TM, Jongen EL, Greenwood RJ (1996) Assessment of post-traumatic amnesia after severe closed head injury: retrospective or prospective? J Neurol Neurosurg Psychiatry 60:422–427
32. Williams DH, Levin HS, Eisenberg HM (1990) Mild head injury classification. Neurosurgery (Baltim) 27:422–428

33. van der Naalt J, Hew JM, van Zomeren AH et al (1999) Computed tomography and magnetic resonance imaging in mild to moderate head injury: early and late imaging related to outcome. Ann Neurol 46:70–78
34. Zafonte RD, Mann NR, Millis SR et al (1997) Posttraumatic amnesia: its relation to functional outcome. Arch Phys Med Rehabil 78:1103–1106
35. Jennett B, Bond M (1975) Assessment of outcome after severe brain damage. Lancet 1:480–484
36. Katz DI, Alexander MP (1994) Traumatic brain injury. Predicting course of recovery and outcome for patients admitted to rehabilitation. Arch Neurol 51:661–670
37. Ellenberg JH, Levin HS, Saydjari C (1996) Posttraumatic amnesia as a predictor of outcome after severe closed head injury. Prospective assessment. Arch Neurol 53:782–791
38. Brooks DN, Aughton ME, Bond MR et al (1980) Cognitive sequelae in relationship to early indices of severity of brain damage after severe blunt head injury. J Neurol Neurosurg Psychiatry 43:529–534
39. Geffen GM, Encel JS, Forrester GM (1991) Stages of recovery during post-traumatic amnesia and subsequent everyday memory deficits. NeuroReport 2:105–108
40. Haslam C, Batchelor J, Fearnside MR et al (1994) Post-coma disturbance and post-traumatic amnesia as nonlinear predictors of cognitive outcome following severe closed head injury: findings from the Westmead Head Injury Project. Brain Inj 8:519–528
41. Sherer M, Sander AM, Nick TG et al (2002) Early cognitive status and productivity outcome after traumatic brain injury: findings from the TBI model systems. Arch Phys Med Rehabil 83:183–192
42. Avesani R, Salvi L, Rigoli G et al (2005) Reintegration after severe brain injury: a retrospective study. Brain Inj 19:933–939
43. Doig E, Fleming J, Tooth L (2001) Patterns of community integration 2-5 years post-discharge from brain injury rehabilitation. Brain Inj 15:747–762
44. Bigler ED (2007) Anterior and middle cranial fossa in traumatic brain injury: relevant neuroanatomy and neuropathology in the study of neuropsychological outcome. Neuropsychology 21:515–531
45. Sabet AA, Christoforou E, Zatlin B et al (2008) Deformation of the human brain induced by mild angular head acceleration. J Biomech 41:307–315
46. Besenski N (2002) Traumatic injuries: imaging of head injuries. Eur Radiol 12:1237–1252
47. Ryan GA, McLean AJ, Vilenius AT et al (1994) Brain injury patterns in fatally injured pedestrians. J Trauma 36:469–476
48. Misra JC, Chakravarty S (1984) A study of rotational brain injury. J Biomech 17:459–466
49. Fijalkowski RJ, Stemper BD, Pintar FA et al (2007) New rat model for diffuse brain injury using coronal plane angular acceleration. J Neurotrauma 24:1387–1398
50. Margulies SS, Thibault LE, Gennarelli TA (1990) Physical model simulations of brain injury in the primate. J Biomech 23:823–836
51. Meythaler JM, Peduzzi JD, Eleftheriou E et al (2001) Current concepts: diffuse axonal injury-associated traumatic brain injury. Arch Phys Med Rehabil 82:1461–1471
52. Black KL, Hanks RA, Wood DL et al (2002) Blunt versus penetrating violent traumatic brain injury: frequency and factors associated with secondary conditions and complications. J Head Trauma Rehabil 17:489–496
53. Povlishock JT, Katz DI (2005) Update of neuropathology and neurological recovery after traumatic brain injury. J Head Trauma Rehabil 20:76–94
54. Bigler ED (2003) Neurobiology and neuropathology underlie the neuropsychological deficits associated with traumatic brain injury. Arch Clin Neuropsychol 18:595–621
55. Phillips LL, Reeves TM (2001) Interactive pathology following traumatic brain injury modifies hippocampal plasticity. Restor Neurol Neurosci 19:213–235
56. Arciniegas DB (2003) The cholinergic hypothesis of cognitive impairment caused by traumatic brain injury. Curr Psychiatry Rep 5:391–399
57. Arciniegas DB, Silver JM (2006) Pharmacotherapy of posttraumatic cognitive impairments. Behav Neurol 17:25–42

58. Markianos M, Seretis A, Kotsou S et al (1992) CSF neurotransmitter metabolites and short-term outcome of patients in coma after head injury. Acta Neurol Scand 86:190–193
59. Markianos M, Seretis A, Kotsou A et al (1996) CSF neurotransmitter metabolites in comatose head injury patients during changes in their clinical state. Acta Neurochir (Wien) 138:57–59
60. McAllister TW, Flashman LA, Sparling MB et al (2004) Working memory deficits after traumatic brain injury: catecholaminergic mechanisms and prospects for treatment – a review. Brain Inj 18:331–350
61. Povlishock JT (1992) Traumatically induced axonal injury: pathogenesis and pathobiological implications. Brain Pathol 2:1–12
62. Salmond CH, Chatfield DA, Menon DK et al (2005) Cognitive sequelae of head injury: involvement of basal forebrain and associated structures. Brain 128:189–200
63. American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders, Text Revision, 4th edn. American Psychiatric Association, Washington, DC
64. Rappaport M (2005) The Disability Rating and Coma/Near-Coma scales in evaluating severe head injury. Neuropsychol Rehabil 15:442–453
65. Trzepacz PT, Mittal D, Torres R et al (2001) Validation of the Delirium Rating Scale-Revised-98: comparison with the delirium rating scale and the cognitive test for delirium. J Neuropsychiatry Clin Neurosci 13:229–242
66. Sherer M, Nakase-Thompson R, Yablon SA et al (2005) Multidimensional assessment of acute confusion after traumatic brain injury. Arch Phys Med Rehabil 86:896–904
67. Hagen C, Malkmus D, Durham P (1972) Rancho Los Amigos Scale. http://www.rancho.org/patient_education/bi_cognition.pdf
68. Wortzel HS, Frey KL, Anderson CA, Arciniegas DB (2009). Subtle neurological signs predict the severity of subacute cognitive and functional impairments after traumatic brain injury. J Neuropsychiatry Clin Neurosci 21:463–466
69. Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res 12:189–198
70. Dubois B, Slachevsky A, Litvan I et al (2000) The FAB: a frontal assessment battery at bedside. Neurology 55:1621–1626
71. Crum RM, Anthony JC, Bassett SS et al (1993) Population-based norms for the mini-mental state examination by age and education level. JAMA 269:2386–2391
72. Appollonio I, Leone M, Isella V et al (2005) The frontal assessment battery (FAB): normative values in an Italian population sample. Neurol Sci 26:108–116
73. Arciniegas DB, Frey K, Alderfer B et al (2006) Impairments of frontally-mediated cognition characterize posttraumatic encephalopathy following resolution of posttraumatic amnesia. J Neuropsychiatry Clin Neurosci 18:281
74. Vanier M, Mazaux JM, Lambert J et al (2000) Assessment of neuropsychologic impairments after head injury: interrater reliability and factorial and criterion validity of the Neurobehavioral Rating Scale – Revised. Arch Phys Med Rehabil 81:796–806
75. McCauley SR, Levin HS, Vanier M et al (2001) The neurobehavioural rating scale-revised: sensitivity and validity in closed head injury assessment. J Neurol Neurosurg Psychiatry 71:643–651
76. Royall DR, Mahurin RK, Gray KF (1992) Bedside assessment of executive cognitive impairment: the executive interview. J Am Geriatr Soc 40:1221–1226
77. Grigsby J, Kaye K, Robbins LJ (1992) Reliabilities, norms and factor structure of the Behavioral Dyscontrol Scale. Percept Mot Skills 74:883–892
78. Kaye K, Grigsby J, Robbins LJ et al (1990) Prediction of independent functioning and behavior problems in geriatric patients. J Am Geriatr Soc 38:1304–1310
79. Cummings JL, Mega M, Gray K et al (1994) The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 44:2308–2314
80. Kalmar K, Novack TA, Nakase-Richardson R et al (2008) Feasibility of a brief neuropsychologic test battery during acute inpatient rehabilitation after traumatic brain injury. Arch Phys Med Rehabil 89:942–949
81. Hanks RA, Millis SR, Ricker JH et al (2008) The predictive validity of a brief inpatient neuropsychologic battery for persons with traumatic brain injury. Arch Phys Med Rehabil 89:950–957

82. Akiyama Y, Miyata K, Harada K et al (2009) Susceptibility-weighted magnetic resonance imaging for the detection of cerebral microhemorrhage in patients with traumatic brain injury. Neurol Med Chir (Tokyo) 49:97–99
83. Arciniegas DB, Anderson CA, Rojas DC (2005) Electrophysiological techniques. In: Silver JM, McAllister TW, Yudofsky SC (eds) Textbook of traumatic brain injury. American Psychiatric Publishing, Washington, DC
84. Rothman MS, Arciniegas DB, Filley CM et al (2007) The neuroendocrine effects of traumatic brain injury. J Neuropsychiatry Clin Neurosci 19:363–372
85. Frey LC (2003) Epidemiology of posttraumatic epilepsy: a critical review. Epilepsia 44(suppl 10):11–17
86. Schierhout G, Roberts I (2000) Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. Cochrane Database Syst Rev 4:CD000173
87. Dikmen SS, Temkin NR, Miller B et al (1991) Neurobehavioral effects of phenytoin prophylaxis of posttraumatic seizures. JAMA 265:1271–1277
88. Smith KR Jr, Goulding PM, Wilderman D et al (1994) Neurobehavioral effects of phenytoin and carbamazepine in patients recovering from brain trauma: a comparative study. Arch Neurol 51:653–660
89. Szaflarski JP, Meckler JM, Szaflarski M et al (2007) Levetiracetam use in critically ill patients. Neurocrit Care 7:140–147
90. Ruegg S, Naegelin Y, Hardmeier M et al (2008) Intravenous levetiracetam: treatment experience with the first 50 critically ill patients. Epilepsy Behav 12:477–480
91. Mula M, Trimble MR, Yuen A et al (2003) Psychiatric adverse events during levetiracetam therapy. Neurology 61:704–706
92. Mula M, Trimble MR, Sander JW (2004) Psychiatric adverse events in patients with epilepsy and learning disabilities taking levetiracetam. Seizure 13:55–57
93. Dikmen SS, Machamer JE, Winn HR et al (2000) Neuropsychological effects of valproate in traumatic brain injury: a randomized trial. Neurology 54:895–902
94. Marion DW (2006) Evidenced-based guidelines for traumatic brain injuries. Prog Neurol Surg 19:171–196
95. Fugate LP, Spacek LA, Kresty LA et al (1997) Measurement and treatment of agitation following traumatic brain injury: II. A survey of the Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation. Arch Phys Med Rehabil 78:924–928
96. Milbrandt EB, Kersten A, Kong L et al (2005) Haloperidol use is associated with lower hospital mortality in mechanically ventilated patients. Crit Care Med 33:226–229
97. Goldstein LB (1993) Basic and clinical studies of pharmacologic effects on recovery from brain injury. J Neural Transplant Plast 4:175–192
98. Goldstein LB (1999) Pharmacological approach to functional reorganization: the role of norepinephrine. Rev Neurol (Paris) 155:731–736
99. Goldstein LB (2003) Neuropharmacology of TBI-induced plasticity. Brain Inj 17:685–694
100. Goldstein LB (2006) Neurotransmitters and motor activity: effects on functional recovery after brain injury. NeuroRx 3:451–457
101. Hoffman AN, Cheng JP, Zafonte RD et al (2008) Administration of haloperidol and risperidone after neurobehavioral testing hinders the recovery of traumatic brain injury-induced deficits. Life Sci 83:602–607
102. Kline AE, Hoffman AN, Cheng JP et al (2008) Chronic administration of antipsychotics impede behavioral recovery after experimental traumatic brain injury. Neurosci Lett 448:263–267
103. Kline AE, Massucci JL, Zafonte RD et al (2007) Differential effects of single versus multiple administrations of haloperidol and risperidone on functional outcome after experimental brain trauma. Crit Care Med 35:919–924
104. Stanislav SW (1997) Cognitive effects of antipsychotic agents in persons with traumatic brain injury. Brain Inj 11:335–341

105. Rao N, Jellinek HM, Woolston DC (1985) Agitation in closed head injury: haloperidol effects on rehabilitation outcome. Arch Phys Med Rehabil 66:30–34
106. Buffett-Jerrott SE, Stewart SH (2002) Cognitive and sedative effects of benzodiazepine use. Curr Pharm Des 8:45–58
107. Bleiberg J, Garmoe W, Cederquist J et al (1993) Effects of dexedrine on performance consistency following brain injury: a double-blind placebo crossover case study. Neuropsychiatry Neuropsychol Behav Neurol 6:245–248
108. Schmitt JA, Kruizinga MJ, Riedel WJ (2001) Non-serotonergic pharmacological profiles and associated cognitive effects of serotonin reuptake inhibitors. J Psychopharmacol 15:173–179
109. McCarter RJ, Walton NH, Moore C et al (2007) PTA testing, the Westmead post traumatic amnesia scale and opiate analgesia: a cautionary note. Brain Inj 21:1393–1397
110. Warden DL, Gordon B, McAllister TW et al (2006) Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. J Neurotrauma 23:1468–1501
111. Cicerone KD, Dahlberg C, Kalmar K et al (2000) Evidence-based cognitive rehabilitation: recommendations for clinical practice. Arch Phys Med Rehabil 81:1596–1615
112. Cicerone KD, Dahlberg C, Malec JF et al (2005) Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. Arch Phys Med Rehabil 86:1681–1692
113. Cappa SF, Benke T, Clarke S et al (2005) EFNS guidelines on cognitive rehabilitation: report of an EFNS task force. Eur J Neurol 12:665–680
114. Cappa SF, Benke T, Clarke S et al (2003) EFNS guidelines on cognitive rehabilitation: report of an EFNS task force. Eur J Neurol 10:11–23
115. Tate RL, Moseley A, Perdices M et al (2006) Update on Cicerone's systematic review of cognitive rehabilitation: the PsycBITE perspective. Arch Phys Med Rehabil 87:446
116. Cicerone KD, Mott T, Azulay J et al (2008) A randomized controlled trial of holistic neuropsychologic rehabilitation after traumatic brain injury. Arch Phys Med Rehabil 89:2239–2249
117. Cicerone KD, Mott T, Azulay J et al (2004) Community integration and satisfaction with functioning after intensive cognitive rehabilitation for traumatic brain injury. Arch Phys Med Rehabil 85:943–950