Chapter 2

Traumatic Brain Injury

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Epidemiology

Traumatic brain injury (TBI) is a serious public health problem, often referred to as a silent epidemic due to lack of public awareness [1]. TBI is still the leading cause of mortality and morbidity in the world for individuals under the age of 45 [2]. In the United States alone, based on population data from 1995 to 2001, 1.4 million people sustained TBI in the United States each year, compared to 176,000 new cases of breast cancer, 43,500 new cases of HIV, and 10,400 new cases of multiple sclerosis [3]. Of these brain injuries, 50,000 died, 235,000 were hospitalized, and 1.1 million were treated and released from hospital emergency departments. Though many patients recover from their injuries, each year an estimated 80,000–90,000 Americans sustain a TBI that results in permanent disability [1]. It is estimated that 5.3 million Americans are living with disability resulting from TBI [3]. Mild TBI alone costs the nation $17 billion annually [4].

Leading causes of traumatic brain injury are falls – 28%, motor vehicle accidents – 20%, being struck by or against objects – 19%, and assault – 11% [1]. In the United States, persons in the 15–24 and 64+ age groups are at highest risk, with males at more risk than females at a ratio of approximately 2.8:1.6 [5]. Sports-related TBI is second only to MVA as a leading cause of injury in the 15–24 age group with 300,000 cases annually in the United States [6].

TBI, particularly closed head injury resulting from blast injury, is a significant source of morbidity in military service personnel in the Iraq and Afghanistan wars [7]. Effects of primary, secondary, and tertiary blast injuries have been an active area of investigation [7–9].

Neurologic consequences of TBI are multiple [10]. Any sensory, motor, or autonomic function may be compromised and long-term sequelae such as movement disorders, seizures, headaches, visual defects, and sleep disorders can result. Non-neurological medical consequences can be pulmonary, metabolic, nutritional, or musculoskeletal. Impairments may be temporary or permanent, causing partial or total functional disability [3, 10]. Even injuries that are classified as mild can result in persistent neurobehavioral impairments.

Etiology

Mechanisms of Injury

While TBI often occurs from a direct blow to the head due to an external physical force such as a blunt object, bullet wound, or fall, injury to the brain can result without direct impact to the head [11]. Mechanisms of injury include contusions (bruises) occurring at the site of impact, known as coup lesions, and bruising due to the force of impact causing the brain to strike the opposite side of the skull, known as contrecoup lesions. The second type of injury is diffuse axonal injury (DAI) which results from sudden momentum or movement change, typically from a motor vehicle accident. DAI

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occurs from unrestricted movement of the head, with the brain lagging behind the movement of the skull, resulting in shear, tensile, and compressive strains [12]. DAI is thought to underlie all forms of traumatic brain injury, including mild TBI, due to the destruction of neurofilaments and microtubules running the length of the axon, leading to axonal swelling and disconnection [13]. DAI is the principal pathology producing the continuum of brain injury from mild to severe [12].

Primary and Secondary Injuries

Primary injury is the mechanical damage occurring at the moment of impact, and secondary injuries are the non-mechanical aspects that result, including altered cerebral blood flow and metabolism, excitotoxicity, edema (swelling), and inflammatory processes [2]. The extensive tearing of nerve tissue throughout the brain causes these additional injuries since neurotransmitters are released, resulting in disruption of the brain's normal communication and chemical processes. Permanent brain damage, coma, or death is possible.

Types of Injury

Traumatic brain injuries are classified as penetrating or closed, and the pathophysiological processes differ for each.

Penetrating Head Injury

Penetrating or open head injuries cause fracture or breach of the skull with laceration or destruction of brain tissue, and the mortality rate is much higher for this type of head injury [14]. Trauma to the skull results from low-velocity bullets, puncture, everyday objects that may become embedded or from a tangential injury whereby an object strikes the skull, causing bone fragments to be driven into the brain [15, 16]. In most cases, such focal lesions cause relatively circumscribed cognitive losses; however, penetrating objects may cause damage throughout the brain depending on

shock wave or pressure effects from the speed and malleability of the penetrating object [15, 16]. With penetrating injuries, prevention of infection is key since brain abscesses may develop. Secondary injuries from metabolic and physiologic processes such as edema, ischemia, or posttraumatic epilepsy can be as or more damaging than the primary injury [2].

Closed Head Injury

In closed head injury (CHI), the most common type of TBI, the skull remains relatively intact. CHI primary effects include both coup and contrecoup contusions. DAI is common and considered to be responsible for persistent neurological effects [13, 16]. CHI impacts the frontal lobes, particularly the orbital and polar aspects [17, 18]. Specificity for the frontal poles and the anterior temporal convexity is due to the proximity of these regions to the bony surfaces of the skull, such that movements of the brain cause compression against the falx and tentorium [19]. Although many lesions can be detected by modern visual imaging techniques, the extent of microscopic damage due to DAI cannot be fully documented; thus it should be emphasized that damage after CHI is never circumscribed [17]. More importantly, frontal dysfunction includes not only damage to the frontal lobes per se but also disconnection to prefrontal regions from lesions elsewhere in the brain, for example, injury to dorsomedial thalamic nuclei or other anterior connections that can imitate effects of a frontal lesion.

Potential secondary effects in CHI include development of subdural hematoma, intracerebral bleeding, increased intracranial pressure, hypoxia, obstructive hydrocephalus, and posttraumatic epilepsy [2]. Cognitive and behavioral changes are often the most salient features after closed head injury of any severity, and the extent of impairment reflects the severity of the DAI, length of posttraumatic amnesia (PTA), extent of generalized atrophy, and the location, depth, and volume of focal cerebral lesions [20]. The nature and frequency of the cognitive and/or behavioral difficulties are due to concentration of damage in the anterior regions of the brain [20].

After a CHI, a person may experience any of the following symptoms: loss of consciousness, dilated/unequal pupils, vision changes, dizziness,

balance problems, respiratory failure, coma, paralysis, slow pulse, slow breathing rate, vomiting, lethargy, headache, confusion, tinnitus (ringing in ears), cognitive changes, inappropriate emotional responses, loss of bowel/bladder control, speech changes, or body numbness or tingling [3].

Rating Severity of TBI

TBI severity is based on rating the presence or extent of loss of consciousness (LOC) and posttraumatic amnesia (PTA). Both LOC and PTA are used in the classification of TBI as mild, moderate, or severe.

Loss of Consciousness

The most commonly used instrument for grading LOC is the Glasgow Coma Scale [21], which rates verbal responses, eye opening behavior, and best motor responses on a 0–15 scale, with 15 indicating best performance. GCS ratings for severity level are as follows: mild = 13–15 points, moderate = 9–12 points, and severe = 8 or fewer points. The GCS appears most sensitive to moderate and severe injuries and less sensitive to mild TBI [16]. More current classification systems have acknowledged that loss of consciousness is not necessary for a diagnosis of TBI [3, 22–24].

Posttraumatic Amnesia

The second measure of TBI severity is posttraumatic amnesia (PTA), defined as anterograde memory loss for events occurring immediately following the injury and retrograde loss for events immediately prior to the injury. During this acute phase, learning and memory are significantly disrupted and memory deficits are on a temporal gradient, with older memories being more resistant to disruption. There are different systems for grading PTA; a commonly used system classifies PTA as follows: mild = PTA of less than 1 hour, moderate = PTA of 1–24 hour, and severe = PTA of greater than 24 hour [16]. Other systems [15] have distinguished six categories: very mild = less than 5 min, mild = 5–60 min, moderate = 1–24 hour, severe = 1–7 days,

very severe = 1–4 weeks, and extremely severe = greater than 4 weeks. PTA length is generally more accurate than duration of LOC in predicting recovery of function, with longer periods of PTA associated with more severe brain injury and poorer recovery.

Because it is a prognostic indicator, acute care facilities place emphasis on measuring PTA [25]. One of the most widely used brief instruments that can be administered bedside is the Galveston Orientation and Amnesia Test (GOAT) [26] which measures orientation, retrograde, and anterograde memory loss. It is most appropriate for use in a hospital setting since PTA is often acute and time limited. Other similar measures of PTA include the Oxford PTA Scale [27] and the Rivermead PTA Scale [28].

Due to the nature of PTA, relying of brief screening measures alone is problematic and can result in misclassification [28]. One reason is that recovery from PTA is gradual and may include periods of intact orientation or memory in a patient who is still in the midst of general confusion and disorientation [29]. Attention in particular is noted to be a key component in early recovery after TBI [30], and postconfusional state or PCS is preferred by some investigators to more fully describe the syndrome that includes impaired cognition, attention, and consciousness. PTA may also be accompanied by significant behavior problems such as agitation, restlessness, confabulation, or lethargy [16, 29]. PTA does not end when the patient begins to register experience again but only when registration is continuous [15]. Another concern is the reliability of the patient's report of the PTA period itself since it can be difficult for the examiner or the patient to distinguish what the patient actually recalls about the time period versus what the patient has been told by others.

For these reasons, in the acute care setting, even though the TBI patient may seem to be improved based on normal screening scores or brief interviews, the examiner should remain cognizant that fluctuations in mental status are likely, and some patients may still be in PTA at the time of discharge from the hospital.

Severity Classifications

Traumatic brain injuries are generally classified as mild, moderate, and severe and some systems have added very mild and very severe categories [3].

1. *Mild TBI*. Several systems have been used for categorizing mild TBI, with differences generally centering around loss of consciousness. More contemporary systems such as the definition proposed by the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine (MTBIC-ACRM) [22] or other systems [23] acknowledge that TBI can and does occur without loss of consciousness. The MTBIC-ACRM definition identifies the mild TBI symptom constellation as including previous labels such as minor head injury, postconcussive syndrome, traumatic head syndrome, traumatic cephalgia, postbrain injury syndrome, and posttraumatic syndrome. The definition further states that only one of the following manifestations is needed to indicate the presence of mild TBI:

a. any period of loss of consciousness,
b. any loss of memory for events immediately before or after the accident,
c. any alteration in mental state at the time of the accident such as feeling dazed, confused, or disoriented, or
b. focal neurological deficit which may or may not be transient.

Furthermore, the severity of the injury cannot exceed loss of consciousness of 30 minutes, initial GCS score of 13–15, or PTA greater than 24 hour. The symptoms may not be documented in the acute stage, and some patients may not become aware of or admit to symptoms until they try to resume their normal daily routines. In such cases, symptomatology which can be linked to a head injury can suggest the existence of a mild TBI [22].

Mild TBI has greater consequences than formerly assumed [31]. Of all hospital emergency department visits for TBI, more than half involve mild closed head injuries that do not require hospital admission, yet a significant percentage of these patients return to the hospital clinic weeks or months afterward complaining of symptoms from the original head injury [32]. Standard neuroimaging, including CT, MRI, and EEG, is often normal yet mental status changes can still occur, indicating that functioning has been altered [22, 33] and that DAI is present, which can result in temporary or permanent damage. Symptoms may also persist for varying periods of time, and some patients will exhibit persistent emotional, cognitive, behavioral, and physical symptoms, alone or in combination, producing a functional disability [22].

2. *Moderate TBI*. Moderate TBI is defined as involving loss of consciousness lasting from a few minutes to no more than 6 hour, a GCS score of 9–12, and PTA from 1 to 24 hours [15]. Confusion may last from days to weeks, and physical, cognitive, and emotional impairments can persist for months or be permanent [3]. Patients with moderate injury may display the full spectrum of cognitive and behavioral impairments. Evidence of contusions, edema, bleeding, etc., on standard CT/MRI will be more likely at this stage.

3. *Severe TBI*. Severe injury involves loss of consciousness with a GCS score of 8 or less, and loss of consciousness can last days, weeks, or months. Recent investigations have noted different subgroups within the severe TBI category [3, 34]. These subgroups include coma, vegetative state, persistent vegetative state, minimally conscious state, akinetic mutism, and locked-in syndrome. *Coma* is a state of unarousable unconsciousness with no eye opening, no command following, no intelligible speech, no purposeful movement, no defensive movements, and no ability to localize noxious stimuli. *Vegetative state* is like coma with no signs of conscious behavior, but differing in that there is spontaneous eye opening, evidence of sleep–wake cycles on EEG, and mechanical respiration or other life support measures are not required. *Persistent vegetative state* is vegetative state with duration longer than 1 month. The *minimally conscious state* is defined as severely altered consciousness in which minimal but definite evidence of self- or environmental awareness is demonstrated with ability to follow simple commands and have intelligible verbalization though these behaviors may occur inconsistently [34]. *Akinetic mutism*, resulting from damage to the dopaminergic pathways, results in minimal body movement, little to no spontaneous speech, infrequent or incomplete ability to follow commands, and preserved eye opening and visual tracking. Akinetic mutism differs from the minimally conscious state in that the lack of movement/speech is not due to neuromuscular disturbance. In the rare neurological condition *locked-in syndrome*, the person cannot physically move any part of the body except the eyes, and vertical eye movements and eye blinks are used to communicate [3]. Finally, *brain death* can also result from severe injury, and in this condition, the brain shows no sign of functioning.

Neuroimaging and TBI

Structural Imaging

Computed tomography (CT) and standard magnetic resonance imaging (MRI) detect structural changes within the brain including tissue or fluid volume and have been the most available and commonly used neuroimaging procedures for detection of damage from TBI; however, they are less sensitive to the diffuse axonal injuries in mild TBI. As noted by Bigler [35], clinically significant injuries from TBI are at the micron level, whereas detection of abnormality via CT or MRI is based on larger resolution capability which is measured in millimeters. Therefore a "normal" scan means the pathology has not reached the threshold of 1 mm or more, so standard MRI or CT cannot image brain lesions that are microscopic and below their level of detection [35].

With these stipulations, CT is still the preferred method of imaging for head trauma in the acute phase, since it can be done quickly and is most appropriate for detection of treatable lesions such as subdural hematoma, cortical contusions, skull fractures, intraparenchymal hemorrhage, or edema [35]. Magnetic resonance imaging is superior to CT in resolution, but is generally not used during the acute phase due to increased chance of motion artifact, length of scan time, and decreased sensitivity in detection of skull fractures. CT has not been useful in predicting outcome of TBI, since it takes days or weeks for brain lesions to evolve and months before stable degenerative patterns are established [31, 35]. MRI imaging studies have been more effective in documenting such chronic effects occurring over an extended period in mild and moderate TBI. Parenchymal and whole brain atrophy after mild and moderate brain injury have been detected on MRI an average 11 months postinjury [31], presumably as a result of cellular loss.

Diffusion Tensor Imaging

Newer tools that use MRI technology such as diffusion tensor imaging (DTI) allow for specific examination of integrity of the white matter tracts which are especially vulnerable to mechanical trauma and are more sensitive in identifying impairment in mild TBI

than standard MRI [33, 36]. DT imaging has detected abnormalities in white matter representing axonal swelling, which is an early step in the process of axonal injury in mild TBI, and such white matter changes have correlated with poor clinical outcome [13]. In some mild TBI patient samples with no macroscopically detectable or obvious lesions, disruptions of the corpus callosum and fornix have been demonstrated [37]. When performed more than 45 days postinjury DT imaging has detected chronic or long-term lesions associated with TBI such as shear injury, white matter abnormalities, and frontal atrophy and these abnormalities have correlated with neurobehavioral deficits [35]. Data indicate that white matter changes exist on a continuum, and TBI patients have reduced white matter integrity relative to controls. An index of global white matter neuropathology has been found to be related to cognitive functioning, such that greater white matter pathology predicts greater cognitive deficits.

Magnetic Resonance Spectroscopy

The prognostic role of magnetic resonance spectroscopy (MRS) in detection of underlying pathophysiology and severity of injury in TBI has also been an active area of investigation [38]. MRS is a noninvasive and quantitative way to evaluate brain changes at the atomic level, including metabolite changes such as N-acetylaspartate (NAA) concentrations which are decreased in areas of contusion as well as normal-appearing frontal white matter, occipital gray matter, and parietal–occipital white matter [38]. MRS is appropriate for evaluating diffuse injury associated with mild TBI and has been found to be more sensitive at detecting metabolic changes that are associated with poor clinical outcomes yet are not observable on CT or MR imaging [39]. MRS has detected widespread metabolic changes following mild TBI in regions that appeared structurally normal on standard MRI at 1 month postinjury. Differences in N-acetylaspartate (NAA), total creatine (Cr), and total choline (Cho) were found in mild TBI as compared to controls, which was consistent with diffuse cellular injury seen in postmortem examinations [39]. Cohen et al. [40] were able to document decline of NAA as well as gray matter and white matter atrophy in mild TBI patients, with whole brain NAA concentrations showing a 12%

deficit on the whole compared with controls, and these findings were apparent in patients with and without visible MRI imaging pathology. In summary, MRS has documented neuronal injury beyond the minimal focal visible lesions in mild TBI.

Functional Imaging

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) involve the use of isotope tracers to measure functional activity in the brain and have been used to evaluate cerebral metabolism in TBI. Magnetoencephalography (MEG) records the brain's magnetic fields produced by electrical activity. Comparison studies of SPECT, MEG, and MRI imaging have found evidence of abnormal cerebral metabolism in mild TBI patients with persistent postconcussive somatic and cognitive symptoms [32]. MEG has been informative in preliminary studies, with significant correlations found between regional abnormalities and specific cognitive problems [32]. SPECT and MEG have demonstrated more sensitivity than routine MRI in detecting abnormalities in mild head trauma patients, with MEG showing the greatest sensitivity; however, MEG is not yet widely available and further studies are needed regarding findings in the TBI population. In one moderate TBI patient sample, PET imaging demonstrated abnormal focal uptake extending beyond the abnormal regions documented on CT and MRI [41]. Ruff et al. [42] demonstrated significant correlation between neuropsychological findings and PET in mild TBI patients, with PET documenting metabolic abnormalities that were pronounced in frontal and anterior temporal regions and no differences were noted in those patients with or without loss of consciousness.

Functional MRI (fMRI), which measures regional changes in blood perfusion and blood oxygenation changes, has also demonstrated ability to detect brain abnormalities in mild TBI that are not detectable on standard imaging [43]. Using fMRI, investigators have shown smaller increases in brain activity in mild TBI patients relative to healthy controls on working memory tasks [44] and have demonstrated significant reductions in activation of right prefrontal and medial temporal regions in mild TBI patients relative to healthy controls [45]. In a study of athletes with mild TBI,

Chen et al. [46] found that normal controls showed the expected frontal cortical activations during a working memory task, whereas all TBI subjects showed significantly weaker and fewer activations; in several subjects who had multiple concussions, there was a complete lack of task-related activation. Self-reported TBI symptoms have been shown to predict changes on fMRI as well, with decreased activity in prefrontal regions corresponding to the extent of complaints, i.e., a high number of complaints was predictive of significantly reduced activity while a mild number of complaints indicated less but still significantly reduced activity [47].

Frontal Systems, Cognition, and Behavior

Both frontal and temporal lobe regions are affected by traumatic brain injury, with the frontal lobes being the most significantly impacted. Effects of TBI on temporal lobe functioning are well known and extensively described in the extant literature; however, adequate characterization of frontal systems and measurement of executive functions are often inadequate; therefore, frontal systems are emphasized in this section.

Distinct behavioral and cognitive syndromes correspond to three frontal lobe systems: the dorsolateral, orbitofrontal, and anterior cingulate circuits [17, 48], with the orbitofrontal system being substantially impacted in TBI of all severities. Each system is considered separately, with particular focus on the orbitofrontal circuit.

Dorsolateral Prefrontal Circuit

The dorsolateral prefrontal circuit consists of the dorsolateral prefrontal cortex which projects to the lateral region of the caudate nucleus. This circuit is the neuroanatomical basis for organizing behavioral responses to solve complex problems, such as learning new information, systematically searching memory, or activating remote memories. Patients with damage to this circuit exhibit poor organization strategies, poor word list generation, reduced design fluency, poor sorting behavior, stimulus-bound behavior, environmental dependency, concrete proverb interpretations,

imitation behavior, utilization behavior, and impaired cognitive set shifting and maintenance [17, 49–51]. Not all skills are affected by any one lesion or process, and patients with dorsolateral prefrontal dysfunction have varied clinical presentations.

Orbitofrontal Circuit

The orbitofrontal circuit includes the lateral orbitofrontal cortex which sends projections to the ventromedial caudate and the medial orbitofrontal cortex which sends projections to the ventral striatum [17]. The two systems overlap in anatomy and behavioral functions [17]. The orbitofrontal circuit mediates empathic, civil, and appropriate social behavior, and damage to this region results in impaired emotional reactivity and processing, personality change, tactlessness, undue familiarity, irritability, poor impulse control, increased aggression, and mood instability [17, 49].

Socially inappropriate behavior is evident in TBI patients and has been well documented in studies of patients with damage to the orbitofrontal regions [52–54]. One of the more famous patients was Phineas Gage, a supervisor of a railroad construction work crew who in the 1800s sustained severe injury to the orbitomedial frontal regions after an explosion. A tamping iron was propelled into his left maxilla, exiting through the mid-frontal regions [55]. After this injury, a significant alteration in personality and judgment was reported by friends and coworkers; Gage apparently changed from a responsible, wellfunctioning individual into one who was no longer employable and was given to "fits" of anger and profanity.

Changes in emotional reactivity and behavior have been demonstrated in more recent studies of orbitomedial damage as well [56–58]. In some investigations, patients with damage to this region exhibited both antisocial behavior and abnormal autonomic responses to socially meaningful stimuli, i.e., "acquired sociopathy" [57]. Damasio et al. [58] found defective emotional responses to socially significant stimuli as measured by skin conductance in subjects with bilateral ventromedial frontal lesions who also had severe deficits in social conduct/social judgment compared with subjects who had brain injury without ventromedial involvement and no acquired deficits in social

conduct. Rolls et al. [59] found orbitomedial pathology to be significantly associated with disinhibited and socially inappropriate behavior and with difficulty in modifying responses when followed by negative consequences.

Orbitomedial frontal dysfunction increases the probability of aggression [60] and several investigators have demonstrated the role of medial and orbital frontal regions in aggressive and violent behavior. Grafman et al. [61], in a study of 279 Vietnam veterans, found that head-injured veterans who had focal ventromedial frontal lobe lesions had a significantly higher frequency of aggressive and violent behavior when compared to controls or subjects who had lesions elsewhere in the brain. Functional neuroimaging has also correlated injury to this region with highly abnormal behavior including reductions in prefrontal lobe glucose metabolism on positron emission tomography (PET) imaging in lateral and medial prefrontal cortex in murderers [62].

The orbitomedial prefrontal circuit is thought to mediate social cognition in general [63–65]. One aspect of social cognition, theory of mind (ToM), defined as the ability to recognize and make inferences about other peoples' intentions and beliefs, is considered necessary for effective social communication [63, 65, 66]. ToM includes the ability of an individual to understand that another may hold a false belief, to recognize faux pas in one's own behavior, for example, that he or she said something they should not have said and realizing they should not have said it, and the ability to detect sarcasm or irony. Theory of mind is frequently disturbed after TBI, as indicated by family reports of TBI patients' changes in behavior including lack of empathy, unconcern, and inability to appreciate humor [66]. Patients with ventromedial, but not dorsolateral, prefrontal lesions were significantly impaired on tests of irony and faux pas compared with patients with posterior lesions or normal controls, and lesions in the right ventromedial area were associated with the most severe ToM deficit [65].

Anterior Cingulate

The "motivation circuit" [67] is the anterior cingulate and includes the forebrain, composed of the anterior cingulum, nucleus accumbens, ventral palladium,

and ventral tegmental area. The anterior cingulate is the neuroanatomical basis of motivated behavior, and apathy is the most distinguishing characteristic of damage [67]. The most severe damage to this circuit, akinetic mutism, results from bilateral lesions of the anterior cingulate, resulting in profound apathy, lack of movement or rare movement, incontinence, eating/drinking only when fed, speech limited to monosyllable responses, and no display of emotions. Unilateral lesions display less dramatic apathetic syndromes, with impaired motivation, marked apathy, poverty of spontaneous speech, and poor response inhibition [17]. A method for evaluating and quantifying apathy or loss of motivation is the Apathy Evaluation Scale (AES) [68] which has strong construct validity and can be administered as a self-rated scale, a caregiver paper-and-pencil test, or a clinician-rated inventory. The AES has been found to be sensitive in a severe TBI population [69].

Neuropsychological Assessment of TBI

Attention, memory, and executive functions are primarily affected in TBI, and each will be discussed separately, with particular attention to executive functions since these functions are critical in TBI yet comprehensive assessment has been incomplete and/or problematic.

Attention

Impaired attention is prevalent, if not universal, after TBI at all levels of injury, whether diffuse or focal [70]. Attention underpins all aspects of cognition and even mild impairments can restrict other processes such as learning or problem solving. Common complaints from patients reflecting attention problems include mental slowing, trouble following conversation, losing train of thought, or difficulty attending to several things simultaneously.

Attention is not a unitary phenomenon, but includes at the most basic level arousal and alertness. Useful tools for evaluation of attention in acute-phase TBI patients include tests of delirium such as the Cognitive Test for Delirium [71] and the Moss Attention Rating

Scale (MARS) [72, 73]. The Cognitive Test for Delirium, which was developed to diagnose delirium on the basis of cognitive functioning, has been noted to have acceptable specificity and sensitivity to delirium in TBI patients in the inpatient setting [71]. The Moss Attention Rating Scale (MARS) has differentiated various aspects of disordered attention in acute TBI, such as restlessness/distractibility, initiation, and sustained/consistent attention, and can be used to monitor changes over time as well as treatment response [72].

Post-acute assessment of attention includes measures of auditory and visual attention, and several tests are well standardized and widely used. Attention tests generally range from simple to more complex tasks that require speed of information processing and working memory. For general span or amount of information that can be held in mind at one time, forward span for digits or visual targets from the Wechsler scales are appropriate [74, 75]. Attentional vigilance or being able to select target information and inhibit irrelevant stimuli can be measured by tasks such as the Continuous Performance Test of Attention [76], the Stroop test [77], or visual search tasks from the Wechsler scale [74]. Shifting or dividing attention between two or more sources of information is generally assessed by tasks such as the Trailmaking Test Part B [78] or the Paced Auditory Serial Addition Test (PASAT) [79]. Visual attention and processing speed can be measured by timed coding tasks such as those on the Wechsler scales [74] or visual scanning via the Trailmaking Test Part A [78], and working memory can also be evaluated by Wechsler subtests of mental arithmetic, digits backward span, and auditory sequencing [74, 75].

Memory

Impairment of memory is also a cardinal feature after TBI and may be temporary or permanent. In penetrating head injuries (PHI), memory deficits may be material specific, depending on the site of the injury.

Two systems, the episodic or knowing "what" and the procedural or knowing "how," comprise memory. Episodic memory is a multifactorial process, and all phases, encoding, consolidation, or retrieval, may be affected in TBI. Episodic memory for personal information or facts is most impacted after TBI, in contrast

to procedural memory, which is outside conscious awareness; includes memory for procedures, conditioning, and priming; and is relatively spared [80]. When evaluating memory both associative processes, served by the medial temporal lobes and hippocampal formation, and strategic processes, associated with dorsolateral prefrontal functions, must be assessed [80]. Both immediate and delayed memory are evaluated. In mild TBI, problems are generally more with acquisition and/or with the strategic aspects of registering material into memory, i.e., immediate recall, than with consolidation or retention of material that is registered. In moderate to severe injuries, acquisition and consolidation are generally affected, reflected by deficits in immediate recall as well as retention.

The neuropsychological evaluation typically involves assessment of acquisition and consolidation aspects of verbal and visual memory. For auditory memory, verbal learning tasks such as the California Verbal Learning Test-II [81] are appropriate due to serial position learning, semantic organization, interference effects, cued recall, recognition, and monitoring aspects. Similar verbal learning/recall tasks include the Hopkins Verbal Learning Test [82] and the Rey Auditory Verbal Learning Test [83]. Additional measures of immediate and delayed auditory verbal memory include paragraph or story recall, such as in the Wechsler Memory tests [75]. Nonverbal memory is generally assessed by visual recall and reproduction of simple designs, recognition memory for faces, or recall of scenes [75]; complex figural memory is evaluated by reproducing complex figures after copying; and tactile and spatial memory can be evaluated by use of tasks that do not allow visual access, such as the Tactual Performance Test from the Halstead–Reitan battery [78].

Executive Functions

There is substantial agreement among investigators that executive functions are significantly impacted by TBI due to the preponderance of frontal system injuries. The definition of executive functions has varied among investigators, but it is generally acknowledged as involving self-regulatory functions that organize, direct, and manage other cognitive activities, emotional responses, and behavior [84]. This regulatory function includes the ability to initiate behaviors, inhibit competing actions or stimuli, select relevant task goals, plan and organize, solve complex problems, shift problem-solving strategies appropriately when necessary, regulate emotions, monitor and evaluate behavior, and hold information in mind in order to guide cognition and behavior [84]. Though executive functions are a critical determinant in functional outcome after TBI [15, 20, 48] and are among the most disabling aspects of cognitive impairment following TBI [85], they continue to be inadequately assessed. Comprehensive evaluation of these functions has been problematic for several reasons, including lack of tests that are sensitive or specific to the differing frontal circuits, lack of recognition of the importance of the orbitofrontal circuit which leads to undertesting and underdetection of deficits associated with this region, and the nature of the standardized testing environment, which is artificial and highly structured and does not elicit the types of errors, commonly reported by TBI patients, that occur during everyday activities. Each of these is considered separately.

1. *Test Sensitivity and Specificity*. While many examiners prefer use of general-purpose or "fixed" batteries such as the Halstead–Reitan Neuropsychological Battery [78], with the advantage that such batteries provide standardized procedures and allow for comparisons, the disadvantage is that none of the fixed batteries are fully appropriate or complete for any one patient [86], and this results in overtesting or undertesting of specific functions. Evaluation of frontal systems functioning has been particularly problematic, as many tests comprising clinical neuropsychological batteries in current usage lack specificity or sensitivity to the differing frontal circuits and/or unique deficits exhibited by the TBI patient and yet are widely used as tests of executive functions [51, 80]. Examples include the Stroop Color–Word Test [77] and the Trailmaking Tests [78] which are sensitive to general cerebral pathology, but are not specific to frontal system functioning in TBI [80]. Widely used tests, such as the Category Test [78], the matrix reasoning subtest from the Wechsler Intelligence Scale [74], the Wisconsin Card Sorting Test [87], and verbal fluency tasks [88], also have demonstrated sensitivity to diffuse cerebral dysfunction in addition to dorsolateral prefrontal functioning. Functional neuroimaging studies using PET, SPECT, and regional cerebral blood flow have demonstrated sensitivity but lack of

specificity of the Wisconsin Card Sorting Test, with widespread activation noted in frontal and non-frontal brain regions during test administration [89], activation of the left dorsolateral prefrontal cortex [90, 91], or activation of the right anterior prefrontal region [92].

Even more recently developed executive function batteries are comprised of tasks that have been linked primarily to general or dorsolateral prefrontal function (card sorting tests, verbal and design fluency tasks, tower tests, etc.), and not orbitofrontal functioning, such as Delis–Kaplan Executive Function System (D-KEFS) [93]. Another example is the Behavioral Assessment of Dysexecutive Syndrome or BADS [94] which has been noted to have few subtests that are sufficiently powerful enough to encompass all executive functions, such that supplementation with other procedures is recommended [95].

2. *Underdetection of Orbitofrontal Functioning*. Though traditionally used tests of general or dorsolateral prefrontal brain function have been valuable in detecting cognitive deficits in patients who might not appear cognitively impaired to the typical observer, they fail to capture the real-life social functioning and behavior linked to the orbitofrontal regions which bear the brunt of TBI [20]. Ways to correct this situation have been recommended including use of adjunctive structured interviews, self-report, and informant report instruments [85, 96] or by use of questionnaires regarding behavioral disorders [97]. Examples include instruments such as the Behavioral Rating Inventory of Executive Function (BRIEF) [84] and Frontal Systems Behavior Scale (FrSBe) [96], which assess degree of apathy, disinhibition, or other behavioral/emotional dysregulation occurring in everyday life and also have the advantage of allowing for comparisons between patient and caregiver ratings.

In addition, as noted by Goldberg and Bougakov [48] most widely used tests of executive functioning are "veridical" in nature rather than "actor centered." Tests of frontal systems functioning commonly used in neuropsychological batteries, i.e., the Wisconsin Card Sort [87], Stroop Color–Word Test [77], Category Test [78], are veridical in that patient responses on these tests are either correct or incorrect. Individual preferences or biases have no bearing on patient responses; their answers are simply "right" or "wrong." In contrast, actor-centered tests are guided by patient priorities, and the responses made depend on the patient needs and/or perception of those needs. Two tasks

noted as actor centered and reviewed by Goldberg and Bougakov [48] are the Cognitive Bias Task (CBT) [98] and the Iowa Gambling Task (IGT) [99]. The CBT requires decision making based on preference rather than stimulus characteristics, i.e., subjects are instructed to look at a target card and two additional stimuli that look either similar to or different from the target and then to select the one of the two stimuli that they "like better." The CBT has demonstrated robust effects in patients with frontal lobe lesions and has demonstrated important hemispheric differences as well as gender differences [48]. The IGT has recently been standardized and validated and has demonstrated sensitivity to ventromedial prefrontal lesions [99]. The IGT requires decision making by use of advantageous and disadvantageous strategies, and failure to choose advantageously results from insensitivity to future consequences, with immediate prospects overriding any future prospects [100]. The IGT simulates a gambling situation with differing cost and payout ratios, i.e., preferences for strategies that result in high immediate reward but lower overall payout vs. strategies that are low in immediate reward but result in higher overall payout in the long run. This test has shown predictive ability in substance abuse, relapse, and ability to hold gainful employment due to decision-making deficits linked to ventromedial prefrontal cortical dysfunction [101]. Performance on the IGT has also correlated significantly with emotional intelligence, as patients with bilateral ventromedial frontal injury and/or right unilateral lesions in the amygdala have demonstrated significantly lowered judgment and decision making as well as lower emotional/social intelligence despite average levels of cognitive intelligence when compared to patients who had lesions outside these regions [102]. In everyday life, such actor-centered decision making is predominant, yet neuropsychological and/or executive function batteries in common usage do not reflect this, but rather are comprised on tests that are veridical [48].

Experimental measures have also been employed to evaluate orbitofrontal functioning. Investigators have differentiated aspects of social cognition in frontal lesion patients using ToM tasks that involve detecting deception, faux pas, irony, or understanding mental states of others. The right hemisphere in particular has been implicated in ToM. Stuss et al. [64] evaluated patients with focal frontal and non-frontal lesions with visual perspective taking (ability to infer the

visual experience of another) and detecting deception (ability of the patient to infer that someone was trying to deceive them). Lesions throughout the frontal lobes, with most robust findings in the right frontal lobe, were predictive of deficits in visual perspective taking, and medial frontal lesions, particularly right ventromedial, were implicated in detection of deception. Bilateral, particularly right orbitomedial, lesions impaired patients' capacity to incorporate the experience of another's deceptions into their own plans, consistent with existing knowledge about damage to this region [64]. ToM tasks are not yet in common clinical usage, as validity and reliability studies are still in progress.

3. *The Laboratory Testing Environment*. A third problem in assessment of executive functions is the failure of laboratory testing to reflect problems in cognition or behavior as they are manifested in everyday life. Executive functions are dynamic, and unlike evaluation of more specific functions such as motor skills, problem-solving behavior that includes planning or decision making is more difficult to fully capture in a controlled environment [63, 84, 103]. In particular, patient errors when performing everyday activities are less likely to be manifested in the laboratory than they are in the natural setting [104]. TBI patients, when compared to normal controls, have been shown to have a high error rate, for both detecting and correcting errors made in performance of everyday actions [104].

The Naturalistic Action Test (NAT) [105] has been developed to assess everyday actions and has shown promise in evaluating functioning in a way that simulates the natural environment. The NAT is sensitive to errors of action in performing basic everyday activities such as making coffee, toast, packing a lunch, etc. The necessary items for a particular task are placed on a table in a standardized fashion in front of the patient, who is then instructed to complete it, and performance is observed and errors are recorded. The complexity of tasks can be manipulated to place increasing demands on attentional resources, for example, in the simple condition, items are placed in front of the subject along with distractor items; in the complex condition, some target items are hidden in a box placed in a particular spot on the table. Competing stimuli can also be introduced to increase complexity. Errors are recorded and coded as to type, such as omitting steps, performing actions at the wrong time, perseveration, using the wrong object in place of the target object, misjudging

the relationship between two objects, omitting use of or misusing tools. Error rates increase with level or severity of the patient and/or task complexity. Reliability and validity of the NAT have been demonstrated in various populations, including stroke and TBI [106], and adaptations of the NAT have been useful in differentiating patients with Alzheimer's dementia from normal controls [107]. Unfortunately, tests of naturalistic action are not part of standard neuropsychological batteries outside of rehabilitation settings, though they clearly capture significant problems experienced and commonly reported by TBI patients and patient caregivers, suggesting possibly greater ecological validity than many tests in common usage.

Executive Functions: The Need for Subcategories

Executive functioning is a multifactorial rather than a unitary construct. Given the diversity of the frontal systems underpinning the executive functions, no one test can be sensitive to all aspects of dysfunction [48, 95, 108].

Subdividing the executive functions to correspond to distinct frontal systems has been recommended [80, 97, 109]. Different systems for this subdivision have been offered, including executive cognitive functions, behavioral self-regulatory functions, activation–regulation functions, and metacognitive processes [80]. In general, subdivisions that capture both the cognitive and the behavioral/emotional aspects of executive functions are emphasized because they provide the necessary framework for a systematic evaluation strategy [80, 97]. Assessment of executive functioning must therefore include measures of the *cognitive* aspects, generally mediated by the dorsolateral prefrontal circuit, such as planning, organizing, monitoring, working memory, set shifting/set maintenance; the *behavioral self-regulatory/social–emotional* aspects regulated by orbitofrontal circuit and limbic nuclei, such as emotional reactivity, preferences and biases in judgment in problem solving, ability to take another's perspective, personality changes, empathy, and mood changes; and the *activation* aspects, served by the anterior cingulate such as activation and motivation.

Accurate assessment of executive functioning that encompasses all frontal systems will best be accomplished by expanding the traditional neuropsychological battery to include standardized procedures in current usage which have demonstrated utility in evaluating general cognitive as well as dorsolateral prefrontal functioning, incorporating newer measures such as self-report inventories, informant report inventories, and actor-centered tests that are sensitive to the orbitofrontal circuit, using apathy evaluation scales for assessment of anterior cingulate functions, such as motivation, and using tasks that assess errors of action in a more natural environment. Supplementation with more experimental procedures such as ToM tasks may also be indicated.

Neuropsychological Assessment as a Dynamic Process

Effects of and recovery from TBI are ongoing, changing processes. Consequently, the neuropsychological evaluation should be dynamic in terms of being flexible and accommodating to the emergent cognitive and behavioral changes marking the phases of recovery.

In the acute phase of TBI recovery, the focus will be on evaluation of attention, information processing, and memory and may require administration of short tests or repeated interviews. Briefer testing of postconfusional state and posttraumatic amnesia via use of short instruments, behavioral observations, and history, as well as attention to mental status observations from treating health professionals and caregivers over the course of days or weeks, will be necessary. Additional measures to evaluate concomitant delirium and agitation should be employed. In the hospital setting where neuropsychological evaluations are generally used to assist with discharge and treatment planning, strengths and limitations of certain assessment instruments (PTA, delirium questionnaires, etc.) should be discussed on an ongoing basis with treating professionals and patient caregivers in order to avoid overemphasis on a "score." This will help with adjusting expectations about the patient's capabilities and insure proper treatment planning. In this phase of recovery, the neuropsychologist must emphasize to those concerned with patient treatment that recovery from the acute confusion, delirium, and/or posttraumatic amnesia can be a slow, nonlinear process.

In the more stable or chronic phase(s) of TBI, after the patient has regained sufficient alertness, attention, and/or motivation, a more thorough evaluation of neurocognitive functioning should be undertaken with a comprehensive battery. Within the context of a comprehensive assessment, there should be detailed and thorough evaluation of functions known to be particularly vulnerable to TBI, i.e., attention, memory, and, most importantly, the executive functions. When evaluating the executive functions multiple procedures will be required, including self-reports, naturalistic observation or tasks measuring everyday action errors, tasks sensitive to dorsolateral and orbitofrontal circuits, and experimental measures. Use of multiple measures that reflect the different frontal circuits will be necessary. Due to the often protracted nature of recovery of TBI, serial evaluations at different points in time will be warranted to coordinate with or help guide rehabilitation efforts.

Summary

Traumatic brain injury is prevalent in the United States and the world, resulting in long-term neurological, cognitive, emotional, and behavioral sequelae and causing long-term disability in a significant number of patients. The economic costs alone are staggering. Mild closed head injury, the most common form of TBI, is prevalent and has greater consequences than previously assumed. Accurate detection of TBI is critical to adequate treatment and recovery.

Neuroimaging, particularly newer functional imaging methods such as diffusion tensor imaging (DTI), positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), and magnetoencephalography (MEG), holds promise in detection of microscopic abnormalities in mild TBI that have been minimized by more conventional structural imaging. These newer imaging methods are also delineating and correlating separate cognitive functions to distinct neuroanatomical regions, furthering understanding of frontal systems and injuries in TBI.

Executive functions, served by three distinct frontal circuits, are particularly impacted by TBI. Neuropsychological evaluation traditionally has employed standardized tests associated with general cerebral and/or dorsolateral prefrontal functioning, with the result that orbitofrontal functions have been underevaluated, despite the vulnerability of this region in TBI. Effective assessment will best be accomplished by understanding executive functioning as multifactorial and consisting of subdivisions and employing tests/procedures that measure those functions associated with each subdivision. A combination of assessment procedures, including standardized tests, informant and self-rating inventories, naturalistic observations, and thorough interview of patients and caregivers, is essential to evaluate all aspects of cognitive, behavioral, emotional, and social consequences of TBI. Use of experimental measures is also advised as supplementary to more standardized procedures.

TBI is not an "event" but an ongoing process in any patient, and neuropsychological evaluation(s) must reflect this. The assessment battery in general should be tailored to the stage of recovery of the patient. Assessment must be dynamic in nature to accommodate the evolving nature of TBI, so serial evaluations will be necessary to adjust patient and caregiver expectations and to help plan future treatments.

References

1. Langlois JA, Rutland-Brown W, Thomas KE. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths. Atlanta, GA: Department of Health and Human Services (US), Centers for Disease Control and Prevention: National Center for Injury Prevention and Control, 2004.
2. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. Br J Anaesth. 2007;99:4–9.
3. Brain Injury Association of America. Types of brain injury 2007: Available online at http://www.biausa.org/aboutbi/htm
4. Centers for Disease Control and Prevention. Heads up: facts for physicians about mild traumatic brain injury (MTBI) 2002: Available on-line at http://www.cdc.gov/ncipc/tbi/TBI.htm
5. Kraus JF, Chu LD. Epidemiology. In: Silver JM, McAllister TW, Yudofsky SC, editors. Textbook of traumatic brain injury. Washington, DC: American Psychiatric Publishing, Inc.; 2005. pp. 3–26.
6. Gessel LM, Fields SK, Collins CL, et al. Concussions among U. S. high school and collegiate athletes. J Athletic Training. 2007;42:495–503.
7. Warden D. Military TBI during the Iraq and Afghanistan wars. J Head Trauma Rehabil. 2006;21:398–402.
8. Sayer NA, Chiros CE, Sigford B, et al. Characteristics and rehabilitation outcomes among patients with blast and other injuries sustained during the global war on terror. Arch Phys Med Rehabil. 2008;89:163–70.
9. Sylvia FR, Drake AI, Wester DC. Transient vestibular dysfunction after primary blast injury. Mil Med. 2001;166:918–20.
10. National Institutes of Health Consensus Conference on Rehabilitation of Persons with Traumatic Brain Injury. Rehabilitation of persons with traumatic brain injury 1998; Available on-line at http://consensus.nih.gov/1998 TraumaticBrainInjury109html.htm
11. Varney NR, Varney RN. Brain injury without head injury: some physics of automobile collisions with particular reference to brain injuries occurring without physical head trauma. App Neuropsychol. 1995;2:47–62.
12. Gennarelli TA, Graham DI. Neuropathology. In: Silver JM, McAllister TW, Yudofsky SC, editors. Textbook of traumatic brain injury. Washington, DC: American Psychiatric Publishing, Inc.; 2005. pp. 27–50.
13. Bazarian JJ, Zhong J, Blyth B, et al. Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study. J Neurotrauma. 2007;24:1447–59.
14. Peek-Asa C, McArthur D, Hovda D, Kraus J. Early predictors of mortality in penetrating compared with closed brain injury. Brain Inj. 2001;15:801–10.
15. Hannay HJ, Howieson DB, Loring DW, et al. Neuropathology for neuropsychologists. In: Lezak MD, Howieson DB, Loring DW, editors. Neuropsychological assessment. 4th ed. New York, NY: Oxford University Press; 2004. pp. 157–85.
16. Lucas JA. Traumatic brain injury and postconcussive syndrome. In: Snyder PJ, Nussbaum PD, editors. Clinical neuropsychology: a pocket handbook for assessment. Washington, DC: American Psychological Association; 1998. pp. 243–65.
17. Chow TW, Cummings JL. Frontal-subcortical circuits. In: Miller BL, Cummings JL, editors. The human frontal lobes: functions and disorders. New York, NY: Guilford Press; 1999. pp. 3–26.
18. Schnider A, Gutbrod K. Traumatic brain injury. In: Miller BL, Cummings JL, editors. The human frontal lobes: functions and disorders. New York, NY: Guilford Press; 1999. pp. 487–506.
19. Adams JH. The neuropathology of head injury. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology: head injury. Amsterdam: Elsevier Science; 1975. pp. 35–65.
20. McCullagh S, Feinstein A. Cognitive changes. In: Silver JM, McAllister TW, Yudofsky SC, editors. Textbook of traumatic brain injury. Washington, DC: American Psychiatric Publishing, Inc.; 2005. pp. 321–35.
21. Teasdale G, Jennett B. Assessment of coma and impairment of consciousness: a practical scale. Lancet. 1974;13:81–84.

22. Kay T, Harrington DE, Adams R. Definition of mild traumatic brain injury: American congress of rehabilitation medicine. J Head Trauma Rehab. 1993;8:86–7.

23. McAllister TW. Mild brain injury and the postconcussion syndrome. In: Silver JM, McAllister TW, Yudofsky SC, editors. Textbook of traumatic brain injury. Washington, DC: American Psychiatric Press; 2005. pp. 279–308.

24. Smits M, Hunink MGM, Nederkoorn PJ, et al. A history of loss of consciousness or post-traumatic amnesia in minor head injury: "conditio sine qua non" or one of the risk factors? J Neurol Neurosurg Psychiatry. 2007;78:1359–64.

25. Pelham MF, Lovell MR. Issues in neuropsychological assessment. In: Silver JM, McAllister TW, Yudofsky SC, editors. Textbook of traumatic brain injury. Washington, DC: American Psychiatric Publishing, Inc.; 2005. pp. 159–72.

26. Levin HS, O'Donnell VM, Grossman RG. The Galveston orientation and amnesia test: a practical scale to assess cognition after head injury. J Nerv Ment Disease. 1979;167:675–84.

27. Fortuny LA, Briggs M, Newcombe F, et al. Measuring the duration of posttraumatic amnesia. J Neurol Neurosurg Psychiatry. 1980;43:377–79.

28. King NS, Crawford S, Wenden FJ, et al. Measurement of posttraumatic amnesia: how reliable is it? J Neurol Neurosurg Psychiatry. 1997;62:38–42.

29. Hillary FG, DeLuca J. Learning and memory dysfunction following traumatic brain injury. In: Feinberg TE, Farah MJ, editors. Behavioral neurology and neuropsychology. 2nd ed. New York, NY: McGraw-Hill; 2003. pp. 463–75.

30. Stuss DT, Binns MA, Carruth FG, et al. The acute period of recovery from traumatic brain injury: posttraumatic amnesia or posttraumatic confusional state? J Neurosurg. 1999;90:635–43.

31. MacKenzie JD, Siddiqi F, Babb JS, et al. Brain atrophy in mild or moderate traumatic brain injury: a longitudinal quantitative analysis. Am J Neurorad. 2002;23:1509–15.

32. Lewine JD, Davis JT, Bigler ED, et al. Objective documentation of traumatic brain injury subsequent to mild head trauma: multimodal brain imaging with MEG, SPECT, and MRI. J Head Trauma Rehabil. 2007;22:141–55.

33. Kraus MF, Susmaras T, Caughlin BP, et al. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. Brain. 2007;130:2508–19.

34. Giacino J, Whyte J. The vegetative and minimally conscious states. J Head Trauma Rehabil. 2005;20:30–50.

35. Bigler ED. Structural imaging. In: Silver JM, McAllister TW, Yudofsky SC, editors. Textbook of traumatic brain injury. Washington, DC: American Psychiatric Publishing, Inc.; 2005. pp. 79–105.

36. Hughes DG, Jackson A, Mason DL, et al. Abnormalities on magnetic resonance imaging seen acutely following mild traumatic brain injury: correlation with neuropsychological tests and delayed recovery. Neuroradiology. 2004;46:550–58.

37. Nakayama N, Okumura A, Shinoda J, et al. Evidence for white matter disruption in traumatic brain injury without macroscopic lesions. J Neurol Neurosurg Psychiatry. 2006;77:850–55.

38. Shutter L, Tong KA, Lee A, Holshouser BA. Prognostic role of proton magnetic resonance spectroscopy in acute traumatic brain injury. J Head Trauma Rehabil. 2006;21:334–49.

39. Govindaraju V, Gauger GE, Manley GT, et al. Volumetric proton spectroscopic imaging of mild traumatic brain injury. Am J Neurorad. 2004;25:730–37.

40. Cohen BA, Inglese M, Rusinek H, et al. Proton MR spectroscopy and MRI-volumetry in mild traumatic brain injury. Am J Neurorad. 2007;28:907–13.

41. Jansen HM, van der Naalt J, van Zomeren AH, et al. Cobalt-55 positron emission tomography in traumatic brain injury: a pilot study. J Neurol Neurosurgery Psychiatry. 1996;60:221–24.

42. Ruff RM, Crouch JA, Troster AI, et al. Selected cases of poor outcome following a minor brain trauma: comparing neuropsychological and positron emission tomography assessment. Brain Inj. 1994;8:297–308.

43. Ptito A, Chen J-K, Johnston KM. Contributions of functional magnetic resonance imaging (fMRI) to sport concussion evaluation. NeuroRehabilitation. 2007;22:217–27.

44. McAllister TW, Saykin AJ, Flashman LA, et al. Brain activation during working memory one month after mild traumatic brain injury: an fMRI study. Neurology. 1999;53:1300–08.

45. McAllister TW, Sparling MB, Flashman LA, et al. Differential working memory load effects after mild traumatic brain injury. NeuroImage. 2001;14:1004–12.

46. Chen JK, Johnston KM, Frey S, et al. Functional abnormalities in symptomatic concussed athletes: an fMRI study. NeuroImage. 2004;22:68–82.

47. Chen JK, Johnston KM, Collie A, et al. A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. J Neurol Neurosurg Psychiatry. 2007;78:1231–38.

48. Goldberg E, Bougakov D. Neuropsychologic assessment of frontal lobe dysfunction. Psychiatr Clin North Am. 2005;28:567–80.

49. Goldberg E. The executive brain. New York, NY: Oxford University Press; 2001.

50. Luria AR. Higher cortical functions in man. New York, NY: Basic Books, Inc.; 1980.

51. Williams AD. Diagnostic decision making in neuropsychology. In: Horton AM, Hartlage LC, editors. Handbook of forensic neuropsychology. New York, NY: Springer; 2003. pp. 113–16.

52. Bibby H, McDonald S. Theory of mind after traumatic brain injury. Neuropsychologia. 2005;43:99–114.

53. Henry JD, Phillips LH, Crawford JR, et al. Theory of mind following traumatic brain injury: the role of emotion regulation and executive dysfunction. Neuropsychologia. 2006;44:1623–28.

54. McDonald S, Flanagan S. Social perception deficits after traumatic brain injury: interaction between emotion regulation, mentalizing ability, and social communication. Neuropsychology. 2004;18:572–79.

55. Stuss DT, Gow CA, Hetherington CR. "No longer Gage": frontal lobe dysfunction and emotional changes. J Consult Clin Psychol. 1992;60:349–59.

56. Saunders JC, McDonald S, Richardson R. Loss of emotional experience after traumatic brain injury: findings with the startle probe procedure. Neuropsychology. 2006;20:224–31.

57. Blair RJR, Cipolotti L. Impaired social response reversal: a case of 'acquired sociopathy'. Brain. 2000;123:1122–41.

58. Damasio AR, Tranel D, Damasio H. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behav Brain Res. 1990;41:81–94.

59. Rolls ET, Hornak J, Wade D, McGrath J. Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. J Neurol Neurosurg Psychiatry. 1994;57:1518–24.

60. Blair JR, Mitchell D, Blair K. The psychopath. Malden, MA: Blackwell Publishing; 2006.

61. Grafman J, Schwab K, Warden D, et al. Frontal lobe injuries, violence, and aggression: a report of the Vietnam head injury study. Neurology. 1996;46:1231–38.

62. Raine A, Buchsbaum MS, Stanley J, et al. Selective reductions in prefrontal glucose metabolism in murderers. Biol Psychiatry. 1994;36:365–73.

63. Wood JN. Social cognition and the prefrontal cortex. Behav Cog Neurosci Rev. 2003;2:97–114.

64. Stuss DT, Gallup GG Jr, Alexander MP. The frontal lobes are necessary for 'theory of mind'. Brain. 2001;124:279–86.

65. Shamay-Tsoory SG, Tomer R, Berger BD, et al. Impaired "affective theory of mind" is associated with right ventromedial prefrontal damage. Cogn Behav Neurol. 2005;18:55–57.

66. Milders M, Ietswaart M, Crawford JR, Currie D. Impairments in theory of mind shortly after traumatic brain injury and at one-year follow-up. Neuropsychology. 2006;20:400–08.

67. Marin RS, Chakravorty S. Disorders of diminished motivation. In: Silver JM, McAllister TW, Yudofsky SC, editors. Textbook of traumatic brain injury. Washington, DC: American Psychiatric Press; 2005. pp. 337–52.

68. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the apathy evaluation scale. Psychiatry Res. 1991;38:143–62.

69. Andersson S, Bergedalen AM. Cognitive correlates of apathy. Neuropsychiat Neuropsychol Behav Neurol. 2002;15:184–91.

70. Gronwall D. Minor head injury. Neuropsychology. 1991;5:254–65.

71. Kennedy RE, Nakase-Thompson R, Nick TG, Sherer M. Use of the cognitive test for delirium in patients with traumatic brain injury. Psychosomatics. 2003;44:283–89.

72. Hart T, Whyte J, Millis S, et al. Dimensions of disordered attention in traumatic brain injury: further validation of the moss attention rating scale. Arch Phys Med Rehabil. 2006;5:647–55.

73. Whyte J, Hart T, Bode RK, Malec JF. The Moss Attention rating scale for traumatic brain injury: initial psychometric assessment. Arch Phys Med Rehabil. 2003;84:268–76.

74. Wechsler D. Wechsler adult intelligence scale. 3rd ed. San Antonio, TX: The Psychological Corporation; 1997.

75. Wechsler D. Wechsler memory scale. 3rd ed. San Antonio, TX: The Psychological Corporation; 1997.

76. Cicerone K. Clinical sensitivity of four measures of attention to mild traumatic brain injury. Clin Neuropsychologist. 1997;11:266–72.

77. Golden CJ. Stroop color and word test. Chicago, IL: Stoelting Co.; 1978.

78. Reitan RM, Wolfson D, eds. The Halstead-Reitan neuropsychological test battery: theory and clinical interpretation. Tucson, AZ: Neuropsychology Press; 1993.

79. Gronwall D. Paced auditory serial addition task: a measure of recovery from concussion. Percept Mot Skills. 1977;44:367–73.

80. Cicerone K, Levin H, Malec J, et al. Cognitive rehabilitation interventions for executive function: moving from bench to bedside in patients with traumatic brain injury. J Cogn Neurosci. 2006;18:1212–22.

81. Delis DC, Kaplan E, Kramer JH, Ober RA. The California verbal learning test. 2nd ed. San Antonio, TX: The Psychological Corporation; 2001.

82. Brandt J. The Hopkins verbal learning test: development of a new memory test with six equivalent forms. Clin Neuropsychol. 1991;5:125–42.

83. Schmidt M. Rey auditory and verbal learning test: a handbook. Los Angeles, CA: Western Psychological Services, Inc.; 1996.

84. Roth RM, Isquith PK, Gioia GA. Behavioral rating inventory of executive function-adult version (BRIEF-A). Lutz, FL: Psychological Assessment Resources, Inc.; 2005.

85. McDonald BC, Flashman LA, Saykin AJ. Executive dysfunction following traumatic brain injury: neural substrates and treatment strategies. NeuroRehabilitation. 2002;17:333–44.

86. Lezak M. Principles of neuropsychological assessment. In: Feinberg TE, Farah MJ, editors. Behavioral neurology and neuropsychology. 2nd ed. New York, NY: McGraw-Hill; 2003. pp. 33–44.

87. Heaton RK. Wisconsin card sorting test. Odessa, FL: Psychological Assessment Resources; 1981.

88. Benton AL, Sivan AB, Hamsher KdeS, et al., eds. Contributions to neuropsychological assessment: a clinical manual. New York, NY: Oxford University Press; 1994.

89. Barcelo F, Calleja-Sandome A. A critical review of the specificity of the Wisconsin card sorting test for the assessment of prefrontal function. Rev Neurol. 2000;30:855–64.

90. Berman KF, Ostrem JL, Randolf C, et al. Physiological activation of a cortical network during performance of the Wisconsin card sorting test: a positron emission tomography study. Neuropsychologia. 1995;33:1027–46.

91. Weinberger DR, Berman KF, Zec RF. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia, I: regional cerebral blood flow evidence. Arch General Psychiatry. 1986;43:114–24.

92. Marenco S, Coppola R, Daniel DG, et al. Regional cerebral blood flow during the Wisconsin card sorting test in normal subjects studied by Xenon-133 dynamic SPECT: comparison of absolute values, percent distribution values, and covariate analysis. Psychiatry Res. 1993;50:177–92.

93. Delis D, Kaplan E, Kramer JH. Delis-Kaplan executive function scale. San Antonio, TX: Psychological Corporation; 2001.
94. Wilson BA, Alderman N, Burgess PW, et al. Behavioural assessment of the dysexecutive syndrome (BADS). Lutz, FL: Psychological Assessment Resources; 1996.
95. Bennett PC, Ong B, Ponsford J. Assessment of executive dysfunction following traumatic brain injury: comparison of the BADS with other clinical neuropsychological measures. J Int Neuropsychol Soc. 2005;11:606–13.
96. Grace J, Malloy PF. Frontal systems behavior scale (FrSBe). Lutz, FL: Psychological Assessment Resources; 2002.
97. Godefroy O. Frontal syndrome and disorders of executive functions. J Neurol. 2003;250:1–6.
98. Goldberg E, Harner R, Lovell M, et al. Cognitive bias, functional cortical geometry, and the frontal lobes: laterality, sex, and handedness. J Cogn Neurosci. 1994;6:276–93.
99. Bechara A. Iowa gambling task. Lutz, FL: Psychological Assessment Resources, Inc.; 2007.
100. Bechara A, Damasio H, Tranel D, Anderson SW. Dissociation of working memory from decision making within the human prefrontal cortex. J Neurosci. 1998;18:428–37.
101. Bechara A, Dolan S, Denburg N, et al. Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. Neuropsychologia. 2001;39:376–89.
102. Bar-On R, Tranel D, Denburg NL, Bechara A. Exploring the neurological substrate of emotional and social intelligence. Brain. 2003;126:1790–800.
103. Tranel D, Anderson SW, Benton AL. Development of the concept of 'executive function' and its relationship to the frontal lobes. In: Boller F, Grafman J, editors. Handbook of neuropsychology. vol 9. Amsterdam: Elsevier Science; 1994. pp. 125–48.
104. Hart T, Giovannetti T, Montgomery MW, Schwartz MF. Awareness of errors in naturalistic action after traumatic brain injury. J Head Trauma Rehabil. 1998;13:16–28.
105. Schwartz MF, Buxbaum LJ, Montgomery MW, et al. The naturalistic action test. New York, NY: Harcourt; 2003.
106. Schwartz MF, Segal M, Veramonti T, et al. The naturalistic action test: a standardized assessment for everyday action impairment. Neuropsychol Rehabil. 2002;12:311–39.
107. Ramsden CM, Kinsella GJ, Ong B, Storey E. Performance of everyday actions in mild Alzheimer's disease. Neuropsychology. 2008;22:17–26.
108. Chaytor N, Schmitter-Edgecombe M. Fractionation of the dysexecutive syndrome in a heterogeneous neurological sample: comparing the dysexecutive questionnaire and the brock adaptive functioning questionnaire. Brain Inj. 2007;21:615–21.
109. Royall DR, Lauterbach EC, Cummings JL, et al. Executive control function: a review of its promises and challenges for clinical research. J Neuropsychiatry Clin Neurosci. 2002;14:377–405.