Psychiatric Disorders and Traumatic Brain Injury: What Is The Connection?

Traumatic brain injury (TBI) may be the disorder that breaks down the remaining barriers between neurology and psychiatry. In many respects, TBI represents the quintessential neuropsychiatric paradigm: It is difficult to appreciate what an individual with TBI and their family experience without understanding the brain regions typically effected by biomechanical trauma. It is equally critical to understand the effect of injury-related neurobehavioral sequelae on rehabilitation and outcome after TBI.

Broadly speaking, the neurobehavioral effects of TBI can be organized as changes in cognition, changes in personality, and enhanced risk for a host of psychiatric disorders. However, these broad categories interact with each other in ways that can challenge clinicians used to

Thomas W. McAllister, MD
conventional psychiatric disorders. This article reviews the interaction between biomechanical trauma and the predictable array of neurobehavioral sequelae associated with this type of injury.

**BIOMECHANICAL ASPECTS OF BRAIN INJURY**

There are two categories of forces that result in brain injury: contact or impact forces and inertial (acceleration or deceleration) forces. Contact injuries result from the brain coming into contact with an object, which might include the skull or some external object.1

The configuration of the external surface of the brain, how it is situated in the skull, and the uneven topography of the inner surface of the skull make certain brain regions, such as the anterior temporal poles, the lateral and inferior temporal cortices, the frontal poles, and the orbital frontal cortices more vulnerable to these forces.2 As discussed below, this has implications for the profile of neurobehavioral problems encountered by survivors of TBI.

**Inertial Injury**

Inertial injury results from rapid acceleration or deceleration of the brain with resultant shear, tensile, and compression forces on axons and blood vessels. In addition to tissue tears and intracerebral hematomas, these forces can produce diffuse injury to white matter [known as diffuse axonal injury (DAI) or diffuse traumatic injury (TAI)]. Certain regions are particularly susceptible, including the corpus callosum, the rostral brainstem, and the subfrontal white matter.1

Small hemorrhages, ranging in size from miniscule petechiae to 1-cm lesions, are characteristically seen in the parasagittal portion of the brain, are associated with DAI, and are caused by acceleration-induced brain damage.1

Mechanical distortion of neurons at the time of injury releases assorted neurotransmitters, which, in turn, trigger complex excitotoxic injury cascades.3 Although this occurs throughout the brain, the excitotoxic cascades and other forms of secondary injury, such as hypoxia and ischemia, have a disproportionate effect on certain brain regions, such as the hippocampus, even in the context of an otherwise fairly mild injury.4

The conflicts in Iraq and Afghanistan have called attention to “blast injury.” An explosion generates a wave of over-heated expanding gases that compress surrounding air. Expansion of the heated gases eventually results in a drop in pressure with resulting reversal of the pressure wave.

These fluctuations in pressure are associated with strain and shear forces (barotrauma) that can be particularly damaging to air- and fluid-filled organs and cavities.5 Animal models suggest that primary blast injury can be associated with neural injury, although the underlying mechanism is not clear.6 In human blast injury, it is important to bear in mind that other factors often come into play, including the head coming into contact with an object, penetrating injuries from fragments and debris (referred to as secondary blast injury), rapid acceleration or deceleration of the brain causing inertial injury (tertiary injury), and exposure to toxic gas or chemicals as a result of the explosion (quaternary injury) debris.7

Brain injury is generally viewed as occurring along a severity spectrum clinically and neuropathologically. However, clinicians and researchers typically categorize injury severity as mild, moderate, or severe. The usual clinical severity indicators include the duration of any period of unconsciousness, the duration of posttraumatic amnesia, and, when available, the Glasgow Coma Scale.8

**MILD TRAUMATIC BRAIN INJURY**

Most diagnostic schema9,10 view mild TBI (mTBI) as encompassing injuries in which there is at least a disturbance of consciousness, the period of any unconsciousness is less than 30 minutes, and the period of posttraumatic amnesia does not exceed 24 hours. Glasgow Coma Scale scores of 13 to 15 are consistent with a mild injury. Most brain injuries, including those from the current conflicts in Iraq and Afghanistan,11,12 fall into the mild category. It is worth considering what is known about the neuropathology of mild brain injury.

A variety of animal models across several species suggest that the neuropathology of brain injury at the mild end of the spectrum are similar qualitatively to more severe injuries.13 Axonal damage may range from stretching with associated poration (that if not severe can seal over), to axotomy,14 either at the time of injury if strain forces are sufficient, or hours to days later related to changes in the permeability of the axonal membrane and disruption of elements of the cytoskeleton, particularly axonal neurofilaments.

Assessing for neuropathological changes after mTBI in humans is limited to convenience samples of individuals who sustained a mild TBI, died shortly thereafter of other causes, and came to autopsy. However, these studies also suggest that mild TBI can be associated with neural damage.15-17

For example, Blumbergs et al.16 using immunostaining for amyloid precursor protein as a marker for axonal injury, reported multifocal axonal injury in five individuals who had sustained very mild injuries with periods of unconsciousness as brief as 1 minute. Bigler15 described subtle neurocognitive and neuropathological abnormalities in a 47-year-old man who died 7 months after a mTBI of unrelated causes. Animal and human studies also suggest that mTBI can result in at least temporary alteration of the normal balance between cellular energy demand and energy supply.18
Therefore, although each brain injury is different, there are certain features that are commonly seen, including a combination of focal and diffuse injury and injury to regions that include the frontal cortex and subfrontal white matter; the deeper midline structures, including the basal ganglia, the rostral brainstem, and the medial temporal regions, including the hippocampi. Certain neurotransmitter systems, particularly the catecholaminergic and cholinergic systems, are altered in TBI.

These systems play critical roles in behavioral homeostasis, including arousal, cognition, reward behavior, and mood regulation. This profile of structural injury and neurochemical dysregulation occurs along a spectrum of injury severity, including “mild” injury.

It is also helpful to place these structural and neurotransmitter vulnerabilities in a broader, circuit-based context. These brain regions are important nodal points in frontal-subcortical circuits that subserve cognition and social behavior. In particular, three major frontal-subcortical circuits have significant roles in nonmotor forms of behavior. These brain regions are important nodal points in frontal-subcortical circuits that subserve cognition and social behavior. In particular, three major frontal-subcortical circuits have significant roles in nonmotor forms of behavior.

A circuit arising in the dorsolateral prefrontal cortex modulates executive functions, such as working memory, decision-making, problem-solving, and mental flexibility. Another, arising from cells in the orbitofrontal cortex, plays a critical role in intuitive reflexive social behaviors and the capacity to self-monitor and self-correct in real time within a social context. A third circuit starting in the anterior cingulate modulates motivated and reward-related behaviors.

Although not a frontal subcortical circuit, per se, circuits traversing medial temporal regions play critical roles in episodic memory and new learning, as well the smooth integration of emotional memory with current experience and real-time assessment of stimulus salience. With that as a backdrop, the typical neurobehavioral sequelae of TBI are briefly reviewed.

**CHANGES IN COGNITION**

Initial and persistent cognitive deficits are the most common complaints after TBI and can present significant challenges to independent living, social re-adaptation, family life, and return to work. Frontal executive functions (problem solving, set shifting, impulse control, self-monitoring), attention, short-term memory and learning, speed of information processing, and speech and language functions are the cognitive domains typically impaired.

**CHANGES IN PERSONALITY**

The term “personality change” is used often by survivors and family/caregivers to describe alterations in emotional and behavioral regulation after brain injury. In some individuals, this presents as exaggeration of preinjury traits (eg, irritability). It is important in this context to ask about changes in the frequency and/or intensity of behaviors or traits that may have been present before the injury took place. Alternatively, these behaviors can present as fundamental changes in response patterns. Several common clusters of symptoms that characterize the “personality changes” are recognizable.

**Impulsivity**

This may be manifest in verbal utterances, physical actions, snap decisions, and poor judgment flowing from the failure to fully consider the implications of a given action. This is closely related to the concept of stimulus boundedness, in which the individual responds to the most salient cue in the environment or attaches exaggerated salience to a particular cue, without regard to previously determined foci of attention or priorities.

**Irritability**

Survivors may be described as more irritable or more easily angered. Responses can range from verbal outbreaks to dangerous aggressive and assaultive behavior. Although a particular cue might be perceived as a legitimate aggravation, the response is characteristically out of proportion to the precipitating stimulus. This modulatory deficit differs in intensity, onset, and duration from the preinjury pattern for any given individual.

**Affective Instability**

Survivors and family/caregivers frequently describe exaggerated displays of emotional expression, out of proportion to the precipitating stimulus and the preinjury range of responses. Additional characteristics include a paroxysmal onset, brief duration, and subsequent remorse. This phenomenon occurs in other central nervous system disorders and has been called pathological affect, affective lability, pseudobulbar affect, and affective incontinence.

**Apathy**

Disorders of motivated behavior can be of concern to family members and can be a barrier to progress in rehabilitation programs. It is often misinterpreted as laziness or depression and may be linked to aggression when attempts to engage the individual in activities in which they have little interest can precipitate assaultive behavior. Kant et al. found that apathy (mixed with depression) occurred in 60% of their sample. Andersson et al. found that almost half of their individuals with TBI had significant degrees of apathy. Deficits in motivated behavior can occur in association with injury to the circuitry of “reward.” Key nodal points in this circuitry include the amygdala, hippocampus, caudate, entorhinal and cingulate cortices, the ventral tegmental area, and the medial forebrain bundle. Catecholaminergic systems, particularly the mesolimbic dopaminergic system, appear to play critical roles in the modulation of the reward system.
Lack of Awareness of Deficits

The personality changes described above are often more difficult to address because the injured individual may be unable to appreciate that his or her behavior is different after the injury.27,28 Of interest is that individuals with TBI are less likely to be aware of changes in behavior and executive function than changes in more concrete domains, such as motor function.32 Furthermore, the degree of awareness has been found to correlate with functional and vocational outcome in many,79-42 although not all,43 studies.

RELATIONSHIP OF TBI TO PSYCHIATRIC DISORDERS

In addition to the changes in cognition, behavior, and personality described above, a significant body of evidence suggests that TBI results in an increased risk of developing psychiatric disorders, including mood and anxiety disorders (see Rapoport article, page 581); sleep disorders (see Vaishnavi et al., page 553); PTSD (see Summerall article, page 563); substance abuse; and psychotic syndromes.44-47 For example, Kopenen et al.47 studied 60 individuals 30 years after their TBI and found that almost half (48%) developed a new Axis I psychiatric disorder after their injury. The most common diagnoses were depression, substance abuse, and anxiety disorders. In individuals with a TBI, rates of lifetime and current depression (26%; 10%), panic disorder (8%; 6%), and psychotic disorders (8%; 8%), were significantly higher than base rates found in the Epidemiologic Catchment Area (ECA) study.48

Hibbard et al.45 studied 100 adults on average 8 years after TBI. A significant number of individuals had Axis I disorders before injury. After TBI, the most frequent diagnoses were major depression and anxiety disorders [ie, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder and panic disorder]. Almost half (44%) of individuals had two or more disorders.

More recently, this group reported a longitudinal study of 188 individuals enrolled within 4 years of injury and assessed at yearly intervals on at least two occasions.49 Once again, they found elevated rates of psychiatric disorders (depression and substance abuse) before injury. Subsequent to TBI, there were increased rates of depression, PTSD, and other anxiety disorders. This was particularly true of those with preinjury psychiatric disorders. Furthermore, the rates were greatest at the initial assessment point after injury and stabilized or decreased over time.

Others have also reported increased indicators of psychiatric illness after TBI and increased medical costs associated with those indicators.50,51 More recently, Bryant et al.52 have shown that there are high rates of psychiatric illness in individuals hospitalized with traumatic injury of any sort (including mTBI) 12 months after the event (31%). Twenty-two percent suffered psychiatric disorders that they had never had before. Having a mTBI was associated with higher rates of PTSD and other anxiety disorders. The combination of mTBI and psychiatric illness was associated with greater degrees of functional impairment. Whelan-Goodinson et al.53 also found a strong relationship between post-TBI depression, anxiety, and outcome.

Furthermore, as with any potentially disabling condition, individuals with TBI report a variety of symptoms in different domains (discouragement, frustration, fatigue, anxiety, etc.). Not all of these symptoms will rise to the level of a disorder.

However, constellations of symptoms that are consistent and sustained over time (usually weeks), and that are of sufficient severity to interfere with social or occupational function or quality of life, are legitimately considered disorders.

The consistent observation that individuals who sustain a TBI have higher base rates of psychopathology before injury also suggests that there is a reciprocal interaction: psychopathology predisposes to TBI, and TBI in turn predisposes the individual to develop psychiatric disorders.

Several studies have raised a concern about the relationship of TBI to progressive dementia.54 For example, TBI-associated disruption of axonal transport results in the rapid accumulation of amyloid precursor protein (APP) in animals54,55 and humans.56,57 APP, Abeta, and other proteins associated with Alzheimer’s and other neurodegenerative disorders accumulate rapidly after a TBI.58-60

Some (but not all) autopsy studies have shown increased amyloid plaques and neurofibrillary tangles in individuals with TBI.50,61 This variation has prompted exploration of the role of genetic factors in modulating risk for Alzheimer’s disease (AD) after TBI.

For example, Mayeux et al.62 retrospectively studied 113 older adults with AD, comparing them with a control group of 123 healthy older individuals. They found that the combination of APOE-e4 and history of TBI increased the risk for AD by a factor of 10. However, not all studies have found such a relationship. A large, prospective population-based study of 6,645 individuals 55 years and older and free of dementia at baseline found that mild brain trauma was not a major risk factor for the development of AD. Moreover, brain trauma did not appear to increase the risk for developing AD in people carrying the APOE-e4 allele.63

One possibility is that diminished cognitive reserve associated with TBI facilitates earlier manifestation of dementia symptoms in individuals already at risk for AD.64 Therefore, although there are some compelling scientific reasons to consider the relationship of
TBI to AD and other neurodegenerative disorders, and some strong evidence suggesting clinical associations, the relationship between TBI and dementia needs further study.

**TREATMENT IMPLICATIONS**

Given the strong link between TBI and the array of neurobehavioral problems described above, an important question is whether a history of TBI alters the response to standard treatments, whether pharmacological agents or psychotherapy, and therefore whether these treatment approaches require modification. Some general principles are highlighted.

**Need for a Comprehensive Approach**

A thorough understanding of the pre-injury history, the profile of the injury, and the context in which the injury occurred is critical to a nuanced appraisal of the current difficulties and how best to attribute the causality to the various presenting symptoms.

It is important to be aware that the sequelae of the injury can alter the presentation of psychiatric and behavioral disorders and, therefore, standard assessment instruments and diagnostic criteria may not completely apply. Emerging neurodiagnostic techniques, such as newer neuroimaging modalities, can be helpful but should not be overly emphasized. An appreciation for the normal trajectory of recovery after injury, particularly mTBI, is critical to putting the current symptoms in perspective.

**Pharmacotherapy**

There are some theoretical reasons to think that response to pharmacological agents might differ after a TBI. TBI is associated with dysregulation of several neurotransmitter systems integral to the homeostasis of mood, emotional control and cognition (eg, the catecholaminergic, serotonergic, and cholinergic systems), raising the possibility that medications that work through modulation of these neurotransmitters might behave differently after an injury. Insofar as a brain injury results in actual loss of neurons in brain regions modulating emotional control and cognition, there might be less substrate on which pharmacologic agents can work, and this might alter the side-effect profile.

Interestingly, a review of the literature found an inadequate evidence base on the pharmacotherapy of the neuropsychiatric sequelae of TBI. Pharmacologic treatments of affective disorders/anxiety/psychosis, cognition, and aggression were reviewed.

For the most part, the evidence base consists of case reports and small case series, or clinical trials with methodological limitations or small sample sizes, greatly limiting the strength of the conclusions that could be drawn. With respect to the treatment of mood disorders, psychosis, and anxiety, evidence in support of the efficacy of standard psychotropic regimens (eg, antidepressants) did not rise above the option level.

For cognition, the evidence supported the use of donepezil and methylphenidate for treatment of attention and speed of information processing at a guideline level, donepezil for the treatment of memory deficits at a guideline level, and bromocriptine for the treatment of executive deficits.

For aggression, evidence for the use of beta-blockers (propranolol, pindolol) was considered at a guideline level. There was no significant evidence that side effects were more evident in individuals with TBI, although many clinicians adopt a lower dosing strategy and slower titration. Starting doses should be reduced, and titration intervals prolonged. Clinicians should be alert to therapeutic responses at lower than expected doses and should not feel compelled to push through to higher “therapeutic” doses unless warranted by an incomplete response.

**Nonpharmacologic Interventions**

It should be emphasized that the effectiveness of medication is greatly enhanced in the context of addressing the full array of an individual’s psychosocial needs. There is a good evidence base supporting the use of cognitive interventions for individuals with TBI, particularly cognitive complaints and deficits.

Of interest is an absence of studies addressing whether the combination of medication and cognitive therapies is more effective than either treatment alone. Combined medication and cognitive therapy approaches have been explored in other psychiatric disorders, such as depression, where it appears that both approaches are fairly similar in efficacy but may differ somewhat in terms of which patients benefit from which intervention. There is some evidence that combination therapy is more effective than either monotherapy for some patients.

**Importance of Diagnostic Clarity**

As with any clinical condition, a proper evaluation is the foundation of a sound treatment plan. TBI occurs at high rates in military and also other populations at high risk for PTSD, including victims of domestic violence and incarcerated populations. The overlap between the symptoms frequently endorsed by individuals with a history of TBI and those with a history of PTSD require careful assessment of both conditions.

For example, both groups may note problems in cognition (memory, attention), somatic concerns (headache), and affective dysregulation (impulsivity, irritability, anxiety), particularly in the time period shortly after the traumatic event (whether psychological, biomechanical, or both) (see Summerall and McAllister article, page 563). Therefore, attribution of specific symptoms to a particular etiology may be difficult, if not impossible.
Clinicians should not feel compelled to be certain and should be forthright about their uncertainty, and one should formulate a clear etiological hypothesis to inform the therapeutic decision-making. As a general rule, treatment trials should be initiated with one agent at a time, with a clear diagnostic formulation (even an uncertain one) and use the treatment trial to inform the formulation.

**Use of Treatment Algorithms for Idiopathic Psychiatric Disorders as Models**

In the absence of a robust evidence base informing us about the treatment of behavioral disorders after TBI, most clinicians use treatment algorithms developed for idiopathic psychiatric disorders. Although a reasonable default position, it is important to consider potential effects of a given agent or class of agent on the domains of cognition, arousal, sleep, and neurological function, as these are domains on which standard psychotropic regimens can have adverse effects after a TBI.

**REFERENCES**