Published in final edited form as:

Ann N Y Acad Sci. 2010 October ; 1208: 46–57. doi:10.1111/j.1749-6632.2010.05720.x.

Effects of psychological and biomechanical trauma on brain and behavior

Thomas W. McAllister^a and Murray B. Stein^b

^aDepartment of Psychiatry, Section of Neuropsychiatry, Dartmouth Medical School, Lebanon, New Hampshire

^bDepartments of Psychiatry, and Family and Preventive Medicine, University of California San Diego, La Jolla, California; and VA San Diego Healthcare System, San Diego, California

Abstract

The current conflicts in Iraq and Afghanistan have resulted in a large cohort of military personnel exposed to combat-related psychological trauma as well as biomechanical trauma, including proximity to blast events. Historically, the long-term effects of both types of trauma have been viewed as having different neural substrates, with some controversy over the proper attribution of such symptoms evident after each of the major conflicts of the last century. Recently, great effort has been directed toward distinguishing which neuropsychiatric sequelae are due to which type of trauma. Of interest, however, is that the chronic effects of exposure to either process are associated with a significant overlap in clinical symptoms. Furthermore, similar brain regions are vulnerable to the effects of either psychological or biomechanical trauma, raising the possibility that shared mechanisms may underlie the clinically observed overlap in symptom profile. This paper reviews the literature on the neural substrate of biomechanical and psychological injury and discusses the implications for evaluation and treatment of the neuropsychiatric sequelae of these processes.

Keywords

traumatic brain injury (TBI); posttraumatic stress disorder (PTSD); psychological trauma; biomechanical trauma; behavior

Introduction

Traumatic brain injury (TBI) has received much attention as a frequent cause of injury and disability in the current conflicts in Iraq and Afghanistan.¹ Questions have been raised about whether the most common mechanism of TBI in these conflicts, blast concussive injury, results in different neuropsychiatric sequelae than those associated with more conventional contact or inertial forces.^{2, 3} Some investigators have suggested that the neuropsychiatric sequelae reported in military personnel returning from combat are better explained as the effects of exposure to psychological trauma with resultant depression or stress related disorders (e.g. posttraumatic stress disorder or PTSD).^{4, 5} The Department of Defense has underwritten an aggressive research program to address these questions, and much emphasis has been placed on the need to distinguish the effects of biomechanical and psychological trauma.

Correspondence: Thomas W. McAllister, M.D., Millennium Professor and Vice Chairman for Neuroscience Research, Director of Neuropsychiatry, Department of Psychiatry, Dartmouth Medical School, One Medical Center Drive, Lebanon, NH 03756, thomas.w.mcallister@dartmouth.edu.

Investigators and clinicians new to this field might think that the neuropsychiatric effects of both biomechanical and psychological trauma have only recently been appreciated, but this is not the case.⁶⁻⁸ In fact, debate about the relative roles of biomechanical and psychological trauma in symptom genesis have been taking place for well over 100 years.^{6,9} Within a military context, these discussions first arose with the emergence of “shell shock” in World War I, a term supplanted by “postconcussional syndrome” (or some variation of that phrase) in World War II (see Jones et al.⁶ for discussion). In each instance inordinate attention was placed on parsing out the neurologic/ “organic” (biomechanical) contributions from the psychological/ “psychoneurotic” contributions, with a reluctance to embrace the possibility that both forms of trauma might operate through overlapping and/or complementary mechanisms.

Older descriptions of military personnel with combat related distress ring quite true with current clinical experience. For example, Cramer, in describing the clinical picture of what he termed “cerebral blast concussion,” wrote in 1949, “... one or more nearby explosions, causing no overt or external harm to the skull, nevertheless render the subject unconscious. After this, he has a retrograde amnesia for all but the flash of the explosion, and thereafter anterograde amnesia for a variable period. During this time he may have great motor unrest and normal or exaggerated responses to stimuli. On regaining consciousness, he has intense and intractable headache, which later gives way to a milder, but constant, headache; tinnitus; intolerance of noises; tremors, and “nervousness”... “Anxiety” is manifest, and “depression” and “regression” are often employed to describe the dejection and muteness that characterize the behavior of the victim. Neurologic examination is, for the most part, “negative” ...the most frequent [symptoms are] the inability to tolerate loud noises or sudden movements; these stimuli sometimes precipitated strong startle responses... either spontaneous or in response to stimuli, such as the explosion of a shell or the passage of aircraft” (p. 6). Once again, there was great debate about the relative contributions of psychogenesis and physiogenesis. Lishman, in his study of World War II veterans with brain injury, posited that the initial insult had its basis in neural injury but psychological factors subsequently assumed greater importance in maintaining persistent symptoms, particularly after MTBI.¹⁰⁻¹²

Before the DSM III adopted the diagnostic category of PTSD, a variety of terms were used to describe behavior attributed to combat-related stress, including acute and chronic combat stress reaction, shell shock, and combat fatigue.¹³ Thus, the interaction of psychological and biological trauma, particularly in a combat or military context, has a rich history that can inform our deliberations today. As a starting point for these considerations, this paper provides an update on what is known about the neuropsychiatric sequelae of biomechanical and psychological trauma, as well as the effects of exposure to both. Clinical implications are also outlined.

Biomechanical aspects of brain injury

There are two broad categories of forces that result in brain injury: 1) contact or impact and 2) inertial acceleration or deceleration. Contact injuries result from the brain coming into contact with an object, which might include the skull or some external object.¹⁴ 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 certain skull regions are factors that result in heightened vulnerability to impact forces for certain brain regions.¹⁵ Frequent sites of such injury are the anterior temporal poles, the lateral and inferior temporal cortices, the frontal poles, and the orbital frontal cortices.

Inertial injury results from rapid acceleration or deceleration of the brain with resultant shear, tensile, and compression forces. These forces have maximum impact on axons and blood vessels, resulting in axonal injury, tissue tears, and intracerebral hematomas. These mechanisms also produce more widespread or diffuse injury to white matter (known as diffuse axonal injury - DAI, or diffuse traumatic injury-TAI). Certain regions have a heightened vulnerability to this injury including the corpus callosum, the rostral brainstem, and the subfrontal white matter.¹⁴ In addition, tissue-tear hemorrhages can occur. These are often small, ranging in size from miniscule petechiae to one-centimeter lesions. They are characteristically located in the parasagittal portion of the brain, are associated with DAI, and are caused by acceleration-induced brain damage.¹⁴ Mechanical distortion of neurons at the time of injury is also associated with release of assorted neurotransmitters and subsequent triggering of complex excitotoxic injury cascades¹⁶. Although this probably 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.¹⁷

The emergence of explosive devices, particularly “improvized explosive devices or IEDs,” as a primary method of attack in the conflicts in Iraq, Afghanistan, and elsewhere, has called attention to “blast injury.” Explosions generate a rapidly moving wave of overheated expanding gases that compress surrounding air. The ongoing 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.¹⁸ For example the tympanic membrane can be ruptured with approximately a 30% increase in atmospheric pressure and is a useful, though not always reliable indicator of blast exposure.¹⁹ Blast can also be associated with significant brain injury.^{20–24} At this time it is not clear if injury associated with blast is due to the high pressure wave with distortion of vascular tissue, neural tissue or both, the inertial effects of buffeting by the alternating high and low pressure events, or some other mechanism. Additional mechanisms often come into play, including impact mechanisms from the head coming into contact with an object or penetrating injuries from fragments and debris (referred to as secondary blast injury), and 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.¹⁹

Animal models suggest that primary blast injury can be associated with neural injury, although the underlying mechanism is not clear.²⁵ For example Cernak et al.^{20, 23} exposed rats to either whole body blast or localized pulmonary blast in which the brain was protected from the pressure wave with a steel plate. Both groups of animals showed hippocampal injury with neuronal swelling, cytoplasmic vacuolization, and loss of myelin integrity. These changes were associated with poorer performance on an active avoidance response task learned prior to the injury. This group has postulated that one potential mechanism is transmission of the pressure wave through cerebral vasculature, with subsequent injury to perivascular neural tissue, axonal stretching, release of neurotransmitters, and precipitation of the usual excitotoxic cascades,^{20, 23, 26} although this is not yet firmly established.

Thus, the typical profile of injury involves a combination of focal and diffuse injury. There are certain brain regions that are particularly vulnerable to injury, including the frontal cortex and sub-frontal white matter; the deeper midline structures including the basal ganglia, the rostral brainstem; and the temporal lobes including the hippocampi. Certain neurotransmitter systems, particularly the catecholaminergic²⁷ and cholinergic systems,²⁸ are altered in TBI. Both of these systems play critical roles in a variety of domains important in behavioral homeostasis including arousal, cognition, reward behavior, and mood regulation. This profile of structural injury and neurochemical dysregulation plays a direct

role in the common neurobehavioral sequelae associated with TBI including problems in cognition, emotional and behavioral regulation, and increased rates of psychiatric disorders.

The majority of brain injuries from the current conflicts fall into the mild category.^{1, 5} Thus, it is worth considering the evidence for neural injury associated with MTBI. Animal models of brain injury using a variety of models across several species fluid percussion, controlled cortical impact, combination models)^{29, 30} suggest that the neuropathology of brain injury occurs across a spectrum and injuries at the mild end of this spectrum are similar qualitatively to more severe injuries with axonal injury to subcortical white matter, hippocampus, thalamus, and cerebellum (e.g. Park et al.³¹). Axonal damage may range from stretching with associated poration that, if not severe, can seal over, to axotomy (see Farkas et al.³² for review) either at the time of injury if strain forces are sufficient, or that evolves over hours to days related to changes in the permeability of the axonal membrane and disruption of elements of the cytoskeleton, particularly axonal neuro filaments.

Assessing for neuropathological changes after MTBI in humans is limited to convenience samples of individuals who sustained an MTBI, died shortly thereafter of other causes and came to autopsy; however these studies also suggest that MTBI can be associated with neural damage.^{33–35} For example, Blumbergs et al.,³⁴ using immunostaining for amyloid precursor protein as a marker for axonal injury, reported multifocal axonal injury in individuals who had sustained very mild injuries with periods of unconsciousness as brief as one minute. Bigler³³ described subtle neurocognitive and neuropathological abnormalities in a 47 year old man who died seven months after a MTBI of unrelated causes. In addition to the microscopic structural changes described above, both animal models and human studies suggest that MTBI can result in at least temporary alteration of the normal balance between cellular energy demand and energy supply (see Oppenheimer³⁶). Both animal and human studies have shown an increase in glucose utilization shortly after MTBI associated with a reduction in cerebral blood flow.^{37–42} The limitations inherent in obtaining human brain tissue after MTBI have driven interest in other avenues to detect neural injury, such as neuroimaging (see Levin et al.⁴³ and Belanger⁴⁴ for reviews). Although CT scanning is most often used clinically, MRI based methods are more sensitive in detecting the diffuse axonal injury and small hemorrhages that are generally believed to be the neuropathology associated with MTBI,^{44, 45} particularly using more recent image acquisition techniques such as susceptibility weighted imaging (SWI),⁴⁵ magnetoencephalography (MEG), and diffusion tensor imaging (DTI) (e.g.^{46–48}). It should be noted, however, that some recent studies, using techniques such as DTI, have failed to find evidence of white matter injury in patients with mild to moderate blast-related TBI,⁴⁹ underscoring the need for more research in this area. Functional imaging techniques, including SPECT, PET, and fMRI, as well as magnetic resonance spectroscopy, also show some promise in clarifying the underlying pathophysiology of the sequelae of MTBI (see Refs. 50–53). It remains to be determined from future longitudinal imaging studies the extent to which detected abnormalities (if any) track with objective dysfunction and subjective complaints.

Psychological trauma and PTSD

PTSD prevalence has been estimated as approximately 17% among veterans of the current war in Iraq,^{54, 55} many of whom have also had a possible MTBI. Investigations into the pathophysiology of PTSD has focused on excessive activation of the amygdala by stimuli perceived to be threatening, and altered response to acute and chronic stress (see Refs. 56–58 for reviews). Amygdala activation produces outputs to a number of brain areas that mediate memory consolidation of emotional events and spatial learning (hippocampus), memory of emotional events and choice behaviors (orbital frontal cortex), autonomic and

fear reactions (LC, thalamus and hypothalamus), and instrumental approach or avoidance behavior (dorsal and ventral striatum).⁵⁹

In PTSD, it is postulated that normal checks and balances on amygdala activation have been impaired so that the restraining influence of the medial PFC (especially the anterior cingulate gyrus and orbitofrontal cortex) is disrupted.^{60, 61} Altered functional connectivity of the amygdala with other brain regions (e.g., Simmons et al.⁶²) and resultant disinhibition of the amygdala may contribute to a vicious spiral of recurrent fear conditioning in which ambiguous stimuli are more likely to be appraised as threatening; mechanisms for extinguishing such responses are nullified, and key limbic nuclei are sensitized thereby lowering the threshold for fearful reactivity.^{61, 63, 64} (see Refs. 57 and 65) A variety of neuroimaging studies (see⁵⁸) have confirmed that key nodal points in this circuitry do not function normally in individuals with PTSD.

Abnormal responses to acute and chronic stress may also play a role in PTSD. Abnormal HPA activity may have neurotoxic effects through activation of excitatory amino acids resulting in calcium influx into susceptible neurons.^{66, 67} Although excessive HPA system activity appears to be associated with trauma exposure and PTSD, the mechanism of its effect is not clearly worked out. For example, it may be expressed by elevated cortisol levels, as has been found in some PTSD patients and in children exposed to sexual trauma. Conversely, it may be expressed by reduced cortisol levels associated with supersensitivity of glucocorticoid receptors.^{68–75}

Co-occurring biomechanical and psychological trauma

There was initially some controversy about the prevalence of co-morbid TBI and PTSD (see Harvey et al.⁷⁶). TBI is associated with partial or complete amnesia for the event, whereas a core symptom of PTSD is recurrent memory and re-experiencing of the event. Thus, at a theoretical level, some questioned the ability to have both conditions, particularly after MTBI.⁷⁷ Alternatively, if one allows for a partial or incomplete PTSD syndrome (i.e., without memory/re-experiencing of the event owing to neurogenic amnesia), others have argued that the two conditions can co-exist. Warden et al.⁷⁸ found that none of 47 military patients with TBI met full criteria for PTSD, because none had re-experiencing symptoms of the event. However 13% of the patients did experience the avoidance and arousal symptom clusters of PTSD, suggesting that individuals can develop a form of PTSD without the re-experiencing symptoms.

The conflicts in Iraq and Afghanistan have spurred additional interest in the relationship between psychological and biomechanical trauma particularly in military populations (e.g. see Refs. 79–81). Although both conditions are quite prevalent in military personnel involved in the current conflict,¹ two recent studies highlight their complex interaction. Hoge et al.⁵ found that 44% of Iraq war returnees reporting a TBI with loss of consciousness met criteria for PTSD, compared to 27% of those reporting altered mental status, 16% with other injuries, and 9% with no injury. Much of the variance observed in these groups with respect to physical health outcomes and symptoms could be accounted for by the presence of PTSD and/or depression. It is important to point out that participants were assessed three to four months after deployment and thus reflect individuals with persistent symptoms. Schneiderman et al.⁸² found that combat-incurred mild TBI approximately doubled the risk for PTSD and that a PTSD diagnosis was the strongest factor associated with persistent postconcussive symptoms. Belanger et al.⁸³ studied patients with mild and moderate-to-severe TBI and found, as expected, that mild TBI was associated with higher levels of postconcussion complaints approximately two years after injury. However, after adjusting for PTSD symptoms, these between group differences were no longer

significant, leading the authors to conclude that much of the persistent symptoms after mild TBI may be attributable to emotional distress.

These studies should not be construed as minimizing the effects of MTBI. Rather, they highlight the permissive or gateway effect that MTBI serves in increasing the relative risk for psychiatric disorders. The civilian literature has emphasized for a decade or more that one of the causes of persistent symptoms after MTBI (the issue the Hoge and Schneiderman papers address) is the development of a psychiatric disorder such as depression or PTSD. As far back as 1973, Lishman¹¹, in his review of the psychiatric sequelae of brain injury, refers to PTSD-like symptoms, including that “the circumstances of the accident may recur vividly in dreams, maintain states of anxiety, or become the focus for obsessional rumination or conversion hysteria” (p. 306). This suggests that it is important to distinguish a history of exposure to MTBI from attribution of current symptoms to that event. If one conceptualizes persistent symptoms as a postconcussive syndrome or “chronic TBI”, one risks missing the diagnosis of a co-morbid psychiatric disorder that could be quite responsive to appropriate treatment.⁸⁰ Bryant and Harvey have reported a series of studies of individuals hospitalized after motor vehicle accidents, some with and some without MTBI. They have shown that rates of acute stress disorder one month after an accident are comparable in the two groups, and that acute stress disorder is a good predictor of those who go on to develop PTSD six months after injury.^{84–87} For example, they studied 46 individuals admitted to a hospital after an MTBI (LOC with PTA <24 hours) and 59 survivors of motor vehicle accidents without evidence of TBI 6 months after their accidents.^{88, 89} Twenty percent of the TBI group and 25% of the non-TBI group had PTSD. The TBI group had more postconcussive symptoms than did the non-TBI group. Furthermore, the TBI group with PTSD was significantly more symptomatic than the TBI without PTSD group. Recently, this group published results of a study of 1,167 traumatic accident survivors, 459 of whom had mild TBI, the rest did not.⁹⁰ Three months after injury the MTBI group had higher rates of PTSD (11.8% vs 7.5%). Taken together, these studies suggest that TBI increases risk for PTSD, and that when present, PTSD can amplify postconcussive symptoms after an MTBI and complicate recovery. In their MTBI sample (LOC <15 minutes), Mayou *et al.*⁹¹ found that an astonishing 48% of those with definite loss of consciousness had PTSD three months after injury, and one-third of their subjects with MTBI had PTSD one year after injury.

It is important to point out that much of the above discussion considers the question of the frequency of co-morbid MTBI and PTSD from the same event and focuses primarily on the civilian population. Little is known about the co-morbid condition in military populations and in those who may have PTSD from exposure to psychologically traumatic events experienced at time points unrelated to the TBI.

Interaction of psychological and biomechanical trauma

There are several issues that highlight the interaction between psychological and biomechanical trauma and suggest that it may make more sense to embrace these interactions rather than struggle to parse out the differences in the downstream effects of these processes.

Links between PTSD and Injury In General

There is an interesting relationship between injury, including brain injury and PTSD. Several studies have suggested that physical injury in the context of a psychologically traumatic event is a risk factor for PTSD.^{81, 92} The link between TBI and subsequent PTSD appears particularly noteworthy (see Vasterling *et al.*⁸¹ for discussion). For example Mollica *et al.*⁹³ found that psychological trauma associated with brain injury in a civilian population was associated with higher rates of PTSD and depression than other types of injury. As

noted earlier, studies by Hoge et al. have found higher rates of PTSD and depression in military personnel who may have had a TBI, particularly those who reported loss of consciousness,⁵ and the Schneiderman et al. study⁸² found that a probable TBI almost doubled the risk for PTSD. Nor is this finding unique to the current conflicts. Vanderploeg et al.,⁹⁴ in a study of Vietnam era veterans, found that self-report of a MTBI was associated with an almost two fold increase in rate of PTSD even after controlling for a variety of other relevant variables; MTBI was also associated with a lower long-term likelihood of having recovered from PTSD. The mechanism for this relationship is not known but several factors may play a role.

Most recently, Bryant et al.⁹⁵ showed, using data from their prospective study of seriously injured trauma victims, that when an injury included MTBI, risk of new-onset PTSD was substantially higher than when the injury did not include MTBI. Surprisingly, however, PTSD was not the only new-onset psychiatric disorder associated with MTBI; new cases of panic disorder, social phobia, and agoraphobia were also seen significantly more often in injured persons with MTBI than in those without MTBI. These data are consistent with the notion of the permissive or gateway effect that MTBI serves in increasing the relative risk for psychiatric disorders.

Common Neural Substrates

As described above, several brain regions at risk for injury from biomechanical trauma overlap with brain regions that appear to be dysfunctional, perhaps in a causative fashion, in PTSD.^{15, 79, 96} For example mesial temporal structures are vulnerable in TBI from both contact/impact forces, as well as increased sensitivity to excitotoxic injury. Hippocampal and amygdala injury are common. Both of these regions play key roles in PTSD as well, both in terms of contextual memory consolidation and fear conditioning. The hippocampus is also felt to be vulnerable to the effects of chronic stress, presumably through the mediating effects of the HPA axis. Thus biomechanical and neurochemically mediated damage could conceivably interact with neurohumoral dysregulation to create a milieu that lends itself to the development of PTSD. Orbitofrontal cortex is also vulnerable to TBI through impact forces as well as frontal subcortical axonal injury.

Neurocognitive Factors

Both TBI and PTSD are associated with effects on cognition (see above). General intellectual function appears to play a role in determining risk for PTSD when exposed to psychological trauma.^{97, 98} In so far as IQ may be a proxy for cognitive reserve and if a TBI reduces cognitive reserve, this could result in an increased association between TBI and PTSD. Vasterling et al.⁸¹ have also suggested that processes such as TBI that might disrupt the processes of memory consolidation and integration and coherent processing and retrieval of emotional memories could put an individual at greater risk for development of PTSD.

Treatment implications

A full discussion of treatment approaches to TBI and PTSD is beyond the scope of this paper (see Refs. 80, 99 for reviews), but several general points are worth making. Although there are evidence based treatments for PTSD⁹⁹ and to a lesser extent TBI,^{100–103} the approach to individuals with co-morbid TBI and PTSD has not been studied to any great extent. We do not know at this point if treatments effective for PTSD are as effective if the individual has had a TBI, nor do we know if the efficacy of treatments that address symptoms attributable to TBI (for example cognitive complaints or deficits) are altered if the person also has PTSD. Most studies of PTSD treatment have excluded persons with a history of TBI, and studies of TBI sequelae typically have excluded persons with significant

psychiatric illness including PTSD. Therefore, the generalizability of treatment approaches to the co-morbid condition is unknown. Furthermore, the recent IOM reports^{99, 101} on both conditions, were rather skeptical of the evidence supporting common practices in both conditions raising further questions about treatment efficacy.

Effect of TBI on Treatment Response

An important question is whether a history of TBI alters the response to standard pharmacological agents or cognitive behavioral treatments, and thus whether conventional treatment approaches require modification. There are some theoretical reasons to think that response to pharmacological agents might differ after a TBI. As described earlier, TBI is associated with dysregulation of several neurotransmitter systems integral to the homeostasis of mood, emotional control, and cognition (e.g. the catecholaminergic, serotonergic, and cholinergic systems), raising the possibility that medications that work through modulation of these neurotransmitters might behave differently after an injury. In so far 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. Alternatively, neurochemical dysregulation from the combination of both biomechanical and psychological trauma might create a milieu in which medication effects are more evident. It is also reasonable to ask whether individuals with cognitive complaints and/or deficits as experienced by many people with TBI will respond to cognitive processing therapy, prolonged exposure, or other cognitive behavioral interventions that are the standard of practice in the non-pharmacological treatment of PTSD.

Evaluation and Attribution of Effects of Biomechanical and Psychological Trauma

As with any clinical condition, a proper evaluation is the foundation of a sound treatment plan. The overlap between the symptoms frequently endorsed by individuals with a history of TBI and those with a history of PTSD requires 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). Thus, accurate causal attribution of specific symptoms to a particular etiology may be difficult if not impossible. It is best in such situations for the clinician to keep an open mind about attribution, while at the same time establishing a clear etiological hypothesis in order 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 (e.g., “I am treating TBI related cognitive deficits” or “I am treating PTSD related sleep disturbance.”). Both TBI and PTSD are associated with a heightened reactivity to environmental changes. Thus, the longer the treatment trial, the more confidence one has in assessing efficacy attributable to the specific intervention rather than to the non-specific elements of treatment. There is also a strong sense among clinicians that the TBI population has a heightened sensitivity to medication side effects, necessitating lower starting doses and longer titration intervals. This also necessitates longer treatment trials.

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. This approach is supported by the limited available evidence¹⁰⁰ as well as expert opinion (e.g., Refs. 104, 105). Although a reasonable default position in the absence of a robust evidence base, this approach can have some pitfalls. It is particularly 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 in one or both populations.

Cognition

Both TBI and PTSD are commonly associated with cognitive complaints and deficits.^{96, 106} Many of the medications commonly used in both conditions, such as antipsychotics, anticonvulsants, and some anxiolytics, can be associated with cognitive slowing and problems with memory and attention. Adrenergic agents can either enhance or impair cognition depending on their receptor agonist profile and their dose. Thus, particular care should be given to monitoring cognitive function when prescribing these agents.

As noted, cognitive behavioral therapies are a mainstay of PTSD treatment.⁹⁹ The impact that psychotropic medications may have on cognitive behavioral therapies shown to be effective in PTSD is unclear. Theoretically, medications known to impact attention and memory processes could alter the efficacy of psychotherapies that depend on intact cognitive processes in order to be effective.

Arousal

Individuals with TBI may complain of excessive fatigue or demonstrate reduced arousal or apathy. Conversely, those with PTSD typically have excessive arousal as a core component of the disorder, particularly in response to certain environmental contexts. Agents such as central nervous stimulants that enhance catecholaminergic tone (e.g., methylphenidate) are commonly used to treat arousal and cognitive deficits in individuals with TBI but in theory (though this has yet to be proven in practice) could exacerbate core symptoms of PTSD.

Sleep

Disordered sleep is common in both individuals with TBI and those with PTSD.^{107–109} Many of the psychotropics have complex effects on sleep, thus it is helpful for clinicians to familiarize themselves with these effects, discuss potential sleep changes with the patient, and monitor changes in sleep as the medication trial progresses.

Neurological Function

Individuals with a history of TBI have higher rates of seizures and may have problems with disequilibrium or balance, vision, and hearing,^{110, 111} as well as other neurological concerns. Individuals with PTSD have less marked neurological abnormalities as a general rule but have been reported to have higher rates of subtle neurological abnormalities.¹¹² Many of the psychotropics can have adverse effects on sensory processing, gait, and balance, and are associated with increased rates of seizures. Thus, again, it is helpful for the clinician to bear these issues in mind when choosing a medication and to monitor for emergence or worsening of these symptoms during treatment.

Alterations in Dosing

Related to the above concerns, most expert opinion suggests that conventional dosing strategies be altered in individuals with a history of TBI and ongoing sequelae.⁹⁶ 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.

Summary

The literature reviewed suggests that the current conflicts in Iraq and Afghanistan are associated with a large cohort of military personnel exposed to episodes of biomechanical force sufficient to cause neurotrauma (sometimes multiple such exposures) and other physical injury, as well as episodes of combat and other forms of deployment related psychological stress. Although such considerations have been associated with other periods of armed conflict, including the World Wars of the previous century, there is a growing appreciation that these different traumas overlap and interact in complex ways, and a better understanding of how common sequelae follow predictably from the profile of brain regions injured by both types of trauma.

From a neural perspective, several brain regions (hippocampus, amygdala, medial and prefrontal cortex) vulnerable to biomechanical forces in the typical TBI, are the same regions implicated in the etiology of PTSD and other stress related disorders, suggesting that although initiating events may differ, there may be a common etiological pathway resulting in the overlapping clinical symptoms. Furthermore, there appears to be a shared cognitive vulnerability. Those with lower cognitive reserve, or those who sustain a TBI, are at substantially greater risk for stress related disorders. Although the mechanism is not clear yet, possibilities include the effects of decreased cognitive reserve with impaired coping capacity, as well as acute TBI-related disruption of the normal processing of emotional and psychologically traumatizing experiences with resultant heightened vulnerability to pathological emotional processing and emergence of stress-related disorders.

At this time, the treatment implications are not clearly established but there are theoretical reasons to question whether the co-morbid occurrence of both types of trauma might render conventional treatment approaches less effective or at least require some alterations in the treatment delivery. Further research should shed some light on this. In the meantime the use of conventional approaches, with modest common sense modifications to accommodate the clinical realities, is advised. These modifications include taking into account the effects of cognitive complaints and possible deficits on the pace of cognitive behavioral interventions, and the effects of psychotropic agents on cognition, arousal, sleep, and sensorimotor function.

Acknowledgments

Supported in part by grants: NICHD R01 HD048176, 1R01HD047242, and 1R01HD48638; NINDS 1R01NS055020; CDC R01/CE001254; DoD/CDMRP PT075446; NIMH K24MH64122; DoD/CDMRP W81XWH08-2-0159

References

1. Tanielian, T.; Jaycox, L.H., editors. Invisible wounds of war: Psychological and cognitive injuries, their consequences, and services to assist recovery. RAND Corporation; Washington, DC: 2008.
2. Sayer NA, Chiros CE, Sigford B, Scott S, Clothier B, Pickett T, Lew HL. Characteristics and rehabilitation outcomes among patients with blast and other injuries sustained during the global war on terror. *Arch Phys Med Rehabil*. 2008; 89:163–170. [PubMed: 18164349]
3. Belanger H, Kretzmer T, Yoash-Gantz R, Pickett T, Tupler L. Cognitive sequelae of blast-related versus other mechanisms of brain trauma. *J Int Neuropsychol Soc*. 2009; 15:1–8. [PubMed: 19128523]
4. Hoge C, Goldberg H, Castro C. Care of war veterans with mild traumatic brain injury - flawed perspectives. *N Engl J Med*. 2009; 360:1588–1591. [PubMed: 19369664]
5. Hoge C, McGurk D, Thomas J, Cox A, Engel C, Castro C. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med*. 2008; 358:453–463. [PubMed: 18234750]

6. Jones E, Fear N, Wessely S. Shell shock and mild traumatic brain injury: A historical review. *Am J Psychiatry*. 2007; 164:1641–1645. [PubMed: 17974926]
7. Cramer F. Cerebral injuries due to explosion waves, cerebral blast concussion; a pathologic, clinical and electroencephalographic study. *Archives of Neurology and Psychiatry*. 1949; 61:1–20.
8. Cramer F. Cerebral injuries due to explosion waves; blast concussion. *J Nerv Ment Dis*. 1947; 106
9. Evans R. The postconcussion syndrome: 130 years of controversy. *Semin Neurol*. 1994; 14:32–39. [PubMed: 8029557]
10. Lishman WA. Brain damage in relation to psychiatric disability after head injury. *Br J Psychiatry*. 1968; 114:373–410. [PubMed: 5656260]
11. Lishman WA. The psychiatric sequelae of head injury: A review. *Psychol Med*. 1973; 3:304–318. [PubMed: 4580811]
12. Lishman WA. Physiogenesis and psychogenesis in the “Post-concussional syndrome”. *Brithish Journal of Psychiatry*. 1988:460–469.
13. Friedman MJ, Schnurr PP, McDonagh-Coyle A. Post-traumatic stress disorder in the military veteran. *Psychiatr Clin North Am*. 1994; 17:265–277. [PubMed: 7937358]
14. Gennarelli, T.; Graham, D. Neuropathology. In: Silver, J.; McAllister, T.; Yudofsky, S., editors. *Textbook of traumatic brain injury*. American Psychiatric Press; Washington, DC: 2005.
15. Bigler ED. Anterior and middle cranial fossa in traumatic brain injury: Relevant neuroanatomy and neuropathology in the study of neuropsychological outcome. [review] [119 refs]. *Neuropsychology*. 2007; 21:515–531. [PubMed: 17784800]
16. Raghupathi R, Graham DI, Al E. Apoptosis after traumatic brain injury. *J Neurotrauma*. 2000; 17:927–938. [PubMed: 11063058]
17. Umile EM, Sandel ME, Alavi A, Terry CM, Plotkin RC. Dynamic imaging in mild traumatic brain injury: Support for the theory of medial temporal vulnerability. *Arch Phys Med Rehabil*. 2002; 83:1506–1513. [PubMed: 12422317]
18. Kocsis JD, Tessler A. Pathology of blast-related brain injury. *J Rehabil Res Dev*. 2009; 46:667–672. [PubMed: 20104396]
19. Depalma RG, Burris DG, Champion HR, Hodgson MJ. Blast injuries. *N Engl J Med*. 2005; 352:1335–1342. [PubMed: 15800229]
20. Cernak I, Wang Z, Jiang J, Bian X, Savic J. Cognitive deficits following blast injury-induced neurotrauma: Possible involvement of nitric oxide. *Brain Inj*. 2001; 15:593–612. [PubMed: 11429089]
21. Cernak I, Savic J, Malicevic Z, Zunic G, Radosevic P, Ivanovic I, Davidovic L. Involvement of the central nervous system in the general response to pulmonary blast injury. *J Trauma*. 1996; 40:S100–104. [PubMed: 8606388]
22. Mayorga MA. The pathology of primary blast overpressure injury. *Toxicology*. 1997; 121:17–28. [PubMed: 9217312]
23. Cernak I, Wang Z, Jiang J, Bian X, Savic J. Ultrastructural and functional characteristics of blast injury-induced neurotrauma. *J Trauma*. 2001; 50:695–706. [PubMed: 11303167]
24. Warden D. Military tbi during the iraq and afghanistan wars. *J Head Trauma Rehabil*. 2006; 21:398–402. [PubMed: 16983225]
25. Chen Y, Smith DH, Meaney DF. In-vitro approaches for studying blast-induced traumatic brain injury. *J Neurotrauma*. 2009; 26:1–16. [PubMed: 19196178]
26. Bhattacharjee Y. Shell shock revisited: Solving the puzzle of blast trauma. *Science*. 2008; 319:406–408. [PubMed: 18218877]
27. Mcallister TW, Flashman LA, Sparling MB, Saykin AJ. Working memory deficits after mild traumatic brain injury: Catecholaminergic mechanisms and prospects for catecholaminergic treatment-a review. *Brain Inj*. 2004; 18:331–350. [PubMed: 14742148]
28. Arciniegas DB. The cholinergic hypothesis of cognitive impairment caused by traumatic brain injury. *Curr Psychiatry Rep*. 2003; 5:391–399. [PubMed: 13678561]
29. Morales DM, Marklund N, Lebold D, Thompson HJ, Pitkanen A, Maxwell WL, Longhi L, Laurer H, Maegele M, Neugebauer E, Graham DI, Stocchetti N, McIntosh TK. Experimental models of

- traumatic brain injury: Do we really need to build a better mousetrap? *Neuroscience*. 2005; 136:971–989. [PubMed: 16242846]
30. Thompson H, Lifshitz J, Marklund N, Grady M, Graham D, Hovda D, McIntosh T. Lateral fluid percussion brain injury: A 15-year review and evaluation. *J Neurotrauma*. 2005; 22:42–75. [PubMed: 15665602]
 31. Park E, Mcknight S, Ai J, Baker A. Purkinje cell vulnerability to mild and severe forebrain head trauma. *J Neuropathol Exp Neurol*. 2006; 65:226–234. [PubMed: 16651884]
 32. Farkas O, Povlishock JT. Cellular and subcellular change evoked by diffuse traumatic brain injury: A complex web of change extending far beyond focal damage. *Prog Brain Res*. 2007; 161:43–59. [PubMed: 17618969]
 33. Bigler E. Neuropsychological results and neuropathological findings at autopsy in a case of mild traumatic brain injury. *J Int Neuropsychol Soc*. 2004; 10:794–806. [PubMed: 15327725]
 34. Blumbergs PC, Scott G, Manavis J, Wainwright H, Simpson DA, Mclean AJ. Staining of amyloid precursor protein to study axonal damage in mild head injury. *Lancet*. 1994; 344:1055–1056. [PubMed: 7523810]
 35. Oppenheimer DR. Microscopic lesions in the brain following head injury. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1968; 31:299–306.
 36. Marcoux J, McArthur D, Miller C, Glenn T, Villablanca P, Martin N, Hovda D, Alger J, Vespa P. Persistent metabolic crisis as measured by elevated cerebral microdialysis lactate-pyruvate ratio predicts chronic frontal lobe brain atrophy after traumatic brain injury. *Crit Care Med*. 2008; 36:2871–2877. [PubMed: 18766106]
 37. Strebel S, Lam AM, Matta BF, Newell DW. Impaired cerebral autoregulation after mild brain injury. *Surg Neurol*. 1997; 47:128–131. [PubMed: 9040813]
 38. Junger EC, Newell DW, Grant GA, Avellino AM, Ghatan S, Douville CM, Lam AM, Aaslid R, Winn HR. Cerebral autoregulation following minor head injury. *J Neurosurg*. 1997; 86:425–432. [PubMed: 9046298]
 39. Arvigo F, Cossu M, Fazio B, Gris A, Pau A, Rodriguez G, Rosadini G, Sehrbundt Viale E, Siccaldi D, Turtas S. Cerebral blood flow in minor cerebral contusion. *Surg Neurol*. 1985; 24:211–217. [PubMed: 4012580]
 40. Lee S, Wong M, Samii A, Al E. Evidence for energy failure following irreversible traumatic brain injury. *Ann N Y Acad Sci*. 1999; 893:337–340. [PubMed: 10672261]
 41. Giza C, Hovda D. The neurometabolic cascade of concussion. *J Athletic Training*. 2001; 36:228–235.
 42. Bergsneider M, Hovda D, Lee S, Al E. Dissociation of cerebral glucose metabolism and level of consciousness during the period of metabolic depression following human traumatic brain injury. *J Neurotrauma*. 2000; 17:389–401. [PubMed: 10833058]
 43. Levine B, Fujiwara E, O'connor C, Richard N, Kovacevic N, Mandic M, Restagno A, Easdon C, Robertson IH, Graham SJ, Cheung G, Gao F, Schwartz ML, Black SE, Levine B, Fujiwara E, O'connor C, Richard N, Kovacevic N, Mandic M, Restagno A, Easdon C, Robertson IH, Graham SJ, Cheung G, Gao F, Schwartz ML, Black SE. In vivo characterization of traumatic brain injury neuropathology with structural and functional neuroimaging. *J Neurotrauma*. 2006; 23:1396–1411. [PubMed: 17020478]
 44. Belanger H, Vanderploeg R, Curtiss G, Warden D. Recent neuroimaging techniques in mild traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2007; 19:5–20. [PubMed: 17308222]
 45. Chastain CA, Oyoyo U, Zipperman M, Joo E, Ashwal S, Shutter L, Tong K. Predicting outcomes of traumatic brain injury by imaging modality and injury distribution. *J Neurotrauma*. 2009; 26:1183–1196. [PubMed: 19317591]
 46. Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM, Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM. White matter integrity and cognition in chronic traumatic brain injury: A diffusion tensor imaging study. *Brain*. 2007; 130:2508–2519. [PubMed: 17872928]
 47. Niogi SN, Mukherjee P, Ghajar J, Johnson C, Kolster RA, Sarkar R, Lee H, Meeker M, Zimmerman RD, Manley GT, Mccandliss BD. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: A 3t diffusion tensor

- imaging study of mild traumatic brain injury. *Ajnr: American Journal of Neuroradiology*. 2008; 29:967–973. [PubMed: 18272556]
48. Huang M, Theilmann RJ, Robb A, Angeles A, Nichols S, Drake A, Dandrea J, Levy M, Holland M, Song T, Ge S, Hwang E, Yoo K, Cui L, Baker DG, Trauner D, Coimbra R, Lee RR. Integrated imaging approach with meg and dti to detect mild traumatic brain injury in military and civilian patients. *J Neurotrauma*. 2009; 26:1213–1226. [PubMed: 19385722]
 49. Levin H, Wilde EA, Troyanskaya M, Petersen N, Scheibel R, Newsome M, Radaideh M, Wu T, Yallampalli R, Chu Z, Li X. Diffusion tensor imaging of mild to moderate blast related tbi and its sequelae. *J Neurotrauma*. 2010; 27:683–694. [PubMed: 20088647]
 50. Hattori N, Swan M, Stobbe G, Uomoto J, Minoshima S, Djang D, Krishnananthan R, Lewis D. Differential spect activation patterns associated with pasat performance may indicate frontocerebellar functional dissociation in chronic mild traumatic brain injury. *J Nucl Med*. 2009; 50:1054–1061. [PubMed: 19525460]
 51. Alavi A, Newberg AB. Metabolic consequences of acute brain trauma: Is there a role for pet? *J Nucl Med*. 1996; 37:1170–1172. [PubMed: 8965190]
 52. Mcallister TW, Flashman LA, Mcdonald BC, Saykin AJ, Mcallister TW, Flashman LA, Mcdonald BC, Saykin AJ. Mechanisms of working memory dysfunction after mild and moderate tbi: Evidence from functional mri and neurogenetics. *J Neurotrauma*. 2006; 23:1450–1467. [PubMed: 17020482]
 53. Gasparovic C, Yao R, Mannell M, Ling J, Elgie R, Phillips J, Doezenia D, Mayer A. Neurometabolite concentrations in gray and white matter in mild traumatic brain injury: An 1h-magnetic resonance spectroscopy study. *J of Neurotrauma*. 2009; 26:1635–1643. [PubMed: 19355814]
 54. Hoge C, Castro C, Messer S, McGurk D, Cotting D, Koffman R. Combat duty in iraq and afghanistan, mental health problems, and barriers to care. *N Engl J Med*. 2004; 351:13–22. [PubMed: 15229303]
 55. Hoge, C. Personal communication. February 21. 2007
 56. Neumeister A, Wood S, Bonne O, Nugent AC, Luckenbaugh DA, Young T, Bain EE, Charney DS, Drevets WC. Reduced hippocampal volume in unmedicated, remitted patients with major depression versus control subjects. *Biol Psychiatry*. 2005; 57:935–937. [PubMed: 15820716]
 57. Friedman, MJ.; Davidson, JRT. Pharmacotherapy for ptsd. In: Friedman, MJ.; Keane, TM.; Resick, PA., editors. *Handbook of ptsd*. Guilford Publications; New York: 2007.
 58. Bremner JD. Functional neuroimaging in post-traumatic stress disorder. *Expert Review of Neurotherapeutics*. 2007; 7:393–405. [PubMed: 17425494]
 59. Davis M, Whalen PJ. The amygdala: Vigilance and emotion. *Mol Psychiatry*. 2001; 1:13–34. [PubMed: 11244481]
 60. Vermetten E, Bremner JD. Circuits and systems in stress. II. Applications to neurobiology and treatment in posttraumatic stress disorder. *Depression & Anxiety*. 2002; 16:14–38. [PubMed: 12203669]
 61. Charney DS. Psychobiological mechanisms of resilience and vulnerability: Implications for successful adaptation to extreme stress. *American Journal of Psychiatry*. 2004; 161:195–216. [PubMed: 14754765]
 62. Simmons A, Paulus M, Thorp S, Matthews S, Norman S, Stein M. Functional activation and neural networks in women with posttraumatic stress disorder related to intimate partner violence. *Biol Psychiatry*. 2008; 64
 63. Charney DS, Deutch AY, Krystal JH, Southwick SM, Davis M. Psychobiologic mechanisms of posttraumatic stress disorder. *Arch Gen Psychiatry*. 1993; 50:295–305. [PubMed: 8466391]
 64. Friedman MJ. Neurobiological sensitization models of post-traumatic stress disorder: Their possible relevance to multiple chemical sensitivity syndrome. *Toxicol Ind Health*. 1994; 10:449–462. [PubMed: 7778107]
 65. Southwick, SM.; Davis, L.; Aikens, DE.; Rasmusson, AM.; Barron, J.; Morgan, CA. Neurobiological alterations associated with ptsd. In: Friedman, MJ.; Keane, TM.; Resick, PA., editors. *Ptsd: Science and practice - a comprehensive handbook*. Guilford Publications; New York: in press

66. Sapolsky RM. The possibility of neurotoxicity in the hippocampus in major depression: A primer on neuron death.[comment]. *Biological Psychiatry*. 2000; 48:755–765. [PubMed: 11063972]
67. McEwen BS, Angulo J, Cameron H, Chao HM, Daniels D, Gannon MN. Paradoxical effects of adrenal steroids on the brain: Protection versus degeneration. *Biol Psychiatry*. 1992; 31:177–199. [PubMed: 1737079]
68. Debellis MD, Chrousos GP, Dorn LD, Burke L, Helmers K, Kling MA, Trickett PK, Putnam FW. Hypothalamicpituitary-adrenal axis dysregulation in sexually abused girls. *J Clin Endocrinol Metab*. 1994; 78:249–255. [PubMed: 8106608]
69. Heim C, Newport JD, Bonsall R, Miller AH, Nemeroff CB. Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *Am J Psychiatry*. 2001; 158:575–581. [PubMed: 11282691]
70. Lemieux AM, Coe CL. Abuse-related posttraumatic stress disorder: Evidence for chronic neuroendocrine activation in women. *Psychosom Med*. 1995; 57:105–115. [PubMed: 7792368]
71. Rasmusson AM, Lipschitz DS, Wang S, Hu S, Vojvoda D, Bremner JD, Southwick SM, Al E. Increased pituitary and adrenal reactivity in premenopausal women with ptsd. *Biol Psychiatry*. 2001; 50:965–977. [PubMed: 11750893]
72. Rasmusson, AM.; Friedman, MJ. The neurobiology of ptsd in women. In: Kimerling, R.; Ouimette, PC.; Wolfe, J., editors. *Gender and ptsd*. Guilford Press; New York: 2002.
73. Yehuda R. Current status of cortisol findings in post-traumatic stress disorder. *Psychiatr Clin North Am*. 2002; 2:341–368. [PubMed: 12136504]
74. Yehuda R, Boissoneau D, Lowy MT, Giller EL. Dose-response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. *Arch Gen Psychiatry*. 1995; 52:583–593. [PubMed: 7598635]
75. Friedman, MJ.; McDonagh-Coyle, AS.; Jalowiec, JE.; Wang, S.; Fournier, DA.; Mchugo, GJ. Neurohormonal findings during treatment of women with ptsd due to childhood sexual abuse. Presented at 17th Annual Meeting of the International Society for Traumatic Stress Studies; New Orleans, LA. 2001.
76. Harvey A, Brewin C, Jones C, Kopelman M. Coexistence of posttraumatic stress disorder and traumatic brain injury: Towards a resolution of the paradox. *J Int Neuropsychol Soc*. 2003; 9:663–676. [PubMed: 12755178]
77. Sbordone RJ, Liter JC. Mtb does not produce post-traumatic stress disorder. *Brain Inj*. 1995; 9:405–412. [PubMed: 7640686]
78. Warden DC, Labbate LA, Salazar AM, Nelson R, Sheley E, Staudenmeier R, Martin E. Posttraumatic stress disorder in patients with traumatic brain injury and amnesia for the event. *J Neuropsychiatry Clin Neurosci*. 1997; 9:18–22. [PubMed: 9017524]
79. Stein MB, McAllister TW. Exploring the convergence of post traumatic stress disorder and mild traumatic brain injury. *Am J Psychiatry*. 2009; 166:768–776. [PubMed: 19448186]
80. McAllister T. Psychopharmacological issues in the treatment of tbi and ptsd. *The Clinical Neuropsychologist*. 2009; 23:1338–1367. [PubMed: 19882475]
81. Vasterling JJ, Verfaellie M, Sullivan KD. Mild traumatic brain injury and posttraumatic stress disorder in returning veterans: Perspectives from cognitive neuroscience. *Clin Psychol Rev*. 2009; 29:674–684. [PubMed: 19744760]
82. Schneiderman A, Braver E, Kang H. Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: Persistent postconcussive symptoms and posttraumatic stress disorder. *Am J Epidemiol*. 2008; 167:1446–1452. [PubMed: 18424429]
83. Belanger HG, Kretzmer T, Vanderploeg RD, French LM. Symptom complaints following combat-related traumatic brain injury: Relationship to traumatic brain injury severity and posttraumatic stress disorder. *J Int Neuropsychol Soc*. 2010; 16:194–199. [PubMed: 19758488]
84. Harvey AG, Bryant RA. Acute stress disorder after mild traumatic brain injury. *J Nerv Ment Dis*. 1998; 186:333–337. [PubMed: 9653416]
85. Harvey AG, Bryant RA. Predictors of acute stress following mild traumatic brain injury. *Brain Inj*. 1998; 12:147–154. [PubMed: 9492962]

86. Bryant RA, Harvey AG. Relationship between acute stress disorder and posttraumatic stress disorder following mild traumatic brain injury. *Am J Psychiatry*. 1998; 155:625–629. [PubMed: 9585713]
87. Broomhall LG, Clark CR, Mcfarlane AC, O'donnell M, Bryant R, Creamer M, Silove D. Early stage assessment and course of acute stress disorder after mild traumatic brain injury. *J Nerv Ment Dis*. 2009; 197:178–181. [PubMed: 19282684]
88. Bryant RA, Harvey AG. Postconcussive symptoms and posttraumatic stress disorder after mild traumatic brain injury. *J Nerv Ment Dis*. 1999; 187:302–305. [PubMed: 10348085]
89. Bryant RA, Harvey AG. The influence of traumatic brain injury on acute stress disorder and post-traumatic stress disorder following motor vehicle accidents. *Brain Inj*. 1999; 13:15–22. [PubMed: 9972438]
90. Bryant RA, Creamer M, O'donnell M, Silove D, Clark CR, Mcfarlane AC. Post-traumatic amnesia and the nature of post-traumatic stress disorder after mild traumatic brain injury. *J Int Neuropsychol Soc*. 2009; 15:862–867. [PubMed: 19703323]
91. Mayou RA, Black J, Bryant B. Unconsciousness, amnesia and psychiatric symptoms following road traffic accident injury. *Br J Psychiatry*. 2000; 177:540–545. [PubMed: 11102330]
92. Koren D, Norman D, Cohen A, Berman J, Klein EM. Increased ptsd risk with combat-related injury: A matched comparison study of injured and uninjured soldiers experiencing the same combat events. *Am J Psychiatry*. 2005; 162:276–282. [PubMed: 15677591]
93. Mollica RF, Henderson DC, Tor S. Psychiatric effects of traumatic brain injury events in cambodian survivors of mass violence. *Br J Psychiatry*. 2002; 181:339–347. [PubMed: 12356662]
94. Vanderploeg R, Belanger H, Curtiss G. Mild traumatic brain injury and posttraumatic stress disorder and their associations with health symptoms. *Arch Phys Med Rehabil*. 2009; 90:1084–1093. [PubMed: 19577020]
95. Bryant RA, O'donnell ML, Creamer M, Mcfarlane AC, Clark CR, Silove D. The psychiatric sequelae of traumatic injury. *Am J Psychiatry*. 2010; 167:312–320. [PubMed: 20048022]
96. Mcallister T. Neurobehavioral sequelae of traumatic brain injury: Evaluation and treatment. *World Psychiatry*. 2008; 7:3–10. [PubMed: 18458777]
97. Breslau N V, Lucia C, Alvarado GF. Intelligence and other predisposing factors in exposure to trauma and posttraumatic stress disorder: A follow-up study at age 17 years. *Arch Gen Psychiatry*. 2006; 63:1238–1245. [PubMed: 17088504]
98. Kremen WS, Koenen KC, Boake C, Purcell S, Eisen SA, Franz CE, Tsuang MT, Lyons MJ. Pretrauma cognitive ability and risk for posttraumatic stress disorder: A twin study. *Arch Gen Psychiatry*. 2007; 64:361–368. [PubMed: 17339525]
99. Institute of Medicine. Treatment of posttraumatic stress disorder: An assessment of the evidence. Washington, DC: 2008.
100. Warden D, Gordon B, Katz D, Mcallister T, Silver J, Sparling M, Whyte J. Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. *J Neurotrauma*. 2006 Oct.23:1468–1501. [PubMed: 17020483]
101. Institute of Medicine. Gulf war and health, volume 7: Long-term consequences of traumatic brain injury. The National Academies Press; Washington, DC: 2009.
102. Cicerone K, Levin H, Malec J, Stuss D, Whyte J. Cognitive rehabilitation interventions for executive function: Moving from bench to bedside in patients with traumatic brain injury. *J Cogn Neurosci*. 2006; 18:1212–1222. [PubMed: 16839293]
103. Cicerone K, Dahlberg C, Kalmar K, Langenbahn DM, Malec J, Bergquist TF, Felicetti T, Giacino JT, Harley JP, Harrington DE, Herzog J, Kneipp S, Laatsch L, Morse PA. Evidence-based cognitive rehabilitation: Recommendations for clinical practice. *Arch Phys Med Rehabil*. 2000; 81:1596–1615. [PubMed: 11128897]
104. Alderfer BS, Arciniegas DB, Silver JM. Treatment of depression following traumatic brain injury. *J Head Trauma Rehabil*. 2005; 20:544–562. [PubMed: 16304490]
105. Silver J, Mcallister T, Arciniegas D. Depression and cognitive complaints following mild traumatic brain injury. *Am J Psychiatry*. 2009; 166:653–661. [PubMed: 19487401]

106. Vasterling JJ, Duke LM, Brailey K, Constans JI, Allain AN Jr, Sutker PB. Attention, learning, and memory performances and intellectual resources in vietnam veterans: Ptsd and no disorder comparisons. *Neuropsychology*. 2002; 16:5–14. [PubMed: 11853357]
107. Raskind M, Peskind E, Hoff D, Hart K, Holmes H, Warren D, Shofer J, O'connell J, Taylor F, Gross C, Rohde K, Mcfall M. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. [see comment]. *Biol Psychiatry*. 2007; 61:928–934. [PubMed: 17069768]
108. Vaishnavi S, Rao V, Fann J. Neuropsychiatric problems after traumatic brain injury: Unraveling the silent epidemic. *Psychosomatics*. 2009; 50:198–205. [PubMed: 19567758]
109. Kraus J, Schaffer K, Ayers K, Stenehjem J, Shen H, Afifi AA. Physical complaints, medical service use, and social and employment changes following mild traumatic brain injury: A 6-month longitudinal study. *J Head Trauma Rehabil*. 2005; 20:239–256. [PubMed: 15908824]
110. Kapoor, N.; Ciuffreda, K. Vision problems. In: Silver, J.; McAllister, T.; Yudofsky, S., editors. *Textbook of traumatic brain injury*. American Psychiatric Publishing; Washington, DC: in press
111. Cosetti, M.; Lalwani, A. Dizziness, imbalance and vestibular dysfunction after traumatic brain injury. In: Silver, J.; McAllister, T.; Yudofsky, S., editors. *Textbook of traumatic brain injury*. American Psychiatric Publishing; Washington, DC: in press
112. Pitman RK, Gilbertson MW, Gurvits TV, May FS, Lasko NB, Metzger LJ, Shenton ME, Yehuda R, Orr SP, Harvard VAPTSI. Clarifying the origin of biological abnormalities in ptsd through the study of identical twins discordant for combat exposure. *Ann N Y Acad Sci*. 2006; 1071:242–254. [PubMed: 16891575]