Behavioral and Psychiatric Comorbidities of TBI

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Introduction

An estimated 1.7 million Americans sustain a traumatic brain injury (TBI) each year [1], and over 5.3 million (2% of the United States [US] population) are currently living with a disability from TBI that requires assistance in activities of daily living [2]. The incidence of TBI, as measured by combined emergency department (ED) visits, hospitalizations, and deaths, has steadily risen from 521 per 100,000 in 2001 to 824 per 100,000 in 2010 [3]. Men are 1.5 times more likely to sustain a TBI than women, and military activities increase the risk of TBI [4]. Approximately 40.5% of TBIs are caused by falls, 14.3% by motor vehicle accidents, 15.5% by being struck by something or striking one's head against something, and 10.7% by assaults [3]. Among military personnel serving in a warzone, explosive blasts are the leading cause of TBI [5]. TBI is associated with a variety of subsequent neurological disorders, including epilepsy,

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Alzheimer's disease, and Parkinson's disease [6]. TBI has also been associated with a number of psychiatric and behavioral effects, including the development of mood and anxiety disorders, psychosis, aggressive behavior, and posttraumatic stress disorder (PTSD).

TBI Psychiatric Comorbidities

There are numerous and varied health and functional consequences of TBI, among the most challenging both to manage, but also to establish the precise link to TBI, are psychiatric problems. Reports of a potential relationship to TBI include disorders of mood, difficulties with anxiety, posttraumatic stress disorder, and behavioral disturbances. Differentiating diagnoses between various issues following TBI is complicated [7], as psychiatric symptoms following TBI, such as irritability and anger, are common to PTSD, depression, aggression, and some neuroanatomical lesions. In addition, substantial comorbidity may occur [8]; for example, Hibbard and associates [9] found that 44% of their sample with TBI reported two or more Axis I disorders on an average of 8 years following injury. Among 1560 adults who completed telephone interviews 1 year following TBI, approximately 40% reported clinically significant symptoms of mood or anxiety disorders [10].

Studies have found that premorbid psychiatric disorders, such as alcohol abuse, anxiety, and depression, increase the risk of postinjury depression or anxiety [7, 9–11]. Although it is unclear what proportion of individuals with TBI have psychiatric disorders prior to their injury, in general, 6.7% of individuals over the age of 18 in the USA experience major depression, and 18% experience an anxiety disorder each year [12].

Research suggests that the development of psychiatric issues following TBI may represent the developmental concept of *equifinality*, in which the same outcome (e.g., depression) may result from disparate causes and circumstances, such as premorbid dysfunction, poor psychosocial functioning after TBI, or nature and anatomic location of TBI.

Mood Disorders

Incidence rates of mood disorders following TBI vary. Prevalence estimates are 6–77% [10]; however, most experts approximate that post-TBI depression is evident in 25–50% of patients within the first year post injury and in 26–64% across the lifespan [9, 13–15]. This wide range in prevalence estimates is believed to result from a variety of methodological factors, including variation across studies in sample characteristics, severity and definition of TBI and depression, and assessment instrument [10]. The problem is further complicated by an overlap in symptoms between TBI, depression, and anxiety disorders (e.g., sleep disturbance, concentration difficulties).

Studies examining risk factors for depression after TBI have yielded mixed results (for discussion, see [11, 16, 17]); for example, some have found that older age [18] and female gender [19] significantly predict postinjury depression, whereas others have reported that these were not significant predictors [20–23]. Depression following TBI has been associated with poorer cognitive functioning [24, 25] and poorer psychosocial functioning [22, 26] than reported by those without depression. It has also been associated with a failure to recover as expected following TBI [20].

Factors that likely influence the risk of depression following TBI include genetic, demographic, developmental, and psychosocial elements [27]. That said, the exact etiology of these symptoms remains unclear; negative outcomes, such as poor psychosocial functioning, have been hypothesized to be both the cause [28] and consequence [26] of depression. Early psychosocial adversity (e.g., abuse), life stress, and limited social support are well-recognized risk factors for the development of psychiatric illness. These factors have not been extensively studied among TBI populations. However, preliminary research suggests that personal history of mood and anxiety disorders as well as previous poor social functioning are associated with the occurrence of major depression after TBI [7, 29]. Similarly, Fann and colleagues observed that the risk of psychiatric illness is highest shortly after injury in persons with no previous psychiatric history,

was unrelated to the severity of TBI, and appeared to increase in subsequent years in persons with premorbid psychiatric disorders [30].

It is also possible that for some individuals, depression following TBI may reflect an organic etiology [18] associated with the neurological issues associated with TBI; for example, lesions in the regions such as the left dorsofrontal cortex, left basal ganglia, or right posterior hemisphere have distinguished depressed and nondepressed patients with TBI [17]. Taken together, this research suggests that the development of psychiatric issues following TBI may represent the developmental concept of *equifinality*, in which the same outcome (e.g., depression) may result from disparate causes and circumstances, such as premorbid dysfunction, poor psychosocial functioning after TBI, or nature and anatomic location of TBI.

Anxiety Disorders

Anxiety disorders (other than posttraumatic stress disorder [PTSD], see below) are relatively common in patients who have sustained a TBI, but estimated prevalence rates vary greatly. Some estimates suggest prevalence of anxiety after TBI is as high as 70%; however, a meta-analytic review by Epstein and Ursano [31] demonstrated prevalence of anxiety disorders being lower – 29% across all severities of TBI. Although some are much more prevalent than others, virtually all types of anxiety disorders have been documented following TBI. Research indicates that the rates of anxiety disorders among patients with TBI are 3–28% for Generalized Anxiety Disorder (GAD), 4–17% for Panic Disorder, 1–10% for phobic disorders, 2–15% for Obsessive-Compulsive Disorder (OCD), and 3–27% for PTSD [15, 32]. Such acquired anxiety disorders are presently coded in the Diagnostic and Statistical Manual-5 (DSM-5) as "Anxiety Disorder Due to Another Medical Condition" [33]. In general, the most common post-TBI anxiety symptoms include free-floating anxiety, fearfulness, intense worry, generalized uneasiness, social withdrawal, interpersonal sensitivity, and anxiety dreams [34]. Increased activity of the aminergic system and decreased activity of the GABA inhibitory network is the proposed mechanism for the clinical manifestation of anxiety [35]. Right-hemispheric lesions are more often associated with anxiety disorder than left-sided lesions [36].

Posttraumatic Stress Disorder

Exposure to trauma, such as the potentially life-threatening events associated with TBI (e.g., motor vehicle accidents and combat), places individuals at risk for various psychiatric disorders, most notably PTSD. As defined by the American Psychiatric Association, PTSD is a constellation of symptoms, including re-experiencing the event, avoidance of reminders of the event, negative alterations in cognitions and emotions, and chronic hyperarousal that persist for 3 months or more after exposure to a trauma [33]. Given the increased risk of both trauma and TBI in combat, the recent wars in Iraq and Afghanistan have highlighted the complications associated with identifying TBI in the context of PTSD and vice versa. In a sample of 100 soldiers with similar combat experience, 16.7% of those who incurred a bodily injury during combat met the criteria for PTSD after deployment, while only 2.5% of those without injury were diagnosed with PTSD [37]. The association between injury and later development of PTSD appears to be even greater in the case of mild TBI (mTBI, or concussion) relative to other bodily injuries. Hoge and associates [38] noted a strong association between combat-related mTBI and screening positive for PTSD. In a stratified sample of soldiers who reported a history of no injury, nonbrain injury, mTBI with altered mental status, and mTBI with loss of consciousness, the rate of positive postdeployment PTSD questionnaire screenings rose steadily from 9.1% in the nonbrain injury group to 43.9% in the mTBI with loss of consciousness group. What remains unclear is if this relation between PTSD and history of mTBI would be changed if more stringent diagnostic standards for PTSD and mTBI (i.e., clinician-confirmed diagnosis) were employed. This frequent occurrence of PTSD symptomatology after mTBI is not unique to military populations. Estimated rates of PTSD

following mTBI have ranged from 17% to 33% in civilians with TBI [39–41], a rate of PTSD considerably higher than 7.8% lifetime prevalence rate noted in the civilian population [42].

The topic of PTSD following mTBI has caused considerable controversy for two reasons. First, the development of PTSD is assumed to stem from intense psychological trauma wherein the perceived potential for loss of life, physical injury, or sexual assault is present. From this perceived threat at the time of the traumatic event, the individual subsequently "cannot forget" the trauma as evidenced through re-experiencing the trauma, avoiding situations, thoughts, and feelings that serve as reminders of the trauma, subsequent changes in one's thinking and emotions, and hypervigilance toward perceived threats. It has been questioned whether this psychological response to a traumatic event can occur in the context of a TBI associated with loss of memory for the event.

An early study on this topic appeared to validate the logical conclusion that mTBI should serve as a protective factor against later PTSD [43]. Of the 70 patients with either PTSD or a history of mTBI included in this study, none of the patients with a history of TBI reported any re-experiencing symptoms, consistent with the expectation that an amnestic state associated with an mTBI would preclude later recall of the event. Of note, the majority of patients in this study either reported loss of consciousness or amnesia for the event (i.e., 85.7% reported a positive loss of consciousness, and 96.4% reported amnesia for the event), suggesting that this sample may have included a disproportionate number of patients with somewhat more significant mTBIs. A more recent study exploring the association between memory for the traumatic event and later development of PTSD suggested that those patients with mTBI without amnesia for the event were at increased risk of developing PTSD relative to those patients without memory for the event [44]. The representativeness of the 120 patients in this study has also been called into question, however, since all the patients required hospitalization for observation.

Other studies, however, have failed to support the hypothesis that amnesia for the traumatic event surrounding the mTBI reduces the likelihood of developing PTSD. Studies of civilians indicated that a history of TBI with loss of consciousness was a risk factor for development of PTSD [45, 46]. King [47] offered three explanations for the paradoxical appearance of PTSD (especially re-experiencing symptoms) following a TBI with apparent loss of consciousness or posttraumatic amnesia proximal to the traumatic event. First, it is possible that islands of memory persist during the period of apparent amnesia. Second, an implicit fear response may still be evoked when a person is exposed to stimuli reminiscent of the traumatic event even if there was a clear loss of consciousness. Lastly, individuals without memory for the traumatic event may develop imagined or reconstructed memories based on information provided by others.

Another problem related to the comorbidity of TBI and PTSD concerns the considerable overlap in PTSD and postconcussion symptoms. Sleep disturbance, irritability, memory and concentration difficulties, reduced speed of processing, depression, fatigue, headaches, and nausea are common to both disorders [47]. As might be expected, the presence of PTSD following mTBI is associated with increased postconcussion symptoms reported, and PTSD symptoms are correlated with postconcussion symptoms. In a sample of 105 motor vehicle collision survivors with and without mTBI, the frequency of reported postconcussion symptoms was greatest in individuals who sustained an mTBI and had been diagnosed with PTSD, and overall report of PTSD symptoms was significantly correlated with the report of postconcussion symptoms [48]. Longitudinal studies of PTSD and postconcussion symptoms demonstrate that PTSD accounts for the lingering postconcussion symptoms rather than the original head injury [49–51].

In the context of combat-related mTBI, the controversy of mTBI as a risk factor for PTSD is different. Unlike the civilian population where a single event is theorized to precipitate both the mTBI and subsequent PTSD, the traumatic event that is associated with a combat-related mTBI often represents perhaps one in a series of psychologically traumatic events and exposure to

heighted combat intensity taking place over several months [38]. In this context, a diagnosis of mTBI simply serves as a proxy indicating a likely history of exposure to repeated, traumatic events, any of which could have contributed to the later development of PTSD. Although further research is needed to better delineate the interplay between these two disorders, it could be hypothesized that an mTBI occurring in the context of acute stress disorder or PTSD has the potential to worsen the psychiatric disorder through a temporary reduction in cognitive resources used to process the ongoing trauma. Conversely, chronic stress associated with the presence of acute stress disorder or PTSD could impede or otherwise alter the trajectory of the course of spontaneous recovery of cognitive functioning following mTBI.

Fortunately, comorbid mTBI and PTSD are generally not associated with greater impairment than either diagnosis alone. There are some exeptions, to include comornid mTBI and PTSD being related to increased medical costs, PTSD symptom severity [52, 53], and increased pain intensity levels [54]. However, the majority of functional outcomes do not appear to be negatively affected by the comorbidity of the disorders. For example, comorbid mTBI did not elevate the risk of suicide [53], negative physical health outcomes (with the exception of headaches; [38]), arrest rates [55], impaired psychosocial functioning [56], or alcohol use disorder [57] above PTSD alone. Similarly, PTSD did not lead to impairments in cognitive ability above mTBI [58]. Psychiatric symptoms and coping abilities may be more important in predicting mTBI complications than the severity of the head injury. A civilian study conducted in the Netherlands demonstrated that patients who experienced an mTBI and reported many postconcussive complaints 2 weeks after the injury were more likely to be female, endorse psychiatric symptoms (anxiety, depression, and/or PTSD), have fewer active coping mechanisms, and have more passive coping tendencies than patients who reported few or no symptoms. The severity of the head injury did not predict complaints [59].

Psychotic Symptoms

Although a relatively rare complication, psychotic symptoms may emerge secondary to TBI. Psychotic symptoms following TBI can manifest as frank delusions, hallucinations, and disordered thinking. They may also be associated with symptoms of agitation, ideas of reference, grimacing, inappropriate laughing, and impulsive aggressiveness (discussed below; [60, 61]). The psychotic features may be acute or chronic, transient or persistent, and may or may not be associated with mood disturbances [62]. Nevertheless, the association between psychosis and TBI remains quite controversial. Psychotic syndromes occur more frequently in individuals who have had a TBI than in the general population. A review by Davison and Bagley [63] revealed that 0.7–9.8% of patients with TBI develop schizophrenia-like psychosis. The majority of those patients did not have a family history of schizophrenia. Other studies have shown that the incidence of head injury predating psychotic symptoms in a population of patients with schizophrenia is about 15% [64]. David and Prince [65] reviewed the literature to identify a causal role of TBI in psychosis and concluded that the evidence for such an association does not exist. They suggest that any association may be the result of reverse causality. It is clear that large-scale epidemiological studies are needed to determine if TBI can be considered to be causally implicated as a risk factor for schizophrenia-like syndromes [66].

Suicide

Just as depression and other psychiatric conditions are associated with an increased risk of suicide [67, 68], a history of TBI must also be considered when assessing suicide risk. In their review of the relation between TBI and suicidality, Simpson and Tate [69] concluded that those recovering from TBI have a three- to four-fold increased risk of committing suicide relative to the general population, and that this increase appears to remain constant at least through the first 15 years post injury. A recent Danish population-based study including nearly 150,000

subjects examined the relationship between TBI severity and suicide risk [70]. While those with severe TBI, as defined by the presence of cerebral contusions or intracranial hemorrhages, demonstrated the highest risk of suicide (i.e., 4.1 times increased risk) relative to the general population, those classified with a concussion still demonstrated an increased risk of suicide (i.e., three times increased risk). It has been suggested, however, that the increased rates of suicide for mTBI are likely related to postinjury and/or concomitant psychosocial factors, whereas suicidality following severe TBI is likely related to the injury and subsequent sequelae [69].

Given that the vast majority of combat-related TBIs from the current wars in Iraq and Afghanistan are classified as mild [68], the relation between TBI severity and suicidality must be carefully considered in order to fully appreciate the potential implications for health management of returning military personnel and veterans. Although causal attribution cannot be drawn from correlational studies, the possibility that such an association exists between combat-related concussion and suicide has extremely important implications for mental health screening and suicide prevention efforts given the relatively high incidence of history of concussion in returning military personnel (estimated to be between 5% and 20% of service members in deployed units [68]). Future attempts to further explicate the complex relation between concussion and suicide must take into account the various shared risk factors between TBI and suicidality (e.g., young age, male gender, substance abuse, aggression/impulsivity) to determine the extent to which concussion uniquely contributes to suicide risk [71].

TBI Behavioral Comorbidities

Aggressive Behavior

Aggressive behavior following TBI complicates rehabilitation [72], is a concern for caregivers [73], and has been associated with lower psychosocial functioning 10 years following injury [26]. The reports of prevalence and frequency of aggression following TBI differs based on definition/severity of TBI, definition and assessment of aggression, reporting period, reporter (self, caregiver, staff), sample, and timing of assessment. Aggression following TBI may be expressed as agitation [72, 74], intimate partner violence [75, 76], suicide attempts [77], sexual violence or sexual disinhibition [78, 79], verbal aggression [80], or physical aggression [81]. As in the general population, verbal aggression typically is more frequent than physical aggression [79, 80]. The frequency of aggression following TBI has ranged from 11% to 96% based on the form of violence and the assessment instrument used (as reported in [82]). Using the Overt Aggressive Scale (OAS, [83]), Tateno and associates [82] found that 33.7% of patients with TBI compared to 11.5% of patients without TBI reported aggressive acts in the 6 months following their injury. Using the Overt Aggression Scale—Modified for Neurorehabilitation (OAS-MNR, [84]), Alderman [81] reported 5548 episodes of aggression perpetrated by 108 patients with severe neurological damage over 14 days on an inpatient unit. The authors noted that the episodes were triggered by staff prompts or erupted with no apparent provocation. Using the OAS, Baguley and associates [85] reported that rates of aggression among patients with moderate-to-severe TBI fluctuated over the 5 years following injury, but that at any given time, approximately 25% of patients with TBI were expressing "severe" aggression. Similarly, among individuals who survived severe TBI and were followed for 3 years, 55% of those whose injury occurred *more than* 18 months ago had verbal or physical aggression as reported by family members compared to 13% of those whose injury occurred *less than* 18 months ago [73]. Thus, frequency and severity of behavioral problems (aggression and other problems) were not related to the time since injury or the severity of head injury, respectively. Using the Buss Perry Aggression Scale (BPAQ, [86]), Dyer and associates [80] compared a sample of participants with TBI to those with spinal cord injury (SCI) and those without injury on measures of anger, aggression, and impulsivity

10 years following injury. Participants with TBI (severity not specified) reported more impulsivity, anger, and verbal aggression than those with SCI. When caregiver's reports were used, participants with TBI were also rated as more verbally aggressive than those with SCI. TBI has also been associated with anger and aggression among forensic samples. Slaughter and coauthors [87] randomly selected 69 inmates of a county jail of whom 87% reported a lifetime history of TBI (67% mild, 33% moderate/severe) and 36% reported a TBI (80% mild, 20% moderate/severe TBI) in the past year. Based on the Brief Anger and Aggression Questionnaire (BAAQ, [88]), more extreme anger and aggression were reported by those with TBI than those without. Similarly, using the index offense of record, Brewer-Smyth and coauthors [89] found that women incarcerated for a violent crime had more TBIs with loss of consciousness in their lifetimes than those incarcerated for a nonviolent crime; however, only one participant convicted of a violent crime reported severe brain injury.

TBI and potential links to aggression have been examined among military samples; Vietnam veterans with TBI from penetrating brain wounds reported more aggression and violence than those without TBI [90]. At the time this chapter was written, the association between TBI and aggression had not been examined systematically among military personnel serving in Operation Enduring Freedom and Operation Iraqi Freedom, but the consequences of TBI are a concern, given the proliferation of improvised explosive devices (IEDs) used in these conflicts. Among the personnel serving in Iraq, it is estimated that approximately 11% meet the criteria for mTBI through surveys [91]. In a similar vein, among a sample of 2525 Army infantry soldiers serving in Iraq, Hoge and coauthors [38] reported that 4.9% reported loss of consciousness and 10.3% reported altered mental status. Although survey data provide clues about the possible scope of the problem, survey reports of TBI symptoms and criteria are not necessarily confirmed by a clinical assessment and, therefore, may not accurately estimate prevalence by overestimating it.

Aggression following TBI often co-occurs with other postinjury psychiatric and psychosocial issues, such as anger [80], hostility [77], impulsivity [80], depression [85], PTSD [92], and substance abuse [26]. Though premorbid factors, such as alcohol use, may influence the presence (TBI versus no TBI, [77]) and etiology (i.e., whether due to violent or nonviolent causes, [93]) of TBI, these factors seem to be less predictive of postinjury aggression than the other postinjury psychosocial issues. For example, in a 5-year follow-up study, age and depressive symptoms, as rated with the Beck Depression Inventory [94], were the only factors that predicted aggression at 6-, 24-, and 60-month follow-up [85].

Impulsivity

Impulsivity and substance use, specifically alcohol use, have been associated with a variety of violent acts and are thought to be associated via shared biological substrates or altered social information processing [95, 96]. The comorbidity may also be an artifact of the diagnostic criteria for psychiatric disorders, which may include irritability, anger, impulsivity, and aggression [97]. Given these similarities, it is unclear what distinguishes TBI aggression from that observed among noninjured individuals and consequently what novel aspects for TBI-aggression treatment would need to be considered. Because TBI involves lesions to the brain, usually in the frontal lobes, it is possible that specific executive function deficits experienced by individuals with TBI and aggression may provide clues to understanding the phenomenology and treatment of this behavioral problem. Group differences on executive deficits have been examined among individuals with TBI based on the etiology of their injury (violent versus nonviolent), with results suggesting that premorbid factors, and not the nature of injury, influence the outcome following TBI [93, 98]. In a study of sex differences in executive functions among individuals with TBI, women outperformed men on neuropsychological assessments, but demographics (e.g., gender, minority status, education), premorbid history (e.g., history of illicit drug use), and factors related

to the injury (e.g., cause of injury, length of coma) were most predictive of neuropsychological functioning among men and women [99]. When comparing men with and without TBI who were receiving court-ordered treatment for intimate partner violence, men with TBI had poorer executive functioning and lower postinjury IQ than the non-TBI batterers [76]. Underscoring the importance of considering premorbid differences, these studies do not yet definitively establish how executive functions may be associated with aggression post TBI.

Orbitofrontal regions have been associated with alterations in behavior, including impulse control, since reports of the prototypical patient with frontal injury, Phineas Gage [100, 101]. Studies specifically of impulsive aggression among individuals with TBI suggest associations with lesions of the ventromedial prefrontal cortex [102] using neuropsychological testing sensitive to this region (e.g., Revised Strategy Application Test). One difficulty in generalizing subtypes of aggression and their relationship to neuroanatomical underpinnings from the extensive literature on aggression in TBI is that impulsivity and impulsive aggression are often equated, whereas, at least in highly impulsive individuals with antisocial behavior, the degree of impulsivity does not itself distinguish those with predatory versus impulsive aggression, but the existence of language impairments and parietal electrophysiological processing differences did distinguish them [103, 104]. This research suggests that impulsivity alone is not sufficient to cause an individual to become impulsively aggressive, and it is likely that additional deficits that may be associated with TBI are important to this condition. Initial work in long-term survivors of severe TBI with impulsive aggression did not demonstrate these specific neuropsychological abnormalities, suggesting that there may be alternative pathways to impulsive aggression [105]. However, in this study, premorbid functioning was associated with impulsive aggression, suggesting that it may be difficult retrospectively to delineate the specific contribution of the TBI to the behaviors of interest.

Treatment of Behavioral Disorders Following TBI

Treatment of behavioral problems following TBI, including impulsive aggression, a hair-trigger response to a threat with a behavioral loss of control [106], has been recently reviewed by Warden and coauthors [107]. This and earlier reviews of therapy (e.g., [108]) demonstrate a paucity of large randomized trials that address behavioral outcomes. While there is little in the way of large randomized, long-term trials specifically in TBI patients to recommend most therapies, promising research implicates certain pharmacological approaches, such as beta-adrenergic-receptor-blocking agents. Other potential agents, in which most work has involved aggression in other conditions but with some support following TBI, include anticonvulsant agents such as carbamazepine and valproic acid [108]. Phenytoin shows a very specific benefit in reducing the severity and frequency of impulsive aggression acts [103, 104, 106], although this work was in patients with no evidence of past symptomatic TBI and with a normal EEG. It remains to be studied whether this work will translate to patients post TBI. As with all of these agents, a thorough understanding of their side effects is necessary to tailor individual assessments of risk and benefits.

Treatment recommendations of behavioral disorders in TBI patients generally involve targeting symptoms, such as attention, mood, and psychotic symptoms. Evidence on effectiveness in the treatment of other psychiatric disorders occurring in the TBI patients is similarly limited, but general treatment recommendations include agents shown to be beneficial in these conditions in non-TBI patients, including selective serotonin-reuptake inhibitors and anticonvulsants as well as nonpharmacological, behavioral therapies [107, 109]. There is currently great interest in the possibility of treatment of PTSD in combat veterans using the adrenergic agent, prazosin [110]. Benefit for nightmares was initially suggested, although a recently published randomized clinical trial failed to demonstrate medication efficacy [111].

There are several reviews addressing the efficacy of treatments for persistent postconcussion symptoms of mTBI (e.g., [112–114]), although there are few well-designed studies. Treatments following mTBI vary depending on factors, such as time since injury and the symptoms experienced following the event. In general, mTBI treatments can be viewed as falling into one or more of the following four categories: cognitive behavioral therapy, cognitive remediation, pharmacotherapy for symptom-based management, and education and support, depending upon the symptoms present. While the TBI symptoms may need to be monitored and treated, it is fortunate that psychotherapy for psychiatric disorders, such as PTSD, is effective for those with and without comorbid mTBI [115]. We present a basic treatment algorithm (Fig. 1) that describes mTBI interventions, both for symptom reduction and prevention of postconcussion symptoms, for military personnel and veterans at various time points postinjury. This model assumes the presence of unit and military medical personnel who are familiar enough with injury severity characteristics to assist in classifying a suspected mTBI (Fig. 1).

Individual- and population-based mTBI screening instruments, such as the Standardized Assessment of Concussion [116] upon which the more recent Military Acute Concussion Evaluation is based [117] and the Brief Traumatic Brain Injury Screen [4], have shown promise, although verification of the diagnosis through follow-up clinical interview is still necessary due to false-positive errors (e.g., [118, 119]. As described earlier in this chapter, consensus criteria for concussion/mTBI are available to improve diagnostic accuracy [120, 121]. Once the diagnosis has been verified and the specific symptoms have been detailed through clinical interview, symptom management and work restrictions should be considered, with the goals being to maximize functional recovery [122]. While these first two aspects of treatment are meant to reduce the immediate impact of mTBI, the third component of treatment is aimed at reducing the subsequent development of postconcussive symptoms. It is during this period of time shortly following mTBI that psycho-education has been determined to be the most effective for the purpose of reducing subsequent postconcussion symptoms [112]. However, it is important to note that in the World Health Organization (WHO) review of mTBI interventions, no treatments were found to provide clinically important effects on symptoms or disability, although there was some evidence to suggest that early education and limited support (e.g., information about common complaints and the likelihood for a good outcome) as to the effects of mTBI may reduce future symptom complaints [112]. This approach of intervening after exposure to a trauma in order to reduce the likelihood of future maladjustment has also met with success in the management of PTS symptoms in military personnel following combat deployment [123].

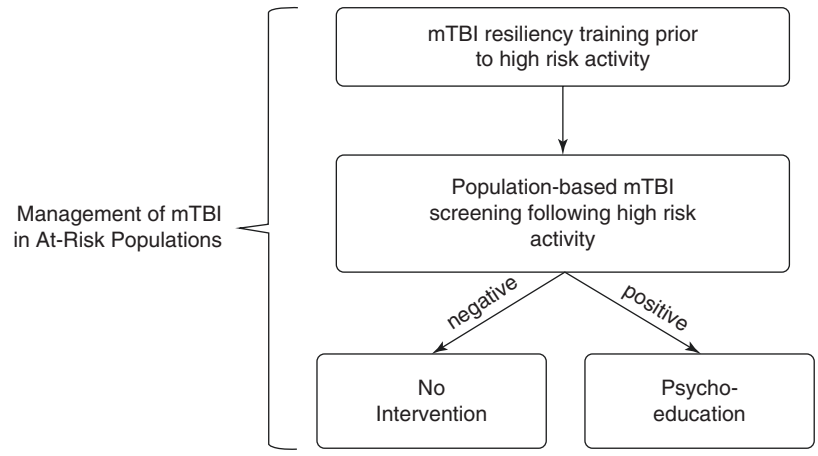

Fig. 1 Management of mTBI during acute recovery. The treatment algorithm for the management of mTBI during acute recovery is based on earlier work by Mittenberg et al. [123], Paniak et al. [126], and others who have demonstrated the effectiveness of brief interventions for reducing the severity of symptoms following mTBI

Based upon their research regarding misappraisal of symptoms in mTBI patients (see above), Mittenberg and coauthors [124] developed an effective, brief 1-hour educational intervention. The effectiveness of this intervention in decreasing later postconcussive symptoms was demonstrated in 58 consecutive mTBI hospital admissions (GCS $\geq$ 13, Galveston Orientation and Amnesia Test score >75, no significant extracranial injuries). Half of the patients were randomized into a treatment arm during which time they met with a therapist to discuss symptoms for approximately 1 hour and were provided with educational materials. The other patients received routine care and were provided with written discharge instructions that were verbally reviewed by a nurse. Six months after admission, mTBI patients in the treatment arm reported reduced symptom duration (33 days versus 51 days) and a lower number of postconcussive symptoms (1.6 symptoms versus 3.1) relative to the patients who received the standard of care [124, 125]. More recently, psychoeducation and support provided via telephone calls (four calls at 2, 4, 8, and 12 weeks postinjury) were also shown to be effective at reducing postconcussive symptoms 6 months post-mTBI relative to standard emergency room care (e.g., instruction handout) [126]. The relative benefit of the follow-up telephone calls is difficult to determine due to the design of the study, although the results of other mTBI intervention studies indicate that more than one treatment session may not have an added benefit [127, 128].

Diagnostic criteria have also been developed to identify those individuals who experience an abnormal persistence of postconcussion symptoms following mTBI. The International Classification of Diseases, Tenth Revision, criteria include a history of TBI and the presence of three or more of the following eight symptoms: headache, dizziness, fatigue, irritability, insomnia, concentration difficulty, memory difficulty, and intolerance of stress, emotion, or alcohol [129]. Boake and colleagues [130] noted that the prevalence of diagnosed postconcussion symptoms was higher 3 months post injury using the ICD-10 criteria (64%) relative to the DSM-IV-TR criteria (11%) in a sample of 178 adults with mild-to-moderate TBI, although both criteria showed poor specificity when tested with a control sample of 104 adults with extracranial injuries. The authors noted that the nonspecific ICD-10 PCS criteria likely contributed to the higher diagnostic rates using that classification scheme, while the lack of specificity demonstrated by both classification schemes was due to frequent endorsement of symptoms by patients without cranial injuries. While the DSM-IV-TR proposed criteria for the diagnosis of postconcussion disorder, the DSM-5 subsumes persisting postconcussion symptoms under the diagnosis of Mild Neurocognitive Disorder due to Traumatic Brain Injury. Injury severity in the DSM-5 framework is loosely based on traditional injury severity characteristics (e.g., LOC, PTA, GCS score), whereas any neurocognitive symptoms, to include postconcussion symptoms, temporally linked to the TBI and persisting beyond the acute postinjury period would be captured as a neurocognitive disorder (NCD). It should be noted that "acute postinjury" is not defined within the DSM-5. While the DSM-5 indicates the "severity of the TBI itself does not necessarily correspond to the severity of the resulting neurocognitive disorder," this is generally inconsistent with extant mTBI literature as well as an indication within the DSM-5 that "neurocognitive symptoms associated with mild TBI tend to resolve within days to weeks after the injury with complete resolution typical by 3 months." The DSM-5 does acknowledge that there are overlapping symptoms between neurocognitive disorder due to TBI and PTSD, including postconcussion symptoms, thus increasing the clinical challenge in considering the differential diagnosis.

For military personnel who subsequently develop postconcussion symptoms, the U.S. Department of Veterans Affairs and Department of Defense recommend a combination of both psychoeducation and symptom management (Fig. 2) [131]. The effectiveness of this treatment paradigm, especially the provision of psychoeducation to veterans who may be several years post injury, has yet to be determined. From a theoretical standpoint, it may be possible that

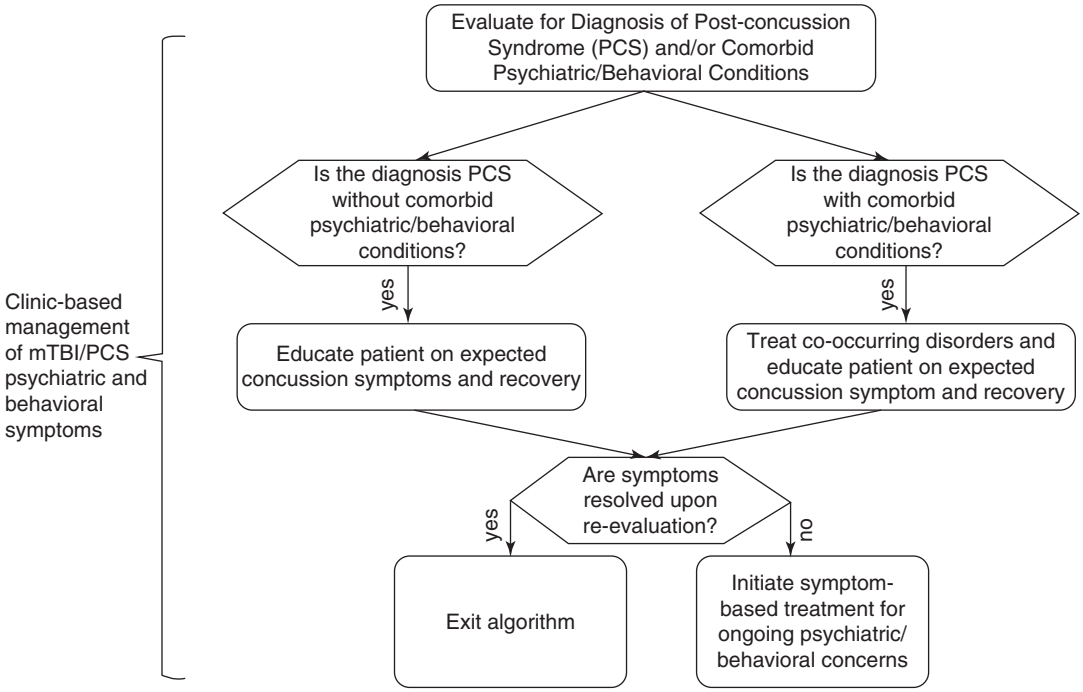

Fig. 2 Management of PCS. The treatment algorithm for the management of PCS is designed in part after the treatment recommendations offered by the U.S. Department of Veterans Affairs and Department of Defense [131]

allowing postconcussion symptoms to develop without early education allows patients to develop resistance to subsequent attempts at reducing postconcussion symptoms through education. That is, once erroneous expectations about consequences of mTBI are left unchecked for many months or years post injury, patients may be reluctant to consider other causes of their symptoms. There may be some benefit to early psychoeducational intervention for military personnel prior to deployment in that education at this level may provide resiliency in terms of subsequent development of postconcussion symptoms following mTBI. More recently, the U.S. Army implemented the Comprehensive Soldier Fitness (CSF) program, designed to increase the psychological resilience and reduce the incidence of maladaptive responses among U.S. Army soldiers [132]. While this training does not appear to directly address TBI and mTBI sequelae, it is possible that some benefit may be seen in terms of the shared PTSD-postconcussion symptoms as the CSF is multifaceted and, among other goals, works to both increase resilience to combat-related stress and also inform soldiers about the psychological consequences of combat exposure to include both PTSD and posttraumatic growth [133]. At present, there are no studies addressing the effectiveness of predeployment resiliency training to include the more recently implemented CSF. We believe, however, that such resiliency training is a natural extension of the literature and is meant to augment, rather than replace, psychoeducational interventions that should occur immediately after a service member sustains an mTBI.

Epidemiology and Classification of mTBI with a Focus on Symptoms

Approximately 70–90% of head injuries are classified as mild in nature [134, 135]. Incidence rates of mTBI in the civilian population, however, are widely considered to be underestimated, since approximately 25% of individuals suffering an mTBI do not seek medical attention [136]. As with moderate-to-severe TBI, the rate of mTBI is

greatest in males and young adults, and the most common mechanisms include motor vehicle accidents and falls [137]. Similar to the civilian population, the majority of military TBIs are mild. In fact, the incidence of mTBI in contemporary warfare may be on the rise due to the prevalent use of explosive munitions (i.e., IEDs and mines). In one study, 22.8% of soldiers returning from the Iraq War were noted to have a history of at least one mTBI during deployment, most of which were mild in nature [138]. It is estimated that by 2008, as many as 300,000 soldiers had suffered an mTBI in the wars in Iraq and Afghanistan [68], although this may be an inflated estimate based on the lack of validity of the diagnostic criteria used to derive the approximation [139]. These issues are important to address as the definitions and context affect our understanding of the psychological and psychiatric effects of TBI.

Characterization of the psychiatric comorbidities of mTBI is complicated by the lack of uniformity in the definition of mTBI [136]. The diagnosis of mTBI is based on the assessment of acute injury severity characteristics immediately following an injury to the head resulting from blunt trauma and/or acceleration or deceleration forces. Most contemporary mTBI classification schemes require a period of impaired consciousness (including loss of consciousness), memory dysfunction for a period of time surrounding the injury (i.e., retrograde or posttraumatic amnesia), or neurological or physiological dysfunction (e.g., seizures, lethargy, and vomiting) proximal to the time of injury. In order to create a clearer boundary between those with mild versus those with moderate-to-severe TBI, the American Congress of Rehabilitation Medicine (ACRM) consensus group suggested that those with mTBI experience a loss of consciousness of no greater than 30 minutes, experience a posttraumatic amnesia of no greater than 24 hours, and should have a Glasgow Coma Scale (GCS) score of 13 or greater within 30 minutes after their injury. The ACRM definition of mTBI has gained traction in the research and clinical community over the last 15 years and has been adapted by other health agencies [136]. Within the field of psychiatry and psychology, the DSM-5 modeled its set of TBI criteria on the ARCM definition described above. TBI and its neuropsychiatric sequelae are addressed principally within framework of the Neurocognitive Disorders.

Although general consensus has been reached regarding the diagnostic criteria for mTBI, several shortcomings of the diagnostic system have been identified. Without direct observation from trained bystanders or emergency medical technicians, there is no way to verify that the minimal criteria for mTBI were present at the time of the injury (i.e., brief period of altered mental status). Despite the apparent fallibility of relying on retrospective, self-reported changes in mental status to establish a history of mTBI, this is considered standard practice in diagnosing mTBI [140, 141] and has been recommended by the Centers for Disease Control in cases of nonmedically attended TBI [136]. Additionally, alcohol and recreational drugs present at the time of injury or therapeutic drugs administered in the immediate postinjury period can cause alterations in consciousness and perturbations in autobiographic memory, all of which can be mistaken for injury-related alterations in mental status [141].

Diagnosing a history of combat-related mTBI presents even greater challenges. First, a brief period of altered mental status may go unreported in the middle of life-threatening events like close proximity to a detonated IED, an event that has been exceedingly common during the Iraq and Afghanistan conflicts [138, 142]. Second, symptoms related to mTBI may be overlooked in the presence of other combat-related injuries that require immediate medical attention (e.g., traumatic amputations, lacerations, and burns). These first two diagnostic issues would result in an underidentification of a history of mTBI. Third, common diagnostic criteria with reasonable specificity in the civilian population, such as feeling dazed or confused, may result in insufficient levels of specificity when applied to injuries incurred during combat deployments. Conversely, a brief period of confusion or disorientation may represent a psychological reaction to an unexpected, highly stressful event rather than a mani-

festation of underlying brain injury. The third diagnostic issue would, thus, result in an overidentification of a history of mTBI.

Because of the definitional issues and difficulty of assessing for TBI criteria immediately postinjury, many studies evaluating the impact of mTBI have had widely different findings (e.g., [143, 144]). For example, many people do not seek treatment following mTBI as there is a likely perception that mTBI will have few meaningful consequences. This sharply contrasts with the established and adverse consequences that are associated with moderate-to-severe TBIs. For those patients that do seek emergent care, a GCS may be obtained, but this instrument is not suited to assess the more subtle cognitive changes that are likely to occur following an mTBI [145]. In both clinical and research settings, comprehensive neuropsychological evaluations in the period following mTBI are typically not undertaken, and even fewer evaluations are likely to occur at more distal time points. For this reason, comparatively less is known about the impact that mTBI has on neuropsychological functioning relative to moderate-to-severe head injuries. Even the most promising prospective studies are often hampered by significant selection biases (i.e., oversampling from emergent care settings and attrition in longitudinal designs), less effective use of appropriate controls, and not controlling for potential confounds [146].

Despite these limitations regarding mTBI, there are several tenets that can be drawn from the literature, and we address these below.

Tenets of Mild Traumatic Brain Injury

mTBI Tenet 1: Injury Severity Is Related to Outcome

In a series of widely recognized studies [147, 148], it was demonstrated that both cognitive and functional outcomes following head injury are related to severity of TBI, with mTBI having better outcomes and severe TBI having the worst outcomes. The strength of these studies is that a large number of patients ($N = 436$), with various injury severities, completed assessments at 1- and 12-months post injury with minimal attrition. In addition to the within-subjects comparisons, their patients were also compared to a matched trauma control sample ($N = 132$) also evaluated at 1-month and 1-year post injury. Patients with a history of TBI increasing in severity from moderate to severe, as measured by increased time to follow commands (the motor score from the GCS), had an incrementally greater chance of having more widespread and persisting neuropsychological and functional impairments 1 year post injury. Among patients with a history of mild head injury (time to following commands <1 hour), however, baseline performance on neuropsychological testing was similar to trauma controls at 1 month [147], and the vast majority were noted to experience good psychosocial outcomes 1 year post injury [148].

mTBI can occur in the context of other factors such as positive CT findings (e.g., "complicated mTBI" [focal brain lesion, skull fracture, etc.]), and this may further cause difficulties in recovery. In keeping with the inverse relationship between injury severity and outcome, patients with a history of complicated mTBI appear to have poorer cognitive function within the first month following mTBI than patients with uncomplicated mTBI [149]. Kwok and coauthors [150] evaluated complicated mTBI patients ($N = 31$) with GCS scores ranging from 13 to 15 with abnormal CT scans (skull fractures, hematomas, subarachnoid hemorrhage) and found persisting impairments in attention at 3 months. The performance of patients with a history of complicated mTBI has also been compared to the performance of patients with a history of moderate TBI. In this study, patients with a history of complicated mTBI ($N = 102$) and moderate TBI ($N = 127$) underwent neuropsychological testing at discharge from a rehabilitation facility and after 1 year. At both time points, there were noteworthy similarities between the mTBI and moderate TBI groups, with mTBI patients evidencing less severely impaired cognitive processing speed. Both groups were also noted to have incomplete recovery in functional status at the 1-year fol-

low-up visit, with no differences found between the groups [151]. There remains some debate as to whether complicated and uncomplicated mTBI patients should be pooled together in studies, or if those with complications should be viewed as a separate diagnostic group.

mTBI Tenet 2: Symptoms Immediately Following an mTBI Are Varied and May Occur Across Cognitive, Physical, and Affective Domains

Self-report symptom inventories (e.g., Rivermead Post-Concussion Symptoms Questionnaire [RPQ], Standardized Assessment of Concussion [SAC], etc.) have been utilized in the period following mTBI and in a variety of different settings [152–154] for review of various inventories). The most frequent subjective complaints following mTBI include headache, dizziness, irritability, poor concentration, fatigue, and memory loss, with the majority of symptoms resolving within 1 month [155, 156]. Across multiple factor analytical studies, these varied symptoms have been noted to load onto cognitive, physical, and affective clusters, although there is some debate as to whether a single factor that some label "concussion" better accounts for the symptoms [152, 157, 158]. A similar pattern of symptoms has also been described in the sports concussion literature, with headache, dizziness, sensitivity to light, and cognitive difficulties (e.g., slowed cognitive processing speed, memory difficulty) reported in the period following mTBI [156].

mTBI Tenet 3: The Vast Majority of mTBI Patients Will Experience Full Cognitive Recovery Within 3 Months

It is generally accepted that among patients sustaining an mTBI, the majority of symptoms resolve during the first week following the injury, with nearly complete resolution of most symptoms for most patients occurring within the first 3 months following the injury [159–161]. Consistent with this, the WHO has concluded the best evidence suggesting: "there are no mTBI-attributable, objectively measured, cognitive deficits beyond 1–3 months post-injury in the majority of cases" [146]. The WHO based their conclusions on a critical review of the literature and parallels the findings from meta-analytic studies evaluating patient performance on cognitive testing following mTBI. Binder and coworkers [143] included studies evaluating the cognitive functioning in adults (11 studies, 314 patients, 308 controls) at least 30 days following mTBI. The overall effect size of cognitive deficits was significant but small (d = 0.18), although a more conservative g statistic was notably smaller and not significant (g = 0.07). Patient performance on cognitive testing was further analyzed using neuropsychological domains of attention, memory acquisition, and performance skills (only three domains were examined across enough of the studies to allow for meaningful analyses). Among these three, only attention emerged as impaired following mTBI with a small effect size (g = 0.17). The authors also found it worthwhile to determine the positive and negative predictive values (PPV and NPV) of neuropsychological testing in patients with mTBI in the reviewed studies, as the detection of more subtle cognitive difficulties is more difficult than obvious neurological impairments. Given the low prevalence of persisting attention impairments based on their data (5%), the likelihood of accurately classifying mTBI with abnormal performance on cognitive measures, even with unrealistic sensitivity and specificity for the cognitive instruments (e.g., 0.9), was small at 0.32, and with smaller sensitivity and specificity test values, the PPVs continued to decrease. In contrast, the NPV of these cognitive measures was consistently high at all sensitivity and specificity levels (>0.98), suggesting much higher accuracy when diagnosing no persisting brain injury following mTBI based on neuropsychological measures.

More pronounced impairments in attention following mTBI have been reported in recent prospective studies (e.g., [150, 162]). Landre and coworkers [162] found mTBI patients (N = 37) to perform worse on measures of vigilance, attention, and memory relative to trauma patients (N = 32) approximately 5 days post injury. The effect sizes for these group differences were in the moderate-to-large range. Interestingly, both

mTBI and the trauma controls reported few concussion symptoms following their injury, and pain levels were controlled for and found not to be associated with cognitive performance in either group. That more pronounced cognitive impairments are found in some studies (e.g., [162]) but not others (e.g., [143]) may, in part, be related to the timing of neuropsychological evaluations relative to the onset of the head injury. For example, in the Binder and coworkers [143] meta-analysis, only studies evaluating cognitive performance 3 months post injury or later were included, whereas other studies may focus on patient cognitive performance within the first or second week following mTBI. Consistent with this, Schretlen and Shapiro [161] examined the effect of mTBI on cognitive performance across different time points post injury. In their meta-analysis, cognitive performance varied as a function of time, with a significant medium effect size reported among patients tested during the first 6 days post injury ($d = 0.41$, mTBI patients performing at the 33rd percentile of matched controls) and a smaller, but significant, effect size reported among patients tested 7–29 days post injury ($d = 0.29$). Patients tested 1–3 months post injury and after 3 months post injury demonstrated no differences from controls. Belanger and coworkers [163] demonstrated a similar finding, with small performance declines across seven of eight cognitive domains for mTBI patients evaluated acutely (<90 days) relative to those mTBI patients evaluated postacutely (≥90 days). Interestingly, in this meta-analysis, there was variability in performance across domains for those mTBI patients evaluated acutely, with the most pronounced effects of mTBI for delayed memory and verbal fluency.

Athletes may be a unique sample as they have extra incentive to have their symptoms improve quickly. In a large sample of college football players prospectively evaluated prior to mTBI and at several time points post injury, more severe symptoms were noted immediately following the mTBI and patterns of symptom recovery emerged as early as 3 hours post injury [164]. Within 7 days post injury, there were no differences relative to baseline scores or matched controls. It is important to mention that there are noteworthy differences between the general population and athletes evaluated in the sports concussion literature, as "motivation to return to play" in the latter may result in underreporting of mTBI symptoms. This likely explains the interesting finding that athletes report faster resolution of symptoms relative to those in the general population, as 85% of athletes reported full symptom recovery within 1 week and fewer than 3% reported symptoms beyond 1 month (see NCAA Concussion Study; [164]), in contrast to an appreciably higher proportion reported in the nonsports concussion literature (e.g., 8–33%; [144, 156, 165]).

mTBI Tenet 4: A Significant Minority of Patients Will Experience Persisting Postconcussive Syndrome Symptoms

It is important to note that individual patients may experience variability, both in terms of rate of recovery during this time period as well as between various symptom clusters [148, 156]. For a "significant minority," there may be mTBI symptoms that extend beyond the expected 3-month recovery period [143, 163]. The persistence of symptoms following mTBI is known as postconcussion syndrome (PCS) (e.g., symptoms persisting typically greater than 3 months post injury), although the nature and reasons for persistence of these symptoms is the source of much debate. The relationship between reported symptoms immediately following mTBI and persistence of postconcussion symptoms remains unclear, in part because there are few studies consistently and systematically evaluating these factors in the literature [146]. There is emerging evidence that suggests that PCS symptoms lasting longer than one year may be related to psychiatric factors as those discussed above rather than the head injury [49–51].

There is limited evidence to suggest that headache and dizziness in the emergency room and dizziness 2 weeks post injury may be predictive of persisting concussion symptoms [166, 167]. However, it is also important to note that many symptoms associated with concussion are also endorsed at high rates in other populations. Headache, fatigue, forgetfulness, frustration,

irritability, concentration difficulty, and sleep disturbance are among many overlapping symptoms reported at high rates and varying severity in college [168], claimant [165], adult control [169], and chronic pain populations [156, 170], although typically at lesser severity levels than those with mTBI within the first month postinjury [146]. In a landmark study that supports a cognitive-behavioral conceptualization for PCS etiology and informs current mTBI treatments, Mittenberg and coworkers [171] suggest that patients have preinjury *expectations* about mTBI symptoms and these, in turn, have the potential to become self-fulfilling. This was based on their finding that healthy adults endorsed symptoms they would expect to have 6 months following an mTBI at similar levels to patients with PCS (i.e., both reported similar levels of anxiety, depression, irritability, fatigue, memory difficulty). Additionally, when PCS patients were asked to estimate the same symptoms prior to their own injuries, compared to a healthy adult sample rating current symptoms, the PCS patients consistently reported fewer preinjury problems. Thus, it is hypothesized that PCS patients have expectations regarding TBI, which have the potential to form internal representations about outcomes. These representations have the potential to become self-fulfilling and may augment perceived intensity and frequency of PCS symptoms [126].

While postconcussion symptoms have been weakly linked to prognosis, multiple studies have demonstrated that compensation-seeking behavior is associated with persistence and severity of impairments as well as a delayed return to work and slowed recovery following mTBI [146, 172, 173]. Belanger and coworkers [163] found that, across studies, clinic-based samples including patients engaged in litigation were likely to have greater cognitive sequelae ($d = 0.74$ after 3 months) and that litigation was negatively associated with improvement of cognitive functioning over time. Conclusions related to the nature of this relationship are not addressed by correlative studies; the association could plausibly reflect more severe impairment independently leading to compensation seeking. Other moderating factors that have been less reliably related to PCS include being female, off-work due to injury, and a history of psychiatric illness. Prior psychiatric illness has also been identified as a risk factor for acute stress disorder following a motor vehicle collision, and this is, in turn, a predictor of the later development of PTSD [146].

mTBI Tenet 5: Neuropsychological Assessment Must Incorporate Both Performance Validity Test (PVT) and Symptom Validity Test (SVT) Measures

The importance of assessing respondent validity has been emphasized by the national boarding organizations of neuropsychology (e.g., the American Academy of Clinical Neuropsychology [AACN] and the National Academy of Neuropsychology [NAN]), with both organizations issuing position papers detailing the importance of including both stand-alone and embedded measures of symptom/performance validity in neuropsychological evaluations [174, 175]. It is important to note that studies have demonstrated how the potential for external incentives [172] and/or poor effort [176] can negatively influence the test results more than the extent of neurological involvement. Similarly, the influence of effort has also been shown to account for a significant portion of variance related to cognitive test performance in veterans reporting mTBI and PTSD symptoms [177]. This recommendation for PVT and SVT use should not be viewed as pejorative, as the use of these measures primarily informs the validity of the testing data rather than the intent of underlying test-taking behavior. It should also be noted that magnification of symptoms and/or PVT failure is not uncommon in the veteran population [178–182]. Given the nature of neuropsychological and psychological evaluations, which are used both to establish current functioning and inform optimal treatments, it is essential to draw on multiple sources of information, and this includes consideration of both PVT and SVT data.

Conclusion: Behavioral and Psychiatric Comorbidities of TBI

Extensive evidence associates TBI with psychiatric and behavioral sequelae. While the design of these studies makes it often difficult to differentiate symptoms based on severity of injury, premorbid deficits, and functioning from the contribution of the, it seems very likely that, at the minimum, TBI is a risk for accentuating premorbid behaviors [106], and individual cases indicate the potential for profound behavioral change [101]. The mechanism of these effects has not been examined, although changes in self-regulation and social information processing may result from neurological insult, psychiatric symptoms, or substance use. On the other hand, it is also conceivable that psychiatric disorder and TBI become difficult to distinguish from an epidemiological perspective, given that circumstances may put an individual at risk for both [38]. In this case, prospective studies and treatment interventions will be needed to identify the salient underlying disorders. Several research groups are pursuing a variety of imaging, neuropsychological, and treatment studies to identify characteristics that would contribute to this distinction. In the interim, it is important from a patient care perspective to identify treatable behaviors that are causing distress to the patients or those around them. While definitive evidence for efficacy is in many cases lacking, a number of reasonable suggestions or extrapolations from other conditions have been reported that provide a starting point to develop a treatment plan. However, lack of definitive evidence for efficacy or the possibility of a unique sensitivity to adverse events affecting TBI patients suggests that treatment should be approached with an appreciation for potential difficulties.

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