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Review

Emotion Dysregulation Following Trauma: Shared Neurocircuitry of Traumatic Brain Injury and Trauma-Related Psychiatric Disorders

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ABSTRACT

The psychological trauma associated with events resulting in traumatic brain injury (TBI) is an important and frequently overlooked factor that may impede brain recovery and worsen mental health following TBI. Indeed, individuals with comorbid posttraumatic stress disorder (PTSD) and TBI have significantly poorer clinical outcomes than individuals with a sole diagnosis. Emotion dysregulation is a common factor leading to poor cognitive and affective outcomes following TBI. Here, we synthesize how acute postinjury molecular processes stemming from either physical or emotional trauma may adversely impact circuitry subserving emotion regulation and ultimately yield long-term system-level functional and structural changes that are common to TBI and PTSD. In the immediate aftermath of traumatic injury, glucocorticoids stimulate excess glutamatergic activity, particularly in prefrontal cortex-subcortical circuitry implicated in emotion regulation. In human neuroimaging work, assessing this same circuitry well after the acute injury, TBI and PTSD show similar impacts on prefrontal and subcortical connectivity and activation. These neural profiles indicate that emotion regulation may be a useful target for treatment and early intervention to prevent the adverse sequelae of TBI. Ultimately, the success of future TBI and PTSD early interventions depends on the fields' ability to address both the physical and emotional impact of physical injury.

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THE MENTAL HEALTH CONSEQUENCES OF TRAUMATIC INJURIES

Each year, more than 50 million people worldwide experience a traumatic brain injury (TBI) (1,2). There is significant overlap in postinjury outcomes that result from the physical damage of TBI (e.g., white matter degradation, neuronal loss, neuroinflammation), the emotional response to the trauma, and the distress related to both physical and psychological symptoms of the TBI and injury event. This combination of physical and emotional trauma increases risk for both acute concussion and stress symptoms as well as the development of persistent postconcussion syndrome (PCS). Both physical and emotional trauma are associated with multiple chronic psychiatric conditions, including posttraumatic stress disorder (PTSD), major depressive disorder, general anxiety disorder, and substance use disorder (3–6). Regardless of previous psychiatric history, there is a markedly increased risk of psychiatric disorders after TBI (7), although previous psychiatric history has been shown to exacerbate psychological symptoms after physical trauma (8–10). One possibility for this heightened risk of psychiatric conditions and associated cognitive, behavioral, and affective outcomes is the presence of acute and chronic emotion dysregulation resulting from physical and/or emotional trauma following traumatic injury.

PTSD is of particular interest after injury because rates of PTSD are high, ranging from 8% to 40% depending on mechanism of injury (3). However, prevalence of comorbid PTSD and TBI is more difficult to estimate owing to numerous factors including, but not limited to, different sample types (civilian vs. military) and sizes, differences in mechanism of injury, and methodological differences in obtaining PTSD and TBI history. Still, a recent 2020 meta-analysis that combined military and civilian samples reported that 27% of those with TBI also met the criteria for PTSD, compared with only 11% without TBI who met the criteria for PTSD (11). Furthermore, the relative risk for PTSD following TBI for civilians and military samples was 1.2 and 4.8, respectively (11). A 2014 review further noted that prevalence of comorbid PTSD and TBI varied according to severity of TBI, with estimates ranging from 3% to 30% for civilian samples and 12% to 89% in military samples, where rates increased with severity of TBI (12). PCS can occur in addition to PTSD, with an estimated half of mild TBI cases also presenting with PCS symptoms (13). Up to 25% of individuals with TBI show persistent PCS symptoms 3 months after injury (i.e., chronic PCS) (14). Importantly, these prevalence estimates, regardless of sample or TBI severity, are significantly higher than the prevalence of PTSD in the general population (~9%) (11), suggesting a shared pathophysiology leading to common symptoms in PTSD and TBI.

Critically, posttraumatic stress symptoms in the acute postinjury window, or symptoms of acute stress disorder (ASD), have been found to be important markers of risk for

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not only nonremitting PTSD (15) but also chronic PCS. For those who experience a traumatic injury, ASD is more likely to occur alongside a mild TBI (mTBI) diagnosis (16). The presence of ASD following TBI also predicts greater severity of chronic PCS (8,10). Moreover, the relationship between PTSD and PCS symptoms becomes stronger as time since injury passes (10). The similarity in rates of PCS and PTSD after TBI is not surprising given the overlap in emotion-related symptoms, particularly hyperarousal (15,17). These findings suggest that acute injury- and stress-driven outcomes contribute to the emotion dysregulation that confers risk for chronic PTSD and PCS following TBI. In fact, this suggests that there are common neurobiological pathways underlying the regulation of emotions impacted by both the physical and/or psychological aspects of traumatic injury.

While the physical damage from TBI leads to an established array of symptoms (e.g., dizziness, confusion, memory impairments, irritability, fatigue, difficulty concentrating), the emotional reactivity to a traumatic event, whether ASD or general anxiety, can mimic many of the same symptoms (e.g., difficulty breathing, headache, stomach pain, nausea) (18,19). Therefore, it is difficult to disentangle the specific effects of the physical trauma of the head injury from the psychological consequences of the injury event (18). However, the combination of PTSD and TBI appears more impactful or more deleterious than the effects of PTSD or TBI alone. Still, it remains unclear whether coexisting PTSD and TBI (this comorbidity is subsequently referred to as PTSD+TBI) produces an additive or multiplicative effect of dysregulation on shared emotion regulation neurocircuitry. Unpacking the neural effects and concurrent behavior of PTSD+TBI is of great clinical importance. Studies on clinical outcomes suggest that a comorbid diagnosis of PTSD+TBI worsens outcomes significantly more than the outcomes associated with a single diagnosis (20). For example, veterans diagnosed with PTSD+TBI are at an elevated risk of suicidality compared with veterans with PTSD only (21,22). The impact of PTSD+TBI is also evident when examining the rates of PCS; those with PTSD have greater PCS symptoms after experiencing an mTBI than those without PTSD (23).

In service of understanding co-occurring and interactive post-TBI outcomes, we review evidence that the shared aspects of persistent cognitive and affective effects in PTSD and TBI arise from molecular changes within emotion regulation circuits. We focus on both injured military personnel and civilians, particularly for non–sports-related traumatic injury. In both of these populations, the prevalence of PTSD and severity of symptoms suggests that the long-term structural and functional neural effect of PTSD+TBI is greater than the effect of either of these diagnoses alone. Indeed, similarities in symptoms of TBI and PTSD may be the result of overlapping disruption at the neural level of emotion regulation networks (12). Finally, we highlight the need to incorporate assessment of emotion dysregulation alongside evaluation of TBI-specific symptoms.

POSTTRAUMA EMOTION DYSREGULATION: A COMMON FRAMEWORK

Although reactions to traumatic injury vary across individuals, emotional responses can range from confusion, sadness, and anxiety to dissociation, depression, and blunted affect (19). One framework shared by research on TBI and trauma-related mental health outcomes involves the role of emotion regulation and the aberrations in brain regions critical for emotion regulation (Figure 1). Emotion regulation broadly refers to complex

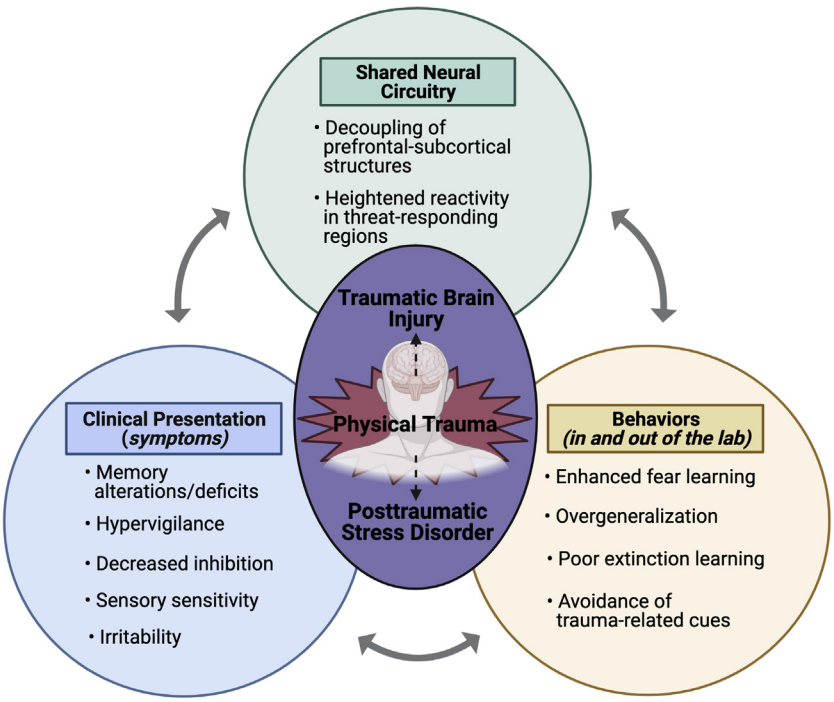

Figure 1. An overview of emotion dysregulation in posttraumatic stress disorder and traumatic brain injury: shared clinical presentations, behaviors, and neural circuitry. Figure created with BioRender.com.

processes underlying how an individual experiences and expresses emotions (24,25). There is significant overlap in the clinical presentation, behaviors, and neural consequences of PTSD and TBI, many of which can be conceptualized as aspects involving or resulting from emotional dysregulation. Dysregulation may represent poor bottom-up processing of emotionally relevant information (e.g., problems with detecting emotions) or maladaptive top-down control of emotions (e.g., difficulty engaging an appropriate coping strategy) (24,25).

Multiple aspects of emotion dysregulation have been linked with chronic poor outcomes of both TBI and non-TBI trauma. Indeed, two of the defining symptom clusters of PTSD involve emotion dysregulation (i.e., re-experiencing/intrusive thoughts and memories, cognitive and emotional avoidance of trauma reminders) (26). Similarly, in addition to physical and physiological symptoms, TBI is often accompanied by changes in mood and cognition (i.e., increased irritability and decreased inhibition), both of which are associated with regulation of emotion (12). Shared behavioral presentations of PTSD and TBI include enhanced fear learning, fear generalization, and avoidance of trauma-related reminders (27–29). We posit that these behavioral profiles are driven by changes in emotion regulation circuitry (reviewed below).

The neural bases of emotion and emotion regulation have been well established and involve both cortical and subcortical brain regions [for review, see (30–33)]. Briefly, motivational features of an emotional stimulus engage primarily subcortical regions, including the amygdala, hippocampus, striatum, periaqueductal gray, and ventromedial prefrontal cortex (PFC) (31,33). Implicit and explicit (i.e., with or without conscious effort) emotion regulation involves complex bidirectional relationships among PFC-subcortical circuitry (25,31). For instance, threat detection and monitoring, which is heightened in PTSD (33), involves deficient cortical modulation of subcortical structures (i.e., inhibited anterior cingulate cortex [ACC] and reduced PFC modulation of amygdala, striatum, and periaqueductal gray) (25,31). Subsequent adaptive conscious reappraisal of threat is achieved through increased modulation of the ACC and PFC over limbic regions (25,30,34). Collectively, subcortical structures subserving emotional response and PFC regulation of response form the core circuitry for emotion regulation. Molecular changes resulting from physical and/or emotional trauma directly impact emotion regulation circuitry, giving rise to the shared emotion dysregulation features of PTSD and TBI.

ACUTE STRESS-RELATED MOLECULAR CHANGES IMPACT EMOTION REGULATION CIRCUITRY

Studies of the acute effects of both noninjury trauma and TBI suggest that a cascade of molecular changes in stress and emotion regulation circuitry (reviewed in Figure 2) may have long-term adverse consequences for this circuitry, increasing risk for PTSD and PCS (35). In this regard, work on the role of neurotransmitters and hormones released through the hypothalamic-pituitary-adrenal (HPA) axis in traumatic injuries has been informative. Briefly, the HPA axis regulates responses to stress by altering levels of neuroendocrine and neural signaling [for review, see (36)]. Poor trauma outcomes are associated with dysregulation of homeostatic HPA func-

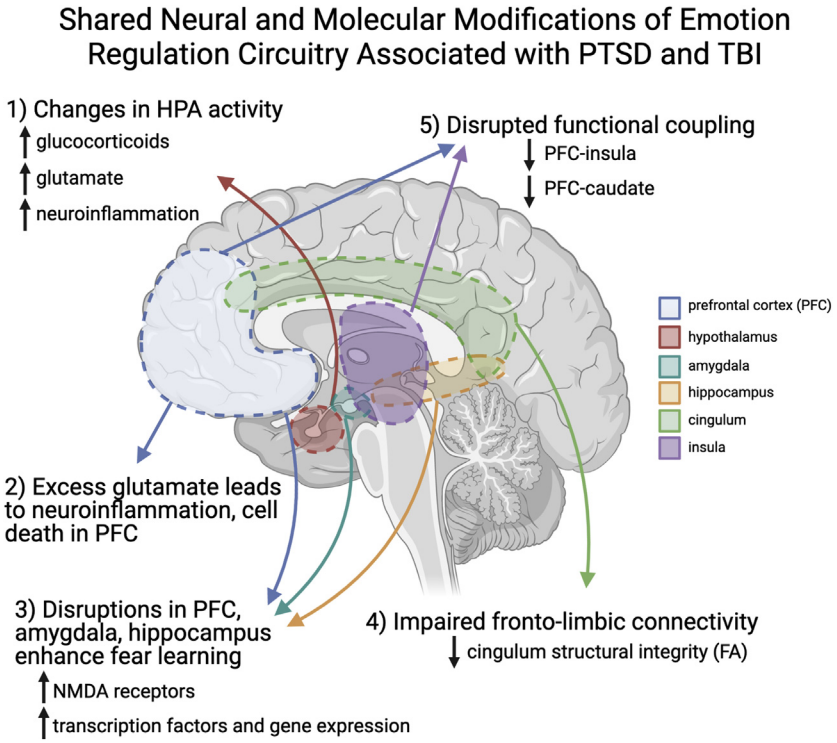

Figure 2. An overview of the shared neural and molecular modifications associated with posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI). Figure created with BioRender.com. FA, fractional anisotropy; HPA, hypothalamic-pituitary-adrenal.

tioning (37). TBI causes an initial surge in glucocorticoids (36,38), followed by continued HPA dysregulation that interferes with adaptive responding to stress (39–41). Over time, this abnormal stress responding is bidirectionally linked to neuroinflammation and worse psychiatric and neurocognitive outcomes after TBI (42).

The HPA axis also plays an important role in stimulating glutamate release following stress, which, if excessive, can adversely impact PFC-subcortical circuitry. Glucocorticoid activity following acute noninjury stress increases release of glutamate (43), especially in the PFC and hippocampus (35,44,45). Heightened glucocorticoid secretion (37,46) and excess glutamatergic activity are also evident acutely following TBI (47–49). Thus, similar glucocorticoid HPA-initiated glutamate release is evident immediately following both noninjury emotional stress and TBI. Moreover, administration of glucocorticoid receptor antagonists blocks this increased glutamate release and reduces anxiety and depressive behaviors (44,50). In addition, CB_1 receptor gating of glutamate, a mechanism reducing its release, has also been shown to blunt these adverse effects on PFC (51). Left unchecked, excess glutamate results in excitatory toxicity, including dendritic atrophy (52) and cell death (53), and inflammation (54,55) in the PFC and hippocampus. Together, these findings suggest that the acute posttrauma stress response following TBI activates this glucocorticoid-glutamate response, which contributes to prolonged distress and neurocognitive problems via its impact on circuitry shared by PTSD and PCS symptoms (56).

Preclinical models of TBI offer an opportunity to better explore how TBI impacts specific emotion regulation behaviors subserved by PFC-subcortical circuitry (57). The numerous molecular and cellular changes resulting from TBI [induced using different experimental methods; models reviewed in (58)] occur in expected subcortical structures, including the amygdala and hippocampus (58). Previous work using Pavlovian conditioning with rodents suggests that TBI broadly enhances fear learning, as evidenced by enhanced fear acquisition, greater generalization to fear-related stimuli, and impaired fear extinction (26,27). Consistent with the stress-induced dysregulation of glutamatergic activity detailed above, disruption of glutamate receptors also disrupts fear learning and memory (59). Importantly, these findings translate well to human work, indicating that TBI is associated with abnormal and heightened fear learning (60). Underlying enhanced fear learning are modifications to specific subregions of the amygdala and hippocampus. For example, TBI induces upregulation of the ionotropic NMDA glutamate receptors in subregions of the amygdala, which supports long-term potentiation, a mechanism by which fear learning and memories can be enhanced and strengthened (27). Additionally, upregulation of transcriptional factors (61) and gene expression in the canonical fear network, including the amygdala (62), PFC, and hippocampus, have been identified following TBI.

As reviewed here, there are common acute stress-induced molecular changes that occur as a result of physical injury and emotional trauma. These modifications appear to disrupt emotion regulation circuitry and alter fear learning and memory processes common to both PTSD and TBI. Although the bidirectional pathways in which TBI may contribute to PTSD+TBI comorbidity have not been fully elucidated, recent work suggests that modifications in sensory systems may create vulnerability to PTSD (63). Indeed, sensitivity to auditory cues and associated increased activation between sensory brain regions and the amygdala was significantly related to greater PTSD-like behavior in rats (63). How higher-order sensory systems may be impacted by TBI and PTSD and the mechanisms by which these systems influence symptoms is a promising direction for future research.

LONG-TERM OVERLAPPING NEURAL CONSEQUENCES OF TRAUMATIC INJURIES IMPACT EMOTION REGULATION CIRCUITRY

The chronic symptoms following TBI likely rest on shared impact of acute and persistent stress-induced molecular changes on emotion regulation neurocircuitry. Of note, there is a significant gap in this literature, because there are few structural and functional magnetic resonance imaging (fMRI) studies evaluating both TBI and psychological symptoms (i.e., PCS and/or PTSD) in either civilian or military samples. While a substantial body of work has examined resting-state fMRI aberrations in TBI along the severity spectrum (64–68), these studies often do not account for possible psychological symptoms that accompany TBI [e.g., (69)]. Similarly, studies in the PTSD literature often neglect to account for TBI (68,70,71), although a few have examined samples with only mTBI [e.g., (71,72)] or a history of head injury [e.g., (73)]. Exclusion of participants with moderate to severe TBI during recruitment is common in the PTSD literature, because TBI is expected to contaminate fMRI signal and analysis of PTSD-related neural processes [e.g., (69)]. Despite the sizable gap in this work, a comprehensive review of the few studies that have examined the overlap in the effects of PTSD+TBI using various neuroimaging techniques has been done previously (74). The commonalities in PTSD and TBI are apparent in brain structural morphology and functional connectivity (74–76). Here, we emphasize how the overlap in regions that underlie emotion regulation may relate to specific affective PTSD and TBI symptoms. Understanding the underlying neurocircuitry of symptoms for those with PTSD+TBI can guide clinical decisions related to treatment, particularly in the acute aftermath of traumatic injury (77).

Diffusion tensor imaging has revealed how the integrity of white matter tracts in the brain is impacted by TBI and PTSD. The majority of studies using diffusion tensor imaging have examined PTSD and TBI separately, although ultimately the findings highlight similarities (74). In both military and trauma-exposed civilian samples with mild to severe TBI, abnormalities in frontolimbic circuits, including cingulum fiber bundles, which connect the cingulate cortex to the hippocampus, have been reported (63,78,79). Although psychological symptoms were not considered in these samples, white matter pathology (decreased fractional anisotropy [FA], an index of structural integrity derived from diffusion tensor imaging) increased with severity of TBI (63,79). Similarly, there is a direct relationship between decreased FA of the cingulum bundles and PTSD symptom severity, as well as chronicity (78,80–82). Similar white matter abnormalities have been described in veterans with comorbid major depressive disorder, PTSD, and mTBI, with more significant decreases of FA in individuals with all

three diagnoses (83). Indeed, in veteran samples, widespread decreases in cerebral white matter FA, particularly in the cingulum, are pronounced in those with both mTBI and PTSD compared with those with only mTBI or PTSD (84,85). Furthermore, in a veteran sample, the number of regions with reduced white matter FA mediated the relationship between mTBI and PCS symptoms (86). The cingulum bundle has been implicated in attention modulation of emotion and memory (78). Therefore, reduced integrity of this frontolimbic pathway may lead to aberrant emotion regulation and memory functions (i.e., hyperarousal, intrusive memories, overgeneralization of fear to trauma-related stimuli), affective symptoms common to both PTSD and TBI (78,87). Collectively, these findings demonstrate that white matter integrity, specifically in frontolimbic circuitry that supports emotion regulation, is not only altered by TBI alone as a result of physical injury but also impacted by and affects the development of psychological symptoms following injury. Still, more longitudinal research is needed to truly determine how white matter integrity reduction, most notably in frontolimbic pathways, corresponds to the interaction between PTSD and TBI.

fMRI is particularly useful in evaluating how symptoms of TBI and psychiatric disorders may independently and mutually alter functional connectivity at rest (i.e., when the participant is not engaged in a task) and during affective tasks. Civilians with mTBI showed decreased resting-state functional connectivity between the insula and PFC, although neither PCS nor posttraumatic stress symptoms were evaluated (88), even though this decreased connectivity is evident in PTSD. In a veteran sample with mTBI, decoupling of insula-PFC and caudate-PFC connectivity at rest was related to greater posttraumatic intrusion symptoms and more errors processing threatening versus safe stimuli (89). This aligns with the emotion dysregulation framework: the anterior insula contributes to interoceptive awareness, suggesting that the observed deficits in PFC inhibition permitted greater internal attention to intrusive thoughts (90). Notably, this reduced connectivity is also linked to impaired cognitive function (e.g., deficits in orientation and abstract thinking), suggesting that insula-PFC circuity may underly both TBI and PTSD symptoms (88).

Previous theoretical reviews have implicated the hippocampus, orbitofrontal cortex, and dorsolateral PFC as potential regions where TBI and PTSD may overlap (91,92). Simmons and Matthews (93) conducted a meta-analysis to identify regions that are disrupted in both PTSD and TBI, thereby providing data-driven regions of interest for future investigations. Both the caudate, a component of the striatum, and the ACC were identified. The caudate is a region important for associative learning processes (93), and the ACC is implicated in the appraisal of emotional stimuli (25). Together, these regions coordinate emotional responses to stimuli and may underlie generalization of responses to trauma- and nontrauma-related cues. The dorsolateral PFC/middle frontal gyrus, a region important for executing goal-directed behavior such as regulating emotional responses (25), also appears vulnerable to both mTBI and PTSD; however, these results have mixed directions, with articles noting both hyper- and hypoactivation (93).

Ultimately, the structural and fMRI work indicates that the circuitry common to PTSD and TBI involves regions supporting emotion regulation and that this circuitry is impacted following physical and emotional traumatic injury.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The neural consequences of acute injury- and stress-driven changes in the brain from molecular- to system-level neurocircuitry contribute to the sequelae of emotion dysregulation that confers risk of PCS and ASD and, ultimately, risk for lasting symptoms of PTSD and major depressive disorder (10). While the impact of TBI on physical and psychological health outcomes has been studied for 2 decades (94), less clear is how and when to intervene to prevent the negative sequelae of PTSD+TBI. This cascade of neural changes highlights the importance of better understanding the timing and type of interventions used to treat, or ideally prevent, PTSD+TBI and PCS.

Decision making in and timing of clinical care during the golden hour after traumatic injury is critical. In addition to standard medical care, consultation from a clinician trained in trauma-informed care could also improve short- and long-term outcomes (19). Given the substantial overlap in neurocircuitry of PTSD+TBI and affected emotion regulation, it is nearly impossible to disentangle which condition is driving symptoms. Akin to most bodily injury, the physical damage of TBI takes time to heal even with early medical care. However, early attention to posttraumatic stress symptoms has been shown to improve chronic psychological outcomes (77,95). Therefore, especially in the acute phase, reducing emotional and psychological response to trauma could free up bodily resources for healing physical trauma of TBI or improve response to clinical treatments (96,97). However, it is unclear how trauma-intensive early treatments are impacted by the symptoms of TBI, a worthy area for future discovery to development of PTSD+TBI–specific interventions.

Improvement of chronic outcomes can be facilitated by ongoing engagement in both physiological/physical and emotional/mental health treatments for the first 6 months to a year following traumatic injury. For example, psychological intervention after concussion reduces depressive symptoms and risk of PCS (98–100). Cognitive behavioral therapies (CBTs) are the gold standard for treating PTSD and have also been shown to be effective in treating those with long-term PTSD+TBI. Cognitive processing therapy (101) and prolonged exposure therapy (two types of CBT for PTSD) (102) reduce symptoms of PTSD, depression, and PCS. The utility of CBT for not only PTSD but also TBI symptoms may be due in part to CBT leading to functional improvements in brain regions responsible for emotion regulation (103) that are impacted, as outlined above. Moreover, evidence suggests that CBT is an effective treatment for ASD+TBI symptoms in the early aftermath of traumatic injury (104), supporting the use of CBT as a secondary prevention technique. Beyond CBT, other common therapeutic techniques (e.g., mindfulness) similarly target emotion regulation processes (19). These promising studies suggest that CBT and other therapies known to directly impact emotion regulation circuitry and processes are effective treatments for TBI symptoms. Early provision of interventions targeting emotion dysregulation may disrupt the cascade of stress-induced molecular changes

following TBI, sparing long-term impacts on emotion regulation circuitry and improving TBI and PTSD symptom trajectories. Certainly, additional work is needed to assess the specificity of these early interventions on emotion regulation circuitry as a mediator of PTSD+TBI outcomes.

Improvements in clinical and medical care have significantly reduced mortality rates of TBI (2); however, long-term outcomes associated with the emotional and psychological distress of the event leading to injury have been infrequently addressed in the treatment of TBI. Lack of consensus and implementation of best practices in clinical treatment of TBI (e.g., different timing of interventions) may explain variability in chronic outcomes (2). However, administration of psychological interventions to treat trauma-related symptoms should be more readily applied within current TBI treatment protocols. Because it remains unclear whether physical damage perpetuates psychological symptoms or vice versa, the medical and psychological clinical care for patients with TBI should be weighted equally, and a more holistic approach to treatment should be taken.

Emotion dysregulation plays a key role in the shared outcomes of PTSD and TBI as evidenced by the overlap in symptom presentation (i.e., hypervigilance, memory deficits, sensory sensitivity, irritability), behavior (i.e., avoidance, overgeneralization of fear), and shared neural circuitry. Ultimately, the field needs additional well-controlled studies, specifically framed through the lens of emotion regulation, to determine best practice for prevention and intervention to improve long-term quality of life for patients with PTSD+TBI.

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ARTICLE INFORMATION

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