Chapter

Suicide Following Traumatic Brain Injury: Pathogenesis and Neurocognitive Mechanisms

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Abstract

Traumatic brain injury (TBI) is associated with varied neuropsychiatric sequelae, including elevated risk for later suicidal behaviors (SBs). This chapter provides a qualitative narrative review of hypothesized biological and neurocognitive mechanisms linking TBI to subsequent SBs. The following selective review specifically highlights: (1) Structural and functional alterations to neural circuitry secondary to common head injuries (e.g., concussions or mild TBI) as well as severe or repetitive TBI (e.g., chronic traumatic encephalopathy); (2) Overlap between post-TBI neuropsychological deficits and proposed bio-behavioral indicators of suicide risk; and (3) Potential neurocognitive mediators of the relationship between TBI and SBs, with a particular focus on executive functions involved in self-regulation (i.e., cognitive and affective inhibitory control) and their neural substrates, e.g., corticolimbic, frontostriatal, and frontoparietal circuitry. The chapter concludes with theoretical and practical implications of this shared pathophysiology, based on the reviewed empirical literature.

Keywords: affective control, chronic traumatic encephalopathy, concussion, executive functioning, mTBI, self-regulation, post-concussive syndrome

1. Introduction

1.1 Clinical description, diagnosis, and epidemiology

1.1.1 Head trauma

Head injuries comprise a broad spectrum of severity, ranging from isolated sub-concussive trauma to repetitive, severe traumatic brain injury (TBI). However, even acute mild TBI (mTBI; c.f., "concussion") can produce lasting neuropsychological deficits and increase risk for progressive neuropsychiatric sequalae, including chronic traumatic encephalopathy (CTE), cognitive decline, neurological diseases (i.e., Parkinson's disease and other dementias), prolonged post-concussive syndrome (diagnosed as "neurocognitive disorder due to traumatic brain injury"), and adverse mental health outcomes [1–5]. CTE – most often a consequence of repetitive mTBI – is especially tied to psychiatric illness [6], and is itself

characterized by dysregulated behavior and mood, beyond non-specific cognitive deficits associated with other forms of TBI, e.g., attentional difficulties, executive dysfunction, and memory impairment [7, 8]. Behavioral and mood symptoms of CTE, which frequently include suicidal ideation [6], implicate impaired *affective control*, or insufficient "top-down" cognitive (inhibitory) control from frontal cortical regions over "bottom-up" stimulus-driven impulses generated by sub-cortical areas, e.g., limbic circuitry [9–13]. Affective control impairment (and consequent behavioral/emotional dysregulation) is a hypothesized central feature of psychiatric conditions trans-diagnostically and proposed latent vulnerability factor for suicide [9, 11–15]. This selective narrative review will provide a focused summary of relevant literature on the association between TBI and psychopathology, highlighting prospective relations between non-penetrative head injuries and later suicidal behaviors (SBs).

Approximately half of the world's population has sustained at least one TBI, with 27–50 million new cases occurring globally each year – although prevalence estimates vary considerably due to inconsistent definitions and diagnostic criteria [1, 4, 16, 17]. Severe TBI is associated with a staggering 30–40% mortality rate [18]; however, mTBI account for the vast majority of cases (up to 95%; [4]). Nonetheless, TBI is the leading cause of mortality among young adults and together, physical head trauma is among the top contributors to disease burden worldwide, costing the global economy approximately $400 billion USD annually [4, 16].

TBI severity is commonly characterized using the Glasgow Coma Scale (GCS; [19]), which assesses visual, verbal, and motor responsiveness on a 3–15 point scale. Current consensus defines mTBI as a GCS score between 13 and 15 at least 30 minutes post-injury, concurrent with one of the following symptoms: (a) < 30 minutes of lost consciousness; (b) < 24 hours of post-traumatic amnesia (PTA); (c) impaired cognition at the time of the accident (e.g., confusion or disorientation); and/or (d) transient neurological consequences, e.g., epilepsy or focal signs [16]. GCS scores between 9 and 12 or lower than 9 indicate "moderate" and "severe" TBI, respectively [19], although there is less agreement regarding these definitions [4]. Regardless, the GCS is a crude (if efficient) assessment of TBI severity with debatable clinical utility [20, 21], given widespread brain damage that may accompany even "mild" closed head injuries [22]. Indeed, chronic cognitive, emotional, and behavioral issues following TBI frequently lead to long-term disability, independent of severity classification derived from GCS scores [22, 23]; for example, while loss-of-consciousness is sometimes considered a pathognomonic diagnostic "threshold" for TBI, this symptom (and other widely-used GCS indicators) are inadequately sensitive to the extent of acute neurological damage and are generally poor prognosticators of clinical outcomes longitudinally, e.g., see [24].

1.1.2 Suicidal thoughts and behaviors

Suicide is the *second* leading cause of death in young adults, accounting for more than 800,000 deaths globally each year – a mere fraction of the estimated 30 million nonfatal suicide attempts occurring annually [25, 26]. Of course, a much larger proportion of individuals endorse a history of suicidal thoughts, with lifetime prevalence estimates of 15–25% in unselected samples [27, 28]. SBs are defined as deliberate self-harm performed with at least some intent to die, reflecting a range of acts with varying levels of intentionality and lethality, e.g., from preparatory behaviors to death by suicide. SB definitions remain disputed even within a single category; for example, the classification of accidental drug overdoses in persons with suicidal thoughts but ambiguous intent remains controversial [29]. The diversity of

these behavioral manifestations contributes to the wide interval of SB prevalence estimates, which may be as high as 3–5% over the lifetime [27, 28].

Prior self-injurious thoughts and behaviors – particularly *non*suicidal self-injury (NSSI), or deliberate self-harm enacted *without* lethal intent – are among the strongest predictors of future SBs [30]. NSSI often involves cutting, burning, and/or self-battery, which are strikingly common behaviors in youth: internationally, approximately one in five adolescents report lifetime NSSI engagement in unselected samples [31]. Prominent suicide theories explain this counterintuitive prospective association as reflecting either (a) a contributory (causal) effect of NSSI on future SBs or (b) shared vulnerability that produces multi-final psychopathological outcomes (possibly depending on the presence of moderating factors; see [32] for a review). The latter position is consistent with the notion of a latent transdiagnostic risk factor implicated across neuropsychiatric syndromes, including aforementioned behavioral and/or emotional symptoms arising from affective control deficits, which commonly characterize nonsuicidal/suicidal self-injury [9–11, 14, 33] *and* repetitive TBI/CTE [5–8].

1.2 Bridging the *g*-a-*p* from TBI to suicide

My colleagues and I recently advanced a novel conceptual framework for understanding relations among NSSI, suicide, and affective control: the *g*-a-*p* model [9], referring to the overlapping roles of (a) the theorized latent "*g* factor" representing general intellectual capacities (c.f. "cognitive reserve"; see [6] and Section 2.2.3 below) and (b) the correspondingly proposed "*p* factor" of underlying vulnerability to diverse manifestations of psychopathology. The *g*-a-*p* model is supported by multiple converging lines of empirical evidence. First, "cool" executive functions (EF) – particular cognitive control or inhibition – provide fundamental scaffolding for higher-order mental operations and ultimately, the *g* factor of intelligence [34, 35]. Second, cognitive control deficits and other aspects of executive dysfunction are present in most psychiatric disorders [36, 37], potentially further implicating EF in the latent *p* factor of psychopathology risk. The extant literature is consistent with this possibility, emphasizing transdiagnostic impairment in *affective* control, i.e., inhibitory processes necessary for regulating stimulus evaluation, motivated action, and emotional reactivity [9]. Affective control thus represents the "hot" EF analogue to cognitive control, relying on shared neural substrates, i.e., functional connectivity within frontoparietal (central executive), frontostriatal (positive affect), and corticolimbic (negative affect) circuitry. The *g*-a-*p* model proposes that affective control represents an "equi-multi-final common pathway" from numerous established risk factors (including TBI) to various psychiatric outcomes and suicide [9, 11, 14].

The empirical literature reviewed in this chapter aligns with the perspective that TBI is similarly characterized by (acquired) impairment in affective control, which comprises a set of candidate neurocognitive mechanisms that undergird prospective associations between head injury and psychopathological phenomena like suicide. The reviewed research specifically suggests that certain forms of TBI may promote neurodegenerative processes that enhance psychopathology risk through acquired deficits in cognitive and/or affective control. Given the chronic course of many TBI cases, this vulnerability might not manifest for some time following the initial injury, obscuring the causal effects of TBI-related neurodegeneration on subsequent psychiatric dysfunction. The central thesis of this chapter accordingly posits that TBI elevates suicide risk via acquired deficits in cognitive – and more specifically, *affective* – inhibitory control.

2. Empirical literature review

2.1 Overlapping neurobiology of TBI and suicide

2.1.1 TBI pathophysiology

The pathogenesis of TBI is dynamic and progressive, involving (a) primary focal lesions due to the index head trauma, both at the impact site as well as its polar opposite location on the skull (i.e., "coup-contrecoup" injury), which in turn promote (b) secondary brain damage arising from localized and systemic dysfunction, manifesting as diminished functional brain connectivity that may worsen over time [38]. In brief, head trauma initiates a "metabolic cascade" via allostatic and epigenetic mechanisms, which produces persistent – if microscopic – brain damage [39]: acute neurological symptoms following TBI may be partially attributable to ionic flux (i.e., trauma-induced alterations in the permeability of lipid membranes that disrupts the flow of calcium, potassium, and sodium ions between neurons and the extracellular matrix), resulting in distributed glutamatergic hyperactivity, generation of free radicals, and increased energy demand in the context of reduced cerebral blood flow. Furthermore, biomechanical force from the impact *directly* damages the delicate cytoskeletal structure of glial cells and neurons (especially unmyelinated axonal projections), facilitating dysconnectivity and a chronic imbalance between excitatory (glutamate) and inhibitory (GABA) neurotransmission. Long-term glutamatergic hyperexcitability resulting from ionic (particularly calcium) dysregulation enhances microglial immune responses (e.g., increased pro-inflammatory cytokine signaling) that promote localized and systemic brain inflammation, thereby accelerating apoptotic and necrotic neuronal cell death via a process termed "immuno-excitotoxicity" [40]. Consequently, oxidative stress due to mitochondrial metabolic dysfunction, persistent inflammation arising from dysregulated immune signaling, and other cytotoxic processes (e.g., blood–brain barrier disruption, genetic damage, etc.) contribute to the progressive neurodegeneration characteristic of TBI; see [18, 39–41] for additional details. TBI therefore alters brain structure and function via multiple pathophysiological pathways at the molecular and cellular levels (some of which unfold acutely post-injury while others unfold longitudinally), ultimately producing the hallmark cognitive, behavioral, and emotional sequelae of head trauma.

TBI is further associated with numerous structural and functional alterations to neural circuitry at the network or systems level, beyond morphological and molecular changes to neurons, glial support cells, and the extracellular matrix. Patterns of neurocognitive dysfunction secondary to TBI are influenced by a host of factors, including those related to the incident (e.g., TBI due to blast injury vs. motor vehicle accident), physical characteristics of the trauma (e.g., site and force of primary impact), as well as the victim's pre-existing vulnerabilities. Relevant patient factors include individual differences in: (a) "cognitive reserve" or baseline intellectual abilities [6]; (b) substance use and neuropsychiatric history, especially prior TBI; as well as (c) comorbid conditions resulting from the trauma, e.g., concomitant post-traumatic stress disorder or spinal cord injury. Neurocognitive deficits associated with TBI are often non-specific, however, most frequently involving impairments in attention, memory, socioemotional abilities (e.g., affective control; mentalization; self-referential processing), and EF, both lower-order cognitive control as well as higher-order mental operations, e.g., abstraction; decision-making; planning; problem-solving, etc. [4, 23]. The prefrontal cortex is considered the most important neurobiological substrate for EF; however, complex cognition relies on distributed activity throughout functional brain networks responsible for all input and output

operations comprising goal-directed behavior, e.g., monitoring, integrating, and inhibiting (task-irrelevant) sensory information in addition to coordinating and inhibiting (task-inappropriate) behavioral responses [23, 35, 38]. Core components of these functional circuits include cortical and subcortical nodes, hubs, and cerebral tracts in the frontal lobes as well as multimodal association cortices in temporoparietal regions [22, 23, 38, 42]. Deficits in EF necessary for activities of daily living may be difficult or impossible to detect with standard neuroimaging techniques routinely used in clinical settings [22, 42–44], and even neuropsychological evaluation may be insufficiently sensitive to fully capture subtle long-term neurocognitive consequences of (especially mild) TBI [2, 23].

Diffuse axonal injury (DAI) is the primary source of TBI-related neural circuit dysfunction, such that prominent researchers have referred to post-concussive syndrome as a "disorder of brain connectivity" involving disruption of multiple functional networks linking brain structure to cognition [38]. DAI refers to acute biomechanically-induced shearing of white matter tracts (i.e., bundles of myelinated axonal fibers), whose integrity is requisite to proper neurotransmission. Partially due to sustained hyperactivity of pro-inflammatory mediators (e.g., cytokines and chemokines; [41]), TBI produces widespread and potentially permanent white matter damage, implicating DAI in TBI-associated neurodegeneration – even in mild cases [22, 42]. Axonal white matter tracts are foundational to all neural circuits and networks; DAI thus interferes with communication throughout the brain, which helps explain the myriad cognitive, behavioral, and emotional symptoms following TBI [6, 22, 38, 45]. A 2018 meta-analytic review of neuroimaging data collected using diffusion tensor imaging – a method adequately sensitive to detect microstructural changes to white matter – indicates that axonal shearing frequently occurs throughout the *whole brain* in TBI (i.e., up to 95% of brain areas in mTBI and 100% in more severe cases), most commonly in subcortical regions of the hindbrain, the corpus callosum (commissural inter-hemispheric fibers), the internal and external capsules, as well as the frontal lobe [2, 22, 38]. These structural alterations may persist for years or even decades post-injury (regardless of TBI severity) with profound long-term impacts on cognition and behavior [2, 38]. Indeed, radiological evidence of DAI is a prognostic indicator of adverse clinical outcomes, which are three times more likely than in TBI cases without DAI, according to a recent meta-analytic review [42].

EF deficits (including impaired cognitive control) are hallmark symptoms of "dysexecutive syndrome" involving frontal areas and associated brain circuitry (e.g., frontoparietal or central executive network) affected by repetitive TBI/CTE, which are further characterized by attention and episodic memory impairment attributable to widespread axonal insult across relevant neural circuitry. Thus, CTE can be conceptualized as the long-term consequence of DAI [4]. Specifically, lesions to the cingulum bundle (connecting the ventromedial prefrontal cortex to the posterior cingulate) and other components of the default mode network correlate with post-TBI deficits in sustained attention and post-concussive symptom severity, whereas lesions to lateral temporoparietal, mesial temporal, and/or posterior cingulate/precuneus tracts contribute to learning and memory problems associated with CTE [6, 38], which are additionally reflected by hippocampal abnormalities observed after TBI [43]. The basal ganglia and limbic structures such as the hippocampus and amygdala are especially susceptible to TBI-related white matter damage [46–48], e.g., to the fornix, which comprises axonal projections originating in hippocampal neuronal cell bodies. In sum, the extant empirical literature suggests that TBI disrupts the functional connectivity of core circuitry necessary for cognitive and affective inhibitory control (e.g., corticolimbic, frontoparietal, and frontostriatal networks), particularly neural tracts connecting prefrontal cortical regions to

subcortical areas via the thalamus and between frontal hemispheres via the genu of the corpus callosum [22, 43–49]. DAI damage to prefrontal white matter tracts thus helps account for heterogeneous deficits in self-regulation capacities secondary to TBI/CTE that overlap considerably with psychiatric disorders and related phenomena, including suicide – one of the leading causes of TBI-related death [6].

2.1.2 Neurobiological correlates of suicide

Suicidal thoughts and behaviors share pathophysiological mechanisms with TBI, particularly disrupted functional connectivity in corticolimbic, frontoparietal, and frontostriatal circuits responsible for affective control and goal-directed behavior [9, 50–56]. The growing literature on the neurobiological underpinnings of suicide is mixed and remains challenging to interpret, however, given inconsistent definitions of SBs and sample heterogeneity. In particular, it is difficult to parse neurocognitive factors *specifically* involved in SBs that are also *not* associated with suicidal ideation, NSSI, and (frequently comorbid) "indirect" self-injurious thoughts and behaviors, e.g., substance misuse, disordered eating, etc. Such etiological commonalities (i.e., multi-final contributors to risk) support the notion of a latent *p* factor reflecting shared variance in these disparate clinical outcomes.

Broadly, SBs are characterized by structural and functional abnormalities in multiple regions of the frontal lobe, e.g., dorsolateral, orbitofrontal, and ventromedial prefrontal cortices, as well as the dorsal anterior cingulate [53, 57]. SBs are specifically associated with altered serotonin signaling in these areas, which may be reflected by cool EF deficits – particularly in cognitive inhibitory control and value-based decision-making; see Section 2.2.2 [50–57]. However, converging evidence indicates that suicide attempts and related self-harm *behaviors* (i.e., SBs and NSSI compared to suicidal thoughts) may be more strongly and/or specifically associated with impaired *hot* EF and corresponding dysfunction in *affective* inhibitory control over negative valence systems [9–11, 14, 33]. This notion aligns with evidence for SB-linked abnormalities in subcortical limbic (particularly morphological changes to the extended amygdala) and striatal regions; see [9] for a recent review.

Extant research on the neurobiological substrates of SBs implicates disruptions to the same neural circuits that are frequently damaged by TBI, albeit via distinct pathogenetic processes – though both often demonstrate a chronic, progressive course of symptoms. The etiology and pathogenesis of SBs, unlike TBI, are most directly influenced by genetic and epigenetic mechanisms (versus traumatic insult). SB heritability estimates range greatly, from 4–55% [9], and evidence suggests a genetic link between predisposition to suicidal thoughts and various domains of cognitive functioning relevant to the *p* factor, e.g., emotion differentiation [58]. Unsurprisingly, we observe similar genetic overlap between TBI outcomes and neurocognitive functioning (particularly EF), partially accounted for by the latent *g* factor of general intelligence [59]. The role of acute or prolonged psychological stress is well-established in SBs, particularly among individuals who are emotionally reactive (e.g., scoring highly on personality traits of neuroticism/negative emotionality/emotional instability) and/or characterized by poor self-regulation, i.e., proposed functional manifestations of the *p* factor. Varied contributors to distress are, correspondingly, known risk factors for SBs. My colleagues and I suggest that these disparate sources of vulnerability operate through a shared "equi-multi-final common pathway", ultimately involving epigenetically-mediated dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and associated stress reactivity. Due to allostasis, HPA axis dysregulation becomes self-maintaining via a positive feedback loop, leading to gray matter volume loss and functional dysconnectivity across multiple brain areas, including major serotonergic and

dopaminergic pathways originating in subcortical areas (i.e., the raphe nuclei and ventral tegmentum/substantia nigra, respectively) that project throughout the frontal cortex. Disruptions to these major neurotransmitter pathways, which are crucial for self-regulation of cognition, emotion, and behavior [60], mirror patterns of white matter damage frequently associated with TBI.

2.2 Overlapping neurocognitive profiles of TBI and suicide

2.2.1 Neuropsychological sequelae of TBI

As mentioned above, common clinical features of TBI include (a) EF deficits contributing to self-regulation impairment of attention, emotion, and motivation as well as (b) memory loss (typically acute in mild cases), whereas cognitive abilities in linguistic and perceptual domains are often relatively spared [4, 7, 8, 61]. Post-concussive neuropsychological dysfunction has profound consequences even in mTBI, however, with over half of patients experiencing continued cognitive decline up to five years post-injury [2, 4, 62], contributing to long-term functional impairment in activities of daily living [48]. Heterogeneity in clinical outcomes is attributable to both pre-TBI individual differences as well as characteristics of the injury itself, e.g., biomechanics of the trauma. Patient variables influencing TBI prognosis span several domains: (a) proxies for cognitive reserve and general intellectual abilities (the *g* factor), e.g., age, education, and genetic polymorphisms linked to neuroplasticity [59, 63]; (b) neuropsychiatric history (the *p* factor), e.g., prior TBI or pre-existing psychopathology [62, 63]; in addition to (c) poor sleep quality [4, 62, 64], which independently predicts psychiatric problems and SBs [9]. Moreover, up to 85% of mTBI patients report persistent sleep disturbances, likely exacerbating ongoing neurodegenerative processes underlying EF and learning/memory deficits [64].

Cognitive inhibitory control is the fundamental capacity that provides scaffolding for all higher-order EFs, comprising interference inhibition (executive attention) as well as early (action suppression) and late response inhibition (action termination; [9, 34]). Even other "low-level" EFs (i.e., shifting/switching and working memory updating) load on a latent factor (c.f.., "the central executive") whose variance is largely accounted for by inhibition [35]. Perhaps unsurprisingly, inhibitory control may be the cognitive capacity most vulnerable to traumatic insult, particularly in pediatric populations for whom TBI occurs within sensitive neurodevelopmental windows [65, 66].

Peri-traumatic and persistent memory impairment are also common in TBI. Autobiographical amnesia surrounding the traumatic insult is perhaps most pathognomonic, likely arising from acute brain damage (and accompanying transient neurological symptoms) sustained during the trauma [67]. Retrospective autobiographical amnesia may continue for a year or more in chronic or severe cases [68]. Learning and memory problems (including anterograde amnesia) are especially characteristic of moderate-to-severe cases, in which these issues demonstrate a more prolonged course than other cognitive symptoms [23, 69]. TBI also frequently involves impaired explicit (verbal and visual) memory on tests of both recall and recognition; however, TBI patients may demonstrate intact memory monitoring, at least retrospectively, i.e., providing accurate judgments regarding their relatively poor recall/recognition accuracy [69, 70].

2.2.2 Neuropsychological deficits in suicide

Cognitive deficits are transdiagnostic characteristics of psychiatric disorders [34, 37], which characterize 90% of individuals who die by suicide [71]. Similar to

TBI, EF and memory abilities comprise the primary affected domains of cognition in suicidal thoughts and behaviors. Meta-analysis indicates substantial episodic memory alterations among individuals with SB history [72], who tend to produce "over-general" descriptions of autobiographical events [73]. Whereas SBs have additionally been tied to diminished domain-general intellectual abilities, suicidal ideation may conversely be associated with *greater* general intelligence, reflecting the abundant mixed findings in this literature [74, 75]. Inconsistent conclusions notwithstanding, meta-analytic evidence confirms the association between SBs and cool EF deficits, particularly in cognitive control, and most reliably, impaired interference inhibition [9, 76–78]. Relatedly, SBs are further linked to poor probabilistic decision-making abilities [74, 77, 79–81], aligning with the fundamental role of inhibitory control to higher-order complex cognition, e.g., hot EF. Multiple studies report associations between self-injurious behaviors (including SBs) and dysfunction in inhibitory control over negative affect, specifically. Deficient affective control associated with deliberate self-harm (i.e., NSSI and SBs) might manifest at the *cognitive* level as poor negative emotional *interference* inhibition (driven by cognitive biases and/or insufficient executive attention) and repetitive negative thinking (e.g., ruminative brooding; [33, 78, 82–84]), whereas at the *behavioral* level, negative emotional *response* inhibition and heightened negative urgency (i.e., impulsive reactions to aversive emotions) likely reflect underlying affective control deficits in suicide and other self-injurious behaviors [9–11, 14, 85, 86]. Our recent work with high-risk psychiatric inpatients suggests that poor negative emotional response inhibition (measured at admission using an emotional stop-signal task [10, 85]) increases the likelihood of subsequent SBs up to one year post-discharge [14]. Difficulty inhibiting negative emotional reactions to self-harm stimuli on this task similarly predicts real-world NSSI urges over the following weeks measured via ecological momentary assessment [86]. Emerging evidence thus supports the notion that affective control impairment is a vulnerability factor for self-injurious behaviors (and not merely a neurobehavioral correlate). I refer readers seeking additional detail to the following contemporary reviews that examine the literature on cognitive deficits in suicide more extensively: [9, 74, 87].

2.2.3 Shared neurocognitive dysfunction as a mechanism linking TBI and suicide

Taken together, epidemiological, neuroimaging, and neuropsychological investigations into TBI and SBs yield several conclusions with important clinical implications. First, both neuropsychiatric phenomena are strikingly prevalent and each is associated with tremendous global economic burden, collectively accounting for over $500 billion USD lost annually to direct and indirect costs [16, 25, 88]. Second, both syndromes involve heterogeneous etiology and clinical presentations, reflecting the inherent multi-finality of established vulnerability factors – many of which are also shared among these conditions, providing corresponding evidence for the equifinality of disparate contributors to neuro-psychopathology risk [4, 9]. Third, relatively more empirical work has sought to elucidate the pathogenesis of TBI, which ultimately reflects dual sources of brain damage that progressively unfold via distinct trajectories and time-courses: (a) acute focal lesions primary to the traumatic insult, both at the impact site and its "contrecoup" location; as well as (b) chronic neurodegenerative processes arising secondarily from host responses to injury, including ischemia, hormonal dysfunction, and disruptions to inflammatory signaling proximately caused by elevated intracranial pressure and maintained via epigenetic changes [4, 41]. Importantly, given that the majority of head injuries are classified as mTBI, the latter set of pathogenetic mechanisms may figure more prominently in chronic disability and dysfunction following repeated concussions [6].

As previously mentioned, head injuries elevate risk for developing later psychopathology, further contributing to the long-term health burden of TBI patients. For example, children who sustain a single mTBI are *twice* as likely to qualify for a psychiatric condition three years post-injury, particularly symptoms of attention deficit/hyperactivity disorder [5]. Overall, TBI is most strongly associated with disorders of emotional distress (i.e., anxiety, stress, and mood disorders), with approximately one-third (and possibly up to three-quarters) of patients experiencing psychiatric illness within five years of head trauma, often major depressive disorder and/or post-traumatic stress disorder (PTSD; [3]).

Much empirical work has focused on TBI-related PTSD, which is linked to the integrity of peri-traumatic memories [89–92] that may be reconstructed over time even without comprehensive encoding during the event [93]. Prolonged reconstruction of traumatic narratives, which characteristically lack consistency and coherence [91, 93], is unlikely to reflect recovery of "true" memories and might rather help explain the delayed onset of PTSD relative to other psychiatric sequelae of TBI [3]. Notably, attention deficit disorders, PTSD, and major depression each increase the likelihood of future SBs independent of brain trauma [71]. However, TBI itself doubles the odds of death by suicide, rates of which are *four times greater* among those with post-TBI psychiatric illness compared to the general population, even according to conservative estimates [94]. This pattern suggests that psychological problems partially mediate the relationship between head injury and SBs, which may occur in up to 60% of TBI cases [71].

The etiologies of depression, PTSD, and SBs following TBI are multifactorial, likely involving the modulation of gene expression associated with persistent inflammation and endocrine dysregulation, which mutually exacerbate continued neurodegenerative processes. Along with chronic pain – another well-established consequence of TBI [4] – depression and PTSD have been classified as "neurosensitization syndromes" maintained via shared epigenetic and neurocognitive mechanisms [95]. Specifically, TBI-induced epigenetic alterations to immune pathway signaling promote microglial dysfunction, triggering a cascade of elevated pro-inflammatory cytokine release and glutamatergic hyperactivity, which interact bidirectionally in a positive feedback loop of immuno-excitotoxicity [40, 96]. Burgeoning evidence similarly implicates epigenetically-mediated immune dysregulation and consequent brain inflammation in the pathophysiology of depressive disorders and SBs [71]. These transdiagnostic immuno-excitotoxic processes facilitate enduring – and potentially permanent (e.g., see [97]) – remodeling of micro-neuronal structure and function, eventually leading to progressive neurodegeneration and dysconnectivity in key brain areas necessary for learning, memory, emotion, and EF.

At the macroscopic level, frontotemporal [6] and limbic structures (e.g., the amygdala and hippocampus) may be most susceptible to morphological changes resulting from sustained release of inflammatory and excitotoxic factors, given the high concentration of glutamate and cytokine receptors in these regions [40]. Glutamate-driven hyperexcitability of the amygdala is hypothesized to generate an electrophysiological "limbic kindling" phenomenon, in which amygdala neurons become progressively sensitized [95]. This "neurosensitization" may be a biological mediator of prospective links between head injury and psychopathology, for example, by decreasing the threshold of limbic reactivity to stress arising from acquired cognitive deficits and socioemotional dysfunction. Secondary brain damage and attendant cognitive deficits arising gradually months or years post-TBI might therefore be comparably conceptualized as a neurosensitization syndrome, supported by high comorbidity rates with chronic pain, depression, and PTSD. Regardless, accumulating research supports the role of excitotoxic glutamate

signaling in neurodegeneration associated with chronic pain, TBI, as well as SBs and related psychiatric illness, e.g., major depressive disorder and PTSD [71].

Acute stress and nerve damage accompanying TBI further alter the expression of neuroendocrine genes, potentiating the secretion and circulation of glucocorticoids (e.g., cortisol) and other steroids that similarly modulate glutamatergic neurotransmission and consequently induce pathophysiological changes to vulnerable corticolimbic, frontoparietal, and frontostriatal circuitry [98, 99]. Coincidentally, functional connectivity in these brain networks is critical for affective and cognitive inhibitory control [9, 35]. Prolonged central nervous system injury secondary to physical trauma thus dysregulates the HPA axis, which relies on negative feedback to function properly, i.e., via hippocampal/pituitary cortisol receptors that eventually decrease in density and binding capacity with the continued release of stress hormones. Morphological alterations associated with chronic HPA axis dysfunction include prefrontal and hippocampal atrophy coupled with biphasic changes in amygdala volume (enlargement followed by reduction), which collectively overlap substantially with the pathophysiology of depression, PTSD, and suicide [71, 95, 98]. HPA axis dysregulation is another transdiagnostic feature of psychopathology and TBI that may ultimately manifest neuropsychologically as impaired affective control and other hot EF deficits associated with SBs [9, 71]. Externalizing variables that putatively reflect insufficient affective control (e.g., aggression, impulsivity, substance misuse) provide additional support for this notion, given their relationships with both elevated suicide risk *and* increased likelihood of head injuries, as well as their proposed role in exacerbating underlying diatheses for SBs unmasked by TBI [71].

3. Conclusions

In sum, compromised self-regulation of affect, behavior, and cognition acquired via neurotoxic molecular cascades following head trauma represent a set of neurocognitive mechanisms that help explain the effects of TBI on suicide vulnerability. These inter-related pathophysiological processes include chronically-enhanced free radical activity, glutamatergic excitotoxicity, and ongoing neuroinflammation triggered primarily by the initial mechanical injury and maintained secondarily by altered gene expression throughout the brain. TBI-induced neurometabolic cascades have profound consequences for neural structure and function, with downstream effects on HPA axis dysregulation, consequent heightened stress reactivity, and diminished affective control.

According to the recently proposed *g*-a-*p* model, domain-general cognitive ability (i.e., the *g* factor) interacts with latent vulnerability to psychopathology (i.e., the *p* factor) – manifesting as impaired affective control – to influence the etiology of transdiagnostic neuropsychiatric phenomena. This framework can be applied across multiple levels of analysis to explain shared risk factors and pathophysiology, high comorbidity rates, and prospective links between TBI and suicide. The *g*-a-*p* model specifically implicates an equi-multi-final common pathway to neuropsychopathology, involving (a) epigenetic alterations to immune/neuroendocrine pathways that disrupt HPA axis function, (b) consequent EF deficits in cognitive (cool) and affective (hot) inhibitory control at the neuropsychological level that manifest as (c) repetitive negative thinking (cognitive dysregulation), (d) urgency (behavioral dysregulation), and/or (e) heightened stress reactivity (emotional dysregulation). The empirical literature reviewed in this chapter aligns with the perspective that cognitive and affective inhibitory control (associated with the *g* and *p* factors, respectively) represent neurocognitive mechanisms underlying the

pathogenesis of SBs following TBI, while also independently elevating the likelihood of both neuropsychiatric phenomena.

From a practical perspective, the relationship between TBI and suicide is sufficiently clear to mandate routine risk assessment in acute care for head injuries. Providers less familiar with psychopathology may initially find such conversations uncomfortable. Suicide risk assessments are generally low-cost and simple to administer, yet avoided in many settings due to unfounded iatrogenic concerns, e.g., asking about suicidal thoughts might increase their incidence. Our recent research with psychiatric inpatients suggests the opposite may be true: evaluating patients' history of suicidal thoughts and behaviors reduces subjective distress and intent [100]. The TBI-suicide link also enjoins mental health clinicians to regularly assess for history of head trauma when evaluating new clients. The extant literature suggests that neurocognitive assessment may be indicated more broadly in determining suicide risk [9, 14], and that clinicians ought to be especially aware of suicidal patients' TBI history, which might necessitate a higher level of care.

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