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Stress and traumatic brain injury: An inherent bi-directional relationship with temporal and synergistic complexities

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ABSTRACT

Traumatic brain injury (TBI) and stress are prevalent worldwide and can both result in life-altering health problems. While stress often occurs in the absence of TBI, TBI inherently involves some element of stress. Furthermore, because there is pathophysiological overlap between stress and TBI, it is likely that stress influences TBI outcomes. However, there are temporal complexities in this relationship (e.g., when the stress occurs) that have been understudied despite their potential importance. This paper begins by introducing TBI and stress and highlighting some of their possible synergistic mechanisms including inflammation, excitotoxicity, oxidative stress, hypothalamic-pituitary-adrenal axis dysregulation, and autonomic nervous system dysfunction. We next describe different temporal scenarios involving TBI and stress and review the available literature on this topic. In doing so we find initial evidence that in some contexts stress is a highly influential factor in TBI pathophysiology and recovery, and vice versa. We also identify important knowledge gaps and suggest future research avenues that will increase our understanding of this inherent bidirectional relationship and could one day result in improved patient care.

1. Introduction

Traumatic brain injury (TBI) is a major health concern worldwide (Maas et al., 2017), with approximately 50 million cases (Feigin et al., 2013) and an economic burden of ~$400 billion USD each year. TBI is caused by external forces acting on the brain, and commonly occurs in vehicle accidents, assaults, sports, falls, and the warzone (Hirtz et al., 2007; Menon et al., 2010). Depending on the setting, the TBI-inducing forces may be blunt, rotational, linear, blast, and/or penetrating in nature, and this may ultimately influence the pathobiology and functional consequences of the injury (Bandak et al., 2015; Brady et al., 2019; Bryden et al., 2019). TBI severity is classified as mild (e.g., concussion), moderate, or severe (Maas et al., 2017) based on a Glasgow Coma Scale assessment, with mild being the most common (Vos et al., 2012). TBI pathology can be the result of both primary and secondary injury mechanisms. Brain damage sustained at the moment of TBI is the result of primary injury mechanisms (e.g., shearing or tearing of brain cells and vasculature, excitotoxicity, cell death, ionic and neurotransmitter imbalance) (Maas et al., 2017), and likely underlies the acute neurological deficits (Rowson et al., 2016; Shetty et al., 2014). TBI pathology can continue to evolve long after the primary injury, as secondary mechanisms such as neuroinflammation, oxidative stress, mitochondrial dysfunction, cerebrovascular disruption, and proteopathies are initiated. (Hua Li et al., 2004; Rehman et al., 2019; van Vliet et al., 2020). These primary and secondary injuries can result in functional consequences including cognitive, emotional, social, and sensorimotor deficits (Pearn et al., 2016; Sulhan et al., 2020). It is important to recognise that TBI is an evolving and heterogeneous condition, and many different factors related to the injury (e.g., type, severity) or the individual (e.g., age, sex, gender) may ultimately influence TBI pathophysiology and outcomes.

One factor that could have a dramatic impact on how the brain responds to TBI is stress. Stress is the brain perceiving an experience or situation as challenging or threatening. Stress has various forms (e.g., physical, emotional, mental) and individual responses to the same experiences or situations are heterogenous (McEwen, 2007). After

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perceiving a situation as stressful, the brain determines which behavioral and physiological responses to utilize in response to the given experience or situation (McEwen, 2007). Exposure to stress causes the human body to deploy an adaptive response that includes the activation of the autonomic nervous system (ANS) and hypothalamus-pituitary-adrenal (HPA) axis. This generates a neuroprotective response that includes brief inflammation and increased heart rate (McEwen, 2007). Afterwards, the body attempts to return to homeostasis, an ability known as allostasis. However, if the stress is chronic and/or the adaptive response is dysregulated, allostatic overload, involving glutamate excitotoxicity, oxidative stress, and neuroinflammation among others can prove detrimental (McEwen, 2007). A constant state of allostatic overload or chronic stress can lead to changes in neural circuitry, cognition, anxiety, and mood (McEwen, 2017).

There is an inherent relationship between TBI and stress because when someone sustains a TBI the event is physically and emotionally stressful in itself, and the TBI may alter important biological pathways required for allostasis. The stress induced by the TBI event is likely influenced by the type and degree/severity of the injury. Beyond this acute stress, TBI survivors may continue to face additional stressors that include pain, medical interventions, loss of independence, disability, and lifestyle changes (Weil et al., 2022). The severity and duration of these consequences could modify the degree of stress. It is also important to consider that individuals at the highest risk of sustaining a TBI may be exposed to dangerous and stressful environments prior to the injury (e.g., warzones, intimate partner violence). Considering the bidirectional and overlapping nature of TBI and stress, it is unsurprising that TBI patients are particularly susceptible to post-traumatic stress disorder (PTSD) – a condition with symptoms that include anxiety, irritability, insomnia, and memory problems; all of which have been mechanistically linked to neuroinflammation, oxidative stress, and excitotoxicity (Howlett and Stein, 2016; Monsour et al., 2022; Vasterling and Dikmen, 2012). While TBI is a risk factor for the development of PTSD, it is important to clarify that TBI-related stress does not always manifest as PTSD. According to the DSM-5-TR, although exposure to an actual or threatened traumatic event or serious injury (e.g., a TBI) is necessary for PTSD diagnosis, it is not sufficient and other criteria must also be met (e.g., presence of intrusion symptoms associated with the traumatic event, beginning after the traumatic event; persistent avoidance of stimuli associated with the traumatic event, beginning after the traumatic event; negative alterations in cognitions and mood associated with the traumatic event, beginning or worsening after the traumatic event occurred; marked alterations in arousal and reactivity associated with the traumatic event, beginning or worsening after the traumatic event occurred), be present for more than one month, cause clinically significant distress or impairment in function, and not be attributable to the physiological effects of a substance or other medical condition (American Psychiatric Association, 2022).

Despite the intrinsic link between TBI and stress, few studies have examined the impact of stress on TBI outcomes and how temporal dynamics influence this relationship. This paper will begin by summarizing the pathophysiology of TBI and stress, with a focus on those with the potential to be synergistic (see Fig. 1). We will then review the available literature pertaining to the different temporal scenarios, identify important knowledge gaps, and suggest areas of future research.

2. Overlapping pathophysiological mechanisms of TBI and stress

The pathophysiological processes involved in TBI and stress are complex and multifaceted, and a comprehensive review of these topics is beyond the scope of this paper (see Giza and Hovda, 2014, Jamjoom et al., 2021, McEwen, 2007, Tian et al., 2014). It is also important to note that differences in the pathophysiology resulting from the various forms of TBI (e.g., blunt versus blast) and stress (e.g., physical versus emotional) are still being elucidated (Aravind et al., 2020; Bryden et al., 2019; Dretsch et al., 2015; Logsdon et al., 2020; Siedhoff et al., 2022). For the purpose of this article, we will therefore focus on mechanisms that are more broadly implicated and overlapping in both TBI and stress including neuroinflammation and immune response, excitotoxicity, HPA axis dysregulation, ANS dysfunction, and oxidative stress.

2.1. Neuroinflammation and immune response

TBI induces a neuroinflammatory cascade that involves a number of cell types including microglia, astrocytes, and infiltrating immune cells (DiSabato et al., 2016; Savage et al., 2012; Bye et al., 2007; Hsieh et al., 2013; Gyoneva and Ransohoff, 2015; Clark et al., 2019). Microglia are

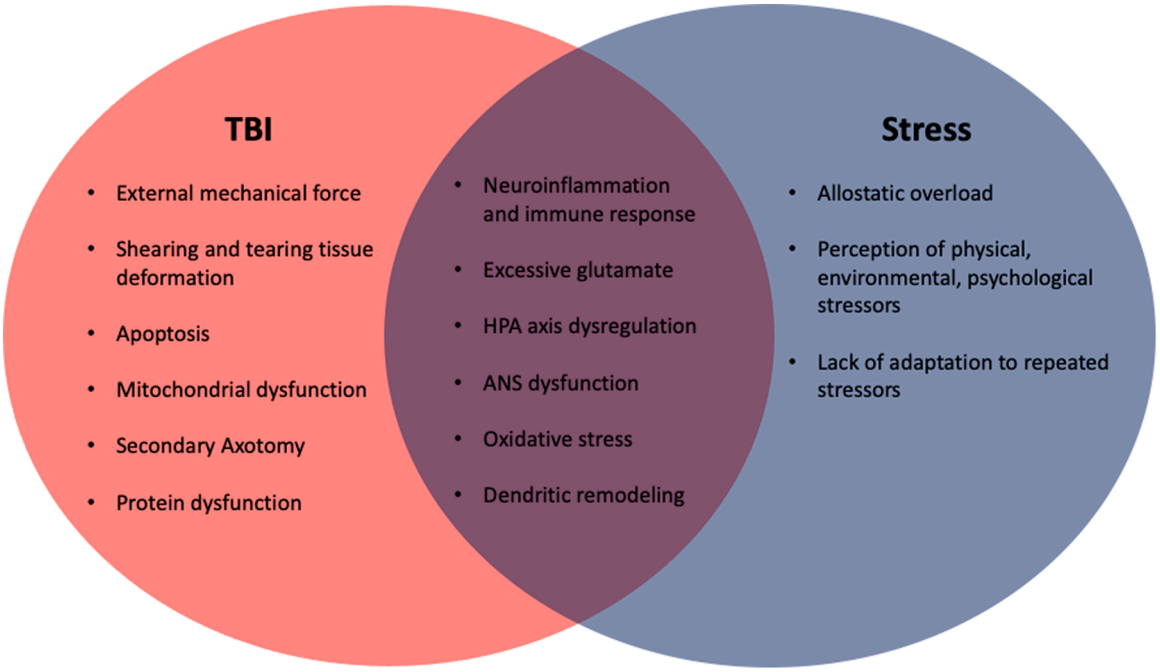

Fig. 1. The pathophysiology of TBI and stress illustrating possible overlapping mechanisms.

the brain's resident immune cells, and are sensitive to changes in the extracellular environment caused by TBI (O'Brien et al., 2020). This can initiate changes in microglial function, morphology, and molecular profile (Paolicelli et al., 2022). Microglia phenotype can transform via distinct signalling pathways regulated at the transcriptional, epigenetic, translational, and metabolic levels, with such regulation thought to determine the function and properties of microglia at that point in time (Paolicelli et al., 2022). Microglia can have both reparative and damaging functions post-TBI. While microglial activation is useful in isolating and scavenging debris from the injury site, microglia can shift to a state known as disease-associated microglia (DAM) that promotes an increase of cytokines (e.g., tumor necrosis factor alpha, TNFα; interleukin-6, IL-6; and interleukin 1 beta, IL-1β), further neuroinflammation, and cell death, whilst interfering with repair mechanisms (Paolicelli et al., 2022; Popiolek-Barczyk and Mika, 2016; Ramlackhansingh et al., 2011; Wang et al., 2014; Wang et al., 2020; Witcher et al., 2015). As microglia are highly plastic, this shift is not necessarily permanent and they possess the ability to shift back to state not associated with disease (Paolicelli et al., 2022). However, following TBI a shift to DAM can be sustained and persist for months to years (Coughlin et al., 2017; Henry et al., 2020; Wu et al., 2021). Following TBI, astrocytes also undergo diverse molecular, structural, and functional changes, known as reactive astrogliosis, that contribute to dysregulated inflammation (as reviewed in Burda et al., 2016). Reactive astrocytes can shift microglia to a DAM state through bidirectional communication furthering proinflammatory cytokine release (Burda et al., 2016; Korotkov et al., 2020; Michinaga and Koyama, 2021; Rosa et al., 2021). Circulating immune cells also play a role in neuroinflammation as they can be actively recruited into the brain after TBI (Bao et al., 2012), with BBB disruption also facilitating the influx of various immune cells such as neutrophils, macrophages, and T-cells (van Vliet et al., 2020). Proinflammatory cytokines in the brain can also enter systemic circulation and have downstream effects on peripheral organs (McDonald et al., 2020). Circulation of these inflammatory mediators can lead to systemic inflammation which is associated with worse outcomes following TBI (Csuka et al., 1999; McDonald et al., 2020; Milleville et al., 2020; Sabet et al., 2021; Xu et al., 2021).

Stress also results in neuroinflammation and an immune response, with microglia shifting to a DAM state (Nair and Bonneau, 2006; Paolicelli et al., 2022; Sugama et al., 2007; Tang and Le, 2015; Tynan et al., 2010). Acute stress may provide some neuroprotective effect by downregulating immunosuppressive proteins and proinflammatory cytokines (McEwen, 2007; Petrovsky, 2001; Zefferino et al., 2020). However, when the stress response becomes dysregulated, such as in chronic stress and PTSD, neuroinflammation follows similar mechanisms of TBI with an increase in DAM and proinflammatory cytokines such as IL-6, TNFα and IL-1β (Frank et al., 2020; Marsland et al., 2017; Mograbi et al., 2020; Rohleder, 2019; von Känel et al., 2007). Stress can also induce the activation of astrocytes, with resulting functional/morphological changes and neurotoxic consequences (Banasr et al., 2010; Du Preez et al., 2021; Liddelow et al., 2017). This dysregulated response also leads to increased recruitment of neutrophils, T-cells, macrophages, and monocytes to the central nervous system (Heidt et al., 2014; Krämer et al., 2019; Woodburn et al., 2021; Zefferino et al., 2020). DAM, proinflammatory cytokines and proinflammatory peripheral cells all contribute to prolonged neuroinflammation and neuronal apoptosis (Estes and McAllister, 2014; Zefferino et al., 2020). Like TBI, chronic stress has also been shown to cause BBB disruption that permits the infiltration of peripheral immune cells and exacerbates neuroinflammation (Menard et al., 2017; Peng et al., 2022). Stress and the resulting proinflammatory cytokines can also cause systemic inflammation that is associated with increased immune dysregulation and disease comorbidities (Barrett et al., 2021; Furman et al., 2019). Taken together, stress prior to and/or following TBI may have the potential to exacerbate or modify the neuroinflammatory and immune response of TBI and result in worse outcomes.

2.2. Glutamate excitotoxicity and calcium overload

At the hyperacute stage of TBI, the mechanical forces cause shearing, tearing, and/or stretching of cell membranes, leading to a rapid and large indiscriminate release of excitatory neurotransmitters (e.g., glutamate). (Giza and Hovda, 2014; Jamjoom et al., 2021; Johnson et al., 2013; Loane and Faden, 2010). This can result in dysregulation of the glutaminergic system and excitotoxicity via excessive stimulation of N-methyl--D-aspartate (NMDA) and *α*-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) receptors (Choi, 1987; Kaplan et al., 2018; McAllister, 2011; Zhou et al., 2013). Damage to astrocytes following TBI also contributes because there can be dysregulation of astrocytic glutamate transporters excitatory amino acid transporter-1 EAAT1 and −2 that limits extracellular glutamate clearance (Dorsett et al., 2017; van Landeghem et al., 2006). A downstream effect of the increased extracellular glutamate and stimulation of NMDA and AMPA receptors is the excessive cellular influx of Ca^{2+}. Increased intracellular levels of Ca^{2+} and dysregulation of Ca^{2+} metabolism can activate caspases and calpains ultimately leading to neuronal necrosis and apoptosis (Choi, 1987; Kaplan et al., 2018; McAllister, 2011; Tehse and Taghibiglou, 2019).

Acute and chronic stress can influence pre-synaptic neurons so that the probability of glutamate release is increased causing glutamate levels to remain elevated (Gunasekaran et al., 2021). Due to the prolonged response or lack of adaptation to stressors, chronic stress results in the persisting elevation of glutamate and subsequent excitotoxic effects (Dunlop et al., 1999; McEwen, 2007; Moghaddam, 2002; O'Shea, 2002; Popoli et al., 2011). Activation of astrocytes leads to impaired glutamate clearance and increased extracellular glutamate (Dang et al., 2022; Liddelow et al., 2017; Yu et al., 2019). Like TBI, the increase in extracellular glutamate leads to excessive activation of NMDA and AMPA receptors followed by influx of Ca^{2+} and destructive downstream effects such as activation of caspases, calpains, and mitochondrial toxicity that ultimately led to neuronal death (Choi, 1987; Edwards et al., 2016; Kaplan et al., 2018; Lau and Tymianski, 2010; McAllister, 2011). Therefore, if stress precedes TBI, the large indiscriminate release of glutamate at the time of injury would occur in what is already an excitotoxic environment. The additional death and activation of astrocytes due to the TBI could further reduce extracellular glutamate clearance. In the context of post-TBI stress, the stress-induced excitotoxicity could exacerbate or prolong the response initiated by the TBI.

2.3. Hypothalamic-pituitary-adrenal (HPA) axis dysregulation

The HPA axis, consisting of the hypothalamus, pituitary gland, and adrenal gland, utilize glucocorticoid hormones, namely cortisol, and feedback loops to control homeostasis (Karaca et al., 2021; Spencer and Deak, 2017). The brain damage caused by TBI can directly affect the HPA axis and cause altered cortisol levels (Barton et al., 2021; Bromberg et al., 2020; Rowe et al., 2016; Taheri et al., 2022). For example, TBI has been linked to atrophy of the hypothalamus and hypopituitarism (Dennis et al., 2017; Klose et al., 2007). Although glucocorticoids have both anti- and pro-inflammatory actions, excessive HPA axis activation at the hyperacute stage of TBI may increase pro-inflammatory markers and DAM in HPA brain regions while HPA axis suppression at more chronic timepoints may limit anti-inflammatory signalling of glucocorticoids, both exacerbating neuroinflammation and cell death (Hill and Spencer-Segal, 2021; Sorrells et al., 2014; Taheri et al., 2022; Tapp et al., 2019).

Stress activates the HPA axis releasing glucocorticoids to act on downstream effectors and negative feedback loops to relieve allostatic load and restore homeostasis (McEwen, 2007; Oyola and Handa, 2017). Acute activation and prompt deactivation can provide protective effects but during events of constant or prolonged stress, the HPA axis and stress response become dysregulated and can be detrimental to health (McEwen, 2007, 2017). The HPA axis dysregulation influences the ANS as these systems are coupled to respond appropriately to various stressors

(Mueller et al., 2022). Overall, pre-existing HPA axis dysregulation could result in excessive activation at the hyperacute stage of TBI; whilst post-TBI stress coupled with TBI-induced damage to the HPA axis damage is likely to result in a sub-optimal response to said stress and be a detriment to health in TBI survivors.

2.4. Autonomic nervous system (ANS) dysfunction

Following TBI, hyperactivation of the sympathetic nervous system (SNS) of the ANS leads to an acute release of catecholamines, also known as sympathetic storming, that gradually declines over time (Lemke, 2004, 2007; McDonald et al., 2020). Dysfunction of the ANS leads to disrupted communication between the SNS and parasympathetic nervous system (PNS) explaining the exaggerated SNS response and lack of opposing PNS response, leading to the sympathetic storming and symptoms of pupil dilation, tachycardia, and hypertension (Lemke, 2004, 2007). This ANS dysfunction can have systemic effects throughout the body affecting a wide range of organs contributing to worsened neurological outcomes following TBI (Esterov and Greenwald, 2017; McDonald et al., 2020).

In the case of stress, the coupling of the HPA axis and the ANS leads to an acute release of catecholamines that act on various bodily systems in response to a stressor (Mueller et al., 2022). When faced with a stressor, the SNS increases activity to modulate heart rate, blood pressure, and respiratory rate amongst others (Daniela et al., 2022). The dysregulation of the SNS and counteracting PNS impair catecholamine release and lead to impaired bodily responses to a subsequent acute stressor and increased allostatic load (Teixeira et al., 2015; Won and Kim, 2016). Together, this dysregulated ANS response, impaired HPA activity and increased allostatic load contribute to promoting neuroinflammation and oxidative stress (Daniela et al., 2022; Teixeira et al., 2015; Won and Kim, 2016). With stress and TBI both capable of dysregulating the ANS response, a subsequent stressor such as a TBI or post-TBI stress, could compound the allostatic load and further dysregulate ANS responses to subsequent stressors.

2.5. Oxidative stress

Following TBI, oxidative stress is a result of an imbalance of production and removal of reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS and RNS increase due to DAM, immune cell activation, excessive glutamate, and increased Ca^{2+} (Chen et al., 2012; Frati et al., 2017; Jamjoom et al., 2021). DAM can lead to increased ROS and RNS via mechanisms related to nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, iron, and mitochondria (Smith et al., 2022). Increased production of these reactive species from TBI depletes the host of antioxidant enzymes creating excess RNS and ROS that can lead to lipid peroxidation and membrane disruption, calpain activation, protein degradation, and DNA deterioration all which contribute to cell death (Frati et al., 2017; Kaplan et al., 2018; Wang et al., 2020).

Facing constant and/or prolonged stressors and subsequent increases in glucocorticoid levels can also lead to oxidative stress via excess production of ROS and RNS (Juszczyk et al., 2021). Similar to TBI, the DAM, excessive glutamate, and increased Ca^{2+} that can occur under stress lead to excessive ROS and RNS (Chen et al., 2012; Frati et al., 2017; Guevara et al., 2020; Jamjoom et al., 2021; Seo et al., 2012; Spencer et al., 2016). Dysregulated production and removal of ROS and RNS that results in excess of reactive species can lead to lipid peroxidation and membrane disruption, calpain activation, protein degradation, and DNA deterioration – all which contribute to cell death (Juszczyk et al., 2021). As stress and TBI can both result in oxidative stress via similar mechanisms, it is reasonable to predict that this may have an additive or synergistic effect when combined.

Broadly speaking, each of the above pathophysiological mechanisms highlighted in this section have overlapping characteristics across TBI and stress. However, it is important to acknowledge that there are also differences between the responses evoked by TBI and stress within these mechanisms, including temporal, spatial, and structural/cellular/molecular subtleties. Temporally, TBI can initiate immediate pathological responses while pathological responses due to stress often require extended periods of time to develop. For example, glutamate release rapidly peaks and then declines after TBI (Giza and Hovda, 2014) whereas chronic stress can eventually result in a dysregulated and persisting increase in glutamate levels (Dunlop et al., 1999; McEwen, 2007; Moghaddam, 2002; O'Shea, 2002; Popoli et al., 2011). Spatially, TBI results in a robust central response that is largely localized to the site of injury whilst having a relatively less profound impact on the periphery (Giza and Hovda, 2014; Monsour et al., 2022). On the other hand, although stress processes inherently involve and impact the brain, the influences of stress are more systemic in nature (McEwen, 2007). At a structural level, TBI can cause immediate and overt damage to brain structures (e.g., lesions observed via conventional imaging) including those that are central to HPA axis regulation (Dennis et al., 2017; Klose et al., 2007). Conversely, stress does not immediately manifest in macroscopic brain damage but instead can lead to malfunction of negative feedback loops within the HPA axis that cause dysregulation overtime (Oyola and Handa, 2017). From a cellular and molecular perspective, there are also differences with regards to specific immune cells and cytokines that are most critically involved in TBI versus stress. Overall, further research is required to provide insight into these condition-specific complexities and how they may interact when combined.

3. Temporal complexities of stress and TBI

As shown in Fig. 2, the combination of stress and TBI can involve different temporal scenarios. The acute event of a TBI is inherently stressful, including disruption of stress regulation pathways. Even in the absence of any overt pre-injury or post-injury stress (e.g. Fig. 2A), TBI can have long lasting consequences. For example, there is strong preclinical evidence from rodent models that TBI induces anxiety-, depression-, and PTSD-like behaviours. (Aravind et al., 2020; Brady et al., 2019; Bray et al., 2022; Elder et al., 2012; Perez-Garcia et al., 2018; Semple et al., 2019; Shultz et al., 2020; Witcher et al., 2021; Zhuang et al., 2021). Generally speaking, human studies appear to corroborate these animal study findings, with TBI survivors at an increased risk of stress-related mood disorders such as depression, anxiety, and PTSD following TBI (Bryden et al., 2019; Dretsch et al., 2015; Howlett et al., 2022; Jorge and Arciniegas, 2014; Semple et al., 2019; Shultz et al., 2020). With the human study conclusions and corroborating animal study conclusions, TBI without pre-injury and post-injury stress is enough to lead to persistent deficits.

3.1. The impact of pre-injury stress on TBI outcomes

The period of pre-injury stress could range from experiencing early life childhood stress to experiencing a high degree of stress in a relatively short time leading up to a TBI (Fig. 2B and D). Early life adversity can lead to dysregulated stress reactivity exacerbating future stress-related disease states following TBI (Russell et al., 2018). Early life adversity increases the incidence and severity of TBI symptoms while impairing recovery after TBI later in life due to an exaggerated response to stress and disease (Weil et al., 2022). This may be due to early life adversity priming the developing immune system to produce an exacerbated inflammatory response to future TBI leading to worse tissue damage and impaired functional recovery. Sanchez et al. (2021) investigated the effects of early life adversity prior to TBI by removing rat pups from their nursing mothers for 3 h/day from post-natal days (PND) 2–14. Following this treatment, the male pups received a mild to moderate TBI via parasagittal fluid percussion injury (FPI) at 2 months of age. Results showed increased corticosterone, increased cortical atrophy, and impairments to hippocampal-dependent learning and memory in early life

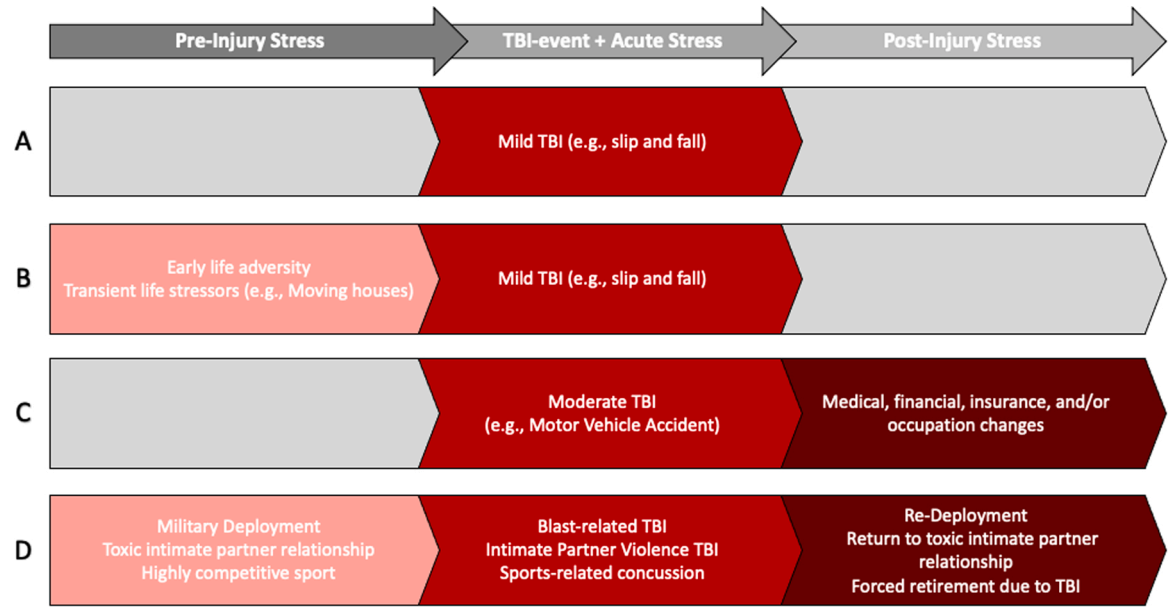

Fig. 2. Temporal scenarios of stress and TBI. The different scenarios of TBI and stress presented here are simply examples of what could occur but it is important to note that TBI severity and stressors are interchangeable across scenarios on a patient to patient basis. **(A)** Each TBI-causing event involves some degree of acute stress. For example, an individual may experience a mild TBI, and associated acute stress; however there was no obvious pre-injury stress and the individual makes a rapid and full recovery (i.e., no obvious post-injury stressors). **(B)** A TBI event is often preceded by some form of pre-injury stress. For example, someone may have experienced an early life adversity or there is a transient life stressor (e.g., moving houses, final exams) ongoing at the time of a mild TBI; however, the individual makes an adequate TBI recovery without any major post-injury stressors. **(C)** Moderate and severe TBI, as well as mild TBI with persisting symptoms, can result in significant post-injury stressors. For example, a previously unstressed individual may suddenly sustain a TBI in a motor vehicle accident and be faced with post-injury stressors such as medical, financial, insurance, and/or occupation changes. **(D)** There are many examples of different scenarios that involve a TBI event that is sandwiched between some combination of pre- and post-injury stressors. For example military personnel, intimate partner violence survivors, and high-level athletes are all individuals that encounter pre-injury stress due to the nature of situation and are at high-risk of sustaining a TBI. Following the TBI the individuals either return to the stressful environment or are faced with major life changes (e.g., cannot return to sport or military due to TBI).

adversity + TBI animals compared to controls and TBI-only groups (Sanchez et al., 2021). Lajud et al. (2021) used a similar stress paradigm by removing rat pups from the mother for 3 h/day from PND 1–21, immediately followed by a mild controlled cortical impact (CCI) to induce TBI in male animals. Pre-injury stress increased the level of the pro-inflammatory cytokine IL-1β after CCI, while IL-6 and TNFα were consistent across stress-only, TBI-only and stress + TBI groups (Lajud et al., 2021).

Other studies have examined the effects of pre-injury stress that occurs later in life. Young-adult male mice were exposed to 4 days of chronic variable stress (cold water swim, cage tilt, food deprivation, restraint, and wet bedding) and then subjected to a closed head impact to induce mild TBI (Fesharaki-Zadeh et al., 2020). Consistent with previous findings (Russell et al., 2018), mice subjected to stress prior to TBI had impaired spatial navigation, increased anxiety-like behaviour, and increased disease state microglia/macrophages compared to controls and TBI-only animals (Fesharaki-Zadeh et al., 2020). Another study examined how exposure to stress followed by a period of no stress prior to TBI altered outcomes in male rats (de la Tremblaye et al., 2021). Animals that had 4 weeks of chronic unpredictable stress (i.e., confinement, cage tilt, isolation, cage shaking, predator sent stress, social instability, tail pinch, restraint, and electric foot shock) from PND30–60 followed by 4 weeks of no stress (PND 60–90) and then a moderate CCI had decreased anxiety-like behaviour and enhanced learning and memory relative to rats experiencing TBI immediately following stress (de la Tremblaye et al., 2021).

In summary, the pre-TBI stress literature to date suggests that early life adversity and a later TBI leads to increased cortical atrophy, memory impairments, and increased IL-1β (Fesharaki-Zadeh et al., 2020; Lajud et al., 2021; Sanchez et al., 2021). Stress without recovery prior to TBI leads to increased DAM, anxiety-like behaviour, and impaired spatial navigation (Fesharaki-Zadeh et al., 2020). On the other hand, stress with adequate recovery prior to TBI may be neuroprotective with reduced anxiety-like behaviour and better cognitive recovery (de la Tremblaye et al., 2021).

3.2. The impact of post-injury stress on TBI outcomes

There are scenarios where an individual may not experience a high degree of stress until after the TBI (e.g., Fig. 2C), at which stage post-injury stressors such as medical bills, job loss, legal cases, disability, and life adjustment enter the equation. Fesharaki-Zadeh et al. (2020) administered male mice a closed head mild TBI followed by four days of chronic variable stress which included cold water swim, cage tilt, food deprivation, restraint, and wet bedding. Mice that received post-injury stress had increased anxiety-like behaviour compared to sham controls and TBI-only groups respectively; however, no significant increase in astrocytic activation or DAM was observed (Fesharaki-Zadeh et al., 2020). Tapp et al. (2020) examined the effects of a moderate lateral FPI followed by three consecutive days of sleep disturbance as a stressor in both male and female mice. At 3 days post-injury there were no differences in plasma corticosterone levels between TBI + post-injury stress and TBI-only groups, but the post-injury stress group did have an enhanced microglial/macrophage response and elevated inflammatory mediators (e.g., TNFα, CCl2, TREM2, and GFAP) in response to TBI (Tapp et al., 2020). At 7 days post-injury, the TBI + post-injury stress group had significantly more of $CD45^{+}$ cells compared to TBI-only mice suggesting persistent inflammation in the ipsilateral cortex (Tapp et al., 2020). Across all timepoints and measures, there were no sex differences identified (Tapp et al., 2020). Using a weight drop moderate TBI model and post-injury restraint stress in male mice, Gao et al. (2022) found that at both 3- and 7-days post-injury, BBB integrity was disrupted with significantly greater leakage in TBI + post-injury stress group compared to TBI-only group. To investigate the impact of stress at more chronic

TBI recovery times in male rats, mild or moderate CCI was followed by a 15-minute forced swim test stressor at 54 days post-injury and 30 min of restraint stress at 70 days post-injury (Taylor et al., 2008). Compared to sham controls, mild CCI led to significant increases in plasma corticosterone whereas moderate CCI led to significant decreases in response to these stressors. At 70 days post-injury, rats subjected to moderate CCI had more cortical tissue loss compared to mild CCI with marked neuronal loss in the CA3 hippocampal region (Taylor et al., 2008). Together, the literature reviewed suggests TBI immediately followed by post-injury stress may reduce BBB integrity while exacerbating the inflammatory response (Gao et al., 2022; Tapp et al., 2020) with cortical loss dependent on severity of injury (Taylor et al., 2008).

3.3. The impact of combined pre- and post-injury stress on TBI outcomes

There are scenarios that can involve high levels of both pre- and post-TBI stress (e.g., Fig. 2D). For example, this may occur in individuals that return to the same stressful environments that they sustained the TBI in (e.g., first responders, soldiers, intimate partner violence survivors, athletes), or may involve different pre- and post-injury stressors (e.g., a soldier that sustains a TBI, is discharged and faces post-injury stressors related to recovery and adjustment). Of relevance, a study of hospitalised medicare found that a diagnosis of depression, anxiety, PTSD, psychosis, or rheumatoid/osteoarthritis prior to experiencing a TBI was significantly associated with a PTSD diagnosis following TBI (Albrecht et al., 2017). Similarly, in a population of intimate partner violence survivors, probable TBI increases the likelihood of comorbid depression and PTSD, as well as worsening symptoms of depression or PTSD (Cimino et al., 2019). Many military veterans also receive a comorbid PTSD diagnosis after TBI. For example, PTSD prevalence was nearly 0% prior to TBI but increased to a prevalence of 39.4% after TBI in active and reserve service members (Hai et al., 2023). Veterans who experienced TBI on deployment were also more likely to have more severe PTSD symptoms, re-experience TBI symptoms and have worse cognitive processing speeds (Jurick et al., 2021; Martindale et al., 2021).

There are few animal model studies that have examined the impact of combined pre- and post-injury stress on TBI outcomes. Acosta et al. (2013) investigated rats allocated to either sham control, stress only (i.e. PTSD group), TBI only, or TBI+PTSD (pre- and post-TBI stress) groups. To model PTSD, rats were exposed to an hour of non-tactile cues from an adult cat on experimental days 1 and 11. From experimental days 1–31, rats were also exposed to social instability daily by pseudorandom changes to pairs of cage cohorts. A moderate CCI was induced on experimental day 12, and rats were euthanized at 8 weeks post-TBI. Both TBI and TBI-PTSD groups had upregulation of DAM in the cortex, striatum, and thalamus, decreased cell survival in the hippocampal CA3 region, and decreased cell proliferation in the dentate gyrus compared to the sham control and PTSD groups. However, there were no significant differences between TBI-only and TBI+PTSD groups, suggesting that the pre- and post-injury stress had no synergistic or additive effects on the above measures (Acosta et al., 2013). A different study exposed mice to 21 days of unpredictable chronic mild stress (i.e., restraint, electric footshock, orbital shaking, forced bath, restraint + shaking, and sleep disruption) before administering repetitive closed head mild TBI combined with a blast injury model followed by social isolation post-TBI (Portillo et al., 2023). Male and female animals subjected to pre-injury stress, TBI, and post-injury stress showed similar increases in anxiety-like behaviour acutely after the injury; whilst only male mice that received the stress (both with and without TBI) had hypersomnia (Portillo et al., 2023).

4. Future directions and conclusions

To briefly summarize the current state of knowledge, early life adversity and a future TBI, stress immediately followed by a TBI, or TBI with post-injury stress may exacerbate TBI injury mechanisms and deficits (Fesharaki-Zadeh et al., 2020, Lajud et al., 2021, Russell et al., 2018, Sanchez et al., 2021, Tapp et al., 2020, Weil et al., 2022). On the other hand, pre-injury stress with adequate recovery followed by TBI may result in resilience and neuroprotection (de la Tremblaye et al., 2021). With that said, the complex temporal relationship between stress and TBI have yet to be comprehensively elucidated.

One avenue to expand our knowledge on this topic is the application of animal models. For example, the use of rodent models would allow for the rigorous, controlled, and efficient examination of questions pertaining to timing (both the sequence of TBI and stress, as well as the recovery time between them) and related long term implications, underlying pathophysiology, and treatments. Such research could be particularly informative in terms of guiding recovery timelines for stressed individuals returning to environments that place them at high-risk of TBI and further stress. This may be particularly relevant to populations such as military personnel and intimate partner violence survivors considering the relatively high incidence of PTSD even before a TBI occurs (Hoge et al., 2008; Kaplan et al., 2018; Monsour et al., 2022). Unfortunately, animal research into the scenario of pre-injury stress + TBI + post-injury stress is nearly non-existent, but should be prioritised in order to improve our understanding and care of these vulnerable individuals. To maximise the clinical relevance of this research it will be important to choose the appropriate animal models (e.g., acute versus chronic stress; variable, maternal separation, social isolation, predator exposure, etc. stress models; mild, moderate, or severe TBI models; single versus repeated TBI model; age; sex), which should ultimately be informed by the specific research question/clinical population at hand. In doing so, animal model research will help bridge important knowledge gaps related to how stress-modifying factors such as the type, severity, and duration of TBI, as well as sex, may differentially impact outcomes. For example, despite evidence indicating that there are sex differences related to both TBI and stress (Bangasser and Wiersielis, 2018; Gupte et al., 2019; Styrke et al., 2013; Verma et al., 2011), the available preclinical literature that was reviewed in this paper is heavily weighted towards males. If we are to one day provide a precision medicine approach for TBI patients that combats the heterogeneity of the condition, the continued investigation of the abovementioned factors in both preclinical and clinical settings will be crucial.

Related to this, if stress is a factor that should be considered in the care of TBI, then measures to quantify stress should be developed/applied in preclinical and clinical settings. This is important because stress and TBI are both heterogenous conditions where similar stressors and/or TBI can ultimately impact individuals differently. In preclinical studies, these measures might include corticosterone (Nakagawa et al., 2019) and glucocorticoid levels (Sze et al., 2018), fluid biomarker profiles (Dion-Albert et al., 2022), and behaviour assays (Cao et al., 2021; Portillo et al., 2023; Tang et al., 2019). Similarly, stress questionnaires (Stryker et al., 2021), as well as cortisol or cortisone measurements (Botía et al., 2023), can be applied in the clinical setting. The inclusion of these measures in future studies will provide a more comprehensive understanding of the various relationships between TBI and stress, including how different types of stressor (e.g., physical, emotional, mental) and TBI (e.g., type, severity) manifest and ultimately influence outcomes and care strategies.

Stress and TBI are both linked to numerous comorbidities that can affect quality of life after TBI. Chronic stress with a dysregulated response is linked to numerous adverse health disorders including anxiety, depression, PTSD, gastrointestinal disorders, cardiovascular disease, Alzheimer's disease, epilepsy, and cancer (Dai et al., 2020; Doney et al., 2022; Juszczyk et al., 2021; McEwen, 2007; Rupasinghe et al., 2022). Similarly, TBI has also been linked to numerous psychiatric disorders such as anxiety, depression, and PTSD, neurodegenerative disorders such as Alzheimer's disease and dementia (Haarbauer-Krupa et al., 2021), and other conditions such as post-traumatic epilepsy (Ali et al., 2019; Christensen et al., 2009; Feigin et al., 2019), gastrointestinal disorders, cardiovascular disease (McDonald et al., 2020) and cancer (Lu

et al., 2022). In order to optimise prevention/treatment of these comorbidities we must first disentangle whether they are being driven by stress and/or TBI. Notably, compared to the available TBI treatment/interventions, stress and stress-related disorders are more advanced and include diet, exercise, mindfulness, relaxation, sleep, and cognitive behavioural therapy (Horn et al., 2022; Lemay et al., 2019; Saeed et al., 2019; van den Berg and Beute, 2021). Therefore, if stress, or the underlying mechanisms that the above interventions are acting on, are a contributing factor to functional deficits in a TBI patient, these interventions may be a useful approach to improve their quality of life (Acabchuk et al., 2021; Bisson et al., 2021; Howlett and Stein, 2016; Lemay et al., 2019; Little et al., 2021; Zaccari et al., 2020).

A major focus of the TBI field is improving diagnosis and prognosis methods that are currently reliant on subjective self-reported symptoms or non-specific clinical signs (Costello et al., 2018). Promising objective biomarkers from biological fluid (e.g., cerebrospinal fluid and blood) including proteins, microRNA, and extracellular vesicles that are sensitive to neuroaxonal and glial injury, inflammation, and/or cerebrovascular damage are now being proposed as means to improve diagnosis, prognosis, and precision therapeutics (Costello et al., 2018; Helmrich et al., 2022; Huibregtse et al., 2021; Korley et al., 2022; Lindblad et al., 2021; McDonald et al., 2023; Mitra et al., 2022; Pleines et al., 2001; Romeo et al., 2005; Shultz et al., 2022; Zetterberg and Blennow, 2016). However, because of the pathophysiological overlap between TBI and stress we must understand how stress influences these biomarkers before we can optimally apply them in the TBI patient setting. As such, human biomarker studies that account for stress, as will animal model studies that are able to tightly control when stress is introduced, will be useful to advance this field. Once developed, one can envision stress and TBI biomarkers being implemented to screen stress levels in individuals at high risk of TBI, monitor recovery after a TBI and help inform return to work/play decisions, and identify pathophysiological mechanisms that can be targeted with interventions. While objective biomarkers would be ideal, even self-reported stress measures pre- and post-TBI would provide the clinician some degree of information to help guide patient care.

In conclusion, there is an inherent and bidirectional relationship between TBI and stress that is arguably present in every TBI patient. Although research into this relationship is still in its infancy, it appears that in at least some contexts stress may be a highly influential factor in TBI pathophysiology and recovery, and vice versa. As such, further studies on this topic should be a priority and may provide a foundation for advancements in patient care related to monitoring or modifying stress to ultimately improve the lives of those affected by TBI.

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