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The role of the stress system in recovery after traumatic brain injury: A tribute to Bruce S. McEwen

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ABSTRACT

Traumatic brain injury (TBI) represents a major public health concern. Although the majority of individuals that suffer mild-moderate TBI recover relatively quickly, a substantial subset of individuals experiences prolonged and debilitating symptoms. An exacerbated response to physiological and psychological stressors after TBI may mediate poor functional recovery. Individuals with TBI can suffer from poor stress tolerance, impairments in the ability to evaluate stressors, and poor initiation (and cessation) of neuroendocrine stress responses, all of which can exacerbate TBI-mediated dysfunction. Here, we pay tribute to the pioneering neuroendocrinologist Dr. Bruce McEwen by discussing the ways in which his work on stress physiology and allostatic loading impacts the TBI patient population both before and after their injuries. Specifically, we will discuss the modulatory role of hypothalamic-pituitary-adrenal axis responses immediately after TBI and later in recovery. We will also consider the impact of stressors and stress responses in promoting post-concussive syndrome and post-traumatic stress disorders, two common sequelae of TBI. Finally, we will explore the role of early life stressors, prior to brain injuries, as modulators of injury outcomes.

1. Bruce McEwen

When Bruce McEwen passed away on January 2nd of 2020, it should have been a portent of the tumultuous year that was to come. In retrospect of course, it was just the beginning of an era marked by tremendous strife, illness, conflict, and loss that represented the ultimate in worldwide allostatic loading. A world without Bruce was always going to be far diminished, as he was among the world's most talented and productive scientists, for decades making fundamental discoveries into the nature of behavioral biology and stress. His intellectual curiosity, penetrating intelligence, and dogged pursuit of biological insight placed him at the center of a scientific field that he helped revolutionize. Remarkably however, Bruce's scientific contributions paled in comparison to his character, warmth, and generosity. Bruce was universally admired by those that knew his work but loved by those that knew him personally. He was a tireless champion of his trainees, collaborators, and colleagues, and took genuine pleasure in seeing them succeed.

One of us (ZMW) had the distinct honor of serving as a postdoctoral researcher in Bruce's lab at Rockefeller (2008–2010). As a scientific trainee being mentored is, at least in part, how we learn how to mentor our own students. Bruce's combination of brilliance and gentleness, kindness and laser focus, productivity and wisdom are both something to aspire to and extremely hard to achieve. As one of the greatest teachers of scientists ever, Bruce's ideas, approach and thoughtfulness are central to our thinking and how we go about doing science (Dhabhar et al., 2020).

2. Introduction

Our lab studies a problem, traumatic brain injury (TBI), and specifically the uneven patterns of recovery among survivors, that on the surface bears little direct relationship to the work conducted in the McEwen lab. Recovery from TBI is largely determined by factors such as TBI severity, age, sex, and preexisting conditions. For example, most noticeable symptoms of mild TBI resolve within a couple of weeks of the initial injury, at least among a substantial majority of individuals. However, there is a group of individuals that experience a very different course of recovery, characterized by significant long-term disability, persistent symptoms, and reduced quality of life (Levin and Diaz-Arrastia, 2015). Moreover, this population of brain injury survivors is also disproportionately vulnerable to other kinds of disease states including post-traumatic stress disorder, substance abuse, depression,

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cardiovascular disease, and a whole host of other maladies (McKinlay et al., 2009; Tremblay et al., 2013). Thus, it is imperative that we understand the source of this variability in outcome if we are to promote optimal recovery among all brain injury survivors.

Bruce's work focused on how the brain, body, and behavior adapt to environmental challenges and how this continued need for adaptation could exert significant costs for the organism. His work focused on psychological stressors and how chronic stress could alter, and in some cases damage, the function of the nervous system (Bulloch and McEwen, 2002). The perception of a psychological stressor leads to a cascade of events that includes activation of stress responsive neuroendocrine systems, rising extracellular excitatory amino acid (EAA) concentrations, and downstream changes in neural structure and function (McEwen and Magarinos, 2001). This process, if repeated or extended in time, could eventually produce permanent alterations in those neuroendocrine systems, the structure of the brain, and in behavior (Lupien et al., 2009). Chronic stress, therefore, could promote many of the maladies that plague our society including mood and anxiety disorders, addiction, and cognitive decline.

From this perspective, TBI, irrespective of severity, can be conceptualized as a physical and emotional stressor and one that produces many parallel physiological responses, including activation of stress systems, inflammatory signaling, metabolic dysfunction, and excess EAA release among many others (Werner and Engelhard, 2007). TBI also has the added effect of (potentially) directly damaging the neural structures that mediate the appraisal of psychological and physical threats, and the regulation of neuroendocrine function. Moreover, individuals that experience a TBI (across all severities) may be forced to adapt to a new situation that can include prolonged hospitalization, absence from school or work, pain, disruption in relationships, and new disabilities (Andelic et al., 2018; Ponsford et al., 2008). Additionally, the physical and mental health history prior to a TBI can be critical determinants of the course of disability and recovery.

In this paper, we will explore the ways in which stress, broadly considered, serves to shape the lives of individuals who have suffered a TBI. Specifically, we will discuss several key intersections between TBI and stress responsive systems. First, we will discuss how TBI contributes to allostatic loading and the ways in which brain injury interacts bidirectionally with the HPA axis system. Next, we will consider how stress responses contribute to the development of two common TBI sequelae, post-concussion syndrome, and posttraumatic stress disorder. Finally, we will consider how early life experiences can shape responses to TBI later in life.

3. Traumatic brain injury, allostasis and allostatic load

The psychological and biomedical costs of chronic stress, long a research interest of the McEwen lab, can vary dramatically among individuals due to genetics, experience, and the specific nature of the stressor (McEwen and Stellar, 1993; Sapolsky et al., 1983, 1986). In order to try to understand the ways in which individuals respond to stress, McEwen and colleagues proposed that exposure to chronic stress exerted its costs by contributing to allostatic loading. Allostasis, as originally defined by Sterling and Eyer (1988) represents the operating range through which the physiological process can adjust. This concept was further refined by McEwen and colleagues to represent the physiological and psychological responses to environmental challenges (McEwen and Stellar, 1993).

Archetypal among these responses is the activation of the hypothalamic-pituitary-adrenal axis (HPA axis) in response to stressors. The HPA axis response to stress, broadly defined as a disruption of homeostasis, is the production of hormones ultimately aimed at restoration of homeostasis (Carrasco and Van de Kar, 2003). Activation of the HPA axis begins in the hypothalamic paraventricular nucleus via production of corticotropin releasing hormone (CRH). CRH is released into hypophyseal portal blood, targets the anterior pituitary gland, and promotes pituitary production of adrenocorticotropic hormone (ACTH). In turn, ACTH release into the blood initiates the production of glucocorticoids by the adrenal glands of the kidneys (Smith and Vale, 2006). Glucocorticoids (i.e. corticosterone, or cortisol in humans) serve a number of critical functions: they restore homeostasis, promote both anti- and pro-inflammatory effects, and exert negative feedback to the hypothalamus thereby inhibiting further CRH release (Herman et al., 2012; Silverman and Sternberg, 2012; Sorrells et al., 2009). At low circulating concentrations, glucocorticoids bind the high affinity mineralocorticoid receptor (MR), however increased production of glucocorticoids during a stressor saturates MR binding and promotes binding of glucocorticoids to the low affinity glucocorticoid receptor (GR) (Herman et al., 2012). GR binding then mediates a negative feedback response and inhibits further production of stress hormones at all three levels of the HPA axis (Herman et al., 2012).

Under normal conditions, organisms can and do respond to homeostatic perturbations appropriately and effectively, meaning that the HPA axis responses are of appropriate magnitude and duration to respond to the challenge. McEwen's major contribution to the theoretical development of this concept was to integrate the total physiological costs associated with *both* the exposure to the stressor *and* the anti-stress responses, together which he called allostatic loading (McEwen and Stellar, 1993). Moreover, in cases of repeated or severe stressors (or in disease states) a mismatch between the stressor and the stress response can emerge which can further tax the system. In the HPA axis example, prolonged exposure to high levels of glucocorticoid hormones can have deleterious effects on neural, immune, and other tissues (McEwen, 2004, 2007). Poor regulation of the HPA axis negative feedback system can result in sluggish termination of the response, thereby exaggerating tissue-level exposure to anti-stress mediators. However, the converse response, that is an inadequate HPA axis response to a stressor, may lead to inappropriate inflammatory responses or other deleterious consequences. Thus, allostatic loading represents the totality of the physiological investment in challenges and can be exacerbated by both over- and under-reactions. Further, the HPA axis response to *perceived* psychological stressors is just one of many potential sets of stimuli and paired physiological responses that accumulate allostatic costs.

TBI is a disease process that is initiated by a single event, a physical blow to the head, but initiates a complex process of biological and psychosocial adaptation that represents a particularly challenging example of allostatic loading that evolves over long time scales after the initial injury (Bay and Donders, 2008; Masel and DeWitt, 2010). Individuals that experience TBI may be forced to deal with a huge variety of potentially stressful events including the actual physical force, medical interventions, potential injuries beyond the TBI, pain, at least a temporary loss of independence, potential disability and sometimes dramatic changes in relationships and careers. Moreover, these processes are superimposed over a nervous system that can have an impaired ability to assess stressors or respond optimally (both physiologically and psychologically). In this section, we will discuss the ways in which TBI can result in and be exacerbated by allostatic loading.

Even mild TBI can both directly damage cerebral structures and set into motion a secondary cascade of events that can further exacerbate tissue damage (Giza and Hovda, 2014). These secondary events, which include excitoxicity, metabolic dysfunction, axonal disconnections and inflammatory events are the focus of much TBI research regardless of severity because they occur after the initial injury, are powerful determinants of long-term outcomes, and at least potentially could be the targets of clinical intervention (Morganti-Kossmann et al., 2019). As allostatic loading theory predicts, glucocorticoid actions on metabolic, inflammatory, and neurochemical signaling are potential regulators of these secondary events after severe TBI (Braakman et al., 1983; Cooper et al., 1979; Muzha et al., 2004). Serum glucocorticoid hormones have a complex relationship with injury outcomes in the early period after TBI. In mild-moderate injuries, glucocorticoid hormone concentrations roughly correlate with injury severity with more seriously injured

individuals tending to bear higher glucocorticoid concentrations (Barton et al., 1987; Cernak et al., 1999). Studies in experimental animals have revealed similar patterns with rapid upregulation of CRH mRNA and increases in serum concentrations of ACTH and glucocorticoids in the first few hours to days after moderate-severe injury (McCullers et al., 2002; Shohami et al., 1995). This is not altogether surprising since TBI very often involves both a psychological stressor and physiological challenges that go beyond the direct injury to the head including loss of blood, fractures, and soft tissue injuries.

However, in more severely injured individuals, the relationship between injury severity and glucocorticoid concentrations can break down and some percentage of individuals will present with acute adrenal insufficiency and low serum cortisol (Cohan et al., 2005). Acute adrenal insufficiency in trauma is a medical emergency and must be treated rapidly to avoid hyponatremia and hypotension (Agha et al., 2007; Hannon et al., 2013). Moreover, insufficient glucocorticoid responses to TBI have the potential to dysregulate neuroinflammatory responses and increase cell death. However, the cause of adrenal insufficiency phenomena remains incompletely understood and likely has several etiologies. For instance, it has been known for over a century that TBI of any severity can result in a general pituitary insufficiency and this was originally interpreted as resulting from direct mechanical damage to the pituitary and portal blood supply (Dusick et al., 2012). Indeed, despite (or perhaps because of) the bony protection afforded by the sella turcica, direct damage to the pituitary itself or the stalk that connects it to the brain is not uncommon (Bistritzer et al., 1981; Kusanagi et al., 2000). Estimates vary, but postmortem and imaging studies have reported that 1/3 or more of individuals that have suffered a moderate to severe TBI exhibit pituitary damage (Benvenga et al., 2000; Ceballos, 1966; Maiya et al., 2008; Salehi et al., 2007). Pituitary dysfunction does not account for all cases of adrenal insufficiency as some patients with low serum cortisol concentrations also exhibit normal (or even enhanced) ACTH responses to exogenous CRH (Cohan et al., 2005; Dimopoulou et al., 2004) indicating that primary adrenal failure can also contribute to adrenal insufficiency.

While HPA axis hypoactivity is potentially dangerous, sustained hyperactivity can also lead to allostatic loading and poorer outcomes. High circulating cortisol that did not decline in the first five days after severe injury predicted poorer cognitive and overall outcomes at 6 months (Barton et al., 2021; Santarsieri et al., 2014) although it remains unclear whether the acutely elevated glucocorticoids are imperiling recovery *per se* or are indicative of greater tissue damage. Thus, as predicted by allostatic theory, optimal recovery seems to occur in conditions when the HPA axis can produce sufficient physiological levels of activation but in a relatively time-limited manner. Low glucocorticoids or sustained exposure to high concentrations of endogenous (or powerful synthetic) steroids also seems to produce poorer outcomes (Santarsieri et al., 2015). This is not entirely surprising given the role that glucocorticoids have in regulating inflammatory responses and other acute reactions to challenge. However, prolonged, or excessive high concentrations of these steroids can have significantly deleterious effects, including promoting inflammatory responses and facilitating neuronal death (Sorrells et al., 2009; Sorrells and Sapolsky, 2007). One potential mechanism underlying this apparent paradox is that both adrenal insufficiency and hypersecretion of glucocorticoids can alter the balance between MR and GR systems. Endogenous glucocorticoids are mixed agonists at both receptors but have a nearly 10-fold higher affinity for MR (Herman et al., 2012; Reul and de Kloet, 1985). In contrast, commonly prescribed synthetic glucocorticoids that are potently immunosuppressive have a higher affinity for the GR. Two synthetic glucocorticoids, dexamethasone and methylprednisolone exacerbate hippocampal apoptosis and cognitive deficits after severe TBI in rats (Zhang et al., 2020). Moreover, treatment with these powerful GR agonists reduced the activity of the HPA axis and reduced plasma corticosterone concentrations. When animals were co-treated with both dexamethasone and corticosterone, the deleterious effects of dexamethasone were significantly reduced, suggesting that activation of both MR and GR systems is required for optimal regulation of inflammatory responses and prevention of cell death (Zhang et al., 2020). The acute stress response after a major injury may be important to help mobilize the emergency metabolic and physiological resources to survive the early post-injury phase.

4. TBI effects on HPA axis regulation and stress responses

Regulation of the HPA axis is the result of the actions of a complex distributed system that includes threat appraisal, hormone production and release, and negative feedback to turn off the stress response. Excessive exposure to stressors (or glucocorticoids) can also impair the function of the cells responsible for negative feedback, creating a vicious cycle (Agorastos and Chrousos, 2022; Miller et al., 2007; Sapolsky et al., 1986). Critically, the structures responsible for threat assessment (and the initiation of stress responses) and negative feedback (for the termination of HPA axis activation) are particularly vulnerable to focal damage and neuronal disconnection following TBI regardless of severity (Cicerone et al., 2006; McAllister, 2011; Zhou et al., 2012).

Experimental and clinical TBI studies have reported disruptions in HPA axis regulation, although the direction of these changes is not always consistent and appears to be dependent on the type and severity of injury, time after injury and stressor type. In experimental animals TBI usually induces acute activation of the HPA axis response as assessed by corticosterone concentration (Grundy et al., 2001; Shohami et al., 1995). However, after the initial period there have been reports of both increased and decreased HPA reactivity, with more severe injuries tending to produce HPA suppression while milder injuries potentiate stress responses. For instance, four weeks after severe cortical contusion injuries (CCI) rats exhibited blunted corticosterone responses to 30 min of restraint stress (Taylor et al., 2006a). However, in a follow-up study the same group reported that a more mild CCI could potentiate HPA responses to restraint out to at least 70 days post injury (Taylor et al., 2008). Similarly, exaggerated glucocorticoid secretion has been reported in rats that underwent restraint stress after a relatively mild fluid percussion injury (Russell et al., 2018). Finally, there are sex differences in HPA responses after TBI. Male mice injured in a mild blast model of brain injuries exhibited increased restraint stress induced corticosterone concentrations, while females exhibited blunted responses relative to sham injured animals (Russell et al., 2018). The neuropathological responses to injury in the brain regions responsible for HPA axis regulation are also sexually differentiated, with greater astro- and micro-gliosis in injured females than males (Bromberg et al., 2020).

The mechanisms underlying these divergent alterations in stress responses are not fully understood. Given that hippocampal cells are critical for mediating negative feedback responses and are often damaged by TBI it could be hypothesized that impairments in negative feedback responses mediate alterations in HPA axis responses. However, dexamethasone suppression tests exhibited intact negative feedback responses after moderate injury suggesting that blunted glucocorticoid responses may be mediated by tighter negative feedback (Taylor et al., 2010). Other groups have reported similar responses to dexamethasone even in animals with blunted stress responses (Blaze et al., 2020; Russell et al., 2018).

Alterations in corticolimbic circuitry with important implication for HPA axis function have been reported after brain injury. For instance, TBI produces structural changes in neuronal architecture that mimic the changes associated with chronic stress even in cases of blunted HPA axis responses. In rats, severe CCI induced reductions in dendritic length and branching in hippocampal CA1 neurons, while a moderate fluid percussion injury induced basolateral amygdalar hypertrophy (Casella et al., 2014; Hoffman et al., 2017). However, it remains unspecified whether alterations in HPA axis physiology are the cause or consequence of these and other circuit-level abnormalities.

5. Postconcussive symptoms

Brain injury symptoms often subside within days or weeks of the injury (Dwyer and Katz, 2018; Rees, 2003). However, for a subset of individuals, symptoms last far longer. Postconcussive symptoms include headaches, blurred vision, insomnia, and attention deficits, among others (Barlow, 2016; Blume and Hawash, 2012). A diagnosis of post-concussive syndrome (PCS) requires 1–3 months of persistent symptoms after injury, though it is not uncommon for patients to report symptoms even 12 months after injury (Dwyer and Katz, 2018). PCS can occur after mild injuries but is more common after moderate or severe TBI (Rees, 2003; Ryan and Warden, 2003; Yeates et al., 2009). While PCS can occur in both children and adults (Barlow, 2016; Blume and Hawash, 2012), it is more likely to develop in women than men (Hanna-Pladdy et al., 2001; Meares et al., 2011; Ponsford et al., 2012). Importantly, one key predictor of PCS is the existence of anxiety and other related psychiatric issues before the injury (Felmingham et al., 2010; Meares et al., 2008).

PCS is a challenge to diagnose, as there are limited tools available to help differentiate it from other related conditions. A high proportion of the general population display traditional 'concussion' symptoms like headaches or impaired concentration, especially in populations that experienced chronic pain or stress-induced headaches (Iverson and McCracken, 1997; Ponsford et al., 2000). Moreover, multiple studies have reported that psychometric assessments of postconcussion symptoms fail to differentiate individuals that have suffered mild TBI from those that have not (Dean et al., 2012; Meares et al., 2011; Ponsford et al., 2012). Diagnostic issues aside, assigning causality to the lasting cognitive and neuropsychiatric symptomology is also a challenge (Rees, 2003; Wojcik, 2014). There is considerable evidence that the psychosocial and cognitive aspects of postconcussive symptoms play a role in symptom duration, in a way that is additive to the initial physical injury (Hanna-Pladdy et al., 2001; Meares et al., 2011; Taylor, 2010). Thus, PCS appears to represent a disease state with multiple etiologies including direct damage to the nervous system, psychosocial disruption associated with injury, *and* preexisting neuropsychiatric issues. The direct contribution of each of these factors remains unknown and likely varies significantly on a case-by-case basis.

6. Postconcussive symptoms and HPA axis physiology

TBI patients in general, and PCS sufferers particularly, exhibit a reduced capacity to manage stressors. For example, individuals with a history of mild TBI are more likely to experience postconcussive symptoms compared to uninjured individuals, including cognitive impairments and mental fatigue (one of the major postconcussive symptoms), especially when exposed to stressful environments (Hanna-Pladdy et al., 2001; Machulda et al., 1998; Taylor, 2010). Indeed, mental fatigue can be observed among brain injured individuals who experience difficulty adapting to an increase in perceived stress (Bohnen and Jolles, 1992; Hinkeldey and Corrigan, 1990). Additionally, individuals who are suffering from postconcussive symptoms may exhibit longer symptom duration when they are in a stressful environment (Hanna-Pladdy et al., 2001). These abnormalities in stressor evaluation, along with disruptions of HPA axis physiology, are potential contributors to PCS.

Although the mechanisms by which the HPA axis contributes to the development of PCS are not fully understood, its direct relationship to several pathological markers of TBI is suggestive of a mediating role. HPA axis-induced activation of microglia contributes to the psychological and cognitive impairments that are hallmarks of post concussive symptoms, typically through increased expression of GR (Sierra et al., 2008; Tapp et al., 2019). Additionally, persistent suppression of the HPA axis after a brain injury, characterized by decreased concentrations of glucocorticoids and CRH release (Hannon et al., 2013; Roe et al., 1998), may lead to a suppression of the immune response acutely after an injury, resulting in prolonged recovery periods associated with PCS (Aimaretti et al., 2004; Lieberman et al., 2001; Tapp et al., 2019). Additionally, cortisol levels are highly variable over the time course of brain injury and are dependent on the severity of the injury. Individuals with mild injuries are more likely to have higher plasma cortisol levels than those with more severe injuries (Bernard et al., 2006; Tanriverdi et al., 2007). Of note, patients with persistently low cortisol levels experience fatigue and weakness (Bushnik et al., 2007; Molaie and Maguire, 2018; Tapp et al., 2019). Moreover, cortisol levels are also predictive of survival after brain injury, with higher mortality rates among moderate-severe TBI patients with persistent cortisol deficiencies (Hannon et al., 2013; Tapp et al., 2019).

Additionally, brain injury survivors may exhibit growth hormone (GH) deficiency associated with lasting cognitive psychiatric symptoms including depression, memory loss, and concentration impairments beyond 6 months after the initial injury irrespective of severity (Elovic and Glenn, 2004; Kelly et al., 2006). GH insufficiencies are tightly correlated with hypopituitarism, which has been studied in clinical populations of TBI survivors and is believed to play a role in many of the behavioral and cognitive abnormalities that last months to years after the brain injury (Karaca et al., 2016; Klose et al., 2007).

7. PCS treatments

Treatment of postconcussive symptoms is conducted on an individualized basis, as many of the lasting impairments have varying causes. The traditional treatment options following brain injury classically included a period of quiet rest to facilitate symptom resolution. However, recent studies have shown that prolonged bed rest increases symptom duration after an injury (Leddy et al., 2012, 2016; Polinder et al., 2018; Thomas et al., 2015). The rest period is dependent on the initial severity of the brain injury, but typically rest therapy is most effective when conducted between a day and a week of the TBI (Haider et al., 2021; Leddy et al., 2016; Makdissi et al., 2017). In contrast to previous dogma in clinical practice, research in recent years has found that mild exercise following a brain injury has been complementary to improving outcomes both acutely and chronically (Broshek et al., 2015; Leddy et al., 2018a, 2018b). Patients who were prescribed bed rest, and to avoid normal activity and exercise, reported higher rates of post-concussive symptoms compared to those who exercised moderately during the recovery period (Broshek et al., 2015; Grool et al., 2016). However, the intensity and timing of exercise are important determinants of TBI outcome, as prolonged or intense periods of exercise during the early period after a mild injury have been shown to increase the rate of recurrent injury and prolong symptoms (Broshek et al., 2015; Silverberg and Iverson, 2013). A growing research interest into the mechanisms of exercise-induced neuroprotection (i.e. reducing inflammation and oxidative stress, and enhancing metabolic health and neural plasticity), suggests that physical exercise may also improve recovery rates via moderating the physiological response to stress, reducing the sensitivity to stress via adaptations of the HPA axis and sympathetic nervous system (Klaperski et al., 2013; Tsatsoulis and Fountoulakis, 2006).

Generally, pharmacological treatment of postconcussive symptoms is focused on addressing symptoms rather than treating the root causes (McAllister, 2016). Affective symptoms have a history of being treated with selective serotonin reuptake inhibitors (SSRIs) among other antidepressants. The prolonged duration of affective symptoms in a subset of TBI individuals often necessitates a lower starting dose of treatment and constant monitoring of symptoms as treatment continues. Anticholinergic drugs may also be prescribed for lasting cognitive impairments after injury, although these are generally avoided as they are known to have off-target effects and often result in adverse side effects (Hadanny and Efrati, 2016). On the other hand, somatic symptoms may be treated non-pharmacologically, with interventions including physical therapy and educational training, as well as sleep hygiene and relaxation techniques. Occasionally, non-steroidal anti-inflammatory analgesics are prescribed to relieve some of the physical pain associated with

symptoms (Grool et al., 2016; Mittenberg et al., 2001). Additionally, neurocognitive rehabilitation is a treatment option to resolve cognitive impairments after concussive brain injuries, as various therapies to improve cognitive processes and maintain attention and memory function can be individualized to the patient (Leddy et al., 2012). In more severe PCS cases, some pharmacological agents that provide physical relief from both somatic symptoms and affective or cognitive impairments are utilized, like tricyclic antidepressants or SSRIs.

8. Posttraumatic stress disorder in TBI patients

TBI and post-traumatic stress disorder (PTSD) are often associated due to their overlapping symptom profiles and the high rates of comorbid TBI/PTSD present in military and civilian populations (Vasterling et al., 2018). Symptoms present in both conditions may include attention deficits, irritability, trouble sleeping, and memory disturbances. The overlap in pathophysiological underpinnings of both TBI and PTSD is evident in the neuroinflammatory response, excitotoxicity cascades, and oxidative damage. The high rates and debilitating effects of comorbid TBI/PTSD suggest the need for the development of novel, effective therapeutic targets (Vasterling et al., 2018).

Not all TBI patients with stress disorders meet the diagnostic criteria for PTSD, rather a subset of this patient population experiences the related acute stress disorder. As a psychiatric diagnosis, acute stress disorder pertains to patients that experience stress-related symptoms within four weeks of a traumatic event (Bryant et al., 2003; Kavan et al., 2012). The addition of acute stress disorder to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) served to address the diagnostic gap for patients experiencing posttraumatic symptoms during the one-month observation period needed before a PTSD diagnosis can be made. According to the DSM-5 criteria for the diagnosis of acute stress disorder, a traumatic event is defined as an event that threatens an individual with serious injury or death (APA, 2013). Stress-related symptoms can be physical, emotional, and mental in nature, including symptoms of intense anxiety, avoidance behaviors, depression, fatigue, fear, dissociation, headaches, and gastrointestinal disruptions (Bryant et al., 2011; Kavan et al., 2012). Among acute stress disorder diagnoses in the DSM-5, the criteria have shifted away from the large emphasis DSM-IV placed on dissociation (Broomhall et al., 2009). For post-traumatic symptoms to be classified as acute stress disorder, the presence of nine or more symptoms from the five predefined categories must occur either during or after the traumatic event (APA, 2013).

Identifying individuals at high risk of developing PTSD can be accomplished through acute stress disorder diagnoses, as 80% of individuals with acute stress disorder develop chronic post-traumatic stress disorder (Bryant and Harvey, 1998; Harvey and Bryant, 2000). PTSD is a psychiatric diagnosis characterized by symptoms of post-traumatic stress, in response to physical or emotional trauma, that persist for more than one month following a traumatic event. Symptoms may include emotional withdrawal, intrusive memory recall or memory loss, increased threat sensitivity, irritability, alterations of consciousness, and poor concentration (Breslau, 2009). PTSD also increases reactivity and arousal, producing symptoms such as heightened startle response and hypervigilance (Gupta, 2013). As a result of the intrusive symptoms associated with PTSD, individuals may engage in behaviors that avoid cues or environments that may trigger memory recall of the trauma. This may be due to brain damage in regions involved in the stress response associated with threat appraisal (Niogi et al., 2008; Vasa et al., 2004). The development of PTSD can occur within months of the traumatic event and persist for months or years (APA, 2013; Agaibi and Wilson, 2005). Similar to TBI outcomes, the severity of PTSD can be worsened by the development of co-occurring conditions such as mood disorders and substance abuse (Yehuda et al., 2015), and the comorbidity of TBI and PTSD is associated with higher rates of neuropsychiatric health problems (Vanderploeg et al., 2009). Patients with comorbid TBI of any severity and PTSD also have greater health risks and cognitive impairments than those without PTSD (Zatzick et al., 2010). Additionally, patients with mild TBI can experience both acute stress disorder and PTSD (Bryant, 2001; Bryant and Harvey, 1999; Carty et al., 2006; Creamer et al., 2005; Harvey and Bryant, 1998; Ohry et al., 1996). Of note, there is overlap between diagnostic features of PTSD and TBI, such as memory loss and altered consciousness. Historically, there had been debate regarding whether someone suffering from TBI can experience PTSD (Sbordone and Liter, 1995). Sbordone and Liter argued that the injury sustained from a mild TBI reduces the capacity in which the traumatic information is encoded and recalled due to a disruption in information recall, which does not allow for a painful recollection of traumatic experience, and thus mitigates the development of trauma-related psychopathology. However, the methodology used in this study has been widely criticized. More recently, both experimental and epidemiological data support the idea that PTSD can develop following a TBI, but the context of the injury itself is the determining factor. For example, patients who remain conscious during a TBI are at a higher risk of developing PTSD (Glaesser et al., 2004).

9. Shared pathophysiology in TBI and PTSD

Dysregulation of glutamatergic mechanisms is implicated in the pathophysiology of TBI and PTSD. Excitotoxicity in TBI occurs as a result of the over-stimulation of glutamate N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Similar pathology is evident in animal models of PTSD, for example, restraint stress increases extracellular glutamate in the medial PFC, nucleus accumbens, striatum, and hippocampus (Moghaddam, 1993a, 1993b). Additionally, an animal model of comorbid mild TBI and PTSD revealed enhanced fear conditioning as well as a delayed extinction, which is associated with an increase in glutamate transmission in the ventral hippocampus and a decrease in glutamate transmission in the dorsal hippocampus (Schneider et al., 2016).

Evidence from both pre-clinical and clinical literature indicates that the comorbidity of mild to moderate TBI/PTSD may also be related to similar mechanisms of neuroinflammation (Acosta et al., 2013; Gill et al., 2014; Kwon et al., 2011). Neuroinflammation is a leading cause of secondary injury mechanism in TBI (Dietrich and Bramlett, 2016; Werner and Engelhard, 2007). Following brain injury, microglial activation occurs early and can persist for years (Chiu et al., 2016). This is coupled with the breakdown of the blood-brain barrier to allow for lymphocytes, neutrophils, and macrophages to participate in phagocytosis, the release of pro- or anti-inflammatory cytokines, and the reduction of local bleeding (Chodobski et al., 2011; Schmidt et al., 2005; Yu et al., 2013). The neuroinflammatory response is vital for restoring cellular processes and promoting the regeneration of damaged brain tissue. However, prolonged microglial activation is attributed to chronic demyelination, neurodegeneration, and neuronal lesion expansion in moderate-severe TBI (Dheen et al., 2007; Glushakova et al., 2014; Loane et al., 2014; Nagamoto-Combs et al., 2007). Neuroinflammation in animal models of PTSD is also linked to neuronal damage and dysfunction (Nair and Bonneau, 2006). Stress leads to activation of microglia in the hippocampus, thalamus, central gray areas, hypothalamus, and substantia nigra, and stress endured early in life produces an exaggerated microglial expression later in life due to the sensitization of microglia (Nair and Bonneau, 2006).

An additional shared pathophysiological marker of TBI and PTSD is oxidative stress. Oxidative stress is the result of excessive production of reactive oxidative species (ROS), resulting in direct damage to cells that can result in cell death (Cobley et al., 2018). Under normal conditions, homeostasis is achieved when ROS are scavenged by antioxidants, however, when the production of antioxidants fails to meet the necessary capacity to reverse the effects of ROS and toxic free radicals, oxidative damage occurs (Cobley et al., 2018). The effects of oxidative damage on neuronal function following TBI is well documented (Toklu and Tümer, 2015). The production of ROS and toxic free radicals in TBI

impairs cerebral vascular function, reduces mitochondrial respiration, and induces DNA dysfunction. This increase of ROS, and the inability to properly respond through the production of host antioxidant enzymes, greatly contributes to the pathophysiology of moderate TBI (Ansari et al., 2008; Khatri et al., 2018). Animal models also indicate that oxidative stress may be a factor in the development of PTSD, as oxidative stress biomarkers are found in the amygdala, PFC, and hippocampus (Liu et al., 2016). However, comorbid models of TBI and PTSD result in a unique profile of oxidative damage that needs to be further investigated (Xing et al., 2013).

Given the complex nature of TBI and PTSD, both individually and as a comorbid condition, a multifaceted therapeutic approach may be necessary. Pre-clinical models have used pharmacological and psychological methods in the development of potential treatments. Some of which include the use of anti-inflammatory agents to suppress damage, extinction learning to reduce response to conditioned traumatic stimuli, and the potential use of stem cell-based therapies (Corps et al., 2015; Snyder and Teng, 2012; Teng et al., 2011). The SMART-CPT protocol integrates a cognitive behavioral therapy for PTSD (i.e. cognitive processing therapy) with an evidence-based transdiagnostic cognitive rehabilitation intervention (i.e. Cognitive Symptom Management and Rehabilitation Therapy) as a means of addressing the broad spectrum of clinical problems potentially associated with the co-morbidity. (Jak et al., 2019). However, differing severities of TBI better respond to certain treatments. For example, the most effective treatment for mild traumatic brain injury (mTBI) is psychoeducation, which dramatically reduces the persistence of long-term post traumatic symptoms (Mittenberg and Strauman, 2000). Psychoeducation is the process of defining and providing explanations for the symptoms following a mTBI and has been shown to decrease negative perceptions of mTBI, which subsequently impacts the persistence of post-concussion syndrome (Hou et al., 2012; Whittaker et al., 2007). Further research will provide us with a greater understanding of the debilitating comorbid TBI/PTSD condition and will aid in the development of more effective therapeutic agents.

10. Health impacts of early life stress

One potential predictor of both the incidence and severity of TBI symptoms is a history of adverse childhood experiences, also known as early life stress (ELS). Chronic exposure to ELS such as neglect, abuse, household dysfunction, witnessing of violence, poverty, or parental death, can have an enduring and devastating effect on both behavior and biology (Brown et al., 2009). A true estimate of the number of individuals facing ELS is difficult to obtain given the broad definition of ELS and unreliably low disclosure rates; however, a recent estimate suggests that as many as 1 in 4 children have been exposed to neglect or abuse by age 17 (Finkelhor et al., 2015). The long-term effects of ELS on social and psychological functioning are well documented. It is well established that adverse childhood experiences, including neglect and abuse of a physical, emotional, or sexual nature, are predictive of increased prevalence of mood and psychiatric disorders (Heim and Nemeroff, 2001; Syed and Nemeroff, 2017), impaired cognitive function (Hedges and Woon, 2011; Pechtel and Pizzagalli, 2011), substance abuse (Enoch, 2011), and suicide (Ng et al., 2018; Raleva, 2018). Moreover, there is a relationship between physical abuse and risk for TBI in children such that 2–12% of all pediatric TBIs (all severities) are caused by child abuse (Davies et al., 2015; Dewan et al., 2016). However, the risk of brain injury caused by physical abuse is highest in young children (most notably 0–2 years of age), and in this most vulnerable population child abuse (including shaken baby syndrome) is a leading cause of severe and fatal TBI (Joyce et al., 2022; Keenan et al., 2003; Theodorou et al., 2021). Among children diagnosed with shaken baby syndrome, fatality and poor outcomes are driven by high incidence of subdural hematoma and seizures (Makaroff and Putnam, 2003). In addition to these well-documented consequences of ELS, it is also now recognized that stress during early developmental periods contributes to poor health in all stages of life. Specifically, ELS increases vulnerability to metabolic disorders (Lehman et al., 2005; Maniam et al., 2014), inflammation (Fagundes and Way, 2014; Taylor et al., 2006b), hypertension (Lehman et al., 2009), and cardiovascular disease (Eriksson et al., 2014; Murphy et al., 2017). Given that these disease states are associated with poor outcomes after brain injury, by extension ELS is also predicted to impair recovery after TBI, particularly moderate and severe TBI (Perez-Arjona et al., 2003; Ransom et al., 2003).

Symptoms of PCS are exacerbated in individuals with a history of significant life stressors, and evidence of exacerbated PCS symptoms in patients who experienced ELS is documented in both children and adult mild TBI survivors (Ruff, 2011; Voormolen et al., 2018). For example, among pediatric patients, post-concussive depression is rarely reported with mild (compared to more severe) TBI, however pediatric mild TBI patients who do report persistent depressive symptoms are more likely to have experienced ELS (Smyth et al., 2014). Adverse childhood experiences are also associated with an exaggerated immune response to pain and increased pain sensitivity after mild TBI in adolescents (Salberg et al., 2020), and the subjective experience of pain is a strong predictor of the development of depressive symptoms. ELS is also a risk factor for TBI in adulthood. Studies of vulnerable populations such as individuals in prison (Ruff, 2011), those with mental illness, and the homeless report a strong association between ELS and likelihood of sustaining a brain injury (all severities) (Colantonio et al., 2014; Ma et al., 2019; Post et al., 2013; Song et al., 2018; Sucher et al., 2012). In most cases, higher rates of abuse (both in severity and cumulative number of adverse events) correspond to higher odds ratios for sustaining a TBI. The neurobiological correlates for these outcomes are becoming better understood as a rapidly expanding body of research, particularly over the past 20 years, has begun to elucidate the mechanisms by which stress impacts the developing nervous system, focusing largely on adaptive changes of the HPA axis. We are now closer than ever to bridging the gap in our understanding of how life challenges that alter neuroendocrine function can have a lasting impact on neurobiological structure/function, behavioral outputs, and health.

11. Impact of early life stress on TBI-related neuropathology

The predominant view of how ELS contributes to enduring emotional and physical harm well into adulthood is that persistent HPA axis activation during a critical period of plasticity can results in adaptations that ultimately predispose an individual to have an exaggerated response to stress and disease later in life. Much of what we know about how HPA axis disruption during early life affects immediate and long-term neuropathology comes from (mostly rodent) animal models. These models commonly induce a stress response in pups via maternal separation (varying from either brief separation periods of as little as 15 min, to prolonged separation of 8 h or more), social stress (single housing pups with different male adults for brief periods daily), or via a disruption of maternal care by reducing or eliminating cage bedding materials (Lo Iacono et al., 2016; Molet et al., 2014; Murthy and Gould, 2018). Numerous studies have demonstrated translational validity of these models, as pups reared under these conditions develop an exacerbated HPA axis response to stressors, and increased anxiety- and depressive-like phenotypes in adulthood (Aisa et al., 2008; Millstein and Holmes, 2007; Nishi et al., 2013). Importantly, many of the adverse health effects observed in adults with a history of ELS are also recapitulated in these models.

Persistent changes in HPA axis activation caused by ELS leave the organism vulnerable to a number of disease states, particularly those with an inflammatory component. Given the central role of inflammatory processes in mediating TBI outcomes, identifying the mechanisms by which they are impacted by chronic stress such as ELS is integral to our understanding of TBI pathophysiology. Glucocorticoids are at the intersection of HPA axis dysregulation and inflammation and are believed to be a key modulator of both processes (Silverman and

Sternberg, 2012). A healthy stress response is characterized by homeostatic regulation of hormone release at each stage of the HPA axis via negative feedback mediated by glucocorticoids (Herman et al., 2012). Chronic activation of the HPA axis results in a hypersecretion of glucocorticoids and a compensatory downregulation of GR, thus impairing the homeostatic control of sustained production of stress-related hormones (Liu and Nusslock, 2018). While there are multiple interrelated health consequences of this dysregulated homeostatic process, here we will focus on immune priming and its relationship to the sequela of TBI.

12. Early life stress exacerbates the inflammatory response to TBI

The inflammatory response to TBI is a dynamic process that is initiated by resident immune cells in the brain. At rest brain microglia have ramified processes that are engaged in surveillance of the central nervous system (CNS) environment, as such they are highly reactive to chemotactic signals that are indicative of immune challenge or injury (Raivich, 2005). Once activated, microglia undergo a morphological change into a reactive state characterized by thicker and shorter processes and a larger cell body. Activated microglia respond to CNS injury via production of pro- and anti-inflammatory cytokines and chemokines, production of reactive oxygen species, and removal of debris via phagocytosis (Loane and Byrnes, 2010). As such, they promote both beneficial and deleterious responses to TBI (particularly in severe TBI) (Lenzlinger et al., 2001). Activated microglia contribute to brain edema, blood brain barrier breakdown (allowing for further extravasation of immune cells into the CNS), cell death, and subsequent functional and cognitive impairment (Morganti-Kossmann et al., 2002). However, microglia also scavenge debris, promote nerve growth factor production and angiogenesis, and can promote cell survival (Chen and Trapp, 2016). This apparent dichotomy is driven by multiple factors, including injury severity, acute vs chronic microglial activation, and a dose-response of cytokine production. While microglial activation is a pathological hallmark of TBI, the conflicting evidence of both detrimental and neuroprotective consequences of microglial activation in the injured brain reflects a need to better understand the mechanisms that drive microglial responses in CNS injury.

What is clear, is that when microglia are primed to produce an exaggerated response to an insult such as TBI, the result is a disproportionate response to injury leading to tissue damage and impaired functional and cognitive recovery, thus tipping the balance away from the neuroprotective effects of microglia. Pre-existing conditions such as aging (Norden et al., 2015; Ziebell et al., 2017) and recent prior injury (Aungst et al., 2014; Weil et al., 2014) prime microglia by increasing baseline microglial expression and lowering the threshold leading to microglial activation in the event of a TBI. Importantly, stress has also been shown to sensitize microglia (de Pablos et al., 2006; Frank et al., 2007) in a process mediated by stress-induced elevation of GC levels (Frank et al., 2012). Less is known about the lasting effects of ELS on microglial function, particularly in the context of TBI, however several new reports provide compelling evidence that ELS affects both the pathophysiology and recovery after moderate focal brain injury in part through microglial priming. Catale and colleagues recently reported evidence of ELS-induced microglial priming after a cerebellar lesion in adulthood. Specifically, early life social stress on postnatal days (PD) 14–21 was found to globally increase the expression of protein markers of microglial activation and significantly alter microglial morphology, resulting in a pattern of exaggerated microglial activation in response to a brain lesion (Catale et al., 2021). Moreover, ELS increased the production of pro-inflammatory cytokines, along with cytochrome-c release and caspase-3 activation in the brain injured mice, resulting in significantly more apoptosis (Catale et al., 2021). Although this study did not assess behavioral or cognitive outcomes, a similar study using the maternal separation model of ELS (PD 2–14) reports substantial behavioral deficits in rats that underwent both ELS and mild to moderate TBI (Sanchez et al., 2021). Behavioral outcomes of fear conditioning and water maze revealed profound ELS-induced learning and memory deficits after brain injury. The lasting impact of ELS is particularly noteworthy here as both studies induced brain injury more than a month after ELS, and in the Sanchez et al. report, a stress challenge (30 min of restraint) 8 weeks after TBI induced an exacerbated increase in glucocorticoids levels in brain injured mice that experienced ELS. These data are consistent with similar reports in other disease states, indicating that neuroinflammatory priming by ELS exacerbates amyloid pathology in a mouse model of Alzheimer's Disease (Hoeijmakers et al., 2017) as well as behavioral and inflammatory responses to an immune challenge in adulthood (Reus et al., 2021; Viola et al., 2019).

13. Conclusion

A subset of individuals that suffer a brain injury may have to deal with an overlapping set of challenges that include pain, adjusting to disability, social isolation, and cognitive problems among many others. These individuals must address these hurdles with a nervous system that is attempting to recover from physical and biochemical insults. Increasing our understanding of the processes that contribute to good outcomes has the potential to greatly improve the lives of brain injured individuals, their caregivers, and community. Taken together it is apparent that stress appraisal and physiology both prior to and after traumatic brain injuries are key predictors of short- and long-term outcomes. The physiologically optimal activation of the HPA axis may be an important determinant of outcomes from brain injury as both hypo- and hyperresponsiveness can be deleterious. Moreover, the ways in which stressors are perceived and managed in the period after injury can have profound implications for the ability of individuals to recover from injury. Disruptions in the ability of the nervous system to appraise and process threats and challenges present a significant barrier to optimal function of the injured brain. Moreover, as there is a relationship between pre-injury stress and anxiety disorders and post-injury neuropsychiatric outcomes, it is not sufficient to address mental health issues that emerge only after injury, rather a lifespan approach is warranted. Individuals that suffer an injury and can still manage the physiological and psychological stressors associated with the recovery process do much better than those that struggle with these issues. Many of the outcomes associated with brain injuries may be influenced by events that long predate the injury itself including, but not limited to, events that occur early in life. Moreover, although research on TBI has traditionally focused on adult and mostly male populations, both experimental and clinical TBI research is rapidly expanding to include a wide age range and both sexes (For examples see: Corrigan et al., 2020; Oliverio et al., 2020; Weil and Karelina, 2019). Thus, our growing understanding of the sequela of both the risk factors that contribute to TBI, and the complicated outcomes related to stress, emotional trauma, and TBI pathophysiology is contributing to better diagnosis and faster recovery. Traumatic brain injuries are a significant allostatic challenge. They represent a time-compressed example of the allostatic loading that Bruce spent a career trying to understand. His loss is a blow to the fields he touched and the many who had the opportunity to work with him.

CRediT authorship contribution statement

Zachary M. Weil: Conceptualization, Writing – original draft, Writing – review & editing. **Brishti White:** Writing – original draft. **Bailey Whitehead:** Writing – original draft. **Kate Karelina:** Conceptualization, Writing – original draft, Writing – review & editing.

Data availability

Data will be made available on request.

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References

Acosta, S.A., et al., 2013. Influence of post-traumatic stress disorder on neuroinflammation and cell proliferation in a rat model of traumatic brain injury. PLoS One 8, e81585.
Agaibi, C.E., Wilson, J.P., 2005. Trauma, PTSD, and resilience: a review of the literature. Trauma Violence Abuse 6, 195–216.
Agha, A., et al., 2007. Hypopituitarism following traumatic brain injury (TBI). Br. J. Neurosurg. 21, 210–216.
Agorastos, A., Chrousos, G.P., 2022. The neuroendocrinology of stress: the stress-related continuum of chronic disease development. Mol. Psychiatr. 27 (1), 502–513.
Aimaretti, G., et al., 2004. Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. Clin. Endocrinol. 61, 320–326.
Aisa, B., et al., 2008. Effects of maternal separation on hypothalamic-pituitary-adrenal responses, cognition and vulnerability to stress in adult female rats. Neuroscience 154, 1218–1226.
American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, (5th ed.). American Psychiatric Publishing.
Andelic, N., et al., 2018. Disability and quality of life 20 years after traumatic brain injury. Brain Behav 8, e01018.
Ansari, M.A., et al., 2008. Oxidative stress and modification of synaptic proteins in hippocampus after traumatic brain injury. Free Radic. Biol. Med. 45, 443–452.
Aungst, S.L., et al., 2014. Repeated mild traumatic brain injury causes chronic neuroinflammation, changes in hippocampal synaptic plasticity, and associated cognitive deficits. J. Cerebr. Blood Flow Metabol. 34, 1223–1232.
Barlow, K.M., 2016. Postconcussion syndrome: a review. J. Child Neurol. 31, 57–67.
Barton, R.N., et al., 1987. Relationships among plasma cortisol, adrenocorticotrophin, and severity of injury in recently injured patients. J. Trauma 27, 384–392.
Barton, D.J., et al., 2021. Acute cortisol profile Associations with cognitive impairment after severe traumatic brain injury. Neurorehabilitation Neural Repair 35 (12), 1088–1099, 15459683211048771.
Bay, E., Donders, J., 2008. Risk factors for depressive symptoms after mild-to-moderate traumatic brain injury. Brain Inj. 22, 233–241.
Benvenga, S., et al., 2000. Clinical review 113: hypopituitarism secondary to head trauma. J. Clin. Endocrinol. Metab. 85, 1353–1361.
Bernard, F., et al., 2006. Incidence of adrenal insufficiency after severe traumatic brain injury varies according to definition used: clinical implications. Br. J. Anaesth. 96, 72–76.
Bistritzer, T., et al., 1981. Anterior hypopituitarism due to fracture of the sella turcica. Am. J. Dis. Child. 135, 966–968.
Blaze, J., et al., 2020. Blast-related mild TBI alters anxiety-like behavior and transcriptional signatures in the rat amygdala. Front. Behav. Neurosci. 14, 160.
Blume, H., Hawash, K., 2012. Subacute concussion-related symptoms and postconcussion syndrome in pediatrics. Curr. Opin. Pediatr. 24, 724–730.
Bohnen, N., Jolles, J., 1992. Neurobehavioral aspects of postconcussive symptoms after mild head injury. J. Nerv. Ment. Dis. 180, 683–692.
Braakman, R., et al., 1983. Megadose steroids in severe head-injury - results of a prospective double-blind clinical-trial. J. Neurosurg. 58, 326–330.
Breslau, N., 2009. The epidemiology of trauma, PTSD, and other posttrauma disorders. Trauma Violence Abuse 10, 198–210.
Bromberg, C.E., et al., 2020. Sex-dependent pathology in the HPA Axis at a sub-acute period after experimental traumatic brain injury. Front. Neurol. 11.
Broomhall, L.G., et al., 2009. Early stage assessment and course of acute stress disorder after mild traumatic brain injury. J. Nerv. Ment. Dis. 197, 178–181.
Broshek, D.K., et al., 2015. A review of post-concussion syndrome and psychological factors associated with concussion. Brain Inj. 29, 228–237.
Brown, D.W., et al., 2009. Adverse childhood experiences and the risk of premature mortality. Am. J. Prev. Med. 37, 389–396.
Bryant, R.A., 2001. Posttraumatic stress disorder and traumatic brain injury: can they co-exist? Clin. Psychol. Rev. 21, 931–948.
Bryant, R.A., Harvey, A.G., 1998. Relationship between acute stress disorder and posttraumatic stress disorder following mild traumatic brain injury. Am. J. Psychiatr. 155, 625–629.
Bryant, R.A., Harvey, A.G., 1999. The influence of traumatic brain injury on acute stress disorder and post-traumatic stress disorder following motor vehicle accidents. Brain Inj. 13, 15–22.
Bryant, R.A., et al., 2003. Treating acute stress disorder following mild traumatic brain injury. Am. J. Psychiatr. 160, 585–587.
Bryant, R.A., et al., 2011. A review of acute stress disorder in DSM-5. Depress. Anxiety 28, 802–817.
Bulloch, K., McEwen, B.S., 2002. Regulation of the injury-immune response in the central nervous system: allostasis and allostatic load in immunity. Hormones, Brain and Behavior 773. -V.).
Bushnik, T., et al., 2007. Fatigue after TBI: association with neuroendocrine abnormalities. Brain Inj. 21, 559–566.
Carrasco, G.A., Van de Kar, L.D., 2003. Neuroendocrine pharmacology of stress. Eur. J. Pharmacol. 463, 235–272.
Carty, J., et al., 2006. Delayed-onset PTSD: a prospective study of injury survivors. J. Affect. Disord. 90, 257–261.
Casella, E.M., et al., 2014. Traumatic brain injury alters long-term hippocampal neuron morphology in juvenile, but not immature, rats. Childs Nerv Syst 30, 1333–1342.
Catale, C., et al., 2021. Early life stress exposure worsens adult remote microglia activation, neuronal death, and functional recovery after focal brain injury. Brain Behav. Immun. 94, 89–103.
Ceballos, R., 1966. Pituitary changes in head trauma (analysis of 102 consecutive cases of head injury). Ala. J. Med. Sci. 3, 185–198.
Cernak, I., et al., 1999. Neuroendocrine responses following graded traumatic brain injury in male adults. Brain Inj. 13, 1005–1015.
Chen, Z., Trapp, B.D., 2016. Microglia and neuroprotection. J. Neurochem. 136 (Suppl. 1), 10–17.
Chiu, C.C., et al., 2016. Neuroinflammation in animal models of traumatic brain injury. J. Neurosci. Methods 272, 38–49.
Chodobski, A., Zink, B.J., Szmydynger-Chodobska, J., 2011. Blood–brain barrier pathophysiology in traumatic brain injury. Transl. Stroke Res. 2, 492–516.
Cicerone, K., et al., 2006. Cognitive rehabilitation interventions for executive function: moving from bench to bedside in patients with traumatic brain injury. J. Cognit. Neurosci. 18, 1212–1222.
Cobley, J.N., et al., 2018. 13 reasons why the brain is susceptible to oxidative stress. Redox Biol. 15, 490–503.
Cohan, P., et al., 2005. Acute secondary adrenal insufficiency after traumatic brain injury: a prospective study. Crit. Care Med. 33, 2358–2366.
Colantonio, A., et al., 2014. Traumatic brain injury and early life experiences among men and women in a prison population. J. Correct. Health Care 20, 271–279.
Cooper, P.R., et al., 1979. Dexamethasone and severe head injury. A prospective double-blind study. J. Neurosurg. 51, 307–316.
Corps, K.N., et al., 2015. Inflammation and neuroprotection in traumatic brain injury. JAMA Neurol. 72, 355–362.
Corrigan, J.D., et al., 2020. Is pediatric traumatic brain injury associated with adult alcohol misuse? J. Neurotrauma 37, 1637–1644.
Creamer, M., et al., 2005. Amnesia, traumatic brain injury, and posttraumatic stress disorder: a methodological inquiry. Behav. Res. Ther. 43, 1383–1389.
Davies, F.C., et al., 2015. A profile of suspected child abuse as a subgroup of major trauma patients. Emerg. Med. J. 32, 921–925.
de Pablos, R.M., et al., 2006. Stress increases vulnerability to inflammation in the rat prefrontal cortex. J. Neurosci. 26, 5709–5719.
Dean, P.J.A., et al., 2012. Post-concussion syndrome: prevalence after mild traumatic brain injury in comparison with a sample without head injury. Brain Inj. 26, 14–26.
Dewan, M.C., et al., 2016. Epidemiology of global pediatric traumatic brain injury: qualitative review. World Neurosurg 91, 497–509 e1.
Dhabhar, F.S., et al., 2020. Reflections on Bruce S. McEwen's contributions to stress neurobiology and so much more. Stress-the International Journal on the Biology of Stress 23, 499–508.
Dheen, S.T., et al., 2007. Microglial activation and its implications in the brain diseases. Curr. Med. Chem. 14, 1189–1197.
Dietrich, W.D., Bramlett, H.M., 2016. Therapeutic hypothermia and targeted temperature management in traumatic brain injury: clinical challenges for successful translation. Brain Res. 1640, 94–103.
Dimopoulou, I., et al., 2004. Hypothalamic-pituitary-adrenal axis dysfunction in critically ill patients with traumatic brain injury: incidence, pathophysiology, and relationship to vasopressor dependence and peripheral interleukin-6 levels. Crit. Care Med. 32, 404–408.
Dusick, J.R., et al., 2012. Pathophysiology of hypopituitarism in the setting of brain injury. Pituitary 15, 2–9.
Dwyer, B., Katz, D.I., 2018. Postconcussion syndrome. Handb. Clin. Neurol. 158, 163–178.
Elovic, E.P., Glenn, M.B., 2004. Anterior pituitary dysfunction after traumatic brain injury, part II. J. Head Trauma Rehabil. 19, 184–187.
Enoch, M.A., 2011. The role of early life stress as a predictor for alcohol and drug dependence. Psychopharmacology (Berl) 214, 17–31.
Eriksson, M., et al., 2014. Early life stress and later health outcomes–findings from the Helsinki Birth Cohort Study. Am. J. Hum. Biol. 26, 111–116.
Fagundes, C.P., Way, B., 2014. Early-life stress and adult inflammation. Curr. Dir. Psychol. Sci. 23, 277–283.
Felmingham, K., et al., 2010. Neural responses to masked fear faces: sex differences and trauma exposure in posttraumatic stress disorder. J. Abnorm. Psychol. 119, 241–247.
Finkelhor, D., et al., 2015. Prevalence of childhood exposure to violence, crime, and abuse: results from the national survey of children's exposure to violence. JAMA Pediatr. 169, 746–754.
Frank, M.G., et al., 2007. Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS pro-inflammatory cytokine responses. Brain Behav. Immun. 21, 47–59.
Frank, M.G., et al., 2012. Glucocorticoids mediate stress-induced priming of microglial pro-inflammatory responses. Brain Behav. Immun. 26, 337–345.
Gill, J., et al., 2014. Lower health related quality of life in US military personnel is associated with service-related disorders and inflammation. Psychiatr. Res. 216, 116–122.
Giza, C.C., Hovda, D.A., 2014. The new neurometabolic cascade of concussion. Neurosurgery 75, S24–S33.
Glaesser, J., et al., 2004. Posttraumatic Stress Disorder in patients with traumatic brain injury. BMC Psychiatr. 4, 5.
Glushakova, O.Y., et al., 2014. Delayed increases in microvascular pathology after experimental traumatic brain injury are associated with prolonged inflammation,

blood-brain barrier disruption, and progressive white matter damage. J. Neurotrauma 31, 1180–1193.
Grool, A.M., et al., 2016. Association between early participation in physical activity following acute concussion and persistent postconcussive symptoms in children and adolescents. Jama-Journal of the American Medical Association. 316, 2504–2514.
Grundy, P.L., et al., 2001. The hypothalamo-pituitary-adrenal axis response to experimental traumatic brain injury. J. Neurotrauma 18, 1373–1381.
Gupta, M.A., 2013. Review of somatic symptoms in post-traumatic stress disorder. Int. Rev. Psychiatr. 25, 86–99.
Hadanny, A., Efrati, S., 2016. Treatment of persistent post-concussion syndrome due to mild traumatic brain injury: current status and future directions. Expert Rev. Neurother. 16, 875–887.
Haider, M.N., et al., 2021. Exercise for sport-related concussion and persistent postconcussive symptoms. Sports Health-a Multidisciplinary Approach 13, 154–160.
Hanna-Pladdy, B., et al., 2001. Stress as a diagnostic challenge for postconcussive symptoms: sequelae of mild traumatic brain injury or physiological stress response. Clin. Neuropsychol. 15, 289–304.
Hannon, M.J., et al., 2013. Acute glucocorticoid deficiency and diabetes insipidus are common after acute traumatic brain injury and predict mortality. J. Clin. Endocrinol. Metab. 98, 3229–3237.
Harvey, A.G., Bryant, R.A., 1998. The relationship between acute stress disorder and posttraumatic stress disorder: a prospective evaluation of motor vehicle accident survivors. J. Consult. Clin. Psychol. 66, 507–512.
Harvey, A.G., Bryant, R.A., 2000. Two-year prospective evaluation of the relationship between acute stress disorder and posttraumatic stress disorder following mild traumatic brain injury. Am. J. Psychiatr. 157, 626–628.
Hedges, D.W., Woon, F.L., 2011. Early-life stress and cognitive outcome. Psychopharmacology (Berl) 214, 121–130.
Heim, C., Nemeroff, C.B., 2001. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol. Psychiatr. 49, 1023–1039.
Herman, J.P., et al., 2012. Neural regulation of the stress response: glucocorticoid feedback mechanisms. Braz. J. Med. Biol. Res. 45, 292–298.
Hinkeldey, N.S., Corrigan, J.D., 1990. The structure of head-injured patients' neurobehavioural complaints: a preliminary study. Brain Inj. 4, 115–133.
Hoeijmakers, L., et al., 2017. Early-life stress lastingly alters the neuroinflammatory response to amyloid pathology in an Alzheimer's disease mouse model. Brain Behav. Immun. 63, 160–175.
Hoffman, A.N., et al., 2017. Early and persistent dendritic hypertrophy in the basolateral amygdala following experimental diffuse traumatic brain injury. J. Neurotrauma 34, 213–219.
Hou, R.H., et al., 2012. When a minor head injury results in enduring symptoms: a prospective investigation of risk factors for postconcussional syndrome after mild traumatic brain injury. J. Neurol. Neurosurg. Psychiatry 83, 217–223.
Iverson, G.L., McCracken, L.M., 1997. 'Postconcussive' symptoms in persons with chronic pain. Brain Inj. 11, 783–790.
Jak, A.J., et al., 2019. SMART-CPT for veterans with comorbid post-traumatic stress disorder and history of traumatic brain injury: a randomised controlled trial. J. Neurol. Neurosurg. Psychiatry 90, 333–341.
Joyce, T., et al., 2022. Pediatric Abusive Head Trauma. StatPearls, Treasure Island (FL).
Karaca, Z., et al., 2016. GH and pituitary hormone alterations after traumatic brain injury. Prog Mol Biol Transl Sci 138, 167–191.
Kavan, M.G., et al., 2012. The physician's role in managing acute stress disorder. Am. Fam. Physician 86, 643–649.
Keenan, H.T., et al., 2003. A population-based study of inflicted traumatic brain injury in young children. JAMA 290, 621–626.
Kelly, D.F., et al., 2006. Neurobehavioral and quality of life changes associated with growth hormone insufficiency after complicated mild, moderate, or severe traumatic brain injury. J. Neurotrauma 23, 928–942.
Khatri, N., et al., 2018. Oxidative stress: major threat in traumatic brain injury. CNS Neurol. Disord. - Drug Targets 17, 689–695.
Klaperski, S., et al., 2013. Does the level of physical exercise affect physiological and psychological responses to psychosocial stress in women? Psychol. Sport Exerc. 14, 266–274.
Klose, M., et al., 2007. Acute and long-term pituitary insufficiency in traumatic brain injury: a prospective single-centre study. Clin. Endocrinol. 67, 598–606.
Kusanagi, H., et al., 2000. Pituitary insufficiency after penetrating injury to the sella turcica. J. Nippon Med. Sch. 67, 130–133.
Kwon, S.K., et al., 2011. Stress and traumatic brain injury: a behavioral, proteomics, and histological study. Front. Neurol. 2, 12.
Leddy, J.J., et al., 2012. Rehabilitation of concussion and post-concussion syndrome. Sport Health 4, 147–154.
Leddy, J.J., et al., 2016. Active rehabilitation of concussion and post-concussion syndrome. Phys. Med. Rehabil. Clin 27, 437–454.
Leddy, J.J., et al., 2018a. Exercise is medicine for concussion. Curr. Sports Med. Rep. 17, 262–270.
Leddy, J.J., et al., 2018b. Active recovery from concussion. Curr. Opin. Neurol. 31, 681–686.
Lehman, B.J., et al., 2005. Relation of childhood socioeconomic status and family environment to adult metabolic functioning in the CARDIA study. Psychosom. Med. 67, 846–854.
Lehman, B.J., et al., 2009. Relationship of early life stress and psychological functioning to blood pressure in the CARDIA study. Health Psychol. 28, 338–346.
Lenzlinger, P.M., et al., 2001. The duality of the inflammatory response to traumatic brain injury. Mol. Neurobiol. 24, 169–181.
Levin, H.S., Diaz-Arrastia, R.R., 2015. Diagnosis, prognosis, and clinical management of mild traumatic brain injury. Lancet Neurol. 14, 506–517.
Lieberman, S.A., et al., 2001. Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury. J. Clin. Endocrinol. Metab. 86, 2752–2756.
Liu, P.Z., Nusslock, R., 2018. How stress gets under the skin: early life adversity and glucocorticoid receptor epigenetic regulation. Curr. Genom. 19, 653–664.
Liu, F.F., et al., 2016. NOX2 mediated-parvalbumin interneuron loss might contribute to anxiety-like and enhanced fear learning behavior in a rat model of post-traumatic stress disorder. Mol. Neurobiol. 53, 6680–6689.
Lo Iacono, L., et al., 2016. Regulation of nucleus accumbens transcript levels in mice by early-life social stress and cocaine. Neuropharmacology 103, 183–194.
Loane, D.J., Byrnes, K.R., 2010. Role of microglia in neurotrauma. Neurotherapeutics 7, 366–377.
Loane, D.J., et al., 2014. Progressive neurodegeneration after experimental brain trauma: association with chronic microglial activation. JNEN (J. Neuropathol. Exp. Neurol.) 73, 14–29.
Lupien, S.J., et al., 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci. 10, 434–445.
Ma, Z., et al., 2019. The association between adverse childhood experiences and adult traumatic brain injury/concussion: a scoping review. Disabil. Rehabil. 41, 1360–1366.
Machulda, M.M., et al., 1998. Relationship between stress, coping, and postconcussion symptoms in a healthy adult population. Arch. Clin. Neuropsychol. 13, 415–424.
Maiya, B., et al., 2008. Magnetic resonance imaging changes in the pituitary gland following acute traumatic brain injury. Intensive Care Med. 34, 468–475.
Makaroff, K.L., Putnam, F.W., 2003. Outcomes of infants and children with inflicted traumatic brain injury. Dev. Med. Child Neurol. 45, 497–502.
Makdissi, M., et al., 2017. Approach to investigation and treatment of persistent symptoms following sport-related concussion: a systematic review. Br. J. Sports Med. 51.
Maniam, J., et al., 2014. Early-life stress, HPA Axis Adaptation, and mechanisms contributing to later health outcomes. Front. Endocrinol. 5, 73.
Masel, B.E., DeWitt, D.S., 2010. Traumatic brain injury: a disease process, not an event. J. Neurotrauma 27, 1529–1540.
McAllister, T.W., 2011. Neurobiological consequences of traumatic brain injury. Dialogues Clin. Neurosci. 13, 287–300.
McAllister, T.W., 2016. Mild traumatic brain injury. Focus 14, 410–421.
McCullers, D.L., et al., 2002. Traumatic brain injury regulates adrenocorticosteroid receptor mRNA levels in rat hippocampus. Brain Res. 947, 41–49.
McEwen, B.S., 2004. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann. N. Y. Acad. Sci. 1032, 1–7.
McEwen, B.S., 2007. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol. Rev. 87, 873–904.
McEwen, B.S., Magarinos, A.M., 2001. Stress and hippocampal plasticity: implications for the pathophysiology of affective disorders. Hum. Psychopharmacol. 16, S7–S19.
McEwen, B.S., Stellar, E., 1993. Stress and the individual: mechanisms leading to disease. Arch. Intern. Med. 153, 2093–2101.
McKinlay, A., et al., 2009. Adolescent psychiatric symptoms following preschool childhood mild traumatic brain injury: evidence from a birth cohort. J. Head Trauma Rehabil. 24, 221–227.
Meares, S., et al., 2008. Mild traumatic brain injury does not predict acute postconcussion syndrome. J. Neurol. Neurosurg. Psychiatry 79, 300–306.
Meares, S., et al., 2011. The prospective course of postconcussion syndrome: the role of mild traumatic brain injury. Neuropsychology 25, 454–465.
Miller, G.E., et al., 2007. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychol. Bull. 133, 25–45.
Millstein, R.A., Holmes, A., 2007. Effects of repeated maternal separation on anxiety- and depression-related phenotypes in different mouse strains. Neurosci. Biobehav. Rev. 31, 3–17.
Mittenberg, W., Strauman, S., 2000. Diagnosis of mild head injury and the postconcussion syndrome. J. Head Trauma Rehabil. 15, 783–791.
Mittenberg, W., et al., 2001. Treatment of post-concussion syndrome following mild head injury. J. Clin. Exp. Neuropsychol. 23, 829–836.
Moghaddam, B., 1993a. Stress preferentially increases extraneuronal levels of excitatory amino acids in the prefrontal cortex: comparison to hippocampus and basal ganglia. J. Neurochem. 60, 1650–1657.
Moghaddam, B., 1993b. Stress preferentially increases extraneuronal levels of excitatory amino-acids in the prefrontal cortex - comparison to Hippocampus and basal ganglia. J. Neurochem. 60, 1650–1657.
Molaie, A.M., Maguire, J., 2018. Neuroendocrine abnormalities following traumatic brain injury: an important contributor to neuropsychiatric sequelae. Front. Endocrinol. 9, 176.
Molet, J., et al., 2014. Naturalistic rodent models of chronic early-life stress. Dev. Psychobiol. 56, 1675–1688.
Morganti-Kossmann, M.C., et al., 2002. Inflammatory response in acute traumatic brain injury: a double-edged sword. Curr. Opin. Crit. Care 8, 101–105.
Morganti-Kossmann, M.C., et al., 2019. The complexity of neuroinflammation consequent to traumatic brain injury: from research evidence to potential treatments. Acta Neuropathol. 137, 731–755.
Murphy, M.O., et al., 2017. Developmental origins of cardiovascular disease: impact of early life stress in humans and rodents. Neurosci. Biobehav. Rev. 74, 453–465.
Murthy, S., Gould, E., 2018. Early life stress in rodents: animal models of illness or resilience? Front. Behav. Neurosci. 12, 157.

Muzha, I., et al., 2004. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. Lancet 364, 1321–1328.
Nagamoto-Combs, K., et al., 2007. Prolonged microgliosis in the rhesus monkey central nervous system after traumatic brain injury (vol 24, pg 1719, 2007). J. Neurotrauma 24, 1889, 1889.
Nair, A., Bonneau, R.H., 2006. Stress-induced elevation of glucocorticoids increases microglia proliferation through NMDA receptor activation. J. Neuroimmunol. 171, 72–85.
Ng, Q.X., et al., 2018. Early life sexual abuse is associated with increased suicide attempts: an update meta-analysis. J. Psychiatr. Res. 99, 129–141.
Niogi, S.N., et al., 2008. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. Am. J. Neuroradiol. 29, 967–973.
Nishi, M., et al., 2013. Effects of early life stress on brain activity: implications from maternal separation model in rodents. Gen. Comp. Endocrinol. 181, 306–309.
Norden, D.M., et al., 2015. Microglial priming and enhanced reactivity to secondary insult in aging, and traumatic CNS injury, and neurodegenerative disease. Neuropharmacology 96, 29–41.
Ohry, A., et al., 1996. Post-traumatic stress disorder in brain injury patients. Brain Inj. 10, 687–695.
Oliverio, R., et al., 2020. Sex, drugs, and TBI: the role of sex in substance abuse related to traumatic brain injuries. Front. Neurol. 11, 546775.
Pechtel, P., Pizzagalli, D.A., 2011. Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology (Berl). 214, 55–70.
Perez-Arjona, E., et al., 2003. Late outcome following central nervous system injury in child abuse. Childs Nerv Syst 19, 69–81.
Polinder, S., et al., 2018. A multidimensional approach to post-concussion symptoms in mild traumatic brain injury. Front. Neurol. 9, 1113.
Ponsford, J., et al., 2000. Factors influencing outcome following mild traumatic brain injury in adults. J. Int. Neuropsychol. Soc. 6, 568–579.
Ponsford, J., et al., 2008. Functional outcome 10 years after traumatic brain injury: its relationship with demographic, injury severity, and cognitive and emotional status. J. Int. Neuropsychol. Soc. 14, 233–242.
Ponsford, J., et al., 2012. Predictors of postconcussive symptoms 3 Months after mild traumatic brain injury. Neuropsychology 26, 304–313.
Post, R.M., et al., 2013. Role of childhood adversity in the development of medical co-morbidities associated with bipolar disorder. J. Affect. Disord. 147, 288–294.
Raivich, G., 2005. Like cops on the beat: the active role of resting microglia. Trends Neurosci. 28, 571–573.
Raleva, M., 2018. Early life stress: a key link between childhood adversity and risk of attempting suicide. Psychiatr. Danub. 30, 341–347.
Ransom, G.H., et al., 2003. Cerebral infarct in head injury: relationship to child abuse. Child Abuse Negl. 27, 381–392.
Rees, P.M., 2003. Contemporary issues in mild traumatic brain injury. Arch. Phys. Med. Rehabil. 84, 1885–1894.
Reul, J.M., de Kloet, E.R., 1985. Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. Endocrinology 117, 2505–2511.
Reus, G.Z., et al., 2021. The impact of early life stress and immune challenge on behavior and glia cells alteration in late adolescent rats. Int. J. Dev. Neurosci. 81, 407–415.
Roe, S.Y., et al., 1998. Evidence for the involvement of corticotrophin-releasing hormone in the pathogenesis of traumatic brain injury. Eur. J. Neurosci. 10, 553–559.
Ruff, R.M., 2011. Mild traumatic brain injury and neural recovery: rethinking the debate. NeuroRehabilitation 28, 167–180.
Russell, A.L., et al., 2018. Differential responses of the HPA Axis to mild blast traumatic brain injury in male and female mice. Endocrinology 159, 2363–2375.
Ryan, L.M., Warden, D.L., 2003. Post concussion syndrome. Int. Rev. Psychiatr. 15, 310–316.
Salberg, S., et al., 2020. The development of adolescent chronic pain following traumatic brain injury and surgery: the role of diet and early life stress. Dev. Neurosci. 42, 2–11.
Salehi, F., et al., 2007. Histologic study of the human pituitary gland in acute traumatic brain injury. Brain Inj. 21, 651–656.
Sanchez, C.M., et al., 2021. Early life stress exacerbates outcome after traumatic brain injury. J. Neurotrauma 38, 555–565.
Santarsieri, M., et al., 2014. Cerebrospinal fluid cortisol and progesterone profiles and outcomes prognostication after severe traumatic brain injury. J. Neurotrauma 31, 699–712.
Santarsieri, M., et al., 2015. Variable neuroendocrine-immune dysfunction in individuals with unfavorable outcome after severe traumatic brain injury. Brain Behav. Immun. 45, 15–27.
Sapolsky, R.M., et al., 1983. The adrenocortical stress-response in the aged male rat: impairment of recovery from stress. Exp. Gerontol. 18, 55–64.
Sapolsky, R.M., et al., 1986. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr. Rev. 7, 284–301.
Sbordone, R.J., Liter, J.C., 1995. Mild traumatic brain injury does not produce posttraumatic-stress-disorder. Brain Inj. 9, 405–412.
Schmidt, O.I., Heyde, C.E., Ertel, W., Stahel, P.F., 2005. Closed head injury–an inflammatory disease? Brain Res. Rev. 48 (2), 388–399.
Schneider, B.L., et al., 2016. Increased cortical gamma-aminobutyric acid precedes incomplete extinction of conditioned fear and increased hippocampal excitatory tone in a mouse model of mild traumatic brain injury. J. Neurotrauma 33, 1614–1624.
Shohami, E., et al., 1995. The effect of the adrenocortical axis upon recovery from closed head injury. J. Neurotrauma 12, 1069–1077.
Sierra, A., et al., 2008. Steroid hormone receptor expression and function in microglia. Glia 56, 659–674.
Silverberg, N.D., Iverson, G.L., 2013. Is rest after concussion "the best medicine?": recommendations for activity resumption following concussion in athletes, civilians, and military service members. J. Head Trauma Rehabil. 28, 250–259.
Silverman, M.N., Sternberg, E.M., 2012. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. Ann. N. Y. Acad. Sci. 1261, 55–63.
Smith, S.M., Vale, W.W., 2006. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin. Neurosci. 8, 383–395.
Smyth, K., et al., 2014. The role of serotonin receptor alleles and environmental stressors in the development of post-concussive symptoms after pediatric mild traumatic brain injury. Dev. Med. Child Neurol. 56, 73–77.
Snyder, E.Y., Teng, Y.D., 2012. Stem cells and spinal cord repair. N. Engl. J. Med. 366, 1940–1942.
Song, M.J., et al., 2018. Childhood trauma and lifetime traumatic brain injury among individuals who are homeless. J. Head Trauma Rehabil. 33.
Sorrells, S.F., Sapolsky, R.M., 2007. An inflammatory review of glucocorticoid actions in the CNS. Brain Behav. Immun. 21, 259–272.
Sorrells, S.F., et al., 2009. The stressed CNS: when glucocorticoids aggravate inflammation. Neuron 64, 33–39.
Sterling, P., Eyer, J., 1988. Allostasis: a new paradigm to explain arousal pathology. In: Fisher, S., Reason, J. (Eds.), Handbook of Life Stress, Cognition and Health. John Wiley & Sons, New York.
Sucher, R., et al., 2012. Hemiface allotransplantation in the mouse. Plast. Reconstr. Surg. 129, 867–870.
Syed, S.A., Nemeroff, C.B., 2017. Early life stress, mood, and anxiety disorders. Chronic Stress 1, 2470547017694461.
Tanriverdi, F., et al., 2007. Pituitary functions in the acute phase of traumatic brain injury: are they related to severity of the injury or mortality? Brain Inj. 21, 433–439.
Tapp, Z.M., et al., 2019. A tilted Axis: maladaptive inflammation and HPA Axis dysfunction contribute to consequences of TBI. Front. Neurol. 10, 345.
Taylor, S.E., 2010. Mechanisms linking early life stress to adult health outcomes. Proc. Natl. Acad. Sci. U. S. A. 107, 8507–8512.
Taylor, A.N., et al., 2006a. Lasting neuroendocrine-immune effects of traumatic brain injury in rats. J. Neurotrauma 23, 1802–1813.
Taylor, S.E., et al., 2006b. Relationship of early life stress and psychological functioning to adult C-reactive protein in the coronary artery risk development in young adults study. Biol. Psychiatr. 60, 819–824.
Taylor, A.N., et al., 2008. Injury severity differentially affects short- and long-term neuroendocrine outcomes of traumatic brain injury. J. Neurotrauma 25, 311–323.
Taylor, A.N., et al., 2010. Injury severity differentially alters sensitivity to dexamethasone after traumatic brain injury. J. Neurotrauma 27, 1081–1089.
Teng, Y.D., et al., 2011. Functional multipotency of stem cells: a conceptual review of neurotrophic factor-based evidence and its role in translational research. Curr. Neuropharmacol. 9, 574–585.
Theodorou, C.M., et al., 2021. Increased mortality in very young children with traumatic brain injury due to abuse: a nationwide analysis of 10,965 patients. J. Pediatr. Surg. 56, 1174–1179.
Thomas, D.G., et al., 2015. Benefits of strict rest after acute concussion: a randomized controlled trial. Pediatrics 135, 213–223.
Toklu, H. Z., Tumer, N., Frontiers in Neuroengineering Oxidative Stress, Brain Edema, Blood-Brain Barrier Permeability, and Autonomic Dysfunction from Traumatic Brain Injury. In: F. H. Kobeissy, (Ed.), Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects. CRC Press/Taylor & Francis© 2015 by Taylor & Francis Group, LLC., Boca Raton (FL), 2015.
Tremblay, S., et al., 2013. Sports concussions and aging: a neuroimaging investigation. Cerebr. Cortex 23, 1159–1166.
Tsatsoulis, A., Fountoulakis, S., 2006. The protective role of exercise on stress system dysregulation and comorbidities. Ann. N. Y. Acad. Sci. 1083, 196–213.
Vanderploeg, R.D., et al., 2009. Mild traumatic brain injury and posttraumatic stress disorder and their associations with health symptoms. Arch. Phys. Med. Rehabil. 90, 1084–1093.
Vasa, R.A., et al., 2004. Neuroimaging correlates of anxiety after pediatric traumatic brain injury. Biol. Psychiatr. 55, 208–216.
Vasterling, J.J., et al., 2018. Traumatic brain injury and posttraumatic stress disorder: conceptual, diagnostic, and therapeutic considerations in the context of Co-occurrence. J. Neuropsychiatry Clin. Neurosci. 30, 91–100.
Viola, T.W., et al., 2019. Acute neuroinflammation elicited by TLR-3 systemic activation combined with early life stress induces working memory impairments in male adolescent mice. Behav. Brain Res. 376, 112221.
Voormolen, D.C., et al., 2018. Divergent classification methods of post-concussion syndrome after mild traumatic brain injury: prevalence rates, risk factors, and functional outcome. J. Neurotrauma 35, 1233–1241.
Weil, Z.M., Karelina, K., 2019. Lifelong consequences of brain injuries during development: from risk to resilience. Front. Neuroendocrinol. 55, 100793.
Weil, Z.M., et al., 2014. Injury timing alters metabolic, inflammatory and functional outcomes following repeated mild traumatic brain injury. Neurobiol. Dis. 70, 108–116.
Werner, C., Engelhard, K., 2007. Pathophysiology of traumatic brain injury. Br. J. Anaesth. 99, 4–9.
Whittaker, R., et al., 2007. Illness perceptions and outcome in mild head injury: a longitudinal study. J. Neurol. Neurosurg. Psychiatry 78, 644–646.
Wojcik, S.M., 2014. Predicting mild traumatic brain injury patients at risk of persistent symptoms in the Emergency Department. Brain Inj. 28, 422–430.

Xing, G.Q., et al., 2013. Impact of repeated stress on traumatic brain injury-induced mitochondrial electron transport chain expression and behavioral responses in rats. Front. Neurol. 4.
Yeates, K.O., et al., 2009. Longitudinal trajectories of postconcussive symptoms in children with mild traumatic brain injuries and their relationship to acute clinical status. Pediatrics 123, 735–743.
Yehuda, R., et al., 2015. Post-traumatic stress disorder. Nat. Rev. Dis. Prim. 1.
Yu, F., Wang, Z., Mikiei, T., Chiu, C.-T., Leeds, P., Zhang, Y., Chuang, De-M., 2013. Posttrauma cotreatment with lithium and valproate: reduction of lesion volume, attenuation of blood-brain barrier disruption, and improvement in motor coordination in mice with traumatic brain injury. J. Neurosurg. 119 (3), 766–773.
Zatzick, D.F., et al., 2010. Multisite investigation of traumatic brain injuries, posttraumatic stress disorder, and self-reported health and cognitive impairments. Arch. Gen. Psychiatr. 67, 1291–1300.
Zhang, B., et al., 2020. Corticosterone replacement alleviates hippocampal neuronal apoptosis and spatial memory impairment induced by dexamethasone via promoting brain corticosteroid receptor rebalance after traumatic brain injury. J. Neurotrauma 37, 262–272.
Zhou, Y., et al., 2012. Default-mode network disruption in mild traumatic brain injury. Radiology 265, 882–892.
Ziebell, J.M., et al., 2017. Aging with a traumatic brain injury: could behavioral morbidities and endocrine symptoms be influenced by microglial priming? Brain Behav. Immun. 59, 1–7.