



# Lifelong consequences of brain injuries during development: From risk to resilience



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## ABSTRACT

Traumatic brain injuries in children represent a major public health issue and even relatively mild injuries can have lifelong consequences. However, the outcomes from these injuries are highly heterogeneous, with most individuals recovering fully, but a substantial subset experiencing prolonged or permanent disabilities across a number of domains. Moreover, brain injuries predispose individuals to other kinds of neuropsychiatric and somatic illnesses. Critically, the severity of the injury only partially predicts subsequent outcomes, thus other factors must be involved. In this review, we discuss the psychological, social, neuroendocrine, and autonomic processes that are disrupted following traumatic brain injury during development, and consider the mechanisms that mediate risk or resilience after traumatic brain injury in this vulnerable population.

## 1. Introduction to traumatic brain injury

Traumatic brain injury (TBI), caused by a bump, blow, jolt, or penetrating injury to the head, is a global health concern capable of causing lifelong consequences. In the United States, on average, 2.8 million people are diagnosed with a TBI every year, although this is likely to be an underestimate of the actual disease burden because many brain injuries are never reported. A staggering 5.3 million individuals are believed to be living with a long-term disability associated with TBI (Thurman et al., 1999). Symptoms of TBI vary by severity and may progress from headaches, poor memory, sleep disturbance, and fatigue to emotional distress, cognitive and psychosocial dysfunction, and posttraumatic stress (Lundin et al., 2006). The tissue damage and functional impairments induced by TBI can be broadly attributed to two types of processes. First, primary injury, is characterized by the direct damage to the brain including shearing of tissue and damage to the vasculature. Injury outcomes, however, are determined by both these primary factors and the subsequent evolution of pathological processes termed secondary injury, which constitutes the physiological response to the trauma, and may include swelling, neuroinflammation, oxidative damage, excitotoxicity, and ultimately cell death (Ghajar, 2000). Medical management of TBI is necessarily aimed at limiting the development of secondary injury to the greatest possible extent.

Although TBIs occur in men, women, and children of all ages, of the

2.5 million emergency room visits related to TBI annually in the U.S., 26% are for children 0–14 years old (Taylor et al., 2017). Children appear to be at elevated risk of long-term cognitive, physical, and psychological consequences from TBI as compared to individuals injured later in life. This is in contrast to the longstanding theory that children should recover faster from TBI due to considerable plasticity during development (Anderson et al., 2005; Anderson et al., 2011). Rather, pediatric TBI (pTBI) places a disproportionately large public health burden on survivors resulting in increased vulnerability to both neurocognitive and psychosocial deficits, particularly in cases involving moderate to severe injuries (Donders and Warschausky, 2007). Moreover, adult survivors of childhood injury are less likely to have achieved high educational levels, less likely to be employed, more likely to develop drug/alcohol dependence, and more likely to be arrested for a violent offense (Anderson et al., 2009; McKinlay et al., 2014).

Brain injury and the resulting pathology are inherently heterogeneous, contributing to patient outcomes that vary across the range from no overt symptoms to life-altering or fatal outcomes. It is important to note, however, that variability in outcomes is not accounted for by heterogeneity in the injury alone, given that a subset of patients exhibit resilience against TBI symptoms even when similarly injured patients have persistent deficits. This divergence in recovery presents both a diagnostic challenge and a gap in our understanding of the mechanisms that contribute to TBI outcomes. For example, mild brain

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injuries, which represent approximately 80% of all TBIs (National Center for Injury Prevention and Control, 2003; World Health Organization, 2006), produce a wide range of symptoms which generally resolve within a few weeks of injury. The post-concussion symptoms typically reported at one week post mild TBI include headache, dizziness, fatigue, irritability, and difficulty concentrating. While a subset of patients (11–30%) report persistent symptoms between three and 12 months after injury, the majority of mild TBI patients recover to pre-injury levels within three months (Ponsford et al., 2000; Sigurdardottir et al., 2009; Barlow et al., 2015; Babcock et al., 2013). Patients with moderate-to-severe TBI are at a higher risk of developing persistent post-concussion symptoms, yet a substantial proportion (40–70%) return to their preinjury level of function (Dikmen et al., 2003).

Moreover, classical post-concussion symptoms are not the only challenges faced by TBI survivors as these injuries can more generally increase vulnerability to disease states across a huge spectrum of etiologies. For instance, individuals with a history of TBI are more likely to suffer from sepsis, digestive disorders, and seizures along with psychiatric and other neurological issues (Corrigan et al., 2013; Bombardier et al., 2010; Vespa, 2017; Masel and DeWitt, 2010; Harrison-Felix et al., 2006). The role of early life experiences in general, and trauma in particular, on subsequent health outcomes has received much attention in recent decades. Pediatric TBI represents a relatively unique form of trauma in that it both evokes the neuronal and neuroendocrine sequelae typically associated with trauma, and also induces direct mechanical damage to the developing nervous system with profound implications for recovery from the trauma and more general nervous system function. Finally, the duration and intensity of the functional outcomes from TBI depend on several risk factors besides injury severity, including point of impact, age at injury, sex, and comorbid health problems. However, even among individuals that share these risk factors, similar injuries can (and often do) have dramatically different outcomes. Thus, this review will address the interaction between TBI and risk/resilience in two ways. First, we will assess the effects of brain injury on the physiological and psychological recovery in pediatric patients. Then, we will interrogate the TBI literature to identify potential factors that contribute to elevated risk of (or resilience to) persistent pTBI symptoms.

## 2. Social/behavioral disorders

Development of persistent behavioral and social disorders is a common post-injury occurrence after pTBI, affecting as many as 48% of pTBI survivors (Bloom et al., 2001). Patients with moderate to severe brain injury are more likely to experience attention and executive dysfunction as well as adverse family functioning (per parental self-reports) compared to patients with an extracranial injury (Schwartz et al., 2003). The presence of preinjury behavioral problems substantially increases the odds ratio for the development of behavioral disorders following pTBI (odds ratios ranging from 1.40 to 27.11 at 12+ month follow up) (Schwartz et al., 2003). Pediatric TBI patients from low socioeconomic status (SES) households are at an even greater risk of poor social and behavioral outcomes (compared to high SES) even when assessed years after the injury (Yeates et al., 2004; Taylor et al., 2002; Wade et al., 2016). The increased risk of poor functional outcome in this patient population is multifactorial and includes contributing factors such as comorbid health problems (i.e. obesity), authoritarian or permissive parenting practices (Wade et al., 2016), disparities in health insurance coverage (McCarthy et al., 2002), and increased risk of enduring a severe brain injury. Overall, poor social outcomes are common among this patient population, in part because the brain areas closely associated with social cognition (frontal and temporal) (Amodio and Frith, 2006; Ross and Olson, 2010) are likely to suffer damage in pTBI (Wilde et al., 2005). Numerous studies of social outcomes in survivors of pTBI reveal significant deficits in social

adjustment and social cognition (typically measured using the Child Behavior Checklist and the Vineland Adaptive Behavior Scales) compared to similarly aged children with either no injury or extracranial injuries (Yeates et al., 2004; Rosema et al., 2012). Social and behavioral deficits following pTBI are typically worse in individuals who sustained injuries at a younger age than those who were older/adolescents at the time of injury, and the severity of these deficits have been shown to increase with time (Yeates et al., 2004). Psychosocial functioning is critical to recovery from TBI and is a determining factor of community integration and life satisfaction even when assessed many years after injury (Stalnacke, 2007; Hoofien et al., 2001), thus early life TBI represents a period of great vulnerability to long-term social and behavioral consequences.

Because TBI patients face challenges reintegrating into their social community, they are also at risk of receiving reduced levels of social support. Adequate social support, from caregivers, family, and friends, serves an important role in patient recovery and the impact of poor social support on well-being extends beyond the well-known risks for depression and anxiety (Segrin, 2000; Teo et al., 2013) to the development of cardiovascular, cerebrovascular, and infectious diseases (Uchino, 2006; Boden-Albala et al., 2005; Brummett et al., 2001; Friedmann et al., 2006; Karelina and DeVries, 2011). Both adult and pediatric TBI survivors who report poor social support are particularly vulnerable to depression and PCS (McCauley et al., 2001; Taylor et al., 1995; Hart et al., 2012; Moldover et al., 2004). Accordingly, social skills training is viewed as an integral component of TBI rehabilitation programs, however the reported benefits of this approach are generally limited to patients without additional cognitive or psychological impairments. Nonetheless, social skills training programs such as training in the decoding of emotional expressions, and interpersonal process recall, in which patient interactions are videotaped and reviewed with the assistance of a therapist, have successfully improved communication skills and overall life satisfaction in adult patients following moderate or severe TBI (Dahlberg et al., 2007; McDonald et al., 2008; Struchen et al., 2014). Similar intervention attempts with pTBI patients who report having fewer friends after injury (Prigatano and Gupta, 2006) have focused on increasing their social network (Glang et al., 1997) and encouraging positive social behavior (Ylvisaker et al., 2005). Efforts to educate the patients on proper behavior for interaction with their peers have been shown to successfully increase social engagement, though the direct relationship between skills training and TBI outcome in the pediatric population has not been well documented. What is clear is that pTBI patients are at risk of losing social support, particularly by their peers, at a time when perceived social support is known to be a critical component of recovery.

## 3. Endocrine dysfunction

Pediatric traumatic brain injury poses unique challenges to long-term recovery because this patient group is vulnerable to developmental disruptions. Endocrine abnormalities in particular are relatively common after pTBI and have been largely attributed to physical damage to the pituitary induced by the injury (Agha et al., 2004; Alatzoglou et al., 2014; Popovic et al., 2005). The anatomical localization of the pituitary within the sella turcica and the relative fragility of the portal blood supply render the pituitary vulnerable to physical damage (Kornblum and Fisher, 1969). Pituitary infarcts were reported in 38% of patients that died after non-missile TBI (Harper et al., 1986). However, there is mounting evidence that brain injuries produce circuit abnormalities that alter synaptic input onto hypothalamic neurons. Although post-traumatic hypopituitarism was first described in 1918 it has only relatively recently received substantial attention (Schneider et al., 2007; Kaulfers et al., 2010). When considered globally (rather than investigating individual hypothalamic-pituitary systems), pituitary dysfunction is an extremely common sequela of pTBI. Retrospective studies of pTBI survivors have reported between 16 and 61%

prevalence of hypopituitarism at 1–5 years post injury (as defined by basal and stimulated hormone concentrations) (Aimaretti et al., 2005; Reifschneider et al., 2015; Einaudi et al., 2006). Among a prospective cohort of children with moderate-severe traumatic brain injuries, endocrine dysfunction peaked at 75% of children six months after injury before declining to 29% at one-year post injury (Kaulfers et al., 2010). The most common manifestations of pituitary dysfunction include hypothyroidism, growth hormone deficiency and precocious puberty. Interestingly, injury severity does not generally predict endocrine outcomes. Although both adult and pediatric patients can suffer endocrine dysfunction after TBI (for a review see Schneider et al., 2007) there are several endocrine syndromes that are particularly salient for (and/or unique to) children and have important implications for long term outcomes.

### 3.1. Growth hormone deficiency

There is disagreement in the literature as to whether pTBI is associated with isolated (single hormone system) or general hypopituitarism. The somatotrope cells that produce growth hormone appear to be more susceptible to damage than the other cell groups (i.e. corticotropes, gonadotropes and thyrotropes) which may be due to their anatomical localization to the wings of the anterior pituitary (Edwards and Clark, 1986). Growth hormone deficiency is the most common chronic isolated endocrine dysfunction in TBI survivors, affecting between 10 and 33% of individuals. However, there has been marked variation in the rates of growth hormone dysfunction (GHD) among studies, with some cross-sectional studies reporting suboptimal growth hormone and pituitary function without reaching clinically significant GHD (Khadr et al., 2010; Moon et al., 2010) and others reporting significant rates of hypopituitarism and GHD (Aimaretti et al., 2005; Niederland et al., 2007; Norwood et al., 2010) in pTBI survivors. There are several reasons for these discrepancies including variation in the age at injury, time since injury, and the methodology for assessing growth hormone function. Assessment of GHD is a multi-step process that involves assessment of growth velocity, and basal and stimulated concentrations of growth hormone (GH) and insulin-like growth factor 1 (IGF1) (Alatzoglou et al., 2014; S. Growth Hormone Research, 2000). Unfortunately, the approaches used are not standardized, and thus can vary significantly among studies. Finally, the prevalence of GHD is difficult to assess from the clinical literature as in the past physicians would rely largely on reduced growth velocity as a sign of GHD before beginning endocrine testing. However, this approach may underestimate the number of children experiencing GHD as it is not useful for acute assessment in very young children or individuals injured at or near their adult height (Bellone et al., 2013).

Although growth hormone is best known for its role in promoting somatic growth, deficiency along the growth hormone axis can have important modulatory roles in recovery from TBI. Individuals with GHD can exhibit reduced bone mineralization, a possible increase in the incidence of fractures and altered body composition with a decrease in the ratio of lean body mass to fat (Boot et al., 1997). Thus, growth hormone axis deficiency may indirectly interfere with successful recovery by reducing participation in physical activities and team sports both of which promote recovery and can increase the social isolation that is common to children reintegrating after an injury (Yeates et al., 2004; Dimech and Seiler, 2011; Eime et al., 2013; Wise et al., 2012). Further, the deconditioning and sedentary pattern of behavior that can result from growth hormone deficiency can exacerbate many of the deleterious consequences of TBI including physical and cognitive fatigue, depression and impairments in the regulation of autonomic physiology and cerebral blood flow (Leddy et al., 2016). Indeed, among adult patients, those that exhibited GHD after moderate-severe injury exhibited more depression and poorer quality of life scores compared to individuals with similar brain injuries but normal function in the growth hormone axis (Kelly et al., 2006).

Components of the growth hormone axis have a number of central effects on normal neurodevelopment and cognitive function as well as processes involved in CNS recovery and regeneration. Critically, growth hormone production from the anterior pituitary stimulates the production and release of IGF1 from the liver (Yakar et al., 2005). After TBI, IGF1 concentrations fall rapidly and remain persistently low in the serum (Agha et al., 2004; Popovic et al., 2004). IGF1 is also made in neurons but is not dependent on growth hormone for its expression, however reductions in systemic IGF1 production may also decrease central IGF1 expression (Mitschelen et al., 2011; Yan et al., 2011). Animal studies have reported that TBI transiently increases central IGF1 gene expression in an NMDA dependent manner (Madathil et al., 2010; Nordqvist et al., 1997).

Both GH and IGF1 receptors are found in the brain and these hormones can both cross the blood brain barrier. Moreover, GH/IGF1 signaling has been implicated in neurogenesis, axon elongation, myelination, regulation of synapse formation and activity, and angiogenesis among many other processes during normal brain development. Moreover, in the acutely injured brain IGF1 appears to have beneficial anti-inflammatory and pro-survival effects along with improving central energy metabolism (Madathil, 2015). Over the longer term, exogenous IGF1 can help promote regeneration including neurite outgrowth, remyelination and functional plasticity. Further, it seems highly likely that inappropriately low levels of GH/IGF1 signals could serve to further imperil ongoing development and repair. Although the precise mechanism is poorly understood (and is likely multifactorial in any case) low growth hormone concentrations have been correlated with cognitive issues, poor quality of life and other issues (Popovic et al., 2004; High et al., 2010). Moreover, there is limited, but positive evidence that growth hormone replacement therapy can improve cognitive function in patients with both traumatic and non-traumatic growth hormone deficiencies (Moreau et al., 2013). Further, dysfunction of IGF1 signaling in children has been shown to positively correlate with neurocognitive function (Gozal et al., 2009; Gunnell et al., 2005). One study reported that in children (8–9 years old), reading, language comprehension, and intelligence scores increased with elevated levels of serum IGF1 (Gunnell et al., 2005). Thus, adolescent GHD may underly an increased risk of slowed neurodevelopment in pTBI patients.

### 3.2. Hypothalamic pituitary gonadal axis

A second neuroendocrine system that is altered by pTBI is the hypothalamic-pituitary-gonadal (HPG) axis. Alterations in HPG physiology are fairly common in adults but have been less studied in pediatric populations. However, given the critical roles of gonadotrophins and sex steroid hormones in puberty, persistent alterations in HPG physiology in children could potentially have long term consequences that could affect TBI outcomes. Analysis of HPG physiology in children is complicated by normal development; for example, hypogonadotrophism, by definition, cannot be diagnosed in prepubertal children. Moreover, normative values change across childhood and into pubertal transitions (Reifschneider et al., 2015), thus, diagnosis of HPG dysfunction requires long term monitoring of development, and dynamic changes in endocrine status and secondary sex characteristics, and is often missed (Boehm et al., 2015; Masel and Urban, 2015).

In general, TBI acutely, but transiently, suppresses HPG activity in a manner that may be an adaptive response to the injury (Woolf et al., 1985; Behan et al., 2008). However, some percentage of children exhibit persistent alterations in HPG physiology (Kaulfers et al., 2010). Interestingly this can manifest in two functionally opposite phenotypes, hypogonadotrophism or precocious puberty. Hypogonadotrophism cannot be diagnosed in prepubertal children and is unlikely to be assessed in any case unless there are other endocrine abnormalities. Thus, it is relatively unsurprising that the rates of reported reduction in HPG hormone levels among pediatric populations are uncommon, with retrospective and prospective studies reporting between 0 and 9% of

survivors exhibiting lower than normal concentrations of HPG hormones (Kaulfers et al., 2010; Einaudi et al., 2006; Poomthavorn et al., 2008). As a general rule, suppression of the HPG axis seems to occur relatively quickly after injury and resolves of its own accord. Thus, it is not entirely clear whether this is the result of frank damage to the pituitary gonadotrophs or hypothalamic regulation thereof.

Interestingly, some children that suffer a TBI exhibit increased activity of the HPG axis that can result in a condition unique to children, precocious puberty (PP) (Blendonohy and Philip, 1991; Sockalosky et al., 1987). PP is defined as onset of puberty before age 9 in boys and 8 in girls. This condition is also likely underestimated following TBI, but studies have reported between 2 and 9% of injured children, of both sexes exhibiting rapid pubertal onset after injury (Kaulfers et al., 2010; Reifschneider et al., 2015; Einaudi et al., 2006; Poomthavorn et al., 2008). Some patients require gonadotropin releasing hormone (GnRH) agonist therapy to block rapid pubertal development (Kaulfers et al., 2010). The precise cause of PP after pTBI is not well understood, and it has been suggested that the rates of PP among pTBI patients do not exceed the general population. However, other acquired brain injuries such as those induced by meningitis, tumors or hydrocephalus, have also been associated with PP (Siddiqi et al., 1999). The loss of inhibitory control over pulse generators and hypothalamic gonadotrophin neurons has been implicated.

Gonadotrophin deficiency/PP can both impair physical development and potentially interfere with social integration (Hohl et al., 2014) and can have similar effects to GHD on muscle development and exercise tolerance. Moreover, natural variation in the timing of puberty is a key predictor of adolescent behavioral outcomes with earlier (but normal) puberty being associated with greater risks of pregnancy, substance abuse and legal issues (Dick et al., 2000; Celio et al., 2006; Wong et al., 2010). Further, children with other pTBI-associated learning deficits and social issues may be comparatively less able to deal with unwanted sexual attention associated with premature puberty. Indeed, individuals with learning disabilities are much more likely to suffer sexual and physical abuse (Stoltenborgh et al., 2011; Westcott and Jones, 1999). Clearly normal levels of sex steroid hormones are critically important for the maturation of brain, body and behavior (Schulz and Sisk, 2016). Of note, it is not exactly clear how much of the pTBI-induced HPG dysfunction is associated with other broader hypothalamic-pituitary dysfunction or even to what extent HPG dysfunction in particular contributes to variation in outcomes after injury. However, the accumulation of social, cognitive and physical consequences that might come from even minor HPG dysfunction could be magnified in brain injured individuals.

### 3.3. Hypothalamic pituitary adrenal axis

Like most acute stressors, TBI can significantly drive activity of the hypothalamic-pituitary-adrenal (HPA) axis. However, the HPA axis response to TBI is complicated and multifactorial as it is driven by both psychological and physiological trauma (which is not always limited to the head but may also include fractures and blood loss etc.), as well as responses to medical interventions. Further, the hypothalamus and pituitary are vulnerable to direct structural damage, as well as to disconnection between the HPA and overlying limbic and cortical regions involved in threat appraisal (Juraneck et al., 2012; Almeida-Suhett et al., 2014; Palmer et al., 2016). Critically, the acute HPA axis response to TBI has significant modulatory effects on early TBI outcomes. In adults, acute cortisol concentrations tend to increase in a manner that roughly correlates with injury severity, at least among those individuals with mild-moderate injuries (Barton et al., 1987; Cernak et al., 1999). However, some individuals with more severe injuries fail to exhibit the expected elevated cortisol concentrations and are more likely to suffer poor outcomes including longer periods of ventilation and greater hospital mortality (Hannon et al., 2013; Kelly et al., 2000). There are several reasons that this phenomenon, termed functional adrenal

insufficiency, is associated with poorer outcomes. First, low ACTH/cortisol concentrations in acute injury can induce severe hyponatremia and require pressor support. Second, the increase in glucocorticoids associated with acute injury is likely an adaptive response to maximize recovery by altering energy metabolism, stimulating endocrine physiology beyond the HPA axis, and modulating inflammatory responses, thus in the absence of increased glucocorticoid signaling these responses would likely be suboptimal (Johnson and Rn, 2006). Finally, adrenal insufficiency seems to occur among those patients with the most severe injuries (Hannon et al., 2011). The use of exogenous steroid therapy for pTBI patients is not universally recommended although guidelines indicate that children with primary or secondary adrenal insufficiency should be treated with exogenous steroids (Hannon et al., 2011; Agha et al., 2005; Kochanek et al., 2019).

Over the long term there is relatively limited evidence for persistent adrenal insufficiency or hypocortisolism among individuals with pTBI. Although these data should be interpreted conservatively because different studies used very different methods of assessing HPA activity, ranging from measuring basal cortisol or ACTH concentrations, to stimulation with ACTH, metyrapone, glucagon or insulin or negative feedback assessments (Reifschneider et al., 2015; Ghigo et al., 2005). For instance, among a cohort of 33 individuals surviving brain injury nine had suboptimal cortisol responses to an insulin tolerance test (Khadr et al., 2010) although none required glucocorticoid replacement therapy. Similarly, 10 out of 23 survivors of pTBI exhibited subnormal cortisol responses to glucagon administration at three months after injury, although they did not meet diagnostic criteria for hypocortisolism and all but three had normal responses to stimulation when re-tested at 12 months post-injury (Casano-Sancho et al., 2013). Other groups have reported no HPA abnormalities in children with a history of TBI (Kaulfers et al., 2010). Taken together it appears that direct HPA insufficiency after pTBI is a relatively rare complication, nonetheless, as we will address below, responses to physiological and psychological stressors are significantly different among those with a history of TBI.

## 4. Stress responses and long-term outcomes

Traumatic events early in life can have profound effects on a number of long term neurobiological, somatic, cognitive, and psychosocial outcomes (Heim and Binder, 2012; Mirescu et al., 2004; Cohen et al., 2013; McEwen, 2003; Heim et al., 2008; Lupien et al., 2009; De Bellis and Zisk, 2014). Some proportion of the long-term neurobehavioral and medical consequences of early life trauma have been shown to be mediated by long term alterations in stress response systems. The long-term impact of TBI during development shares many similarities to other traumatic experiences, such as childhood abuse or maltreatment, neglect, accidental injuries to other parts of the body and the loss of a parent (Bloom et al., 2001; Lupien et al., 2009; Pechtel and Pizzagalli, 2011). These events can activate stress response systems, lead to the development of post-traumatic stress symptoms, alter school and social outcomes, and increase the likelihood of developing various psychiatric and non-psychiatric diseases later in life (Pechtel and Pizzagalli, 2011; Taylor, 2010). We now understand that these events, when they occur during critical developmental epochs, can profoundly alter the developmental trajectory of neuronal and neurobiological circuitry and subsequently alter the way in which the nervous system functions throughout the rest of the individual's life (Corrigan et al., 2013; Oomen et al., 2010). The neuropathology associated with pTBI is also associated with physical damage to the developing nervous system, thus among children that experience injuries of comparable severity, injuries to the brain are much more closely associated with the development of enduring post-traumatic stress symptoms than those that are injured elsewhere on the body (Levi et al., 1999). Moreover, in injured children, acute stress axis responses are of critical importance in mediating both the tissue damage induced by brain injury and the likelihood of developing post-traumatic stress symptoms (Delahanty et al.,

2000). Thus, to fully understand the variations in the long-term consequences of pTBI we need to consider the manifestation of TBI-related symptoms in children, and the ways in which TBI alters stress responsive systems in this age group.

#### 4.1. Post-concussive syndrome

Most individuals that experience mild-moderate TBI experience transient symptoms and gradually recover over a relatively short time period. However, a subset of individuals experience lasting symptoms that include memory issues, headaches, dizziness, as well as somatic and emotional symptoms that can persist for months after the injury (Barlow et al., 2010). This set of persistent symptoms is termed post-concussive syndrome (PCS) and as a diagnostic entity there has been substantial controversy as to whether it exists at all (Barlow, 2016) or specifically in children (Yeates et al., 1999; Moran et al., 2012; Zemek et al., 2013). There are several reasons why there has been debate as to the existence of PCS, or more specifically whether brain injury (and in particular mild brain injury) can directly cause persistent post concussive symptoms. First, symptoms associated with PCS are certainly not unique to individuals with a history of head injury. Second, there is often concern about litigation as a motivation to report continuing symptoms (Binder and Rohling, 1996). Third, premorbid variables including psychiatric conditions are often powerful predictors of the development of PCS, thus many of the symptoms have been attributed to premorbid variables rather than the injury itself (Wojcik, 2014). Finally, a recall bias is often active where individuals recovering from TBI often overestimate the level of functioning prior to injury and thus attribute greater loss of function to their injury than is warranted (Whittaker et al., 2007; Brooks et al., 2014).

While there is debate as to the precise etiology of persistent post-concussive symptoms approximately one out of seven children that experience mild pTBI will report symptoms that persist for three months or longer after their injuries (Barlow et al., 2010). Further, children with brain injuries are more likely to report post-concussion-like symptoms than are individuals with other kinds of physical trauma (Barlow et al., 2010; McCauley et al., 2011). Moreover, PCS symptoms are associated with substantial distress for children and their families (Moran et al., 2012; Ganesalingam et al., 2008) so it is worth examining the predictors and physical correlates of these symptoms.

Yeates and colleagues described four general courses of recovery after injury (Yeates et al., 2009). As stated above, the majority of children have minimal and transient symptoms that resolve within three months of injury. Among those with persistent symptoms, some children recover within around three months, another group experiences symptoms that gradually increase over time and a third subset report symptoms that are relatively stable across time (Yeates et al., 2009). This is important because the extant evidence suggests that the etiology of symptoms changes over time. In the early period after injury (generally defined as within three months), symptom severity is strongly associated with injury characteristics such as loss-of-consciousness, additional orthopedic injury, or positive neuroimaging results. Interestingly, with increasing time after injury, injury parameters become less prominent predictors of PCS and a variety of non-injury related variables serve as predictors of symptoms. Particularly prominent among these are family variables, premorbid stressors, school difficulties, age, sex and retrospective assessments of preinjury function (Barlow, 2016; McNally et al., 2013). There is also strong evidence that individuals with lower pre-injury IQ or learning disabilities are more likely to develop persistent symptoms suggesting that cognitive reserve can serve to moderate the vulnerability to PCS (Fay et al., 2010).

#### 4.2. Post traumatic stress symptoms/post traumatic stress disorder.

Post-traumatic stress symptoms (PTSS) are a relatively common result of pTBI that can significantly alter the course of recovery. These

symptoms can include re-experiencing the traumatic event (both psychologically and physiologically), avoidance and withdrawal, and hyperarousal (again both physiologically and psychologically). That said, post-traumatic stress disorder (PTSD) in the context of brain injury (especially in children) is also associated with direct damage to the nervous system, including injury to some brain regions involved in threat appraisal and the subsequent stress response (Niogi et al., 2008; Vasa et al., 2004).

The diagnosis of PTSD is challenging in individuals recovering from pTBI. There is substantial evidence that the strict diagnostic criteria for PTSD in adults does not fully capture those with significant disabling symptoms, (Cohen and Scheeringa, 2009; de Vries et al., 1999) thus it is common in the pediatric literature to describe individuals with PTSS. One study reported that although 70% of children hospitalized for pTBI exhibited PTSS, only 5% met the diagnostic criteria for PTSD (Max et al., 1998). Moreover, memory loss and alterations of consciousness are key diagnostic features of PTSD but also extremely common sequela of TBI (King, 2008). Similarly, there is substantial overlap among PTSS and features common to normal development, such as short tempers and fussiness. Additionally, younger children may have difficulty verbally expressing their symptoms (Scheeringa et al., 2005). Finally, it was thought previously that lack of memory for the traumatic injury (which is common in TBI patients) precludes the development of PTSD/PTSS (Sbordone and Liter, 1995) although recall of the trauma is no longer considered a necessary precondition (Harvey et al., 2005).

Diagnostic issues aside, the presence of PTSS significantly impairs recovery. For example, in a cohort of 205 children with mild-severe injuries, the presence of PTSD (as diagnosed with a modified scale for children and adolescents), even after controlling for premorbid behavioral and emotional problems, predicted significantly poorer psychosocial recovery and a trend towards poorer physical recovery compared to individuals with a similar injury but without PTSD. Psychosocial recovery over time was actually better in children with severe injuries but without PTSD than in those with much milder injuries but with PTSD over an 18-month postinjury period (Kenardy et al., 2012). There is also evidence for overlap between individuals suffering from PCS and PTSS. In a study that assessed PCS in children with either a mild pTBI or a comparable orthopedic injury, there was a strong correlation between the symptoms of PTSD and PCS. Interestingly, the individuals with an orthopedic injury exhibited more symptoms of PTSD, suggesting that injury to the nervous system has effects that differ from physical trauma (Hajek et al., 2010).

Much like PCS, premorbid variables are strong predictors of the development of post-traumatic stress after pTBI. In particular, female sex, lower socioeconomic status, anxiety, internalizing psychopathology, and poor problem-solving skills, as well as more severe injuries predicted the development of PTSS after brain injury (Max et al., 1998; Rhine et al., 2018; Gerring et al., 2002). The findings relating persistent PCS and PTSS to premorbid variables at first may seem to suggest that neurological damage resulting from the injury is not responsible for the emergence of these symptoms. It could be argued instead, that pTBI simply exacerbates preexisting symptoms or, if taken even further, is simply the convenient explanation for symptoms that were already present. This, however, greatly oversimplifies the complex processes at play in children that experience brain injury. These injuries can alter the way in which stressors are processed both physiologically (i.e. in terms of neuroendocrine and autonomic physiology) and psychologically in terms of threat appraisal and coping strategies (Bay and Liberzon, 2009; Meiser-Stedman et al., 2007). Additionally, other new-onset psychiatric symptoms including anxiety disorders other than those associated with PTSS also occur after brain injury and are associated with some specific neuroimaging findings including damage to frontal gyri and white matter tracts that connect cortical and subcortical structures (Max et al., 2011)

A general theory regarding the development of PTSS in injured children suggests pTBI, related medical treatments, and other injury-

associated stressors produce a significant stress response (Donlon and Jones, 2015). The magnitude of the stress response is associated most directly with the psychological assessment of the threat of injury rather than the injury itself (Langeland and Olff, 2008). Manipulations that reduce the sense of threat, in one case by simply providing an informational packet about brain injury, can significantly reduce PTSS in injured children (Ponsford et al., 2001). As the individual recovers, PTSS is induced and propagated by dysfunction in the neuronal and peripheral control over physiological stress systems, impairments in neuronal substrates required for threat assessment, and the inhibition of stress responses in the absence of actual threat (Bay and Liberzon, 2009; Dalgleish et al., 2005). Finally, less than optimal coping skills can help reinforce PTSS.

There are two other key factors important for the consideration of PTSS development. First, injury to a child is traumatic for the child but also for the parents. PTSS may even occur in uninjured parents due to the psychological trauma associated with their injured children (Balluffi et al., 2004). This is critically important because parental stress responses and coping mechanisms are key determinants of outcome for the injured children (Anderson et al., 2001; Wade et al., 2001; Ganesalingam et al., 2008). Second, both trauma and TBI often occur more than once. Indeed, TBI is a major risk factor for subsequent TBI. Younger children are thought to be less likely to have experienced a previous traumatic experience or head injury but prior trauma has major effects on the course of both TBI and PTSS outcomes and thus needs to be considered (Pervanidou, 2008).

## 5. Autonomic dysfunction

The autonomic nervous system (ANS) is both a key regulator of cognitive and physical outcomes after TBI and is itself dysregulated by injury. The autonomic regulation of the cardiovascular system represents a highly clinically relevant and a readily assessable readout of integrated physiological and psychological processes (Blake et al., 2016). In general, TBI reduces the coupling between the cardiovascular and autonomic systems and generally increases the ratio of sympathetic:parasympathetic activity under resting and active conditions, relationships that are exacerbated as injury severity increases (Goldstein et al., 1998). This manifests as greater basal heart rate and blood pressure along with reduced heart rate variability. This type of dysregulation is associated with a variety of poor health outcomes including psychiatric and cardiovascular disease and reduced tolerance for exertion (Alvares et al., 2016; Thayer et al., 2010; Kop et al., 2010). There has been comparatively little research on ANS function in pTBI, particularly with milder head injuries and over longer periods of time after injury.

A subset of TBI patients experience a characteristic autonomic syndrome that has come to be called paroxysmal sympathetic hyperactivity (PSH). This syndrome, which was first described by Wilder Penfield in the 1920s (Penfield and Jasper, 1954), constitutes a series of symptoms including instances of tachycardia, arterial hypertension, hyperthermia and tachypnoea (Bower et al., 2010; Perkes et al., 2010). Although there has been comparatively little study of this phenomenon in children, it appears that it affects around 10–15% of individuals hospitalized for moderate-severe TBI (Kirk et al., 2012; Krach et al., 1997). The symptoms associated with this syndrome typically manifest in the first weeks post injury and, although they can occur spontaneously, they may also represent exaggerated responses to previously non-noxious stimuli such as turning, endotracheal tube suction or muscle stretching (Baguley, 2008; Baguley et al., 2009). The symptoms generally resolve or at least become less severe over the subsequent months (Baguley et al., 1999). Although this sympathetic dysautonomic syndrome was previously thought to be epileptic in origin, it is now thought to represent a dysregulation of the excitatory/inhibitory balance in spinal and brain centers (Penfield and Jasper, 1954; Baguley, 2008). Paroxysmal sympathetic hyperactivity is a predictor of poorer

outcomes among TBI patients, resulting in longer ICU stays, reduced neuropsychological recovery and more readmissions (Baguley et al., 1999; Lv et al., 2010). Further, although individuals with PSH tend to have more severe injuries, there is some evidence that PSH itself can independently exacerbate TBI outcomes and impair the effectiveness of rehabilitative therapy (Kirk et al., 2012; Lv et al., 2010).

Early reductions in heart rate variability (an index of parasympathetic activity) are also predictive of poorer outcomes. Among children with moderate-severe pTBI, there were strong correlations between reductions in heart rate variability and Glasgow coma scale at intake, up to and including the complete loss of HRV in brain dead children. More importantly, however, HRV was a better predictor of Glasgow Outcome Scale scores than either coma scale scores or assessments of injury severity (Goldstein et al., 1996; Goldstein et al., 1993). Among adults, early post-injury heart rate variability (in one case as early as 12 h after injury) can predict outcomes out to at least a year after injury (Norris et al., 2005; Henden et al., 2014; Sung et al., 2016). The precise causes of acute alterations in ANS physiology likely represent a combination of acute stress responses, inflammation, increases in intracranial pressure, focal lesions and axonal disconnections (Goldstein et al., 1998; Gang and Malik, 2002; Leitman, 2012)

Among individuals that experience mild-moderate TBI as adults, relatively subtle autonomic dysfunction is not uncommon and can persist. For instance, whereas at rest reduced HRV and other sympathetic parameters may not be present, exertions such as exercise, stress, or manipulations that activate the ANS such as the Valsalva maneuver can reveal underlying impairments (Hilz et al., 2016; Blake et al., 2016; Hilz et al., 2015). This is important because the assessment of autonomic responses with exertion is increasingly being advocated as a marker of recovery in making return to play decisions after sports-related injuries (La Fontaine et al., 2009), ensuring that if exercise produces symptoms potentially associated with autonomic dysfunction (exercise intolerance, dizziness, postural hypotension etc.), then individuals would not (or should not) be cleared for return to play (McCroory et al., October 2016). However, at least one study reported that autonomic dysfunction (increased heart rate and reduced heart rate variability) persisted after symptom resolution and return to play (Gall et al., 2004).

More relevant to the current review, is whether autonomic dysfunction persists among injured children and can serve as a predictor and/or mediator of differential outcomes. There have been extremely few investigations into long term autonomic dysfunction among injured children. One study reported that after a minimum of one-year post-severe pTBI, heart rate was elevated and heart rate variability was reduced at rest. Moreover, six minutes of walking on a treadmill produced impaired autonomic adjustments to exercise among injured children relative to typically developing children (Sorek et al., 2018; Katz-Leurer et al., 2010). Importantly, autonomic dysfunction is bidirectionally linked to the critical outcome measures associated with recovery from pTBI. For instance, if pTBI transiently impairs autonomic function, children may become less exercise tolerant and thus gradually decondition, a state of affairs that can itself promote (or exacerbate) autonomic impairments (Leddy et al., 2017; Leddy et al., 2018). Similar relationships exist between negative affect and autonomic dysfunction (Thayer and Lane, 2000). Thus, there is a critical need for assessment of long-term impairments in autonomic function following mild-moderate TBI among children and whether these impairments can predict and/or mediate differential outcomes.

## 6. Contribution of stress system dysregulation to adverse outcomes

TBI generally induces a physiological stress response characterized by both HPA and ANS activation. Importantly, this stress response is induced at the same time as histopathological injury to regions responsible for control of stress responses, together these factors can lead

to persistent stress-system dysfunction (Bay and Liberzon, 2009). Indeed, increases in both heart rate and urinary cortisol concentrations immediately following injury predicted later development of PTSD (Delahanty et al., 2000; Bryant et al., 2004). Although TBI is known to produce a persistent dysregulation of both the HPA and ANS and their responses to stressors, HPA axis responses to stressors after pTBI have not received a tremendous amount of attention. Thus, it remains unclear whether pTBI results in alteration of glucocorticoid responsivity to stressors. What is relatively clear, at least for other traumatic events beyond TBI is that children and adolescents that develop PTSD exhibit transient increases in HPA activity that gradually resolve toward pre-injury levels (although studies report both persistent reductions and elevations in HPA reactivity (Goenjian et al., 1988; Cicchetti and Rogosch, 2001)). This impairment in glucocorticoid signaling occurs in the presence of greater central corticotrophin releasing factor (CRF) production and release. Thus, the system becomes less responsive to subsequent stressors as the pituitary sensitivity to CRF is gradually downregulated (De Bellis and Zisk, 2014). Additionally, CRF can promote sympathetic activity which remains persistently high after pTBI (Pervanidou et al., 2007). Given the critical role for noradrenergic signaling in attentional processes, emotional tagging of memories, and physiological arousal, dysregulation of this system seems sufficient to produce PTSD (Pervanidou, 2008; Williamson et al., 2013).

In a recent study, there were differential age- and injury-dependent alterations in stress reactivity to the Trier social stress test six months after injury. Injured preadolescent children exhibited elevated basal cortisol compared to uninjured children, however, in response to social stress, injured children showed significant impairments in cortisol production (Ewing-Cobbs et al., 2017). Moreover, salivary alpha amylase (sAA) concentrations, a measure of sympathetic activity, increased to a greater degree in adolescents with a history of TBI than it did in those with extracranial injuries (Ewing-Cobbs et al., 2017). Importantly, sAA concentrations were negatively correlated with avoidance behaviors. These data indicate that TBI can persistently alter the stress response and have important implications for PTSS. Critically, although these data were considered in the context of PTSS, persistent alterations in stress reactivity more generally has important implications for recovery and resilience even among children without PTSS.

## 7. Other factors

Endocrine, psycho-social, and autonomic disruption play an important role in determining recovery from pTBI. However, these processes must also be considered in the context of heterogeneous genetic factors and how they contribute to risk or resilience in pTBI outcome. Specifically, pediatric and adult genetic association studies have identified a number of genes that are associated with standard TBI outcome measures such as the Glasgow Outcome Scale (a scale commonly used to assess functional recovery after TBI), disability, presence/persistence of mood disorders, cognitive disorders, and pathology [see ref Kurowski et al., 2012 for review]. For example, the presence of the APOE  $\epsilon 4$  allele is associated with unfavorable neurological outcome (Brichtova and Kozak, 2008), altered cerebral perfusion pressure (Lo et al., 2009), and a greater likelihood of having a Glasgow Coma Scale score of  $< 15$  in children (Moran et al., 2009). These findings suggest an important association between genotype and TBI recovery, and support the idea that the  $\epsilon 4$  allele can be used to predict greater trauma severity and poor outcome compared with patients that express alternative APOE genotypes typically associated with neuroprotection (i.e. APOE  $\epsilon 2$  or  $\epsilon 3$ ). Similar relationships between genotype and recovery have been identified via analysis of the gene that encodes the enzyme Catechol-O-methyltransferase (COMT). The primary function of COMT is to metabolize catecholamines, thus regulating the activity of dopamine, epinephrine, and norepinephrine, which has important implications for TBI recovery and cognitive function (Lipsky et al., 2005; Willmott et al., 2014; Rizoli et al., 2017). The specific role of COMT in cognitive

function remains under investigation, with some studies reporting that healthy individuals that possess the low activity COMT genotype exhibit better attention than those with the high activity genotype, while other studies report that prefrontal processing is improved in individuals with the high activity COMT genotype (Blasi et al., 2005; Kramer et al., 2007). Among both adult and pediatric TBI patients, those who possess the low activity COMT genotype (associated with decreased degradation of catecholamines) exhibit improved executive function compared to patients with the high activity COMT genotype (Lipsky et al., 2005; Blasi et al., 2005; Kramer et al., 2007; Kurowski et al., 2016). Larger clinical studies are necessary to both replicate and expand upon the link between genetics and pTBI outcome in children, however these data offer an important insight into the role of genetic variation on recovery from pTBI. Implementation of genotyping to the routine clinical assessment of TBI in children may be a useful method for determining risk of complications and may be informative for the development of an appropriate treatment strategy. However, it should be pointed out that the above referenced studies examined genotypic differences but did not directly assess the phenotypic outcomes (e.g. changes in catecholamine metabolism in individuals with COMT polymorphisms) which somewhat limits causal inference.

## 8. Conclusions

Children with brain injuries face significant challenges to optimal recovery and reintegration into their pre-injury lives. These challenges exist at multiple physiological, psychological and social levels. Despite these challenges most children, especially those with relatively mild injuries, recover well and suffer minimal long-term issues. However, a subset of individuals experience long term dysfunction that can persist for many years or permanently after injury. Much emphasis has been placed on correlating injury severity to long term outcomes and while this is undoubtedly a critical determinant it is becoming increasingly clear that many variables, at least partially separate from the injury itself, can significantly alter recovery. Although there are many physiological systems that are vulnerable to disruption by pediatric brain injury. The ability to assess and respond physiologically and psychologically to stressors is central to resilience and these processes appear to be disrupted in children with TBI. Thus, it is critical that we understand how these variables such as endocrine and autonomic physiology or familial support after traumatic brain injury can influence stress responses and subsequent recovery. Perhaps most importantly more research attention has to be paid to individuals who do recover well, rather than just those that suffer adverse consequences if we are to fully understand why some children exhibit robust resilience.

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