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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 the mediate risk or resilience after traumatic brain injury in this vulnerable population.

Keywords

traumatic brain injury; risk; resilience; stress; autonomic; HPA axis; pituitary dysfunction

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 [1]. 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 [2]. The tissue damage and functional impairments induced by TBI can be broadly attributed to two types of processes.

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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 [3]. 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 [4]. 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 [5; 6]. 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 [7]. 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 [8; 9].

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 injuries, which represent approximately 80% of all TBIs [10; 11], 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 [12; 13; 14; 15]. 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 [16].

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 [17; 18; 19; 20; 21]. 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 sequela 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 [22]. 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 [23]. 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 – 27.11 at 12+ month follow up) [23]. 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 [24; 25; 26]. 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 [26], disparities in health insurance coverage [27], 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) [28; 29] are likely to suffer damage in pTBI [30]. 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 [24; 31]. 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 [24]. 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 [32; 33], 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 [34; 35] to the development of cardiovascular, cerebrovascular, and infectious diseases [36; 37; 38; 39; 40]. Both adult and pediatric TBI survivors who report poor social support are particularly vulnerable to depression and PCS [41; 42; 43; 44]. 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 [45; 46; 47]. Similar intervention attempts with pTBI patients who report having fewer friends after injury [48] have focused on increasing their social network [49] and encouraging positive social behavior [50]. 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 [51; 52; 53]. 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 [54]. Pituitary infarcts were reported in 38% of patients that died after non-missile TBI [55]. 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 [56; 57]. 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 16–61% prevalence of hypopituitarism at 1–5 years post injury (as defined by basal and stimulated hormone concentrations) [58; 59; 60]. 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 [57]. 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 [56]) 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 [61]. Growth hormone deficiency is the

most common chronic isolated endocrine dysfunction in TBI survivors, affecting between 10–33% 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 [62; 63] and others reporting significant rates of hypopituitarism and GHD [58; 64; 65] 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) [52; 66]. 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 [67].

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 [68]. 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 [24; 69; 70; 71]. 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 [72]. 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 [73].

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 [74]. After TBI, IGF1 concentrations fall rapidly and remain persistently low in the serum [51; 75]. 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 [76; 77]. Animal studies have reported that TBI transiently increases central IGF1 gene expression in an NMDA dependent manner [78; 79].

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 IGF-1 appears to have beneficial anti-inflammatory and pro-survival effects along with improving central energy metabolism [80]. 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 [75; 81]. 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 [82]. Further, dysfunction of IGF1 signaling in children has been shown to positively correlate with neurocognitive function[83; 84]. One study reported that in children (8–9 years old), reading, language comprehension, and intelligence scores increased with elevated levels of serum IGF-1[84]. 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 [59], 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 [85; 86].

In general, TBI acutely, but transiently, suppresses HPG activity in a manner that may be an adaptive response to the injury [87; 88]. However, some percentage of children exhibit persistent alterations in HPG physiology [57]. 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 0–9% of survivors exhibiting lower than normal concentrations of HPG hormones [57; 60; 89]. 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) [90; 91]. 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 2–9% of injured children,

of both sexes exhibiting rapid pubertal onset after injury [57; 59; 60; 89]. Some patients require gonadotropin releasing hormone (GnRH) agonist therapy to block rapid pubertal development [57]. 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 [92]. 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 [93] 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 [94; 95; 96]. 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 [97; 98]. Clearly normal levels of sex steroid hormones are critically important for the maturation of brain, body and behavior [99]. 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 [100; 101; 102]. 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 [103; 104]. 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 [105; 106]. 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 [107]. Finally, adrenal insufficiency seems to occur among those

patients with the most severe injuries [108]. 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 [108; 109; 110].

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 [59; 111]. For instance, among a cohort of 33 individuals surviving brain injury nine had suboptimal cortisol responses to an insulin tolerance test [62] 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 retested at 12 months post-injury [112]. Other groups have reported no HPA abnormalities in children with a history of TBI [57]. 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 [113; 114; 115; 116; 117; 118; 119]. 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 [22; 118; 120]. 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 [120; 121]. 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 [17; 122]. 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 [123]. 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 [124]. 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 [125]. 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 [126] or specifically in children [127; 128; 129]. 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 [130]. 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 [131]. 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 [132; 133].

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 [125]. Further, children with brain injuries are more likely to report post-concussion-like symptoms than are individuals with other kinds of physical trauma [125; 134]. Moreover, PCS symptoms are associated with substantial distress for children and their families [128; 135] so it is worth examining the predictors and physical correlates of these symptoms.

Yeates and colleagues described four general courses of recovery after injury [136]. 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 [136]. 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 [126; 137]. 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 [138].

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 [139; 140].

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, [141; 142] 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 [143]. Moreover, memory loss and alterations of consciousness are key diagnostic features of PTSD but also extremely common sequela of TBI [144]. 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 [145]. 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 [146] although recall of the trauma is no longer considered a necessary precondition[147].

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 [148]. 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 [149].

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 [143; 150; 151]. 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 [152; 153]. 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 [154]

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 [155]. The magnitude of the stress response is associated most directly with the psychological assessment of the threat of injury rather than the injury itself [156]. 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 [157]. 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 [152; 158]. 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 [159]. This is critically important because parental stress responses and coping mechanisms are key determinants of outcome for the injured children [160; 161; 162]. 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 [163].

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 assessible readout of integrated physiological and psychological processes [164]. 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 [165]. 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 [166; 167; 168]. 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 [169], constitutes a series of symptoms including instances of tachycardia, arterial hypertension, hyperthermia and tachypnoea [170; 171]. 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 [172; 173]. 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 [174; 175]. The symptoms generally resolve or at least become less severe over the subsequent months [176]. 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 [169; 174]. Paroxysmal sympathetic hyperactivity is a predictor of poorer outcomes among TBI patients, resulting in longer ICU stays, reduced neuropsychological recovery and more readmissions [176; 177]. 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 [172; 177].

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 [178; 179]. Among adults, early post-injury heart rate variability (in one case as early as 12h after injury) can predict outcomes out to at least a year after injury [180; 181; 182]. 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 [165; 183; 184]

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 [185; 186; 187]. 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 [188], 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 [189]. 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 [190].

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 [191; 192]. 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 [193; 194]. Similar relationships exist between negative affect and autonomic dysfunction [195]. 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. 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 [152]. Indeed, increases in both heart rate and urinary cortisol concentrations immediately following injury predicted later development of PTSD [124; 196]. 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 [197; 198]). 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 [119]. Additionally, CRF can promote sympathetic activity which remains persistently high after pTBI [199]. 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 [163; 200].

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 [201]. 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 [201]. 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 202 for review]. For example, the presence of the APOE ε4 allele is associated with unfavorable neurological outcome [203], altered cerebral perfusion pressure [204], and a greater likelihood of having a Glasgow Coma Scale score of < 15 in children [205]. These findings suggest an important association between genotype and TBI recovery, and support the idea that the ε4 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 ε2 or ε3). 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 [206; 207; 208]. 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[209; 210]. 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 [206; 209; 210; 211]. 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.

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.

References

[1]. Thurman DJ, Alverson C, Dunn KA, Guerrero J, and Sniezek JE, Traumatic brain injury in the United States: A public health perspective. J Head Trauma Rehabil 14 (1999) 602–15. [PubMed: 10671706]

[2]. Lundin A, de Boussard C, Edman G, and Borg J, Symptoms and disability until 3 months after mild TBI. Brain Inj 20 (2006) 799–806. [PubMed: 17060147]

[3]. Ghajar J, Traumatic brain injury. Lancet 356 (2000) 923–9. [PubMed: 11036909]

[4]. Taylor CA, Bell JM, Breiding MJ, and Xu L, Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2007 and 2013. MMWR Surveill Summ 66 (2017) 1–16.

[5]. Anderson V, Catroppa C, Morse S, Haritou F, and Rosenfeld J, Functional plasticity or vulnerability after early brain injury? Pediatrics 116 (2005) 1374–82. [PubMed: 16322161]

[6]. Anderson V, Spencer-Smith M, and Wood A, Do children really recover better? Neurobehavioural plasticity after early brain insult. Brain 134 (2011) 2197–221. [PubMed: 21784775]

[7]. Donders J, and Warschausky S, Neurobehavioral outcomes after early versus late childhood traumatic brain injury. J Head Trauma Rehabil 22 (2007) 296–302. [PubMed: 17878771]

[8]. Anderson V, Brown S, Newitt H, and Hoile H, Educational, vocational, psychosocial, and quality-of-life outcomes for adult survivors of childhood traumatic brain injury. J Head Trauma Rehabil 24 (2009) 303–12. [PubMed: 19858964]

[9]. McKinlay A, Corrigan J, Horwood LJ, and Fergusson DM, Substance abuse and criminal activities following traumatic brain injury in childhood, adolescence, and early adulthood. J Head Trauma Rehabil 29 (2014) 498–506. [PubMed: 24263173]

[10]. National Center for Injury Prevention and Control. Report to congress on mild traumatic brain injury in the United States: steps to prevent a serious public health problem., Atlanta, GA, 2003.

[11]. World Health Organization. Neurological disorders: public health challenges., World Health Organization Press, Geneva, Switzerland, 2006.

[12]. Ponsford J, Willmott C, Rothwell A, Cameron P, Kelly AM, Nelms R, Curran C, and Ng K, Factors influencing outcome following mild traumatic brain injury in adults. J Int Neuropsychol Soc 6 (2000) 568–79. [PubMed: 10932476]

[13]. Sigurdardottir S, Andelic N, Roe C, Jerstad T, and Schanke AK, Post-concussion symptoms after traumatic brain injury at 3 and 12 months post-injury: A prospective study. Brain Injury 23 (2009) 489–497. [PubMed: 19484622]

[14]. Barlow KM, Crawford S, Brooks BL, Turley B, and Mikrogianakis A, The Incidence of Postconcussion Syndrome Remains Stable Following Mild Traumatic Brain Injury in Children. Pediatr Neurol 53 (2015) 491–7. [PubMed: 26421987]

[15]. Babcock L, Byczkowski T, Wade SL, Ho M, Mookerjee S, and Bazarian JJ, Predicting postconcussion syndrome after mild traumatic brain injury in children and adolescents who present to the emergency department. JAMA Pediatr 167 (2013) 156–61. [PubMed: 23247384]

[16]. Dikmen SS, Machamer JE, Powell JM, and Temkin NR, Outcome 3 to 5 years after moderate to severe traumatic brain injury. Arch Phys Med Rehabil 84 (2003) 1449–57. [PubMed: 14586911]

[17]. Corrigan JD, Bogner J, Mellick D, Bushnik T, Dams-O'Connor K, Hammond FM, Hart T, and Kolakowsky-Hayner S, Prior History of Traumatic Brain Injury Among Persons in the Traumatic Brain Injury Model Systems National Database. Arch Phys Med Rehab 94 (2013) 1940–1950.

[18]. Bombardier CH, Fann JR, Temkin NR, Esselman PC, Barber J, and Dikmen SS, Rates of major depressive disorder and clinical outcomes following traumatic brain injury. JAMA 303 (2010) 1938–45. [PubMed: 20483970]

[19]. Vespa P, Traumatic brain injury is a longitudinal disease process. Curr Opin Neurol 30 (2017) 563–564. [PubMed: 29095717]

[20]. Masel BE, and DeWitt DS, Traumatic Brain Injury: A Disease Process, Not an Event. J Neurotraum 27 (2010) 1529–1540.

[21]. Harrison-Felix C, Whiteneck G, DeVivo M, Hammond FM, and Jha A, Causes of death following 1 year postinjury among individuals with traumatic brain injury. J Head Trauma Rehab 21 (2006) 22–33.

[22]. Bloom DR, Levin HS, Ewing-Cobbs L, Saunders AE, Song J, Fletcher JM, and Kowatch RA, Lifetime and novel psychiatric disorders after pediatric traumatic brain injury. J Am Acad Child Adolesc Psychiatry 40 (2001) 572–9. [PubMed: 11349702]

[23]. Schwartz L, Taylor HG, Drotar D, Yeates KO, Wade SL, and Stancin T, Long-term behavior problems following pediatric traumatic brain injury: prevalence, predictors, and correlates. J Pediatr Psychol 28 (2003) 251–63. [PubMed: 12730282]

[24]. Yeates KO, Swift E, Taylor HG, Wade SL, Drotar D, Stancin T, and Minich N, Short- and long-term social outcomes following pediatric traumatic brain injury. J Int Neuropsychol Soc 10 (2004) 412–26. [PubMed: 15147599]

[25]. Taylor HG, Yeates KO, Wade SL, Drotar D, Stancin T, and Minich N, A prospective study of short- and long-term outcomes after traumatic brain injury in children: behavior and achievement. Neuropsychology 16 (2002) 15–27. [PubMed: 11853353]

[26]. Wade SL, Zhang N, Yeates KO, Stancin T, and Taylor HG, Social Environmental Moderators of Long-term Functional Outcomes of Early Childhood Brain Injury. JAMA Pediatr 170 (2016) 343–9. [PubMed: 26902662]

[27]. McCarthy ML, Serpi T, Kufera JA, Demeter LA, and Paidas C, Factors influencing admission among children with a traumatic brain injury. Acad Emerg Med 9 (2002) 684–93. [PubMed: 12093708]

[28]. Amodio DM, and Frith CD, Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci 7 (2006) 268–77. [PubMed: 16552413]

[29]. Ross LA, and Olson IR, Social cognition and the anterior temporal lobes. Neuroimage 49 (2010) 3452–62. [PubMed: 19931397]

[30]. Wilde EA, Hunter JV, Newsome MR, Scheibel RS, Bigler ED, Johnson JL, Fearing MA, Cleavinger HB, Li X, Swank PR, Pedroza C, Roberson GS, Bachevalier J, and Levin HS, Frontal and temporal morphometric findings on MRI in children after moderate to severe traumatic brain injury. J Neurotrauma 22 (2005) 333–44. [PubMed: 15785229]

[31]. Rosema S, Crowe L, and Anderson V, Social function in children and adolescents after traumatic brain injury: a systematic review 1989–2011. J Neurotrauma 29 (2012) 1277–91. [PubMed: 22260408]

[32]. Stalnacke BM, Community integration, social support and life satisfaction in relation to symptoms 3 years after mild traumatic brain injury. Brain Inj 21 (2007) 933–42. [PubMed: 17729046]

[33]. Hoofien D, Gilboa A, Vakil E, and Donovick PJ, Traumatic brain injury (TBI) 10–20 years later: a comprehensive outcome study of psychiatric symptomatology, cognitive abilities and psychosocial functioning. Brain Inj 15 (2001) 189–209. [PubMed: 11260769]

[34]. Segrin C, Social skills deficits associated with depression. Clin Psychol Rev 20 (2000) 379–403. [PubMed: 10779900]

[35]. Teo AR, Lerrigo R, and Rogers MA, The role of social isolation in social anxiety disorder: a systematic review and meta-analysis. J Anxiety Disord 27 (2013) 353–64. [PubMed: 23746493]

[36]. Uchino BN, Social support and health: a review of physiological processes potentially underlying links to disease outcomes. J Behav Med 29 (2006) 377–87. [PubMed: 16758315]

[37]. Boden-Albala B, Litwak E, Elkind MS, Rundek T, and Sacco RL, Social isolation and outcomes post stroke. Neurology 64 (2005) 1888–92. [PubMed: 15955939]

[38]. Brummett BH, Barefoot JC, Siegler IC, Clapp-Channing NE, Lytle BL, Bosworth HB, Williams RB, and Mark DB, Characteristics of socially isolated patients with coronary artery disease who are at elevated risk for mortality. Psychosom Med 63 (2001) 267–272. [PubMed: 11292274]

[39]. Friedmann E, Thomas SA, Liu F, Morton PG, Chapa D, Gottlieb SS, and Sudden I Cardiac Death in Heart Failure Trial, Relationship of depression, anxiety, and social isolation to chronic heart failure outpatient mortality. Am Heart J 152 (2006) 940 e1–8. [PubMed: 17070164]

[40]. Karelina K, and DeVries AC, Modeling social influences on human health. Psychosom Med 73 (2011) 67–74. [PubMed: 21097660]

[41]. McCauley SR, Boake C, Levin HS, Contant CF, and Song JX, Postconcussional disorder following mild to moderate traumatic brain injury: anxiety, depression, and social support as risk factors and comorbidities. J Clin Exp Neuropsychol 23 (2001) 792–808. [PubMed: 11910545]

[42]. Taylor HG, Drotar D, Wade S, Yeates K, Stancin T, and Klein S, Recovery from traumatic brain injury in children: The importance of the family. Traumatic head injury in children (1995) 188–216.

[43]. Hart T, Hoffman JM, Pretz C, Kennedy R, Clark AN, and Brenner LA, A longitudinal study of major and minor depression following traumatic brain injury. Arch Phys Med Rehabil 93 (2012) 1343–9. [PubMed: 22840833]

[44]. Moldover JE, Goldberg KB, and Prout MF, Depression after traumatic brain injury: a review of evidence for clinical heterogeneity. Neuropsychol Rev 14 (2004) 143–54. [PubMed: 15673235]

[45]. Dahlberg CA, Cusick CP, Hawley LA, Newman JK, Morey CE, Harrison-Felix CL, and Whiteneck GG, Treatment efficacy of social communication skills training after traumatic brain injury: a randomized treatment and deferred treatment controlled trial. Arch Phys Med Rehabil 88 (2007) 1561–73. [PubMed: 18047870]

[46]. McDonald S, Tate R, Togher L, Bornhofen C, Long E, Gertler P, and Bowen R, Social skills treatment for people with severe, chronic acquired brain injuries: A multicenter trial. Arch Phys Med Rehab 89 (2008) 1648–1659.

[47]. Struchen MA, Social Communication Interventions. in: S. M., and S. A., (Eds.), Handbook on the Neuropsychology of Traumatic Brain Injury. Clinical Handbooks in Neuropsychology., Springer, New York, NY, 2014, pp. 213–231.

[48]. Prigatano GP, and Gupta S, Friends after traumatic brain injury in children. J Head Trauma Rehabil 21 (2006) 505–13. [PubMed: 17122681]

[49]. Glang A, Todis B, Cooley E, Wells J, and Voss J, Building social networks for children and adolescents with traumatic brain injury: A school-based intervention. J Head Trauma Rehab 12 (1997) 32–47.

[50]. Ylvisaker M, Adelson PD, Braga LW, Burnett SM, Glang A, Feeney T, Moore W, Rumney P, and Todis B, Rehabilitation and ongoing support after pediatric TBI: twenty years of progress. J Head Trauma Rehabil 20 (2005) 95–109. [PubMed: 15668573]

[51]. Agha A, Rogers B, Sherlock M, O'Kelly P, Tormey W, Phillips J, and Thompson CJ, Anterior pituitary dysfunction in survivors of traumatic brain injury. J Clin Endocrinol Metab 89 (2004) 4929–36. [PubMed: 15472187]

[52]. Alatzoglou KS, Webb EA, Le Tissier P, and Dattani MT, Isolated growth hormone deficiency (GHD) in childhood and adolescence: recent advances. Endocr Rev 35 (2014) 376–432. [PubMed: 24450934]

[53]. Popovic V, Aimaretti G, Casanueva FF, and Ghigo E, Hypopituitarism following traumatic brain injury. Growth Horm IGF Res 15 (2005) 177–84. [PubMed: 15935980]

[54]. Kornblum RN, and Fisher RS, Pituitary lesions in craniocerebral injuries. Arch Pathol 88 (1969) 242–8. [PubMed: 5800923]

[55]. Harper CG, Doyle D, Adams JH, and Graham DI, Analysis of abnormalities in pituitary gland in non-missile head injury: study of 100 consecutive cases. J Clin Pathol 39 (1986) 769–73. [PubMed: 3734113]

[56]. Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, and Agha A, Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. JAMA 298 (2007) 1429–38. [PubMed: 17895459]

[57]. Kaulfers AM, Backeljauw PF, Reifschneider K, Blum S, Michaud L, Weiss M, and Rose SR, Endocrine dysfunction following traumatic brain injury in children. J Pediatr 157 (2010) 894–9. [PubMed: 20797728]

[58]. Aimaretti G, Ambrosio MR, Di Somma C, Gasperi M, Cannavo S, Scaroni C, De Marinis L, Baldelli R, Bona G, Giordano G, and Ghigo E, Hypopituitarism induced by traumatic brain injury in the transition phase. J Endocrinol Invest 28 (2005) 984–9. [PubMed: 16483176]

[59]. Reifschneider K, Auble BA, and Rose SR, Update of Endocrine Dysfunction following Pediatric Traumatic Brain Injury. J Clin Med 4 (2015) 1536–60. [PubMed: 26287247]

[60]. Einaudi S, Matarazzo P, Peretta P, Grossetti R, Giordano F, Altare F, Bondone C, Andreo M, Ivani G, Genitori L, and de Sanctis C, Hypothalamo-hypophysial dysfunction after traumatic brain injury in children and adolescents: a preliminary retrospective and prospective study. J Pediatr Endocrinol Metab 19 (2006) 691–703. [PubMed: 16789636]

[61]. Edwards OM, and Clark JD, Post-traumatic hypopituitarism. Six cases and a review of the literature. Medicine (Baltimore) 65 (1986) 281–90. [PubMed: 3018425]

[62]. Khadr SN, Crofton PM, Jones PA, Wardhaugh B, Roach J, Drake AJ, Minns RA, and Kelnar CJ, Evaluation of pituitary function after traumatic brain injury in childhood. Clin Endocrinol (Oxf) 73 (2010) 637–43. [PubMed: 20681995]

[63]. Moon RJ, Sutton T, Wilson PM, Kirkham FJ, and Davies JH, Pituitary Function at Long-Term Follow-Up of Childhood Traumatic Brain Injury. J Neurotraum 27 (2010) 1827–1835.

[64]. Niederland T, Makovi H, Gal V, Andreka B, Abraham CS, and Kovacs J, Abnormalities of pituitary function after traumatic brain injury in children. J Neurotrauma 24 (2007) 119–27. [PubMed: 17263675]

[65]. Norwood KW, Deboer MD, Gurka MJ, Kuperminc MN, Rogol AD, Blackman JA, Wamstad JB, Buck ML, and Patrick PD, Traumatic brain injury in children and adolescents: surveillance for pituitary dysfunction. Clin Pediatr (Phila) 49 (2010) 1044–9. [PubMed: 20724335]

[66]. S. Growth Hormone Research, Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab 85 (2000) 3990–3. [PubMed: 11095419]

[67]. Bellone S, Einaudi S, Caputo M, Prodam F, Busti A, Belcastro S, Parlamento S, Zavattaro M, Verna F, Bondone C, Tessaris D, Gasco V, Bona G, and Aimaretti G, Measurement of height velocity is an useful marker for monitoring pituitary function in patients who had traumatic brain injury. Pituitary 16 (2013) 499–506. [PubMed: 23179963]

[68]. Boot AM, Engels MA, Boerma GJ, Krenning EP, and De Muinck Keizer-Schrama SM, Changes in bone mineral density, body composition, and lipid metabolism during growth hormone (GH) treatment in children with GH deficiency. J Clin Endocrinol Metab 82 (1997) 2423–8. [PubMed: 9253311]

[69]. Dimech AS, and Seiler R, Extra-curricular sport participation: A potential buffer against social anxiety symptoms in primary school children. Psychol Sport Exerc 12 (2011) 347–354.

[70]. Eime RM, Young JA, Harvey JT, Charity MJ, and Payne WR, A systematic review of the psychological and social benefits of participation in sport for children and adolescents: informing development of a conceptual model of health through sport. Int J Behav Nutr Phy 10 (2013).

[71]. Wise EK, Hoffman JM, Powell JM, Bombardier CH, and Bell KR, Benefits of exercise maintenance after traumatic brain injury. Arch Phys Med Rehabil 93 (2012) 1319–23. [PubMed: 22840829]

[72]. Leddy J, Hinds A, Sirica D, and Willer B, The Role of Controlled Exercise in Concussion Management. PM R 8 (2016) S91–S100. [PubMed: 26972272]

[73]. Kelly DF, McArthur DL, Levin H, Swimmer S, Dusick JR, Cohan P, Wang C, and Swerdloff R, Neurobehavioral and quality of life changes associated with growth hormone insufficiency after complicated mild, moderate, or severe traumatic brain injury. J Neurotrauma 23 (2006) 928–42. [PubMed: 16774477]

[74]. Yakar S, Kim H, Zhao H, Toyoshima Y, Pennisi P, Gavrilova O, and Leroith D, The growth hormone-insulin like growth factor axis revisited: lessons from IGF-1 and IGF-1 receptor gene targeting. Pediatr Nephrol 20 (2005) 251–4. [PubMed: 15645308]

[75]. Popovic V, Pekic S, Pavlovic D, Maric N, Jasovic-Gasic M, Djurovic B, Medic-Stojanoska M, Zivkovic V, Stojanovic M, Doknic M, Milic N, Djurovic M, Dieguez C, and Casanueva FF, Hypopituitarism as a consequence of traumatic brain injury (TBI) and its possible relation with cognitive disabilities and mental distress. Journal of Endocrinological Investigation 27 (2004) 1048–1054. [PubMed: 15754737]

[76]. Mitschelen M, Yan H, Farley JA, Warrington JP, Han S, Herenu CB, Csiszar A, Ungvari Z, Bailey-Downs LC, Bass CE, and Sonntag WE, Long-term deficiency of circulating and hippocampal insulin-like growth factor I induces depressive behavior in adult mice: a potential model of geriatric depression. Neuroscience 185 (2011) 50–60. [PubMed: 21524689]

[77]. Yan H, Mitschelen M, Bixler GV, Brucklacher RM, Farley JA, Han S, Freeman WM, and Sonntag WE, Circulating IGF1 regulates hippocampal IGF1 levels and brain gene expression during adolescence. J Endocrinol 211 (2011) 27–37. [PubMed: 21750148]

[78]. Madathil SK, Evans HN, and Saatman KE, Temporal and Regional Changes in IGF-1/IGF-1R Signaling in the Mouse Brain after Traumatic Brain Injury. J Neurotraum 27 (2010) 95–107.

[79]. Nordqvist ACS, Holmin S, Nilsson M, Mathiesen T, and Schalling M, MK-801 inhibits the cortical increase in IGF-1, IGFBP-2 and IGFBP-4 expression following trauma. Neuroreport 8 (1997) 455–460. [PubMed: 9080428]

[80]. Madathil SK, and Saatman KE, IGF-1/IGF-R Signaling in Traumatic Brain Injury: Impact on Cell Survival, Neurogenesis, and Behavioral Outcome. in: Kobeissy FH, (Ed.), Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects, Boca Raton (FL), 2015.

[81]. High WM, Briones-Galang M, Clark JA, Gilkison C, Mossberg KA, Zgaljardic DJ, Masel BE, and Urban RJ, Effect of Growth Hormone Replacement Therapy on Cognition after Traumatic Brain Injury. J Neurotraum 27 (2010) 1565–1575.

[82]. Moreau OK, Cortet-Rudelli C, Yollin E, Merlen E, Daveluy W, and Rousseaux M, Growth hormone replacement therapy in patients with traumatic brain injury. J Neurotrauma 30 (2013) 998–1006. [PubMed: 23323993]

[83]. Gozal D, Sans Capdevila O, McLaughlin Crabtree V, Serpero LD, Witcher LA, and Kheirandish-Gozal L, Plasma IGF-1 levels and cognitive dysfunction in children with obstructive sleep apnea. Sleep Med 10 (2009) 167–73. [PubMed: 18314384]

[84]. Gunnell D, Miller LL, Rogers I, Holly JM, and Team AS, Association of insulin-like growth factor I and insulin-like growth factor-binding protein-3 with intelligence quotient among 8- to 9-year-old children in the Avon Longitudinal Study of Parents and Children. Pediatrics 116 (2005) e681–6. [PubMed: 16263982]

[85]. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dode C, Dunkel L, Dwyer AA, Giacobini P, Hardelin JP, Juul A, Maghnie M, Pitteloud N, Prevot V, Raivio T, Tena-Sempere M, Quinton R, and Young J, EXPERT CONSENSUS DOCUMENT European Consensus Statement on congenital hypogonadotropic hypogonadism-pathogenesis, diagnosis and treatment. Nat Rev Endocrinol 11 (2015) 547–564. [PubMed: 26194704]

[86]. Masel BE, and Urban R, Chronic Endocrinopathies in Traumatic Brain Injury Disease. J Neurotrauma 32 (2015) 1902–10. [PubMed: 25325517]

[87]. Woolf PD, Hamill RW, McDonald JV, Lee LA, and Kelly M, Transient hypogonadotropic hypogonadism caused by critical illness. J Clin Endocrinol Metab 60 (1985) 444–50. [PubMed: 3919042]

[88]. Behan LA, Phillips J, Thompson CJ, and Agha A, Neuroendocrine disorders after traumatic brain injury. J Neurol Neurosurg Psychiatry 79 (2008) 753–9. [PubMed: 18559460]

[89]. Poomthavorn P, Maixner W, and Zacharin M, Pituitary function in paediatric survivors of severe traumatic brain injury. Arch Dis Child 93 (2008) 133–7. [PubMed: 17986604]

[90]. Blendonohy PM, and Philip PA, Precocious puberty in children after traumatic brain injury. Brain Inj 5 (1991) 63–8. [PubMed: 2043909]

[91]. Sockalosky JJ, Kriel RL, Krach LE, and Sheehan M, Precocious puberty after traumatic brain injury. J Pediatr 110 (1987) 373–7. [PubMed: 3819938]

[92]. Siddiqi SU, Van Dyke DC, Donohoue P, and McBrien DM, Premature sexual development in individuals with neurodevelopmental disabilities. Dev Med Child Neurol 41 (1999) 392–5. [PubMed: 10400173]

[93]. Hohl A, Ronsoni MF, Sande-Lee S.v.d., Vieira F.C.d.F., Schwarzbold ML, Diaz AP, and Walz R, Androgens, Male Hypogonadism and Traumatic Brain Injury. Open Journal of Endocrine and Metabolic Diseases 04 (2014) 13–23.

[94]. Dick DM, Rose RJ, Viken RJ, and Kaprio J, Pubertal timing and substance use: Associations between and within families across late adolescence. Dev Psychol 36 (2000) 180–189. [PubMed: 10749075]

[95]. Celio M, Karnik NS, and Steiner H, Early maturation as a risk factor for aggression and delinquency in adolescent girls: a review. Int J Clin Pract 60 (2006) 1254–1262. [PubMed: 16930146]

[96]. Wong TML, Slotboom AM, and Bijleveld CCJH, Risk factors for delinquency in adolescent and young adult females: A European review. Eur J Criminol 7 (2010) 266–284.

[97]. Stoltenborgh M, van Ijzendoorn MH, Euser EM, and Bakermans-Kranenburg MJ, A global perspective on child sexual abuse: meta-analysis of prevalence around the world. Child Maltreat 16 (2011) 79–101. [PubMed: 21511741]

[98]. Westcott HL, and Jones DPH, Annotation: The abuse of disabled children. J Child Psychol Psyc 40 (1999) 497–506.

[99]. Schulz KM, and Sisk CL, The organizing actions of adolescent gonadal steroid hormones on brain and behavioral development. Neurosci Biobehav R 70 (2016) 148–158.

[100]. Juranek J, Johnson CP, Prasad MR, Kramer LA, Saunders A, Filipek PA, Swank PR, Cox CS Jr., and Ewing-Cobbs L, Mean diffusivity in the amygdala correlates with anxiety in pediatric TBI. Brain Imaging Behav 6 (2012) 36–48. [PubMed: 21979818]

[101]. Almeida-Suhett CP, Prager EM, Pidoplichko V, Figueiredo TH, Marini AM, Li Z, Eiden LE, and Braga MF, Reduced GABAergic inhibition in the basolateral amygdala and the development of anxiety-like behaviors after mild traumatic brain injury. PLoS One 9 (2014) e102627. [PubMed: 25047645]

[102]. Palmer CP, Metheny HE, Elkind JA, and Cohen AS, Diminished amygdala activation and behavioral threat response following traumatic brain injury. Exp Neurol 277 (2016) 215–226. [PubMed: 26791254]

[103]. Barton RN, Stoner HB, and Watson SM, Relationships among plasma cortisol, adrenocorticotrophin, and severity of injury in recently injured patients. J Trauma 27 (1987) 384–92. [PubMed: 3033260]

[104]. Cernak I, Savic VJ, Lazarov A, Joksimovic M, and Markovic S, Neuroendocrine responses following graded traumatic brain injury in male adults. Brain Inj 13 (1999) 1005–15. [PubMed: 10628505]

[105]. Hannon MJ, Crowley RK, Behan LA, O'Sullivan EP, O'Brien MM, Sherlock M, Rawluk D, O'Dwyer R, Tormey W, and Thompson CJ, Acute glucocorticoid deficiency and diabetes insipidus are common after acute traumatic brain injury and predict mortality. J Clin Endocrinol Metab 98 (2013) 3229–37. [PubMed: 23690314]

[106]. Kelly DF, Gonzalo IT, Cohan P, Berman N, Swerdloff R, and Wang C, Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report. J Neurosurg 93 (2000) 743–52. [PubMed: 11059653]

[107]. Johnson KL, and Rn CR, The hypothalamic-pituitary-adrenal axis in critical illness. AACN Clin Issues 17 (2006) 39–49. [PubMed: 16462408]

[108]. Hannon MJ, Sherlock M, and Thompson CJ, Pituitary dysfunction following traumatic brain injury or subarachnoid haemorrhage – In "Endocrine Management in the Intensive Care Unit". Best Practice & Research Clinical Endocrinology & Metabolism 25 (2011) 783–798. [PubMed: 21925078]

[109]. Agha A, Sherlock M, and Thompson CJ, Post-traumatic hyponatraemia due to acute hypopituitarism. Qjm-Int J Med 98 (2005) 463–464.

[110]. Kochanek PM, Tasker RC, Carney N, Totten AM, Adelson PD, Selden NR, Davis-O'Reilly C, Hart EL, Bell MJ, Bratton SL, Grant GA, Kissoon N, Reuter-Rice KE, Vavilala MS, and Wainwright MS, Guidelines for the Management of Pediatric Severe Traumatic Brain Injury, Third Edition: Update of the Brain Trauma Foundation Guidelines. Pediatr Crit Care Med 20 (2019) S1–S82. [PubMed: 30829890]

[111]. Ghigo E, Masel B, Aimaretti G, Leon-Carrion J, Casanueva FF, Dominguez-Morales MR, Elovic E, Perrone K, Stalla G, Thompson C, and Urban R, Consensus guidelines on screening for hypopituitarism following traumatic brain injury. Brain Inj 19 (2005) 711–24. [PubMed: 16195185]

[112]. Casano-Sancho P, Suárez L, Ibáñez L, García-Fructuoso G, Medina J, and Febrer A, Pituitary dysfunction after traumatic brain injury in children: is there a need for ongoing endocrine assessment? Clinical Endocrinology 79 (2013) 853–858. [PubMed: 23650946]

[113]. Heim C, and Binder EB, Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene-environment interactions, and epigenetics. Experimental Neurology 233 (2012) 102–111. [PubMed: 22101006]

[114]. Mirescu C, Peters JD, and Gould E, Early life experience alters response of adult neurogenesis to stress. Nat Neurosci 7 (2004) 841–846. [PubMed: 15273691]

[115]. Cohen MM, Jing DQ, Yang RR, Tottenham N, Lee FS, and Casey BJ, Early-life stress has persistent effects on amygdala function and development in mice and humans. P Natl Acad Sci USA 110 (2013) 18274–18278.

[116]. McEwen BS, Early life influences on life-long patterns of behavior and health. Ment Retard Dev D R 9 (2003) 149–154.

[117]. Heim C, Newport DJ, Mletzko T, Miller AH, and Hemeroff CB, The link between childhood trauma and depression: Insights from HPA axis studies in humans. Psychoneuroendocrino 33 (2008) 693–710.

[118]. Lupien SJ, McEwen BS, Gunnar MR, and Heim C, Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nature Reviews Neuroscience 10 (2009) 434–445. [PubMed: 19401723]

[119]. De Bellis MD, and Zisk A, The biological effects of childhood trauma. Child Adolesc Psychiatr Clin N Am 23 (2014) 185–222, vii. [PubMed: 24656576]

[120]. Pechtel P, and Pizzagalli DA, Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology (Berl) 214 (2011) 55–70. [PubMed: 20865251]

[121]. Taylor SE, Mechanisms linking early life stress to adult health outcomes. Proc Natl Acad Sci U S A 107 (2010) 8507–12. [PubMed: 20442329]

[122]. Oomen CA, Soeters H, Audureau N, Vermunt L, van Hasselt FN, Manders EM, Joels M, Lucassen PJ, and Krugers H, Severe early life stress hampers spatial learning and neurogenesis, but improves hippocampal synaptic plasticity and emotional learning under high-stress conditions in adulthood. J Neurosci 30 (2010) 6635–45. [PubMed: 20463226]

[123]. Levi RB, Drotar D, Yeates KO, and Taylor HG, Posttraumatic stress symptoms in children following orthopedic or traumatic brain injury. J Clin Child Psychol 28 (1999) 232–43. [PubMed: 10353082]

[124]. Delahanty DL, Raimonde AJ, and Spoonster E, Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. Biol Psychiat 48 (2000) 940–947. [PubMed: 11074232]

[125]. Barlow KM, Crawford S, Stevenson A, Sandhu SS, Belanger F, and Dewey D, Epidemiology of postconcussion syndrome in pediatric mild traumatic brain injury. Pediatrics 126 (2010) e374–81. [PubMed: 20660554]

[126]. Barlow KM, Postconcussion Syndrome: A Review. J Child Neurol 31 (2016) 57–67. [PubMed: 25330797]

[127]. Yeates KO, Luria J, Bartkowski H, Rusin J, Martin L, and Bigler ED, Postconcussive symptoms in children with mild closed head injuries. J Head Trauma Rehabil 14 (1999) 337–50. [PubMed: 10407207]

[128]. Moran LM, Taylor HG, Rusin J, Bangert B, Dietrich A, Nuss KE, Wright M, Minich N, and Yeates KO, Quality of life in pediatric mild traumatic brain injury and its relationship to postconcussive symptoms. J Pediatr Psychol 37 (2012) 736–44. [PubMed: 21994421]

[129]. Zemek RL, Farion KJ, Sampson M, and McGahern C, Prognosticators of persistent symptoms following pediatric concussion: a systematic review. JAMA Pediatr 167 (2013) 259–65. [PubMed: 23303474]

[130]. Binder LM, and Rohling ML, Money matters: a meta-analytic review of the effects of financial incentives on recovery after closed-head injury. Am J Psychiatry 153 (1996) 7–10.

[131]. Wojcik SM, Predicting mild traumatic brain injury patients at risk of persistent symptoms in the Emergency Department. Brain Injury 28 (2014) 422–430. [PubMed: 24564636]

[132]. Whittaker R, Kemp S, and House A, Illness perceptions and outcome in mild head injury: a longitudinal study. J Neurol Neurosur Ps 78 (2007) 644–646.

[133]. Brooks BL, Kadoura B, Turley B, Crawford S, Mikrogianakis A, and Barlow KM, Perception of Recovery After Pediatric Mild Traumatic Brain Injury Is Influenced by the “Good Old Days” Bias: Tangible Implications for Clinical Practice and Outcomes Research. Arch Clin Neuropsych 29 (2014) 186–193.

[134]. McCauley S, Wilde E, Pedroza C, Barnes A, Ibarra A, and Levin H, Patterns of Early Emotional and Neuropsychological Sequelae Following Mild Traumatic Brain Injury. J Neurotraum 28 (2011) A41–A41.

[135]. Ganesalingam K, Yeates KO, Ginn MS, Taylor HG, Dietrich A, Nuss K, and Wright M, Family burden and parental distress following mild traumatic brain injury in children and its relationship to post-concussive symptoms. Journal of Pediatric Psychology 33 (2008) 621–629. [PubMed: 18227110]

[136]. Yeates KO, Taylor HG, Rusin J, Bangert B, Dietrich A, Nuss K, Wright M, Nagin DS, and Jones BL, Longitudinal Trajectories of Postconcussive Symptoms in Children With Mild Traumatic Brain Injuries and Their Relationship to Acute Clinical Status. Pediatrics 123 (2009) 735–743. [PubMed: 19254996]

[137]. McNally KA, Bangert B, Dietrich A, Nuss K, Rusin J, Wright M, Taylor HG, and Yeates KO, Injury Versus Noninjury Factors as Predictors of Postconcussive Symptoms Following Mild Traumatic Brain Injury in Children. Neuropsychology 27 (2013) 1–12. [PubMed: 23356592]

[138]. Fay TB, Yeates KO, Taylor HG, Bangert B, Dietrich A, Nuss KE, Rusin J, and Wright M, Cognitive reserve as a moderator of postconcussive symptoms in children with complicated and uncomplicated mild traumatic brain injury. J Int Neuropsych Soc 16 (2010) 94–105.

[139]. Niogi SN, Mukherjee P, Ghajar J, Johnson C, Kolster RA, Sarkar R, Lee H, Meeker M, Zimmerman RD, Manley GT, and McCandliss BD, 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. AJNR Am J Neuroradiol 29 (2008) 967–73. [PubMed: 18272556]

[140]. Vasa RA, Grados M, Slomine B, Herskovits EH, Thompson RE, Salorio C, Christensen J, Wursta C, Riddle MA, and Gerring JP, Neuroimaging correlates of anxiety after pediatric traumatic brain injury. Biol Psychiatry 55 (2004) 208–16. [PubMed: 14744460]

[141]. Cohen JA, and Scheeringa MS, Post-traumatic stress disorder diagnosis in children: challenges and promises. Dialogues Clin Neurosci 11 (2009) 91–9. [PubMed: 19432391]

[142]. de Vries AP, Kassam-Adams N, Cnaan A, Sherman-Slate E, Gallagher PR, and Winston FK, Looking beyond the physical injury: posttraumatic stress disorder in children and parents after pediatric traffic injury. Pediatrics 104 (1999) 1293–9. [PubMed: 10585980]

[143]. Max JE, Castillo CS, Robin DA, Lindgren SD, Smith WL, Sato Y, and Arndt S, Posttraumatic stress symptomatology after childhood traumatic brain injury. J Nerv Ment Dis 186 (1998) 589–596. [PubMed: 9788634]

[144]. King NS, PTSD and traumatic brain injury: folklore and fact? Brain Inj 22 (2008) 1–5. [PubMed: 18183503]

[145]. Scheeringa MS, Zeanah CH, Myers L, and Putnam FW, Predictive validity in a prospective follow-up of PTSD in preschool children. J Am Acad Child Adolesc Psychiatry 44 (2005) 899–906. [PubMed: 16113618]

[146]. Sbordone RJ, and Liter JC, Mild Traumatic Brain Injury Does Not Produce Posttraumatic-Stress-Disorder. Brain Injury 9 (1995) 405–412. [PubMed: 7640686]

[147]. Harvey AG, Kopelman MD, and Brewin CR, PTSD and traumatic brain injury, Guilford Press, 2005.

[148]. Kenardy J, Le Brocque R, Hendrikz J, Iselin G, Anderson V, and McKinlay L, Impact of Posttraumatic Stress Disorder and Injury Severity on Recovery in Children with Traumatic Brain Injury. J Clin Child Adolesc 41 (2012) 5–14.

[149]. Hajek CA, Yeates KO, Gerry Taylor H, Bangert B, Dietrich A, Nuss KE, Rusin J, and Wright M, Relationships among post-concussive symptoms and symptoms of PTSD in children following mild traumatic brain injury. Brain Inj 24 (2010) 100–9. [PubMed: 20085447]

[150]. Rhine T, Cassedy A, Yeates KO, Taylor HG, Kirkwood MW, and Wade SL, Investigating the Connection Between Traumatic Brain Injury and Posttraumatic Stress Symptoms in Adolescents. J Head Trauma Rehab 33 (2018) 210–218.

[151]. Gerring JP, Slomine B, Vasa RA, Grados M, Chen A, Rising W, Christensen JR, Denckla MB, and Ernst M, Clinical predictors of posttraumatic stress disorder after closed head injury in children. J Am Acad Child Adolesc Psychiatry 41 (2002) 157–65. [PubMed: 11837405]

[152]. Bay EH, and Liberzon I, Early stress response: a vulnerability framework for functional impairment following mild traumatic brain injury. Res Theory Nurs Pract 23 (2009) 42–61. [PubMed: 19418887]

[153]. Meiser-Stedman R, Smith P, Glucksman E, Yule W, and Dalgleish T, Parent and child agreement for acute stress disorder, post-traumatic stress disorder and other psychopathology in a prospective study of children and adolescents exposed to single-event trauma. J Abnorm Child Psychol 35 (2007) 191–201. [PubMed: 17219079]

[154]. Max JE, Keatley E, Wilde EA, Bigler ED, Levin HS, Schachar RJ, Saunders A, Ewing-Cobbs L, Chapman SB, Dennis M, and Yang TT, Anxiety disorders in children and adolescents in the first six months after traumatic brain injury. J Neuropsychiatry Clin Neurosci 23 (2011) 29–39. [PubMed: 21304136]

[155]. Donlon K, and Jones RT, Applying a traumatic stress approach to understanding PCS following pediatric mild TBI. Child Neuropsychol 21 (2015) 803–22. [PubMed: 25103672]

[156]. Langeland W, and Olff M, Psychobiology of posttraumatic stress disorder in pediatric injury patients: a review of the literature. Neurosci Biobehav Rev 32 (2008) 161–74. [PubMed: 17825911]

[157]. Ponsford J, Willmott C, Rothwell A, Cameron P, Ayton G, Nelms R, Curran C, and Ng K, Impact of early intervention on outcome after mild traumatic brain injury in children. Pediatrics 108 (2001) 1297–303. [PubMed: 11731651]

[158]. Dalgleish T, Meiser-Stedman R, and Smith P, Cognitive aspects of posttraumatic stress reactions and their treatment in children and adolescents: An empirical review and some recommendations. Behav Cogn Psychoth 33 (2005) 459–486.

[159]. Balluffi A, Kassam-Adams N, Kazak A, Tucker M, Dominguez T, and Helfaer M, Traumatic stress in parents of children admitted to the pediatric intensive care unit. Pediatr Crit Care Med 5 (2004) 547–53. [PubMed: 15530191]

[160]. Anderson VA, Catroppa C, Haritou F, Morse S, Pentland L, Rosenfeld J, and Stargatt R, Predictors of acute child and family outcome following traumatic brain injury in children. Pediatr Neurosurg 34 (2001) 138–48. [PubMed: 11359102]

[161]. Wade SL, Borawski EA, Taylor HG, Drotar D, Yeates KO, and Stancin T, The relationship of caregiver coping to family outcomes during the initial year following pediatric traumatic injury. J Consult Clin Psychol 69 (2001) 406–15. [PubMed: 11495170]

[162]. Ganesalingam K, Yeates KO, Ginn MS, Taylor HG, Dietrich A, Nuss K, and Wright M, Family burden and parental distress following mild traumatic brain injury in children and its relationship to post-concussive symptoms. J Pediatr Psychol 33 (2008) 621–9. [PubMed: 18227110]

[163]. Pervanidou P, Biology of post-traumatic stress disorder in childhood and adolescence. J Neuroendocrinol 20 (2008) 632–8. [PubMed: 18363804]

[164]. Blake TA, McKay CD, Meeuwisse WH, and Emery CA, The impact of concussion on cardiac autonomic function: A systematic review. Brain Inj 30 (2016) 132–45. [PubMed: 26671602]

[165]. Goldstein B, Toweill D, Lai S, Sonnenthal K, and Kimberly B, Uncoupling of the autonomic and cardiovascular systems in acute brain injury. Am J Physiol 275 (1998) R1287–92. [PubMed: 9756562]

[166]. Alvares GA, Quintana DS, Hickie IB, and Guastella AJ, Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: a systematic review and meta-analysis. J Psychiatry Neurosci 41 (2016) 89–104. [PubMed: 26447819]

[167]. Thayer JF, Yamamoto SS, and Brosschot JF, The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol 141 (2010) 122–31. [PubMed: 19910061]

[168]. Kop WJ, Stein PK, Tracy RP, Barzilay JI, Schulz R, and Gottdiener JS, Autonomic nervous system dysfunction and inflammation contribute to the increased cardiovascular mortality risk associated with depression. Psychosom Med 72 (2010) 626–35. [PubMed: 20639389]

[169]. Penfield W, and Jasper H, Autonomic seizures. Epilepsy and the functional anatomy of the human brain. London: J & A Churchill Ltd (1954) 412–37.

[170]. Bower RS, Sunnarborg R, Rabinstein AA, and Wijdicks EF, Paroxysmal sympathetic hyperactivity after traumatic brain injury. Neurocrit Care 13 (2010) 233–4. [PubMed: 20517713]

[171]. Perkes I, Baguley IJ, Nott MT, and Menon DK, A review of paroxysmal sympathetic hyperactivity after acquired brain injury. Ann Neurol 68 (2010) 126–35. [PubMed: 20695005]

[172]. Kirk KA, Shoykhet M, Jeong JH, Tyler-Kabara EC, Henderson MJ, Bell MJ, and Fink EL, Dysautonomia after pediatric brain injury. Dev Med Child Neurol 54 (2012) 759–64. [PubMed: 22712762]

[173]. Krach LE, Kriel RL, Morris WF, Warhol BL, and Luxenberg MG, Central autonomic dysfunction following acquired brain injury in children. J Neurol Rehabil 11 (1997) 41–45.

[174]. Baguley IJ, The excitatory:inhibitory ratio model (EIR model): An integrative explanation of acute autonomic overactivity syndromes. Med Hypotheses 70 (2008) 26–35. [PubMed: 17583440]

[175]. Baguley IJ, Nott MT, Slewa-Younan S, Heriseanu RE, and Perkes IE, Diagnosing dysautonomia after acute traumatic brain injury: evidence for overresponsiveness to afferent stimuli. Arch Phys Med Rehabil 90 (2009) 580–6. [PubMed: 19345772]

[176]. Baguley IJ, Nicholls JL, Felmingham KL, Crooks J, Gurka JA, and Wade LD, Dysautonomia after traumatic brain injury: a forgotten syndrome? J Neurol Neurosurg Psychiatry 67 (1999) 39–43. [PubMed: 10369820]

[177]. Lv LQ, Hou LJ, Yu MK, Qi XQ, Chen HR, Chen JX, Hu GH, Luo C, and Lu YC, Prognostic influence and magnetic resonance imaging findings in paroxysmal sympathetic hyperactivity after severe traumatic brain injury. J Neurotrauma 27 (2010) 1945–50. [PubMed: 21028988]

[178]. Goldstein B, Kempski MH, DeKing D, Cox C, DeLong DJ, Kelly MM, and Woolf PD, Autonomic control of heart rate after brain injury in children. Crit Care Med 24 (1996) 234–40. [PubMed: 8605794]

[179]. Goldstein B, Deking D, Delong DJ, Kempski MH, Cox C, Kelly MM, Nichols DD, and Woolf PD, Autonomic Cardiovascular State after Severe Brain Injury and Brain-Death in Children. Critical Care Medicine 21 (1993) 228–233. [PubMed: 8428474]

[180]. Norris PR, Morris JA, Ozdas A, Grogan EL, and Williams AE, Heart rate variability predicts trauma patient outcome as early as 12 h: Implications for military and civilian triage. J Surg Res 129 (2005) 122–128. [PubMed: 15978622]

[181]. Henden PL, Sondergaard S, Rydenhag B, Reinsfelt B, Ricksten SE, and Aring A; neman, Can Baroreflex Sensitivity and Heart Rate Variability Predict Late Neurological Outcome in Patients With Traumatic Brain Injury? J Neurosurg Anesth 26 (2014) 50–59.

[182]. Sung CW, Lee HC, Chiang YH, Chiu WT, Chu SF, Ou JC, Tsai SH, Liao KH, Lin CM, Lin JW, Chen GS, Li WJ, and Wang JY, Early dysautonomia detected by heart rate variability predicts late depression in female patients following mild traumatic brain injury. Psychophysiology 53 (2016) 455–64. [PubMed: 26560198]

[183]. Gang Y, and Malik M, Heart rate variability in critical care medicine. Curr Opin Crit Care 8 (2002) 371–5. [PubMed: 12357103]

[184]. Leitman IM, Understanding the brain-heart axis in neurological trauma. J Surg Res 173 (2012) e33–5. [PubMed: 22221598]

[185]. Hilz MJ, Liu M, Koehn J, Wang R, Ammon F, Flanagan SR, and Hosl KM, Valsalva maneuver unveils central baroreflex dysfunction with altered blood pressure control in persons with a history of mild traumatic brain injury. BMC Neurol 16 (2016) 61. [PubMed: 27146718]

[186]. Blake TA, McKay CD, Meeuwisse WH, and Emery CA, The impact of concussion on cardiac autonomic function: A systematic review. Brain Injury 30 (2016) 132–145. [PubMed: 26671602]

[187]. Hilz MJ, Aurnhammer F, Flanagan SR, Intravooth T, Wang RH, Hosl KM, Pauli E, and Koehn J, Eyeball Pressure Stimulation Unveils Subtle Autonomic Cardiovascular Dysfunction in Persons with a History of Mild Traumatic Brain Injury. J Neurotraum 32 (2015) 1796–1804.

[188]. La Fountaine MF, Heffernan KS, Gossett JD, Bauman WA, and De Meersman RE, Transient suppression of heart rate complexity in concussed athletes. Auton Neurosci-Basic 148 (2009) 101–103.

[189]. McCrory P, Meeuwisse W, Dvorak J, Aubry M, Bailes J, Broglio S, Cantu RC, Cassidy D, Echemendia RJ, Castellani RJ, Davis GA, Ellenbogen R, Emery C, Engebretsen L, Feddermann-Demont N, Giza CC, Guskiewicz KM, Herring S, Iverson GL, Johnston KM, Kissick J, Kutcher J, Leddy JJ, Maddocks D, Makdissi M, Manley GT, McCrea M, Meehan WP, Nagahiro S, Patricios J, Putukian M, Schneider KJ, Sills A, Tator CH, Turner M, and Vos PE, Consensus statement on concussion in sport-the 5th international conference on concussion in sport held in Berlin, October 2016. Brit J Sport Med 51 (2017) 838–847.

[190]. Gall B, Parkhouse W, and Goodman D, Heart rate variability of recently concussed athletes at rest and exercise. Med Sci Sport Exer 36 (2004) 1269–1274.

[191]. Sorek G, Shaklai S, Meyer S, and Katz-Leurer M, Autonomic cardiac control response to walking and executive cognitive task in adolescents with acquired brain injury and typically developed controls. Brain Injury 32 (2018) 770–775. [PubMed: 29533099]

[192]. Katz-Leurer M, Rotem H, Keren O, and Meyer S, Heart rate and heart rate variability at rest and during exercise in boys who suffered a severe traumatic brain injury and typically-developed controls. Brain Injury 24 (2010) 110–114. [PubMed: 20085448]

[193]. Leddy J, Baker JG, Haider MN, Hinds A, and Willer B, A Physiological Approach to Prolonged Recovery From Sport-Related Concussion. J Athl Training 52 (2017) 299–308.

[194]. Leddy JJ, Haider MN, Ellis M, and Willer BS, Exercise is Medicine for Concussion. Curr Sport Med Rep 17 (2018) 262–270.

[195]. Thayer JF, and Lane RD, A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord 61 (2000) 201–16. [PubMed: 11163422]

[196]. Bryant RA, Marosszeky JE, Crooks J, and Gurka JA, Elevated resting heart rate as a predictor of posttraumatic stress disorder after severe traumatic brain injury. Psychosom Med 66 (2004) 760–1. [PubMed: 15385703]

[197]. Goenjian AK, Yehuda R, Pynoos RS, Steinberg AM, Tashjian M, Yang RK, Najarian LM, and Fairbanks LA, Basal cortisol, dexamethasone suppression of cortisol, and MHPG in adolescents after the 1988 earthquake in Armenia. Am J Psychiatry 153 (1996) 929–34. [PubMed: 8659616]

[198]. Cicchetti D, and Rogosch FA, Diverse patterns of neuroendocrine activity in maltreated children. Dev Psychopathol 13 (2001) 677–93. [PubMed: 11523854]

[199]. Pervanidou P, Kolaitis G, Charitaki S, Lazaropoulou C, Papassotiriou I, Hindmarsh P, Bakoula C, Tsiantis J, and Chrousos GP, The natural history of neuroendocrine changes in pediatric posttraumatic stress disorder (PTSD) after motor vehicle accidents: progressive divergence of noradrenaline and cortisol concentrations over time. Biol Psychiatry 62 (2007) 1095–102. [PubMed: 17624319]

[200]. Williamson JB, Heilman KM, Porges EC, Lamb DG, and Porges SW, A possible mechanism for PTSD symptoms in patients with traumatic brain injury: central autonomic network disruption. Front Neuroeng 6 (2013) 13. [PubMed: 24391583]

[201]. Ewing-Cobbs L, Prasad MR, Cox CS Jr., Granger DA, Duque G, and Swank PR, Altered stress system reactivity after pediatric injury: Relation with post-traumatic stress symptoms. Psychoneuroendocrino 84 (2017) 66–75.

[202]. Kurowski B, Martin LJ, and Wade SL, Genetics and outcomes after traumatic brain injury (TBI): what do we know about pediatric TBI? J Pediatr Rehabil Med 5 (2012) 217–31. [PubMed: 23023254]

[203]. Brichtova E, and Kozak L, Apolipoprotein E genotype and traumatic brain injury in children--association with neurological outcome. Childs Nerv Syst 24 (2008) 349–56. [PubMed: 17932679]

[204]. Lo TY, Jones PA, Chambers IR, Beattie TF, Forsyth R, Mendelow AD, and Minns RA, Modulating effect of apolipoprotein E polymorphisms on secondary brain insult and outcome after childhood brain trauma. Childs Nerv Syst 25 (2009) 47–54. [PubMed: 18839184]

[205]. Moran LM, Taylor HG, Ganesalingam K, Gastier-Foster JM, Frick J, Bangert B, Dietrich A, Nuss KE, Rusin J, Wright M, and Yeates KO, Apolipoprotein E4 as a predictor of outcomes in pediatric mild traumatic brain injury. J Neurotrauma 26 (2009) 1489–95. [PubMed: 19645623]

[206]. Lipsky RH, Sparling MB, Ryan LM, Xu K, Salazar AM, Goldman D, and Warden DL, Association of COMT Val158Met genotype with executive functioning following traumatic brain injury. J Neuropsychiatry Clin Neurosci 17 (2005) 465–71. [PubMed: 16387984]

[207]. Willmott C, Withiel T, Ponsford J, and Burke R, COMT Val158Met and cognitive and functional outcomes after traumatic brain injury. J Neurotrauma 31 (2014) 1507–14. [PubMed: 24786534]

[208]. Rizoli SB, Jaja BNR, Di Battista AP, Rhind SG, Neto AC, da Costa L, Inaba K, da Luz LT, Nascimento B, Perez A, Baker AJ, and Manoel ALD, Catecholamines as outcome markers in isolated traumatic brain injury: the COMA-TBI study. Crit Care 21 (2017).

[209]. Blasi G, Mattay VS, Bertolino A, Elvevag B, Callicott JH, Das S, Kolachana BS, Egan MF, Goldberg TE, and Weinberger DR, Effect of catechol-O-methyltransferase val158met genotype on attentional control. J Neurosci 25 (2005) 5038–45. [PubMed: 15901785]

[210]. Kramer UM, Cunillera T, Camara E, Marco-Pallares J, Cucurell D, Nager W, Bauer P, Schule R, Schols L, Rodriguez-Fornells A, and Munte TF, The impact of catechol-O-methyltransferase and dopamine D4 receptor genotypes on neurophysiological markers of performance monitoring. J Neurosci 27 (2007) 14190–8. [PubMed: 18094258]

[211]. Kurowski BG, Backeljauw B, Zang H, Zhang N, Martin LJ, Pilipenko V, Yeates K, Taylor HG, and Wade S, Influence of Catechol-O-methyltransferase on Executive Functioning Longitudinally After Early Childhood Traumatic Brain Injury: Preliminary Findings. J Head Trauma Rehabil 31 (2016) E1–9.

Highlights:

- Outcomes from pediatric TBI are highly heterogeneous
- TBI-induced disruption of neuroendocrine development impairs psychosocial recovery
- Persistent dysregulation of autonomic physiology may predict long-term outcome
- The development of PTSS is associated with impaired pediatric TBI recovery