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Review Article

Determinants of social behavior deficits and recovery after pediatric traumatic brain injury

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ABSTRACT

Traumatic brain injury (TBI) during early childhood is associated with a particularly high risk of developing social behavior impairments, including deficits in social cognition that manifest as reduced social interactions, with profound consequences for the individuals' quality of life. A number of pre-injury, post-injury, and injury-related factors have been identified or hypothesized to determine the extent of social behavior problems after childhood TBI. These include variables associated with the individual themselves (e.g. age, genetics, the injury severity, and extent of white matter damage), proximal environmental factors (e.g. family functioning, parental mental health), and more distal environmental factors (e.g. socioeconomic status, access to resources). In this review, we synthesize the available evidence demonstrating which of these determinants influence risk versus resilience to social behavior deficits after pediatric TBI, drawing upon the available clinical and preclinical literature. Injury-related pathology in neuroanatomical regions associated with social cognition and behaviors will also be described, with a focus on findings from magnetic resonance imaging and diffusion tensor imaging. Finally, study limitations and suggested future directions are highlighted. In summary, while no single variable can alone accurately predict the manifestation of social behavior problems after TBI during early childhood, an increased understanding of how both injury and environmental factors can influence social outcomes provides a useful framework for the development of more effective rehabilitation strategies aiming to optimize recovery for young brain-injured patients.

1. Introduction

Young children in their first years of life are at high risk of sustaining a traumatic brain injury (TBI), resulting predominantly from falls, motor vehicle accidents, and non-accidental head trauma (Araki et al., 2017). It has been estimated that around 300 per 100,000 children experience a TBI annually (Crowe et al., 2009), making it one of the most common causes of morbidity and mortality in children worldwide. Strikingly, children under the age of 4 years have a particularly high incidence of TBI, and further, appear to be at elevated risk of poorer neuropsychological, psychosocial and neurocognitive outcomes compared to when injuries are sustained during later childhood or adulthood (Crowe et al., 2009; Anderson et al., 2012; Kraus, 1995).

Our ability to interact in a social capacity is crucial to human survival and life satisfaction. Social interactions form the basis of our everyday lives, allowing us to function in public, school, and workplace environments, establish and maintain relationships, and relate appropriately to those around us. Social skills, the underlying social cognition that these skills require, and the neural circuitry that mediates these abilities, is not established at birth – instead, they develop across a protracted time course from early childhood through to adolescence and beyond (Nelson et al., 2016a). Brain maturation correlates with a child's increasing capacity for social information processing, requiring increased regional specialization and connectivity between a complex system of neuroanatomical regions often referred to as the "social brain network" (Adolphs, 2001; Ryan et al., 2016a). This in turn manifests as changes in the complexity of their social behavior (Yeates et al., 2007). It is not surprising, therefore, that brain injuries acquired during childhood can disrupt an individual's social abilities. Poor social functioning secondary to TBI has been largely underappreciated to date, but is increasingly recognized as having widespread and detrimental consequences for quality of life among young TBI survivors (Ryan et al., 2016b; Di Battista et al., 2012; Rosema et al., 2012; Li and Liu, 2013).

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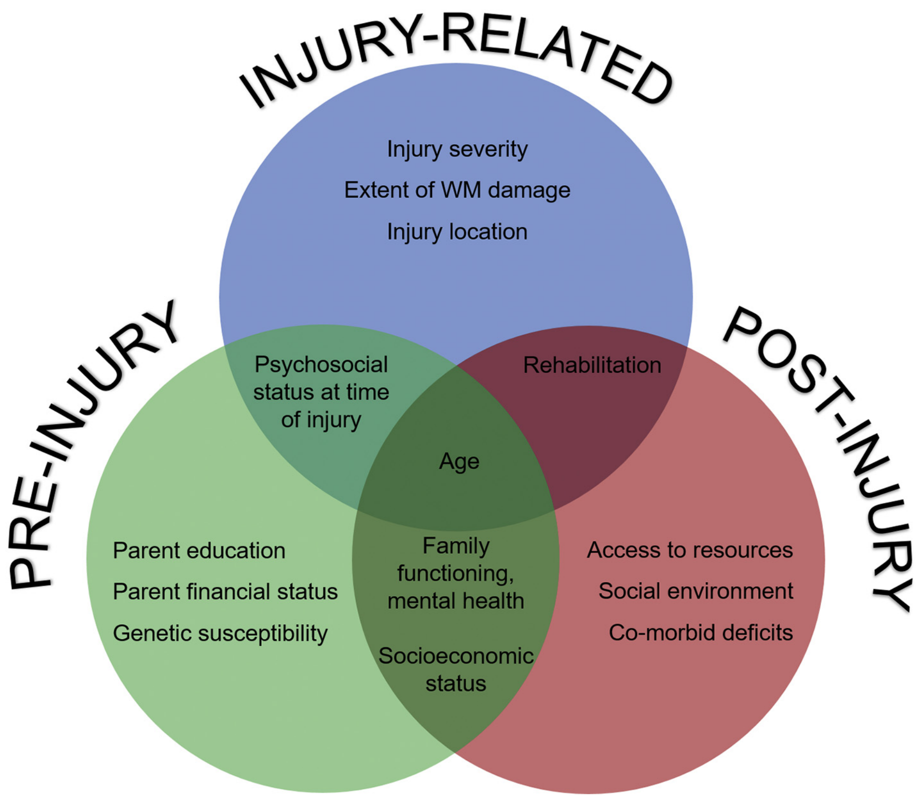

Fig. 1. Summary of the key pre-, post- and injury-related factors that have been identified as contributors to social behavior outcomes after traumatic brain injury during childhood, from both preclinical and clinical studies. Several factors, such as family functioning, family mental health, and socio-economic status, are considered to be determinants of social outcomes by having influence both pre-injury and post-injury. Other factors will influence only one time period – e.g. co-morbid deficits in cognitive function will only affect post-injury social behavior development. Some variables such as genetic predisposition or susceptibility to social behavior impairments have been minimally investigated to date. WM = white matter.

Specifically, studies have found that children sustaining a TBI during early life are at elevated risk of enduring social behavior problems, including decreased social responsiveness, abnormal social interactions, reduced social competence, social communication deficits (including verbal and non-verbal, usage and comprehension), and impaired adaptive behaviors (Ryan et al., 2016a). Social competence is the effectiveness of a persons' functioning as an individual, both in a dyadic relationship as well as in group settings (Yeates et al., 2007). These deficits are most apparent when TBI is sustained prior to school age, and may reflect not only the loss of pre-existing social function but also an inability to acquire new skills as a consequence of the brain injury, alongside potentially concurrent problems with cognition, executive function or attention (Anderson and Moore, 1995; Anderson et al., 2009). Social behavior dysfunction commonly surfaces over time after early life TBI, becoming apparent as the child re-integrates into home and school environments (Ryan et al., 2016b). Many children may initially appear to be on par with their age-matched peers for some time after TBI, but subsequently fall behind as they struggle to establish the new skills required to keep up developmentally (Giza et al., 2009). This progressive emergence of social behavior deficits has been associated with concomitant progressive neuropathology in the injured brain, whereby a severe TBI in particular disrupts connectivity of the distributed neural networks mediating social functioning (Anderson et al., 2009; Ryan et al., 2015). Such behavioral problems in children are reported to linger for years after injury, while other functional or behavioral consequences such as motor and non-social cognition deficits are more likely to resolve or stabilize over time (Wozniak et al., 2007; Cicerone and Tanenbaum, 1997).

Chronically, social behavior problems can impact many facets of an individuals' life. Poor social function has consequences for appropriate and satisfying social interactions in school, work and home environments. Severe TBI during childhood results in a high risk of a reduction in social support and friendships, as well as a reduction in opportunities to establish new social contacts (Morton and Wehman, 1995). Family lives must also adjust to the presence of a brain-injured child, which can cause significant emotional distress for all involved (Brown et al., 2013).

Comorbid psychiatric morbidities such as anxiety and depression are also common in this population (Sariaslan et al., 2016). Increased risk-taking behavior during adolescence and young adulthood, including consumption of illicit and addictive substances or involvement in criminal activities, has also been associated with childhood TBI (Kennedy et al., 2017a; Kennedy et al., 2017b), with a recent review concluding that TBI is a risk factor for earlier, and more violent, offending (Williams et al., 2018). While pediatric TBI is known to result in impulsivity, poor social communication skills and concomitant externalizing behaviors (e.g. aggression), which may result in poor decision-making leading to crime, dissecting out the contribution of post-injury social impairments in particular to such complex outcomes is challenging (Williams et al., 2018).

A common framework for the development of social skills, Beauchamp and Anderson's SOCIAL model proposes that three main components contribute to social maturation: *brain development and integrity*, *internal and external factors*, and *current cognitive and psychosocial function* (Beauchamp and Anderson, 2010). This model provides a foundation upon which to understand both how a TBI may affect social behavior – i.e. by influencing brain development and integrity - as well as how injury at different developmental stages can differentially compromise social functioning (Ryan et al., 2015). Further, it introduces the concept that variables both intrinsic and extrinsic to the individual can influence social outcomes after a TBI.

Traumatic brain injury is a very heterogeneous condition, spanning a wide range of injury severities, impact locations and mechanisms (Bigler et al., 2013a). While mild and concussive head injuries are the most prevalent, moderate and severe TBI account for the majority of mortality and morbidity in this population (Kraus, 1995). Even amongst children with severe TBI for whom social behavior deficits are reportedly most common, substantial variability in outcomes has been noted between individuals (Anderson et al., 2005; Catroppa et al., 2008). Not all patients with a TBI will develop abnormal social functioning, and the causes of social impairments after TBI are poorly understood. This uncertainty renders clinicians poorly equipped to identify children at greatest risk, knowledge which would then guide towards more appropriate intervention strategies (Ryan et al., 2016b). Such observations have spurned increasing interest in the factors that may predict individual differences in outcome among young children with TBI (Anderson et al., 2012).

A number of pre-injury, post-injury, and injury-related factors have been identified that influence the manifestation of social behavior problems after childhood TBI (Fig. 1). These include variables associated with the injured individual (e.g. age, genetics, the extent of white matter damage), proximal environmental factors (e.g. family functioning), and more distal environmental factors (e.g. socioeconomic status, access to resources) (Ryan et al., 2015; Yeates et al., 2004; Anderson et al., 2006; Wade et al., 2016). Many of these factors have been identified in clinical populations, mostly by retrospective, cross-sectional study designs, as well as in preclinical settings by the use of experimental animal models of TBI. In this review, we aim to synthesize the evidence for known and hypothesized determinants of social outcome after pediatric TBI, focusing in on neuroanatomical correlates, and suggest avenues for future study.

2. Preclinical evidence of factors influencing social behavior following TBI

Social behaviors have a multifaceted role in promoting survival and fitness, and are just as important to inherently social species like rodents as they are to humans (Pellis et al., 2010; Feldman et al., 2016). The importance of social cognition (the ability to recognize, attend to, and interpret social cues, in a context-specific manner) cannot be understated, yet it is infrequently studied in preclinical models of TBI. In preclinical studies, social behaviors encompass numerous activities, including but not limited to: play fighting, mating rituals, social investigation, scent/olfactory identification, and various forms of communication [for review see (Ryan et al., 2016c)]. Play fighting is a complex array of behaviors that are greatly influenced by motivational and reward circuits, as well as the individual's energy reserves and availability of play partners. Juvenile play is believed to provide an array of benefit to the participants, including development of the social brain (Pellis et al., 2010; Pellis and Pellis, 2007). Analysis of play fighting is commonly used to measure complex social behaviors in rodents.

Social interaction and social recognition are two aspects of social cognition that are also commonly explored in preclinical models, using the three-chamber test and the resident-intruder or reciprocal interactions task. The three-chamber test provides researchers with a measure of sociability attributed solely to the social approach behaviors of the test rodent towards an unknown conspecific, and permits subsequent investigation of social memory and recognition (Yang et al., 2016). In contrast, the resident-intruder task allows for quantification of social interest as well as antagonistic or aggressive behavior in a freely-interacting setting (Koolhaas et al., 2013). Although not used as regularly, the social odor recognition task has been employed to examine social memory for distinctive conspecifics (Dudchenko et al., 2000), while ultrasonic vocalization recordings have also been incorporated into preclinical testing paradigms as an ethologically valid measure of social communication (Knuston et al., 2002).

The utility of animal models in preclinical experiments arise from similar brain maturation patterns with condensed developmental time courses (Semple et al., 2013). The basic principles of brain and social behavior development appear to be consistent for mammals other than humans, including common laboratory animals such as rats and primates, albeit with shortened timelines. In comparison to humans, rats and mice are born developmentally younger (approximately at the end of the human 2nd trimester) and they mature more rapidly (Kolb et al., 2012). Weaning for a rodent occurs at roughly postnatal day 21 (P21), which can be considered the end of toddlerhood and beginning of the childhood period (2 – 4 years of age). Although many have argued that adolescence is a uniquely human aspect of development (Bogin, 1994), there are a plethora of physiological and neurobehavioral factors that corroborate the occurrence of an adolescent period in species such as rodents and primates. Primates, for example, have extended periods of adolescence whereby the brain undergoes significant anatomical and neuro-functional changes that are comparable to those identified in human populations (Schwandt et al., 2010). Similarly, rodents undergo accelerated brain growth rates that mimic spurts during human adolescent periods (Kennedy, 1967). For the purpose of this review, in rodents the neonatal period is considered to span from birth to P21, childhood or the juvenile period will be considered to encompass P21-P27, adolescence P28-P45, and late-adolescence P46-P56, with the onset of adulthood at 8 weeks of age (Semple et al., 2013). For primates, the neonatal period will range from birth to age 2, with adolescence spanning between 2 and 6 years of age.

In the context of preclinical pediatric TBI, there are numerous factors that contribute to social outcomes ranging from parental genetic and epigenetic influences, early life experiences such as diet and stress, characteristics of the injury itself, and post-injury manipulations such as environmental enrichment. This section will focus on factors identified in the preclinical literature that modify social outcomes and neuroplasticity following neurological insult in the pediatric period.

2.1. Characteristics of the injury differentially influence social behaviors

Given the functional distribution of the brain, and the heterogeneity of brain injury locations and etiologies, it is not surprising that variations in these factors result in different social deficits. With respect to social cognition, two brain regions appear to be particularly important, the temporal lobe and the prefrontal cortex (PFC), which is further divided into the orbital frontal cortex (OFC), medial prefrontal cortex (mPFC) and the dorsolateral prefrontal cortex (dlPFC) (Overwalle, 2009). For example, one of the easiest variables to manipulate in preclinical TBI studies is location of the insult. In rodents, neonatal lesions to the OFC, mPFC and motor cortex all impair social behavior but in different ways. Specifically, neonatal rats with bilateral surgical lesions of the motor cortex do not exhibit age-dependent changes in play behavior (Kamitakahara et al., 2007). Similarly, unilateral focal lesions generated by controlled cortical impact to the frontal lobe focused on the primary motor cortex in P21 mice also failed to generate social deficits (Chen et al., 2013). Conversely, rats with neonatal OFC surgical lesions do exhibit typical age-dependent maturation in play, but are hyperactive, and cannot modify their play behavior with respect to the identity of their play partner (i.e. they engage in the same behaviors regardless of whether or not their playmate is dominant or subordinate to them) (Pellis et al., 2006). Finally, neonatal surgical lesions to the mPFC reduce the complexity of defensive tactics, but not the overall level of play (Bell et al., 2009). Interestingly, complete neonatal decortication does not affect the overall vigor of play behavior, but merely reduced the frequency of pinning actions and the duration of the pin (Panksepp et al., 1994). These findings suggest that the motivation to play remains intact following brain injuries to the PFC; however, deficits arise in formulating and executing complex context-specific behaviors.

Localization of neurological insult has also been examined in primate models. Studies have demonstrated that surgical lesions to the perirhinal cortex impair a monkey's ability to modulate their behaviors in response to complex social situations, reduces hostile behaviors, and increases cooing vocalizations in adulthood (Ahlgrim et al., 2017). Neonatal aspiration lesions to the medial temporal lobe produce different social deficits than lesions to the inferior temporal lobe (Bachevalier et al., 2001). Of significance, deficits were more severe following medial temporal lobe lesions as compared to inferior temporal lobe lesions. In addition, medial temporal lobe damage resulted in an inability to develop and maintain social bonds, whereby monkeys with medial temporal lobe injuries initiated fewer social interactions and actively avoided social contact (Bachevalier et al., 2001). They also failed to convey socially relevant facial and postural expressions and displayed an increase in self-directed behaviors (Bachevalier et al., 2001). On the contrary, deficits following neonatal lesions of the inferior temporal lobe were less severe; these monkeys engaged in less social behavior compared to controls, but did generate weak social bonds and could produce socially relevant facial expressions and posture when required, although it was rarely spontaneous (Bachevalier et al., 2001).

The severity, timing, and etiology of the injury also influences subsequent social behaviors. One study of young mice found that repeated mild closed head injury was associated with social passiveness that was not evident following moderate TBI (Bajwa et al., 2016). Similarly, when severe experimental TBI (controlled cortical impact) was produced at P21, but not P35, investigators found a reduction in social investigation and impaired sociosexual behavior in adulthood (Semple et al., 2014). This latter study parallels what is seen in the clinical population in terms of a higher vulnerability to social behavior impairments after injury at a younger age (Anderson et al., 1997; Ewing-Cobbs et al., 1997).

2.2. Genetic and epigenetic factors influence TBI-related social deficits

Growing literature has highlighted the importance of gene – environment interactions on almost all aspects of brain development and behavioral functioning. Social outcomes following TBI are no different and demonstrate significant variation with respect to genetic and epigenetic factors. First and foremost, research has demonstrated that sex substantially influences social behaviors post-TBI. In a study of mild experimental TBI (mTBI) and play fighting behaviors in adolescent rats (P35-40), being female was associated with increased risk for poor social outcomes. While all sham rats exhibited a reduced interest in playing with brain injured rats, thereby decreasing their exposure to normal social interaction, this was particularly reduced in female pairs (Mychasiuk et al., 2014). Conversely, in a model of neonatal hypoxic-ischemic (HI) brain injury, reduced ultrasonic vocalizations were identified in all brain injured animals, but the effects were more significant in males (Saucier et al., 2008). Sex also differentially influenced social deficits following severe pediatric TBI (controlled cortical impact) in mice. In this particular study males exhibited deficits in sociability and social recognition, while females exhibited a reduction in sociability and increased sociosexual avoidance (Semple et al., 2017). Similar to the clinical literature, there does not seem to be a consensus regarding sex effects as social determinants in the preclinical data; rather it appears that sex differentially moderates outcomes dependent upon other injury related characteristics.

With the advancement of personalized medicine and the known contributions of genetic susceptibility to disease, there is growing investigation into gene-dependent risk factors for TBI-related deficits. Preclinical models provide an ideal mechanism for the study of specific genes in relation to social cognition following TBI. For example, Klaric and colleagues studied the role of the Npas4 gene on sociability in mice following HI (Klaric et al., 2017). Npas4 is an activity-dependent transcription factor with a known role in synaptic plasticity. Although all mice with HI spent less time with the stranger mouse compared to the empty cage in the three-chamber test, indicating a reduction in sociability, these effects were attenuated somewhat in Npas4 knockout mice (Klaric et al., 2017). This interesting finding highlights the role of genetics in social behavior and underscores the need for future research within this context. There have been a plethora of genes, such as the oxytocin receptor and the arginine vasopressin receptor, linked to sociability and social cognition [for reviews see (Ebstein et al., 2010; Robinson et al., 2008)], but they have not been thoroughly examined in the context of TBI and provide a fruitful opportunity for future research endeavors.

Maternal and paternal experiences, and the role of epigenetics, in TBI-dependent social functioning is another emerging field of research. Variations in maternal diet ranging from caloric restriction to high fat/high sugar, have been shown to change gene expression and thereby influence offspring recovery from experimental mTBI in adolescence (Mychasiuk et al., 2015a). While this study did not specifically examine social behavior, a subsequent study from the same laboratory examined variations in social play behavior associated with maternal diet, and found significant changes to the frequency and complexity of offspring play patterns that were dependent upon the mothers' diet (Hehar et al., 2016a). Given that maternal diet altered cognitive and emotional recovery from mTBI, as well as modified play behavior in healthy offspring, one could presume that maternal diet would likely also influence social play post-mTBI, and this hypothesis should be further explored. In a similar fashion, paternal experiences have also been demonstrated to modify anxiety- and depressive-like behaviors following mTBI through epigenetic programming of sperm in fathers and their offspring (Hehar et al., 2016b; Hehar et al., 2017). Again, although sociability was not specifically tested, change in cognition and emotional functioning are likely to also influence social behaviors. While the mechanisms driving the neurological effects of TBI on sociability have not been fully elucidated, it is feasible that epigenetic changes in gene expression are involved and provide a means by which environmental factors can influence functional recovery and social cognition.

2.3. Experiences prior to the injury modify subsequent social behaviors

Just as lesion studies can teach us about the localization of social cognition, manipulation of early life factors in the context of TBI can also highlight important social processes. Given that there is a dearth of literature regarding the role of early life factors on specific social behaviors, this section will more broadly focus on emotional and executive functions that likely contribute to social cognition. Children are exposed to a vast array of experiences and events during their life, and we therefore require an understanding of how various experiences contribute to the heterogeneity in post-injury social functioning. For example, simply being exposed to a prior injury influences recovery from future injuries, with some studies indicating that a single previous TBI may be neuroprotective (Mychasiuk et al., 2015b; McColl et al., 2018).

In addition, just as cognitive reserve influences recovery from TBI in clinical populations, Yamakawa and colleagues found that in a rodent study of experimental mTBI, not only did pre-injury environment (enrichment vs. deprivation) modify behavioral outcomes such as anxiety and depression, it also altered the rodents' response to pharmacological treatment (Yamakawa et al., 2017). Moreover, consistent with findings that parental diet influences social cognition following TBI, early life dietary manipulations have also demonstrated the ability to modulate TBI-dependent changes in sociability. When young rats were fed a diet supplemented with resveratrol, prebiotics, and omega fatty acids prior to an experimental mTBI in adolescence, they exhibited attenuated emotional and cognitive deficits and improved recovery (Salberg et al., 2017). Conversely, when adolescent rats were exposed to chronic caffeine in their drinking water prior to repeated mTBI, they exhibited a worsening of emotional and cognitive outcomes, with effects being more significant in males (Yamakawa et al., 2017). These findings are in alignment with evidence from clinical studies, as described above, suggesting that individual variations in environment may contribute to the dramatic heterogeneity in TBI-induced social dysfunction.

2.4. Post-injury manipulations modify injury-induced social deficits

Given that one of the primary goals of TBI research is the development of effective therapeutics, the effects of post-injury manipulations on social behaviors is one of the more thoroughly studied facets. Although not always beneficial, post-injury manipulations provide a valuable opportunity to examine the progression of TBI-induced deficits. In the context of worsening social function, chronic cannabinoid treatment in adolescence exacerbated social deficits following neonatal mPFC surgical lesions, further reducing the rat's interest in playful activities and their overall tendency to initiate play with their peers (Schneider and Koch, 2005). Another study, utilizing the three-chamber social approach test, found that severe controlled cortical impact in adolescence produced impairments in social interactions which were exacerbated by exposure to post-TBI hypoxia (Davies et al., 2018). Following from this, additional research has demonstrated that exposure to stress in the context of a foot shock, following repeated experimental mTBI in adolescence, impaired social recognition and increased depression (Klemenhage et al., 2013).

There are also numerous post-injury manipulations that result in attenuation of social deficits and improvements in overall recovery. In a model of neonatal HI, rats that experienced HI were impaired socially; exhibiting reduced overall play and reductions in the number of playful approaches and play initiations. However, post-injury treatment with estradiol remediated the injury-induced effects and eliminated all of the social deficits (Waddell et al., 2016). Similarly, Panksepp et al., found that while neonatal surgical ablation of the frontal lobe induced hyperactivity and excessive playfulness, rough and tumble play therapy with normal rats was able to remediate these effects (Panksepp et al., 2003). Finally, post-injury exercise was also shown to actually improve emotional and cognitive recovery in rats, while social isolation had deleterious effects (Mychasiuk et al., 2016). In a similar study with mice, socialization with normal mice was critical for recovery from ischemic brain injury (Venna et al., 2014), suggesting that supporting the social environment post-injury can be a positive modulator of outcome. These studies demonstrate that post-injury social deficits are amendable to targeted interventions but require further investigation to maximize efficacy in a context-specific manner.

In summary, the preclinical literature demonstrates that genetic and epigenetic influences, premorbid experiences, characteristics of the injury itself, and post-injury manipulations contribute to different injury trajectories and the presentation of different social deficits, making prognosis difficult. The occurrence and severity of the social dysfunction is dependent upon a complex and multifaceted array of factors. When extended to humans, these findings may have important implications for the clinical management and prognosis of TBI outcomes in children and youth. Our results suggest that expectations for social recovery will need to be adjusted as a function of the factors presented above.

3. Clinical evidence of factors influencing post-injury social functioning

3.1. Injury-associated predictors of social outcomes after pediatric TBI

Studies of patient populations have identified several factors intrinsic to the injury itself as predictors of long-term psychosocial outcomes. Injury severity is the most obvious of these, with several studies showing an association between severity and aspects of social functioning in TBI survivors (Ryan et al., 2016b). In one longitudinal prospective study, children with severe TBI demonstrated significantly worse social problems compared to typically-developing age-matched controls, as well as compared to children with mild or moderate TBI, and further, these problems significantly increased between 12 to 24 months post-injury (Ryan et al., 2016b). This is largely in agreement with earlier studies, such as Rivara and colleagues (1993) who reported the greatest decline in post-injury social function in children with severe TBI compared to those with mild or moderate TBI, and only minimal improvements noted by one year post-injury (Rivara et al., 1993). Further investigations have found that severe TBI in particular was linked with poorer social participation and social adjustment (Ryan et al., 2015; Yeates et al., 2004; Anderson et al., 2013), and the extent to which children achieve developmentally-appropriate goals (Yeates et al., 2007). Yet other studies have demonstrated that injury severity is associated with poorer social cognitive function (Dennis et al., 2012; Ryan et al., 2014a; Muscara et al., 2009), and reduced maintenance of peer friendships (Prigatano and Gupta, 2006).

As introduced earlier, social cognition and information processing capacity in the brain develops with increasing brain maturation (Yeates et al., 2007). Injuries to any of the many brain regions involved in social functioning, particularly during early stages of brain maturation, are therefore likely to influence subsequent manifestation of social skills. Indeed, age at the time of injury is another consistently-reported risk factor for the development of social behavior problems after TBI (Ryan et al., 2016a; Wells et al., 2009). Broadly, TBI sustained during preschool age is associated with more persistent functional deficits compared to brain injuries occurring during adolescence or adulthood (Anderson et al., 2005; Anderson et al., 1997; Ewing-Cobbs et al., 1997). Two studies specifically compared those who sustained a TBI prior to or after 12 years of age, and found that earlier injuries resulted in worse social integration and reduced independent living (Hanten et al., 2008; Donders and Warschausky, 2007). Both age and injury severity have also been associated with language performance, with severe injury at a younger age resulting in greater linguistic impairments such as reduced fluency, vocabulary and verbal comprehension (Anderson et al., 1997; Ewing-Cobbs et al., 1987).

TBI results in both primary and secondary damage to the brain which may be either focal or diffuse in nature, or a combination of these. After pediatric TBI, as detailed in a subsequent section below, neuropathology has been reported in many regions of the social brain network including the hippocampus, amygdala, temporal lobe, thalamus and white matter tracts, associated to various extents with measures of social dysfunction (Bigler et al., 2013b; Ryan et al., 2016d). Interestingly, it has been noted that injury-related factors, such as injury severity and the location/spread of brain pathology, appears to be most relevant to early outcomes after childhood TBI, but is of lesser importance with the passage of time post-injury (Anderson et al., 2012). Indeed, several studies have shown that injury severity, while the most consistent predictor of social outcomes, does not account for a significant proportion of the variance seen between patients (Anderson et al., 2005; Catroppa et al., 2008; Wells et al., 2009). Such observations suggest that additional factors modulate and shape the manifestation of social behavior deficits in survivors of TBI.

3.2. Pre-injury and post-injury modifiers of social behavior outcomes after pediatric TBI

The health and status of an individual prior to sustaining a TBI has been found to be a significant predictor of social outcomes and recovery. For example, the presence of pre-existing social and cognitive problems is associated with lower levels of social participation in survivors of childhood TBI (Ryan et al., 2015); on the contrary, a high cognitive reserve may yield a degree of neuroprotection. Pre-injury risk factors may be defined as either intrinsic (i.e. features of the individual) or extrinsic (i.e. features of the pre-injury environment). Intrinsically, biological sex is hypothesized to influence social functioning after a brain insult; however, findings to date in this arena are conflicting. Among adult survivors of pediatric TBI, females report an increased incidence of internalizing problems such as depression and anxiety, while males are more likely to report externalizing behaviors such as aggression (Despins et al., 2015; Scott et al., 2015).

Several longitudinal studies have suggested that the quality of an individual's pre-injury environment can interact with a TBI to have either positive or negative consequences on social outcomes. Strong family functioning is reported to have a positive influence on psychosocial development after injury (Yeates et al., 2010). The home or family environment, including family structure, stability, financial status, and social resources, appears to significantly moderate developmental outcomes after an injury to either stunt or maximize potential recovery (Yeates et al., 2004; Kurowski et al., 2011). Anderson and colleagues (2012) examined 40 children with TBI using a family functioning questionnaire, and found a robust correlation between family intimacy and social outcomes at 10 year post-injury (Anderson et al., 2012). A much larger study of over 500 children between 2.5 – 15 years after TBI, found that a high social capital (an index reflecting an individual's perceptions of their personal, family, neighborhood and spiritual community support) contributed to positive social outcomes (Keenan et al., 2018). This is in agreement with other studies from school-aged children after TBI, in which outcomes were examined at earlier time points post-injury (Catroppa et al., 2008; Yeates et al., 2010; Anderson et al., 2004).

Family functioning is influenced by parental beliefs, parenting styles and behaviors, disciplinary practices, and the quality of the relationship between the child and parent or caregiver (Wade et al., 2016). Even in uninjured children, warm and authoritative parenting styles have previously been shown to predict more socially appropriate behavior and better social adjustment (Ladd and Pettit, 2002; Rubin et al., 2002). In a landmark study by Yeates and colleagues (2010), *authoritative parenting* (defined as high acceptance and expectations, warmth, and autonomy development) was found to be predictive of better social competence at 18 months post-injury, whereas *permissive parenting* (low expectations of appropriate behaviors, little instruction, and high responsiveness to child's needs) was predictive of worse social competence across time. Further, this relationship was evident not only in children with TBI but also in age-matched orthopedic-injured controls (Yeates et al., 2010). Similarly, another prospective, longitudinal observational cohort study examining TBI children an average of 6.7 years after injury found that less-favorable home environments, defined as those with higher levels of permissive parenting or *authoritarian parenting* (parent-centered, demanding, unresponsive, and punishment-heavy) were associated with more pronounced functional impairments, even in those with relatively mild TBI (Wade et al., 2016). This finding suggests that a suboptimal home environment is a considerable risk factor for poor social outcomes, whereby even children with less severe TBI may develop social deficits relative to their age-matched peers. On the contrary, a supportive home environment may enhance the capacity for recovery.

Intricately linked with family functioning is the influence of socioeconomic status. While some studies have failed to detect a relationship between the family's socioeconomic status and social or behavioral outcomes (Ryan et al., 2015), several studies have indeed demonstrated a link whereby lower financial standing and fewer family resources can exacerbate the negative social consequences following a pediatric TBI (Yeates et al., 2004). Differences between studies may be due to differences in the sensitivity of the assessment tool used, or the time point when social functioning was assessed. Socioeconomic status is also a strong predictor of language and vocabulary difficulties after TBI (Catroppa and Anderson, 2004). These observations suggest that families with higher social and financial resources may have greater access to medical resources, and may experience less stress, although the precise mechanisms of this interaction are likely to be complex and nuanced. A potential confound is that differences in quality of and/or access to education and parental involvement in language development can also influence language skills, regardless of TBI status (Head Zauche et al., 2017).

In summary, pre- and post-injury factors, including both those intrinsic to the injured child as well as extrinsic environmental variables, have been identified from clinical studies to independently predict or at least modify social outcomes after pediatric TBI. While it can be challenging to differentiate between the pre- versus post-injury timing of when these factors (e.g. family functioning and socioeconomic status) have their greatest effect, together, the evidence strongly suggests that a developing child's environment is crucial to how social functioning is affected by pediatric TBI.

4. Neuroanatomical damage underlying social deficits after TBI

Social cognition is reflective of the development of multiple brain regions across infancy, childhood and adolescence (Nelson et al., 2016b). Functions crucial to social processing such as facial expressions, speech and body perception, or executive functions, while connected, are all mediated by different brain regions. Regions in the temporal lobe form connections with other regions such as the dorsomedial and ventromedial prefrontal cortex, anterior insula, amygdala, fusiform and occipital face area and together form the "social brain network", as introduced earlier (Adolphs, 2001; Ryan et al., 2016a). It is therefore not surprising that injury to the brain results in a spectrum of social impairments depending on the location and severity of injury. Early during normal childhood development, the brain size and gray matter volume starts to increase, but as the brain continues to mature and the social brain network starts to develop, the ratio of gray to white matter decreases, indicating the establishment and consolidation of complex network connections (Mills et al., 2014). Injury at a young age not only disrupts the newly formed connections, but also changes the development of the networks that are to be formed later in life. This makes longitudinal studies on children that have sustained an injury at a young age much more important, particularly when social cognition is impaired.

Due to the bony structure of the skull and brain orientation, focal injury affects brain regions differently. Therefore, some parts of the brain are more susceptible to injury, specifically where the frontal and temporal lobes are enclosed by the anterior and cranial fossa (Bigler, 2007). Sudden movements, severe acceleration/deceleration or a blow to the head causes the soft brain tissue to have contact with the bony edges of the skull, which consequently damages the frontotemporal area (Hardman and Manoukian, 2002). Although the frontal and temporal areas are the primary regions to be affected by focal injury, deeper located structures particularly in the pediatric population can also be readily damaged, due to the stretching and shearing of axonal tracts (Donders and Warschausky, 2007; Bigler and Maxwell, 2011; Yuan et al., 2007). Due to the cascade of secondary cellular events that follow the primary traumatic insult, including Wallerian degeneration, functional deficits can occur months to years following the initial injury (Wilde et al., 2005; Meythaler et al., 2001). Secondary pathology can extend to both the gray matter located deep in the brain as well the white matter fibers that connect these regions together (Mills et al., 2014). As described earlier, patients who sustain a TBI in their early years commonly suffer from neuropsychological impairments and fail to interpret the social and emotional cues needed to sense the social situation (Levin et al., 2004; Anderson et al., 2017). This is especially evident in adults who have sustained injury during their developing childhood years (Anderson et al., 2012; Yeates et al., 2004; Ryan et al., 2014b), suggesting an association between these observations and the developmental trajectory of the underlying neuroanatomical regions. In this section, we examine evidence for the involvement of key regions of the social brain network in mediating the social behavior deficits seen in patients after pediatric TBI.

4.1. Hippocampal pathology following pediatric TBI

The most common way of detecting brain changes is through volumetric analysis of magnetic resonance imaging (MRI). MRI has revolutionized the detection of brain damage in acute, subacute and chronic stages after TBI, and has made longitudinal investigations in still-developing populations possible.

Brain scans of children with moderate to severe TBI, compared to age-matched uninjured controls, show gray matter structures such as the amygdala and hippocampus undergoing significant volume loss for at least 10 years post-TBI (Wilde et al., 2005; Wilde et al., 2007).

Damage along the anterior-posterior axis of the hippocampus most commonly affects the CA1 region (Ariza et al., 2006), which be both due to the region's orientation in the brain and also to its high vulnerability to neuronal loss in acute and chronic stages post-TBI (Bigler and Maxwell, 2011)(Maxwell et al., 2003; DeMaster et al., 2017). Given that memory formation and retrieval is one of the main functions of the hippocampus (Brickman et al., 2011; Budson, 2009), it is unsurprising that memory dysfunction is a common chronic pathology of TBI. The level and type of memory loss varies among individuals depending on the extent of hippocampal volume loss, with one study demonstrating that a definite memory impairment is apparent when the hippocampus undergoes a substantial (≥ 40%) loss in volume (Rempel-Clower et al., 1996). This is particularly important in the context of pediatric TBI given the positive correlation between memory function and bilateral hippocampal volume in the developing brain (Ostby et al., 2012), as well as the propensity for progressive neurodegeneration over time post-injury. Hippocampal damage after pediatric TBI likely contributes to deficits in social recognition memory, which has been associated with dorsal hippocampal lesions in particular, and is required to remember familiar faces, objects and places, thereby facilitating navigation through social challenges (Tanimizu et al., 2017). Evidence of mood disorders and anxiety have also been linked to chronic hippocampal atrophy that continues months to years after TBI and can have devastating negative consequences for the patients' social life (DeMaster et al., 2017; Terpstra et al., 2017).

4.2. Amygdala volume changes post-TBI

In addition to the hippocampus, other regions in the temporal lobe such as the fornix and limbic regions undergo progressive damage and volume loss after pediatric TBI (Bigler, 2007). The amygdala, an important component of the limbic system and with close proximity to the hippocampus, undergoes volume changes after injury (Moreno and Gonzalez, 2007); however, different studies have found contradictory evidence on the direction of these changes. While Wilde and colleagues (2007) reported that the amygdala undergoes volume loss over years following pediatric TBI, in contrast, Beauchamp and colleagues (2011) found that the amygdala was abnormally enlarged by 10 years post-injury (Wilde et al., 2007; Beauchamp et al., 2011). Further, a subacute study failed to report any changes in amygdala volume (Juranek et al., 2012). However, microstructural changes were evident using advanced MRI techniques, which correlated with increased anxiety in the patients. The amygdala has been implicated in social and emotional processing, social anxiety, social recognition, as well as social communication (Gupta et al., 2011; Wang et al., 2014). Of note, an increase in amygdala volume observed in the abovementioned study is consistent with patients' suffering from other disorders associated with social dysfunction, such as emotional dysregulation (Tottenham et al., 2010; Bornhofen and McDonald, 2008), anxiety (De Bellis et al., 2000), depression (Lange and Irle, 2004) and autism (Schumann et al., 2004).

4.3. Thalamus atrophy following TBI

Despite its deep location, the thalamus is not protected from the damage of head impact (Sidaros et al., 2009). Located in the core center of the brain, the thalamus forms afferent and efferent connections with distinct regions of the cortex and is therefore involved in complex information processing between multiple regions to play an important role in cognitive function and executive processing as well as social functioning (Izhikevich and Edelman, 2008; Law et al., 2018).

MRI volumetric analysis shows the vulnerability of thalamus in moderate to severe adult TBI, with reduced tissue volume and disrupted white matter connections regardless of the lesion site (Zhang et al., 2004; Viano et al., 2005; Sabet et al., 2008; Bayly et al., 2005) (Anderson et al., 1996; Natale et al., 2002; Little et al., 2010). The corticospinal tract passing through the thalamus, and multiple white matter fibers within the thalamus, are highly vulnerable to the shear and tear that result from diffuse traumatic injuries (Maxwell et al., 2006; Maxwell et al., 2004). Reduced thalamic volume and lost connections in thalamic white matter tracts has been correlated with deficits in cognition (Grossman et al., 2012; Messe et al., 2011), learning and memory (Ge et al., 2009), executive functioning (Little et al., 2010; Ge et al., 2009) and associative learning (Fernandez-Espejo et al., 2010; Salmond et al., 2005). While not yet examined in depth after TBI during early childhood, after TBI in adults, changes identified by diffusion tensor imaging in the bilateral thalamus were also found to be a significant contributor to socio-cognitive performance and the processing of complex social information (McDonald et al., 2018a).

4.4. White matter microstructural changes following TBI – use of advanced neuroimaging

While brain regions of the gray matter each contribute to aspects of social cognition [i.e. hippocampus involved in learning and memory (Brickman et al., 2011), amygdala involved in emotion and face recognition (Brickman et al., 2011; McDonald et al., 2018a) and the thalamus involved in executive processing and attention (Law et al., 2018)], it is through the social brain network of connections between these individual regions that social cognition emerges (Wang and Olson, 2018). White matter connects a large body of brain tissue, and as a result, white matter deficits are commonly seen in patients with different injury severity and locations; particularly in children in whom the white matter is still developing. Considering the ongoing maturation-dependent development of myelin, axons in the developing brain in highly vulnerable to injury (Yeates et al., 2007; Ryan et al., 2014b). The resulting loss of connection between brain regions or hemispheres is observed as neuropathology years after a brain injury, when children are seen to have impaired social functioning compared to typically-developing controls (Ryan et al., 2014b).

While volumetric MRI analysis serves as a good indicator of gray matter damage, it doesn't appear to be as sensitive to subtle changes that occur in white matter tracts, especially in mild TBI and diffuse injury (Gentry et al., 1988). Volumetric MRI scans of children with TBI in comparison to age-matched controls showed that relying on the lesion size, severity and location does not suffice to predict the children's performance in a social test (Yeates et al., 2007). Even without a focal lesion, shearing of unmyelinated axonal fibers resulting in diffuse axonal injury can occur, although more sensitive tools than standard MRI are needed to accurately detect such damage.

Advanced imaging techniques have made imaging the white matter and small axonal injuries possible. In particular, diffusion weighted imaging (DWI) utilizes the natural water diffusion through brain tissues as a qualitative measure for structural differences. White matter is a highly organized structure that greatly hinders water diffusion; water would have a direction of movement that is quantified by *fractional anisotropy* (FA) values (Assaf et al., 2004; Mori et al., 2001). The direction of water movement fits into a tensor model and is analyzed by diffusion tensor imaging (DTI) (Basser et al., 1994). Any injury that disrupts the fiber bundle and modifies water diffusion can be detected with DTI. Typically, the FA value is highest in normal white matter tissue and lowest in gray matter and cerebrospinal fluid (Neil et al., 2002; Singh et al., 2010). While FA shows the direction of water diffusion, the amount of diffusion is measured by the *apparent diffusion coefficient* (ADC) which is another commonly used estimate of white matter structure in clinical settings; as is *mean diffusivity* (MD). MD is the average of the longest and shortest axes of water direction in a voxel (pixel with volume). The tensor fits an ellipsoid model with the longest axis measured as *axial diffusivity* (AD) and the sum of the two shorter axes measured as *radial diffusivity* (RD). AD and RD are other DTI metrics used in analyzing white matter damage (Song et al., 2002). The majority of studies in both pediatrics and adults use DTI metrics to quantify white matter integrity.

Reduced FA, predominately seen following TBI, may be a result of demyelination, axonal injury, inflammation or edema. This makes FA a good model for detecting damage but not a specific measure of the underlying microstructural damage. Other measures are used to give a more comprehensive interpretation of changes happening within a voxel. MD is an indication of myelination/demyelination, fiber density and axonal packing following injury and the extracellular space. RD and AD represent the myelin and axon integrity, respectively. Based on the type of injury and severity, and the developmental stage of the brain, these values can change in both directions. In addition, in recent years, new analysis techniques have been developed to complement these highly used DTI metrics, such as tractography, which provides a more comprehensive interpretation of white matter damage (Hofer and Frahm, 2006; Correia et al., 2008).

4.5. White matter changes following pediatric TBI are associated with social behavior deficits

Since the initiation of clinical evaluations of white matter in TBI (Arfanakis et al., 2002), there have been numerous studies using DTI to show microstructural progression of neurodegeneration in the pediatric population after brain injury [see review (Hulkower et al., 2013)]. Analyzing white matter tracts of childhood TBI patients at a sub-acute 1 month post injury and a chronic stage of 2 years, found that MD and AD values were the most sensitive indices to detect microstructural changes in correlation with impairments in information processing (Genc et al., 2017). Over the past decade, increasing studies have sought to identify such changes after TBI alongside how they relate to measures of social functioning.

The corpus callosum is the largest white matter in the brain, and is involved in social information processing through connecting areas of the cortical gray matter and transferring information between hemispheres (Hofer and Frahm, 2006). Wilde and colleagues showed that FA was reduced in all areas of the corpus callosum of children after TBI; however, low FA in the splenium was seen particularly in patients with larger lesions and correlated with poor cognition (Wilde et al., 2006). The splenium connects the superior temporal and posterior parietal regions and is involved in social cognition (Adolphs, 2001). A subsequent study also found a significant reduction and increase in respective FA and RA measures, respectively, primarily in the posterior section of genu along with the body and splenium, with the highest significance reported in the splenium (Ewing-Cobbs et al., 2008). In another study, the corpus callosum of brain-injured children with low IQ levels, slow processing speed, cognitive and motor deficits, showed microstructural changes such as low FA at a sub-acute time point, which continued to decline chronically associated with an increase in MD, AD and RD at 1 year post injury. Interestingly, low FA and high MD levels also correlated with poor signal transfer between hemispheres and slow processing speed (Dennis et al., 2015; Dennis et al., 2017). This emphasizes the importance of white matter integrity in information processing, which is an important aspect of social cognition (Arioli et al., 2018).

Yet another study (Wozniak et al., 2007) reported low FA values in inferior and superior frontal and supra-callosal white matter tracts after pediatric TBI, correlating with slow processing, memory and executive functional deficits. This is in agreement with findings from Wu and colleagues (2010), in which children with poor processing speed at 3 months post-injury were reported to have low FA and high ADC levels in the splenium of the corpus callosum (Wu et al., 2010). However, a follow up at 18 months showed an increase in FA, which could have been interpreted as corpus callosum recovery, albeit when combined with other metric such as ADC, suggested otherwise. ADC levels also continued to increase over time. This suggests that the temporary reduction in FA levels at subacute levels might be due to acute post-injury biological events such as edema, that is resolved by 18 months. Similar to these cases in pediatric TBI, demonstrating an association between brain structural changes and behavior impairments, low FA was also detected in adults after TBI alongside deficits in social interpretation. Specifically, low FA was also reported in the splenium along with other white matter tracks such as corticospinal tract and fornix, and correlated with social and cognitive impairments (McDonald et al., 2017; McDonald et al., 2018b).

Contrary to the majority of studies, Ryan and colleagues (Ryan et al., 2018) showed that FA was not different in pediatric TBI patients at 24 months after injury compared to typically-developing controls; however, MD, RA and AD values of the white matter tracts such as cerebro-cerebellar and commissural tracts, uncinate fasciculus, and dorsal cingulum were increased. These MRI analyses also correlated with attention deficits, speech and cognitive impairments, all of which are involved in social cognition.

Injury progression in other white matter tracts also shows correlation with social cognition impairments. Children with moderate to severe TBI were found to have low FA and increased ADC of the cingulum (Hanten et al., 2008; Wilde et al., 2010), coinciding with poorer cognitive measures when compared to orthopedic injury controls. WM tracts such as the inferior longitudinal fasciculus (ILF) showed increased MD, RD and AD levels, while the inferior fronto-occipital fasciculus (IFOF) showed reduced FA levels. Importantly, changes in both tracts correlated with poor facial discrimination, which may underlie reported social recognition deficits. Impairments in the ability to identify facial emotions in brain-injured children was also associated with reduced hippocampal volume (Genova et al., 2015).

In summary, pediatric TBI results in diverse and heterogeneous neuropathology detectable by MRI and DTI. Increasing evidence demonstrates progressive and chronic damage in both gray and white matter regions of the social brain network, which likely underlie the observed social behavior deficits in this patient population.

5. Contribution of co-morbid behavioral deficits to social problems

Social behavior deficits rarely present in isolation after a pediatric TBI, and instead, are more likely to be observed alongside concurrent impairments in aspects of cognition as well as behavioral changes. Longitudinal studies on adults who sustained a childhood brain injury show that injury can also lead to comorbidities, most commonly seen as depression and anxiety (Juranek et al., 2012; Jorge et al., 2004; Max et al., 2006; Kirkwood et al., 2000; Holsinger et al., 2002). Studies have suggested that the extent of depression in brain-injured children at 6-12 months post injury is associated with damage in both the gray and white matter of the prefrontal and temporal lobe (Terpstra et al., 2017; Max et al., 2012), and is modulated by other factors including age of injury and family history of depression and anxiety. Inflicted TBI injury in patients under 6 years old has also been shown to affect their mental state in later stages of life (Ewing-Cobbs et al., 1998). This also applies for significant intellectual and cognitive deficits seen in children with severe TBI; similar to their influence on social outcomes, family dysfunction, psychiatric history and family income are factors that can worsen cognitive outcomes in these children (Max et al., 1999). These neurocognitive and behavioral impairments in turn (for example, difficulties controlling impulsive behaviors) can contribute to additional challenges when navigating social scenarios (Wells et al., 2009). As social deficits often also coexist alongside other neurobehavioral changes such as anxiety and depression, it can be challenging to therefore dissect out the underlying biological mechanisms of social dysfunction specifically.

6. Limitations and future directions

There are several limitations, in terms of the abovementioned clinical and preclinical studies, that hinder our ability to synthesize these findings into a comprehensive predictive model of chronic social behavior deficits after pediatric TBI. Firstly, many studies focused on patient populations are underpowered and cross-sectional in design, capturing one moment in time. For longitudinal studies, issues with attrition may inadvertently create bias, via a disproportional drop-out rate for extended follow-up being reported in particular amongst children from lower socioeconomic families, limiting the generalizability of study findings to the general population of children with TBI (Yeates et al., 2004). Variation in the measurement tools used, the age range of the populations being studied, and the choice of control groups (e.g. age-matched uninjured peers, or orthopedic-injured children) also confound the ability to compare findings between studies. Interestingly, there is sometimes variation in the measurement tools used even within the same study, to account for different aged children over time (e.g. preschool versus school-aged versions of the task) (Yeates et al., 2010). Many studies of social and psychosocial outcomes, particularly in pediatric populations, are based upon parent or caregiver reports. However, these reports are subject to observer and recall bias and provide only an indirect indicator of an individual's social function. When incorporated, more direct measures such as peer interactions and the extent of social networks, provide data that is less subjective to how a brain-injured patient is perceived.

There are also limitations associated with the interpretations of preclinical findings. Few studies to date have incorporated etiologically-appropriate experimental models of TBI, and there is some resistance from the research community regarding the utility of social behavior assays in rodent models in terms of their applicability to the human condition. Due to a lack of data, we have here also drawn upon other models of brain injury (e.g. ischemic stroke, and HI injuries at various developmental ages), which have some parallels with traumatic injuries but also some distinct differences.

Advanced neuroimaging techniques can assist in identifying the progressive neuroanatomical damage resulting from a pediatric TBI that contributes to the development of social behavior deficits. Novel metrics such as tract density imaging, tract-weighted imaging, average path length mapping and curvature of tractography data from DTI, appear to be more sensitive to detecting subtle white matter changes after injury, although these have not yet been applied in the context of sociability following pediatric TBI (Calamante et al., 2010; Calamante, 2017; Calamante et al., 2017; Pannek et al., 2011a; Pannek et al., 2011b; Wright et al., 2017; Willats et al., 2014).

Finally, we are only just beginning to appreciate how social behavior deficits evolve after injury in the broader context of other neurocognitive, behavioral and emotional problems, such as depression and anxiety. Other comorbidities including post-traumatic epilepsy likely also perpetuate these behavioral and functional consequences (Semple et al., 2018). Our understanding of how many of the identified risk factors for social dysfunction interact with each other is also in its infancy; for example, how a combination of younger age and greater injury severity results in the worst outcomes (Anderson et al., 2005).

Despite these limitations, knowledge of individual, injury-related and environmental factors which influence and shape the degree of social behavior impairments that manifest after a pediatric TBI can now be applied to better predict patient outcomes, as well as assist in the development of appropriate rehabilitation strategies. Ongoing work to define the progressive neuroanatomical changes after pediatric TBI hopes to identify prognostic neuroimaging biomarkers that would identify the subset of patients at greatest risk of social behavior deficits. Evidence that post-injury modifiers such as the family environment, socioeconomic status, and social participation level, can influence the social outcomes following a brain injury, suggests that efforts to optimize a child's environment and strengthen the family's coping mechanisms, even many years post-injury, may be an effective strategy to promote and enhance optimal recovery of social problems after pediatric TBI (Ryan et al., 2016b; Ryan et al., 2016c). Pilot studies have indeed found evidence that rehabilitation strategies targeting not only the child but also the child's family and caregivers in terms of education and interventions is beneficial (Yeates et al., 2010; Woods et al., 2014).

7. Conclusions

In summary, the extent of social behavior impairments after pediatric TBI can be moderated by several variables related with the injury itself, as well as pre- and post-injury factors associated with the individual and their environment (Fig. 1). No single factor can accurately predict the manifestation of social behavior problems, due to the complexity of how an injury interacts with the particular developmental stage of the child's brain, their premorbid functional status, as well as their family and broader community support network. The known evolution of neuropathology over time post-injury, and the emergence and/or varying functional and behavioral deficits during this time, highlights the need for additional longitudinal follow-up studies (Keenan et al., 2018). Over the past decade, advances in our understanding of social neuroscience and developmental psychology, alongside the application of clinically-relevant animal models and advanced neuroimaging methodologies, has resulted in identification of the above-described factors that mediate risk versus resilience to poor social outcomes after a brain injury. However, there remains a pressing need for ongoing research into the nature, trajectory and consequences of social dysfunction after pediatric TBI, which has such a profound influence on quality of life for survivors (Stancin et al., 2002).

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