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A comprehensive and multi-modal approach to studying neural and social outcomes after pediatric traumatic brain injury

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A comprehensive and multi-modal approach to studying neural and social outcomes after pediatric traumatic brain injury

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Résumé

Les traumatismes crânio-cérébraux (TCC) pédiatriques (c.-à-d., subis entre la naissance et 18 ans) constituent l'une des principales causes de décès et d'invalidité chez les enfants et les adolescents à travers le monde. Durant la période pédiatrique, les fonctions cognitives, affectives et sociales émergent progressivement, sous-tendues par la maturation cérébrale et l'établissement de réseaux neuronaux complexes. Un TCC subi durant l'enfance ou l'adolescence peut donc causer des dommages au cerveau immature et entrainer des difficultés dans ces domaines. La présentation clinique et les facteurs environnementaux sont très variables d'un enfant ou adolescent à l'autre, de sorte qu'il est difficile d'identifier qui aura un rétablissement optimal et qui aura des séquelles persistantes. Bien que la recherche ait identifié plusieurs facteurs qui contribuent au rétablissement post-TCC pédiatrique, notamment ceux liés à la blessure, à l'enfant et à l'environnement familial, les modèles de prédiction à ce jour ne sont pas toujours exhaustifs et ne tiennent pas compte des facteurs génétiques qui pourraient aider le pronostic.

Parmi l'ensemble des séquelles liées au TCC, les problèmes sociaux (ex: participation sociale réduite, comportements sociaux inappropriés) sont parmi les plus néfastes et peuvent considérablement affecter la qualité de vie. Ces difficultés sociales peuvent résulter d'une perturbation des habiletés socio-cognitives sous-jacentes, mais les mécanismes exacts et les bases neuronales de tels problèmes sont encore inconnus. Notamment, les connaissances actuelles sur la manière dont le TCC pédiatrique affecte les connexions entre les régions cérébrales durant le développement demeurent limitées.

Considérant ces lacunes relatives aux connaissances sur les TCC pédiatriques, cette thèse avait pour but 1) de déterminer les facteurs qui contribuent à la compétence sociale durant la petite enfance (c.-à-d., entre 18 et 60 mois), afin d'établir des pistes normatives pour comprendre l'émergence de problèmes sociaux suite à un TCC pédiatrique, 2) d'établir un modèle pronostique exhaustif du devenir (mesuré par la qualité de vie) après un TCC léger pédiatrique durant la petite enfance, et 3) d'examiner l'impact d'un TCC pédiatrique de sévérité modérée à sévère sur les réseaux cérébraux structurels et fonctionnels, notamment, ceux qui sous-tendent le fonctionnement social et cognitif. Afin d'atteindre ces objectifs, les données de deux cohortes longitudinales ont été analysées et présentées sous forme de quatre articles scientifiques.

Le premier article visait à valider empiriquement le modèle 'SOCIAL' (Beauchamp & Anderson, 2010) pour identifier les facteurs qui contribuent à la compétence sociale. Ce modèle théorique postule que des facteurs internes (liés à l'enfant), externes (liés à l'environnement) et cognitifs (fonctions attentionnelles et exécutives, communicatives et socio-cognitives) déterminent la compétence sociale de l'enfant. Les résultats d'un modèle de régression analysé chez un groupe d'enfants neurotypiques âgés de 18 à 60 mois indiquent que les facteurs internes, externes et cognitifs contribuent tous significativement à la compétence sociale de l'enfant. Les facteurs internes ainsi que les fonctions exécutives et socio-cognitives jouent un rôle particulièrement important. En effet, les enfants avec peu d'affect négatif, moins de difficultés exécutives, une meilleure communication non-verbale et une meilleure théorie de l'esprit ont un niveau de compétence sociale plus élevé.

Le deuxième article visait à examiner les facteurs qui contribuent à la qualité de vie six et 18 mois après un TCC léger subi entre l'âge de 18 et 60 mois. Plusieurs prédicteurs potentiels provenant de quatre catégories de facteurs (biologie, environnement, blessure, comportement/cognition) ont été entrés dans un modèle de régression hiérarchique. Les résultats indiquent qu'un facteur génétique, le polymorphisme Val66Met du gène codant pour la protéine BDNF (*Brain-Derived Neurotrophic Factor*), contribue positivement à la qualité de vie six mois après le TCC, alors qu'un an plus tard, un plus faible niveau de stress parental prédit une meilleure qualité de vie chez l'enfant.

Le but du troisième article était d'étudier l'organisation fonctionnelle du réseau cérébral soutenant les habiletés sociales (le cerveau social) chez les enfants et les adolescents qui ont subi un TCC de sévérité modérée à sévère entre l'âge de neuf et 15 ans. Les participants ont complété un protocole d'acquisition d'imagerie par résonance magnétique fonctionnelle au repos 24 mois après la blessure. Dans deux échantillons indépendants, les résultats indiquent une connectivité fonctionnelle altérée entre les régions cérébrales frontales et le gyrus fusiforme bilatéral dans le groupe TCC (connectivité positive) par rapport au groupe contrôle (connectivité négative).

Le quatrième article a exploré les changements à long terme dans les réseaux de covariance structurelle du cerveau (c.-à-d., des régions cérébrales qui sont structurellement connectées) après un TCC pédiatrique de sévérité modérée à sévère subi entre neuf et 14 ans. L'objectif était d'étudier les différences de covariance structurelle au sein de trois réseaux cognitifs (réseau par défaut [*DMN*], réseau exécutif central [*CEN*], réseau de la salience [*SN*]) entre les enfants avec un TCC

et les enfants sans blessure, trois et 24 mois post-TCC. Aucune différence de groupe n'a été trouvée après trois mois. Cependant, 24 mois après la blessure, le groupe TCC montrait une covariance structurelle réduite dans le DMN et le CEN par rapport au groupe contrôle.

Dans leur ensemble, ces résultats suggèrent que des modèles exhaustifs incluant un large éventail de facteurs provenant de plusieurs sphères du fonctionnement sont essentiels afin de comprendre les éléments qui placent un enfant à risque de séquelles après un TCC pédiatrique. Ils mettent également en évidence l'importance de considérer parmi les facteurs de prédiction des marqueurs génétiques impliqués dans les mécanismes de neuroplasticité, et confirment l'influence de facteurs parentaux, notamment la santé mentale du parent, sur le rétablissement post-TCC chez les jeunes enfants. De plus, les résultats montrent qu'un TCC pédiatrique de sévérité modérée à sévère peut induire des altérations à long terme au niveau des réseaux neuronaux sous-jacents aux fonctions sociales et cognitives. Ces résultats permettent de mieux comprendre comment un TCC pédiatrique affecte les circuits cérébraux pendant le développement, ce qui contribue à clarifier les bases neuronales des problèmes sociaux post-TCC. Finalement, les trouvailles et réflexions issues de la thèse supportent l'idée de considérer plusieurs facteurs liés à la blessure, à l'enfant, et à l'environnement familial ainsi que des facteurs génétiques pour le diagnostic, le pronostic, et le rétablissement après un TCC subi durant l'enfance ou l'adolescence.

Mots clés: Traumatisme crânio-cérébral, enfant, compétence sociale, BDNF, génétique, prédiction, réseaux cérébraux, connectivité fonctionnelle, covariance structurelle, longitudinal.

Abstract

Pediatric traumatic brain injury (TBI; sustained between birth and 18 years) is one of the leading causes of death and disability among children and adolescents worldwide. During development, cognitive, affective and social functions emerge gradually, supported by rapid brain maturation and the establishment of complex neural networks. TBI sustained during childhood or adolescence can therefore cause damage to the immature brain and lead to difficulties in these domains. Clinical presentation and environmental factors vary greatly, rendering it difficult to identify who will recover well and who will experience persistent sequelae. Although research has identified several factors that contribute to recovery after pediatric TBI, including injury, child-related, and family-environmental variables, existing prediction models are not always comprehensive, and they do not account for genetic factors which could contribute to prognosis.

Among all consequences associated with pediatric TBI, social problems (e.g., reduced social participation, maladaptive social behaviours) may be the most debilitating, and can considerably affect quality of life (QoL). These social difficulties can stem from a disruption of underlying socio-cognitive skills, but the exact mechanisms and neural bases of such problems are still unknown. In particular, current knowledge of how pediatric TBI affects connections between brain regions during development remains limited.

Considering these gaps in the pediatric TBI literature, this thesis aimed to 1) determine factors that contribute to social competence in early childhood (i.e., between 18 and 60 months) in order to establish normative avenues for understanding the emergence of social problems following pediatric TBI, 2) establish a comprehensive prognostic model of outcome (assessed by QoL) after early mild TBI (mTBI), and 3) examine the impact of pediatric moderate to severe TBI on structural and functional brain networks, notably those underlying social and cognitive functioning. In order to meet these objectives, data from two longitudinal cohorts were analyzed and are presented in the form of four scientific articles.

The first article aimed to empirically validate the “SOCIAL” model (Beauchamp & Anderson, 2010) to identify factors that contribute to social competence. This theoretical model posits that internal (child-related), external (environment-related) and cognitive (attentional-executive, communicative and socio-cognitive) factors determine a child's social competence. The results of a regression model analyzed in a sample of neurotypical children aged 18 to 60 months

indicate that internal, external and cognitive factors all contribute significantly to a child's social competence. Internal variables, executive functions, and socio-cognitive factors play a particularly important role. Indeed, children with lower levels of negative affect, fewer executive difficulties, greater non-verbal communication and better theory of mind had better social competence.

The objective of the second article was to examine which factors predict QoL six and 18 months following early mTBI sustained between 18 and 60 months of age. Several potential predictors from four domains (biology, environment, injury and behaviour/cognition) were entered into a hierarchical regression model. The results indicate that a genetic factor, the Val66Met polymorphism of the gene coding for the BDNF protein (Brain-Derived Neuroptrophic Factor), positively contributes to QoL six months after TBI, while a year later, lower parental distress predicts better child QoL.

The aim of the third article was to study the functional organization of the brain network supporting social skills (the social brain) in children and adolescents who sustained moderate to severe TBI between nine and 15 years of age. Participants completed a protocol for the acquisition of functional resting magnetic resonance images 24 months post-injury. In two independent samples, the results indicate altered functional connectivity between frontal brain areas and bilateral fusiform gyrus in the TBI group (positive connectivity) compared to the control group (negative connectivity).

The fourth article explored long-term changes in the brain's structural covariance networks (i.e., brain regions that are structurally connected) following pediatric moderate to severe TBI sustained between nine and 14 years of age. The aim was to investigate differences in structural covariance within three core cognitive networks (i.e., default-mode [DMN], central executive [CEN], salience [SN]) between children with TBI and typically developing controls, three and 24 months post-injury. No group difference was found after three months. However, at 24 months post-injury, the TBI group showed reduced structural covariance within the DMN and the CEN compared to the control group.

Taken together, these findings suggest that comprehensive models including a wide range of factors from several domains of functioning are essential for understanding the elements that put a child at risk for poor recovery after TBI. They also highlight the importance of considering, among potential predictors, genetic factors involved in mechanisms of neuroplasticity, and confirm the role of parental factors, in particular parent mental health for post-TBI recovery in young

children. In addition, the results show that moderate-severe pediatric TBI can induce long-term alterations in neural networks underlying social and cognitive functions. These findings provide insights into how pediatric TBI affects brain circuits during development, and may help to elucidate the neural underpinnings of social problems after pediatric TBI. Finally, the findings and implications from the thesis support the notion that several injury, child-related, family-environmental as well as genetic factors should be considered for diagnosis, prognosis, and recovery after TBI sustained during childhood or adolescence.

Keywords : Traumatic brain injury, child, social competence, BDNF, genetics, prediction, brain networks, functional connectivity, structural covariance, longitudinal.

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Appendix I

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List of acronyms

ABAS: Adaptive Behavior Assessment System

ACC: Anterior Cingulate Cortex

AIS: Abbreviated Injury Scale

ANOVA: ANalysis Of VAriance

ANZSCO: Australian and New Zealand Socioeconomic Classification of Occupations

ApoE: Apolipoprotein E

ASD: Autism Spectrum Disorders

BDNF: Brain-Derived Neurotrophic Factor

BOLD: Blood-Oxygen-Level-Dependent

BRIEF: Behavior Rating Inventory of Executive Function

CANTAB: CAmbridge Neuropsychological Test Automated Battery

CBCL: Child Behavior Checklist

CCC: Children's Communication Checklist

CEN: Central Executive Network

CNS: Central Nervous System

CSF: Cerebrospinal Fluid

CT: Computed Tomography

dlPFC: dorsolateral Prefrontal Cortex

DMN: Default Mode Network

dmPFC: dorsomedial Prefrontal Cortex

DNA: Deoxyribonucleic Acid

DTI: Diffusion Tensor Imaging

ECBQ/CBQ: Early Child Behavioral Questionnaire/Child Behavioral Questionnaire

ED: Emergency Department

EEG: Electroencephalography

EF: Executive Functioning

FAD: Family Assessment Device

FBU: False Belief Understanding

FC: Functional Connectivity

fMRI: functional Magnetic Resonance Imaging

FSIQ: Full Scale Intelligence Quotient

GCS: Glasgow Coma Scale

GEM: Griffith Empathy Measure

GM: Grey Matter

IPC: Inferior Parietal Cortex

IQ: Intelligence Quotient

MAR: Missing At Random

MEG: Magnetoencephalography

mPFC: medial Prefrontal Cortex

MRI: Magnetic Resonance Imaging

MRO: Mutually Responsive Orientation

mTBI: mild Traumatic Brain Injury

NEPSY: NEuroPSYchological Assessment

OCTC: Object Classification Task for Children

OFC: Orbitofrontal Cortex

OI: Orthopedic Injury

PCC: Posterior Cingulate Cortex

PCS: Postconcussive Symptoms

PCS-I: Postconcussive Symptoms Interview

PedsQL: Pediatric Quality of Life Inventory

PEERS-Q: Paediatric Evaluation of Emotions, Relationships, and Socialisation

PSI: Parenting Stress Index

QA: Quality Assurance

QoL: Quality of Life

rDLPFC: right Dorsolateral Prefrontal Cortex

ROI: Region Of Interest

rsfMRI: resting-state functional Magnetic Resonance Imaging

SBN: Social Brain Network

SCN: Structural Covariance Network

SES: Socioeconomic Status

SFG: Superior Frontal Gyrus

SN: Salience Network

SNP: Single Nucleotide Polymorphism

SOCIAL: Socio-Cognitive Integration of Abilities modeL

STS: Superior Temporal Sulcus

SWI: Susceptibility Weighted Imaging

TBI: Traumatic Brain Injury

TDC: Typically Developing Control

TMS: Transcranial Magnetic Stimulation

ToH: Tower of Hanoi

ToM : Theory of Mind

TPJ: Temporoparietal Junction

vlPFC: ventrolateral Prefrontal Cortex

vmPFC: ventromedial Prefrontal Cortex

WASI: Wechsler Abbreviated Scale of Intelligence

WISC: Wechsler Intelligence Scale for Children

WM: White Matter

WPPSI: Wechsler Preschool and Primary Scale of Intelligence

List of abbreviations

e.g.: For example

i.e.: That is

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Introduction

Rationale

Pediatric traumatic brain injury (TBI; sustained before the age of 18 years) is a major public health burden, and a leading cause of death and disability in children and adolescents worldwide (Dewan et al., 2016). During development, TBI can disrupt various areas of functioning such as in physical, cognitive, affective, behavioural, and social domains, and, in some cases, results in lifelong disabilities (Babikian & Asarnow, 2009; Beauchamp & Anderson, 2013; Catroppa, Anderson, Morse, et al., 2008; Ryan, Hughes, et al., 2015). Many of the domains affected by TBI are known to follow a protracted developmental course, evolving continuously from infancy through childhood and well into adolescence and early adulthood. This development is paralleled by the maturation of the brain's structural and functional circuitry which underpins these domains of functioning (Mills et al., 2012; Shaw et al., 2008; Thompson & Nelson, 2001). Brain insult sustained during such sensitive developmental periods can cause damage to the immature brain, disrupt cognitive, affective, behavioural or social functioning and their neural substrates, and consequently lead to deviations from the expected developmental trajectory (Anderson, Spencer-Smith, et al., 2011). Repercussions of such disturbances are reflected in the frequent occurrence of cognitive, affective, or socio-behavioural problems after pediatric TBI which can considerably affect quality of life (QoL). Although most consequences disappear in the first few months after TBI, especially in the case of injuries that are mild in nature, others may persist for several months, years and into adulthood when they can further compromise QoL (Anderson, Brown, et al., 2011; Ryan et al., 2019). Given that early childhood and adolescence coincide with important periods of brain maturation and intense socio-cognitive development (Soto-Icaza et al., 2015), sustaining a TBI during these periods may represent a high risk for social difficulties and long-term impairments. Moreover, a dose-response relationship can typically be observed with more severe injuries generally resulting in more negative outcomes.

Among all TBI-related sequelae, social disturbances have been shown to be among the most debilitating consequences. Social problems such as reduced social participation, socially maladaptive behaviours or social isolation often appear in the long-term, sometimes years following the brain insult, and have the potential to compromise children's QoL (Anderson et al.,

2017; Yeates et al., 2004). Social dysfunction is likely to be, at least in part, the result of a disruption of underlying socio-cognitive abilities, but the exact mechanisms are still unknown, as is the neural basis of such problems. Given the various factors that influence the emergence and maintenance of social competence, including cognitive, environmental or innate child characteristics, disruption in any of these areas may also contribute to poor social skills following pediatric TBI (Beauchamp & Anderson, 2010). Indeed, pediatric TBI is an extremely heterogeneous condition, with recovery depending on the interplay of a broad range of variables (Catroppa, Anderson, Morse, et al., 2008; Zamani et al., 2019). Over the past years, several prognostic models have examined the role of various factors for determining outcomes after pediatric TBI. However, most of these models include only a limited range of predictors and focus on specific rather than global outcomes, which can provide a comprehensive index of recovery. Emerging literature suggests that genetic predispositions, in particular genes involved in neuroplasticity, could contribute to explaining diverging recovery trajectories in children with seemingly similar injuries (Kurowski et al., 2012), yet, existing prognostic models have not tested the contribution of genetic factors.

At the neural level, it remains unclear what mechanisms underlie social disturbances. Given its diffuse nature, pediatric TBI has the potential to perturb the emerging formation of large-scale brain networks that sub-serve social cognition (Ryan et al., 2014). In other words, damage to any given brain region has the potential to alter the overall network architecture and can interfere with brain and social development. In this regard, social problems after pediatric TBI may result from structural or functional disruptions to a set of brain regions that are involved in social functioning, called the social brain network (SBN; Adolphs, 2009). To date, little research exists on the impact of pediatric TBI on the structural and functional organization of large-scale brain networks including the SBN, as most studies have focused on individual brain regions in isolation. In addition, few neuroimaging studies have employed a longitudinal perspective. In sum, the literature lacks a comprehensive outlook on the specific underlying neural mechanisms of social dysfunction after pediatric TBI from a network perspective and it is unclear how pediatric TBI affects brain development over time.

The objectives of the present thesis were therefore to 1) set the stage for understanding social development and social problems in the context of pediatric TBI by comprehensively investigating the factors that contribute to normative social development in early childhood, 2) examine which factors determine long-term (i.e., six and 18 months post-injury) QoL after early

mild TBI (mTBI; sustained before the age of six years), including the role of genetic factors, and 3) assess the impact of moderate-severe TBI sustained in childhood and adolescence on the brain's structural and functional organization with a particular focus on the social brain and core neurocognitive networks.

The thesis introduction provides the theoretical background that supports the thesis rationale, including epidemiological, pathophysiological, and methodological aspects related to pediatric TBI, emphasizing the unique developmental context of pediatric brain injury. Predictors of outcome and recovery will be presented, as well as an overview of the short- and long-term consequences of pediatric TBI, with a focus on social problems. Emergence of social competence in normative development as well as the role of socio-cognitive skills in typical development will be discussed as a basis for understanding social disturbances in the context of pediatric TBI. This information will be followed by a section covering evidence from structural and functional neuroimaging pertaining to the neural correlates of social deficits and the SBN. Finally, the specific thesis objectives and hypotheses will be presented. Four empirical studies are then included in the main part of the thesis, followed by a general discussion of the thesis findings. Two articles which complement the work presented here are included as appendices.

Pediatric traumatic brain injury

Epidemiology

Worldwide, over three million children and adolescents are affected by TBI every year (Dewan et al., 2016). As such, pediatric TBI ranks among the most common causes of childhood morbidity and mortality on a global scale (Zamani et al., 2019). Considering its prevalence and the presence of associated post-injury symptoms that require both acute and long-term rehabilitation and medical support, pediatric TBI constitutes a significant medical and public health burden (Gardner & Zafonte, 2016; Zaloshnja et al., 2008).

Reports converge on the observation of a bimodal age distribution indicating that the early childhood (five years and less) and late adolescence (15-19 years) periods have the highest incidence of TBI (Dewan et al., 2016; Thurman, 2016). While the rate is higher for younger children (< five years) than for those aged five to 14 years, adolescents aged 15 years and older are more likely to sustain more severe injuries which require medical attention and hospital treatment, as well as more frequent fatal injuries (Thurman, 2016). Overall, mTBI (also commonly called

"concussion") represents the majority of all pediatric TBIs (> 80%), followed by moderate (10%) and severe TBI (10%; Dewan et al., 2016; Gardner & Zafonte, 2016). Across all age groups, the incidence rates of TBI are almost twice as high in boys compared to girls with the male-to-female ratio becoming more salient with increasing age, especially after the age of three (Dewan et al., 2016; Langlois et al., 2006; McKinlay, Kyonka, et al., 2010; Thurman, 2016). This could reflect higher risk-taking activities, more physical play, as well as sports-related injuries that become more frequent with increasing age in boys (Dewan et al., 2016). In addition, socioeconomic factors such as unemployment or social disadvantage have been consistently associated with higher rates of TBI in children (Hawley, Ward, Long, et al., 2003; Parslow et al., 2005).

Overall rates of pediatric TBI vary worldwide, with highest hospital admissions reported in the U.S. (Dewan et al., 2016). A general increase in pediatric TBI prevalence has been observed, also in the Canadian context, where numbers nearly doubled between 2006 and 2011 (Stewart et al., 2014). Variation between epidemiological studies is likely due to differences in the methodology used (e.g., data sources such as hospitalizations, emergency department [ED] visits), definitions of TBI (e.g., severity), participant characteristics (e.g., ages included, sample size and sampling method), and ways incidence rates are measured across studies. Furthermore, many statistics do not include unattended injuries, that is, injuries for which no medical consultation is sought, as is frequently the case for mTBI (Thurman, 2016). Thus, since some injuries go undiagnosed or do not receive follow-up medical care (Cassidy et al., 2004; Langlois et al., 2006; McKinlay et al., 2008), the true incidence of mTBI is unknown and many TBI-related sequelae may develop silently. In addition, most statistics are based on high-income countries only and thus, global numbers are likely underestimated.

Etiology

Causes of pediatric TBI vary as a function of demographic (i.e., societal, ethnic) and geographic context, as well as age (Dewan et al., 2016). Overall, in children under the age of 14 years, falls present the vast majority of TBI mechanisms (Centers for Disease Control and Prevention, 2015; Dewan et al., 2016). Before the age of five years, TBI results predominantly from falls, but nonaccidental trauma including abusive head trauma, and motor vehicle accidents also occur (Araki et al., 2017; Keenan et al., 2003; Koepsell et al., 2011). Falls remain the leading cause between the ages of five and 14 years, followed by traffic- and sports-related injuries, such as pedestrian, bicycle or motor vehicle accidents (Centers for Disease Control and Prevention,

2015; Thurman, 2016). In youth aged 15 years and older, the primary cause of TBI are motor vehicle accidents, followed by assault and head injuries sustained during sports (Araki et al., 2017; Thurman, 2016). This likely reflects higher-risk taking behaviour in older children, such as engaging in contact sports or risks in the context of driving (Williams, 2009).

Definitions and injury classification

TBI can be defined as a non-degenerative, non-congenital insult to the brain caused by an external physical force, such as a bump, blow, or jolt to the head or penetrating head injury which disrupts normal brain functioning (Centers for Disease Control and Prevention, 2015; World Health Organization, 2006). Two injury mechanisms can be distinguished: a) an object penetrating the head, or b) an acceleration-deceleration movement. In the case of the latter, when an external force is applied to the head, it can lead to a displacement of the brain inside the skull due to an acceleration-deceleration movement and disrupt nervous tissue and blood vessels when the brain hits against the solid meningeal membrane, the dura mater, or the neurocranium (Menon et al., 2010; World Health Organization, 2006). Accordingly, TBIs can be distinguished as open/penetrating (i.e., a foreign object penetrating the skull) or closed/non-penetrating head injuries, which constitute the vast majority (approximately 90%) of pediatric TBIs (Anderson et al., 2014; Greve & Zink, 2009). Generally, open head injuries lead to focal lesions (i.e., at the site of the impact or in a brain area at the opposite side) as a result of penetration as well as edema and increased intracranial pressure (Greve & Zink, 2009). Altered brain function and neuropathology in the case of closed head injury is typically dependent on the force of the external object and the acceleration-deceleration movement of the brain inside the cranium, leading to diffuse injury due to the shearing and tearing caused by the movement. The present thesis focuses on accidental, closed head injuries.

Though numerous characteristics of the injury can alter the outcome of TBI, they are usually grossly classified into mild, moderate, and severe categories according to a limited set of clinical criteria. The Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974), which measures the degree of altered consciousness, is the most common classification system of TBI severity. The GCS consists of three parts (eye opening, verbal response, and motor response) which are combined to create an overall score ranging from three to 15. Given the limited verbal abilities of children under the age of three years, an adapted version of the GCS is used, taking the child's non- or pre-verbal

reaction to speech or pain into account, such as coos, babbles, irritability, or crying (Holmes et al., 2005; Reilly et al., 1988).

Additional criteria used for diagnosis and classification are based on the occurrence of one or more of the following clinical signs: (i) a period of loss of or altered consciousness or amnesia, (ii) neurological or neuropsychological symptoms (e.g., muscle weakness, loss of balance and coordination, disrupted vision, sensory loss, change in speech and language), (iii) altered mental state at the time of the injury (confusion, disorientation), (iv) skull fractures, (v) traumatic intracranial lesions (Menon et al., 2010; Thurman, 2016). In addition, the presence of intracranial pathology on computed tomography (CT) or magnetic resonance imaging (MRI) scans is also taken into account in order to facilitate rapid and sensitive diagnosis (Pinto et al., 2012).

Classification is typically established as follows: (i) mild TBI is associated with a GCS between 13 and 15 in addition to some alteration of consciousness (e.g., drowsiness, disorientation), but no mass lesion on CT or MRI; (ii) mild complex (or mild complicated) TBI is associated with a GCS of 13 to 15, some alteration of consciousness and the presence of intracranial lesions on CT/MRI; (iii) moderate TBI refers to a GCS of 9 to 12 on admission together with significant alterations of consciousness, reduction of responsiveness and/or mass lesion or other specific injury visible on CT/MRI, and/or other neurological deficits; (iv) severe TBI is classified by a GCS of 3 to 8 which represents coma, in addition to mass lesion or other specific injury on CT/MRI as well as neurological deficits (Beauchamp & Anderson, 2013; Carroll, Cassidy, Holm, et al., 2004; Williams et al., 1990). Of note, a dose-response relationship is generally present, with more severe injuries typically leading to poorer outcomes, though exceptions do occur.

Pathophysiology

Due to the rapid maturation of the brain from early childhood through adolescence, including anatomical changes and age-specific properties of the skull, face, brain, and neck muscles, clinical presentations of pediatric TBIs vary considerably depending on severity and age (Araki et al., 2017). In addition, given intrinsic structural and functional differences of the developing versus adult brain, pathophysiology mechanisms as well as subsequent recovery differ for pediatric compared to adult TBI. For example, compared to adults, young children are at higher risk for hemorrhagic shock as the infant scalp is highly vascularized (Araki et al., 2017). In addition, their head is relatively heavy and disproportionally larger in relation to the body size. Consequently, together with a poorer control of head and neck movements, children (especially the

youngest age groups) have increased risk of head injury compared to adults (Burdi et al., 1969; Noppens & Brambrink, 2004). In addition, the developing brain is less well protected from exterior forces due to lower levels of cerebrospinal fluid (CSF), less myelinated brain tissue, and thinner skull bones compared to the adult brain (Noppens & Brambrink, 2004), leading to considerable risk of diffuse edema and increased intracranial pressure following TBI (Aldrich et al., 1992). Finally, frontal brain regions are particularly vulnerable to injury given that in the pre-programmed developmental sequence, they are the last part of the brain to be myelinated, and thus less protected from external forces (Araki et al., 2017).

Generally, when external energy is transferred to the head, three biomechanical forces have to be considered: acceleration, deceleration and rotation of the brain inside the cranial vault (Meaney & Smith, 2011). Subsequent damage to brain tissue can result from either a primary or a secondary insult (Araki et al., 2017).

Primary insult refers to a direct mechanical alteration of brain structures as an immediate consequence of the impact of external forces to the head (Centers for Disease Control and Prevention, 2015). Primary insult includes skull fractures, intracranial injuries such as intracranial haematoma or acute and sub-acute hemorrhages, as well as injury to white matter (WM) pathways and cerebral contusions in grey matter (GM; Mower et al., 2005; Pinto et al., 2012). These are all common forms of primary injuries which often occur at the site of the insult, and depend on the physical force of the impact on the head (Greve & Zink, 2009). The frontal and temporal regions tend to be particularly affected by contusions (Bigler, 2013; Wilde et al., 2005), given that they are located above boney skull surfaces which have a higher vulnerability to injury from an external force (Bigler, 2007). Due to contre-coup mechanisms (a forth and back movement of the brain within the skull), brain areas opposite the site of the impact can also be affected. Primary insult can also involve vascular injury or intra-parenchymal injury such as diffuse axonal injury (Araki et al., 2017; Giza et al., 2007). Diffuse axonal injury results from a sudden rotational movement of the brain inside the cranial vault, which leads to additional stretching and shearing of axons (Greve & Zink, 2009; Johnson et al., 2013). The extent, severity and location of primary injury play a critical role in determining functional outcome (Pinto et al., 2012).

Secondary injury develops gradually, as a result of the physiological and biochemical mechanisms associated with the primary injury, occurring hours, days or even months after the initial trauma (Greve & Zink, 2009; Kaur & Sharma, 2018; Pinto et al., 2012). Secondary injury

involves a metabolic cascade of events, and includes, for example, diffuse cerebral edema, increased intracranial pressure, altered blood flow to the brain due to damage to the blood-brain barrier, cerebral hypoxia, or mitochondrial dysfunction (Araki et al., 2017; Kaur & Sharma, 2018). Cell death can occur through neuro-metabolic changes such as a reduction of oxygen or increased intracranial pressure following the trauma (Kaur & Sharma, 2018). In addition, release of neurotransmitters can be altered, which can increase the likelihood of hypoxic ischemia (Greve & Zink, 2009; Werner & Engelhard, 2007). The release of free radicals, inflammation as well as alterations in glucose metabolism and oxygen proliferation to neurons can interrupt cell function, leading to further cell death (Greve & Zink, 2009; Pinto et al., 2012).

Recovery and determinants of post-injury outcomes

TBI in the context of ongoing brain development: Plasticity or vulnerability?

Childhood and adolescence represent unique developmental contexts, times of rapid brain maturation and sensitive periods that follow a precise pre-programmed sequence. In order to explain the various clinical presentations, differences in outcome, and diverging recovery profiles following pediatric TBI, two perspectives have been proposed.

The "early plasticity theory" or "young age plasticity privilege" (Dennis, Spiegler, et al., 2013) was originally inspired by experiments with primates which showed that infant primates recovered better from injury to the motor cortex than adult primates (Dennis, 2010; Kennard, 1938, 1942). This theory suggests that because the pediatric brain is less functionally and structurally refined, it can reorganize and adapt to injury more easily compared to the adult brain (Ballantyne et al., 2008; Dennis, 2010). More specifically, neural plasticity, that is, molecular and neuroanatomical changes such as synaptic reorganization and axonal sprouting that occur as a result of learning, experience or in response to injury (Su et al., 2016), may serve as a buffer against sequelae. As such, sustaining a TBI at a younger age may be less detrimental than at an older age given the enhanced potential for structural and functional malleability. This theory found support in early studies of young children with focal unilateral brain lesions (e.g., Alajouanine & Lhermitte, 1965; Woods & Carey, 1979) and studies showing good outcomes in children with TBI in terms of cognitive and intellectual abilities, with most evidence coming from studies of severe injuries (Aram & Ekelman, 1986; Ballantyne et al., 2008; Dennis, 1980; Smith & Sugar, 1975).

However, while the views on plasticity appear to hold for focal lesions, they may not apply to generalized and diffuse brain injuries such as TBI which can perturb several brain regions and circuits, leading to more widespread impairment (Anderson et al., 2005b; Anderson, Spencer-Smith, et al., 2009; Donders & Warschausky, 2007). In addition, they do not account for observations that early TBI, even when mild in nature, can sometimes lead to unfavourable outcomes (Bellerose et al., 2015; Crowe et al., 2013; Dégeilh et al., 2018; Gagner et al., 2018; Keenan et al., 2018; Lalonde et al., 2018; Landry-Roy et al., 2018; Séguin et al., 2020). Furthermore, neural plasticity is not synonymous with functional recovery, and although it is generally considered as beneficial, it can also be maladaptive (Anderson, Spencer-Smith, et al., 2011; Dennis, Spiegler, et al., 2013; Felderhoff-Mueser & Ikonomidou, 2000; Gagner, Tuerk, et al., 2020; Raja Beharelle et al., 2010). Indeed, in the unique context of brain development, sustaining a brain injury may be detrimental (Anderson, Spencer-Smith, et al., 2009). As such, the "early vulnerability theory" posits that the immature brain may be particularly vulnerable to the effects of brain insult as it can derail the genetically determined and delicate blueprint of brain maturation occurring during specific periods (i.e., sensitive periods). Consequently, TBI can lead to negative consequences for early developing skills (e.g., cognitive, affective and social) and compromise future development (Anderson et al., 2005b; Anderson, Spencer-Smith, et al., 2009; Dennis et al., 2014; Ewing-Cobbs et al., 1997). Hence, the developing brain is susceptible to TBI-induced difficulties because cognitive and social functioning requires the timely and optimal development of brain structures and networks (Anderson et al., 2005b; Thompson & Nelson, 2001). In turn, injuries to the immature brain can have adverse effects on behaviour and cognitive development, which are typically more severe than similar injuries sustained during adulthood (Anderson et al., 2005b). This has further been supported by evidence showing that younger age at the time of the TBI, such as during early and middle childhood can result in poorer cognitive and psychosocial outcomes than when injury occurs later during development (Donders & Warschausky, 2007; Duval et al., 2008; Hessen et al., 2007; Keenan et al., 2018; Strauss et al., 1995). Importantly, however, the relationship between injury age and any functional outcome is likely not to be a simple linear association, but instead depends on which developmental stage injury occurs at and how sensitive this period is in terms of brain plasticity and cognitive maturation (Hudspeth & Pribram, 1990); this notion is discussed further in the 'Injury characteristics' section.

Although both theories are useful to conceptualize TBI recovery, they cannot fully explain variations in post-injury outcomes. Other than the plasticity or vulnerability of the brain, there is evidence that a complex and dynamic interaction of several factors, including child-related variables, injury characteristics, and environmental factors need to be considered to determine short- and long-term consequences of pediatric TBI (Anderson, Spencer-Smith, et al., 2011; Beauchamp & Anderson, 2013; Crowe et al., 2015; Zamani et al., 2019). The synergy of these factors determines where along a recovery continuum an individual's outcome after TBI is situated.

Predictors of outcome after pediatric TBI

Age at injury considerations notwithstanding, TBI results in a wide range of clinical presentations and recovery trajectories. Some children recover rapidly with no detectable symptoms or impairment within days or months of the injury (as it is often the case for mTBI), others show difficulties or impairments immediately after injury but catch up with their peers over time, and still others have chronic problems that may last throughout their life (Anderson, Spencer-Smith, et al., 2011; Dennis, 1988; Luciana, 2003). Some TBI-related issues may not even be apparent initially after injury, but only emerge later in development when environmental demands increase (Beauchamp & Anderson, 2013; Taylor et al., 2002). Although some of the variability observed in published studies may be due to methodological differences across studies, it is clear that outcomes after pediatric TBI depend on several factors and their interplay. For example, despite overall good outcomes following mTBI, injuries sustained in the first years of life or in the context of poor family functioning or premorbid behavioural problems may result in unfavourable or incomplete recovery (Anderson, Spencer-Smith, et al., 2011). As such, no single variable alone can predict post-injury outcome. Instead, multiple premorbid, injury as well as environmental and neural factors are assumed to play a role in determining child outcome after TBI (Beauchamp & Anderson, 2013; Zamani et al., 2019). Figure 1 presents a visual depiction of some of the factors known to be associated with outcome of childhood TBI which will be briefly discussed in the following section. Please note that this does not represent an exhaustive review of all potential influencing factors, but focuses on those that were candidate predictors in this thesis.

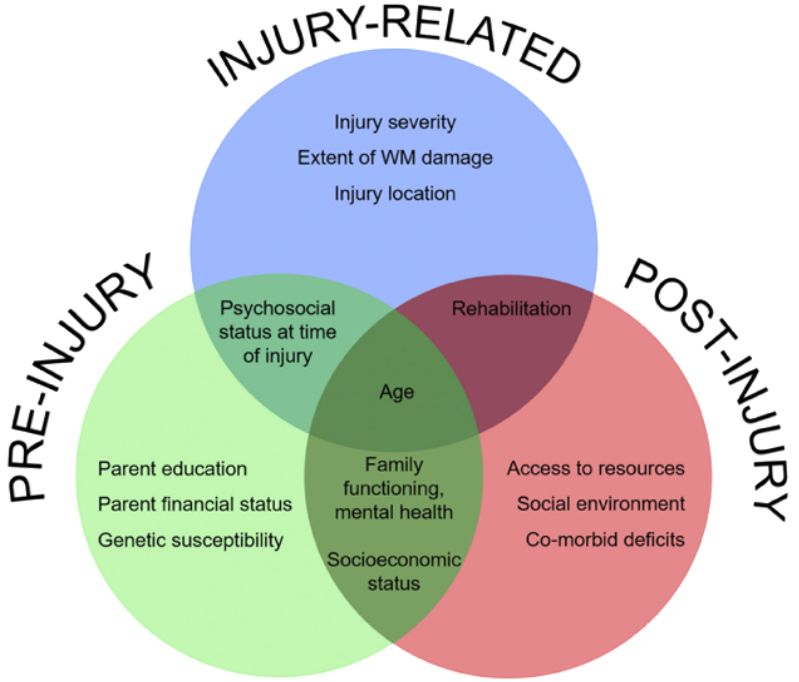

Figure 1. Pre-injury, injury and post-injury factors that have been shown to be implicated in (socio-behavioural) outcomes after pediatric TBI.
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Injury characteristics

Severity and age at injury. Severity of childhood TBI naturally has a considerable impact on recovery. Across age groups, the majority of children with mTBI recover well, while only about half of those with moderate-severe TBI show full or good recovery, that is, they remain delayed when compared to their peers and/or do not attain pre-injury levels of functioning (for a review see Dewan et al., 2016). A dose-response relationship between TBI severity and outcome tends to occur, according to which more severe injuries generally result in worse outcomes. For example, children with severe TBI have more neuropathology (Araki et al., 2017; Genc et al., 2017), lower health-related QoL in the first year post-injury (Brown et al., 2016), and overall poorer neuropsychological outcomes (i.e., attention, language, emotion, social cognition, intellectual, executive and adaptive functioning) when compared to children with moderate or mTBI or uninjured controls, independent of age at injury (e.g., Anderson et al., 2005b; Babikian & Asarnow, 2009; Crowe, Catroppa, Babl, & Anderson, 2012; Ewing-Cobbs et al., 1998; Ewing-Cobbs, Prasad, et al., 2004; Keenan et al., 2018; Ryan, Catroppa, Cooper, Beare, Ditchfield, Coleman, Silk,

Crossley, Rogers, et al., 2015; Ryan, van Bijnen, et al., 2016; Trenchard et al., 2013). In addition, lower rates of improvement in adaptive and social functioning have been demonstrated one year post-injury in children with severe TBI (Rivara et al., 1993), as well as and a reduced likelihood to achieve developmentally-appropriate goals (Babikian & Asarnow, 2009) when compared to children with mild to moderate injuries. However, although children who sustain mTBI generally show fast and favourable recovery, a minority of children experiences persistent postconcussive symptoms (PCS), behavioural or social disturbances even several months post-injury (Bellerose et al., 2017; Gagner, Dégeilh, et al., 2020; Zemek et al., 2016; Zemek et al., 2013).

Age at injury, and the developmental stage at which injury occurs, play an important role in recovery (Anderson, Spencer-Smith, et al., 2009; Anderson, Spencer-Smith, et al., 2011; Crowe, Catroppa, Babl, Rosenfeld, et al., 2012; Dennis et al., 2014). More specifically, brain development occurs in a stepwise manner consisting of peaks and plateaus (called critical or sensitive periods) and follows a distinct orchestrated order of events which are necessary to acquire specific skills and behaviours, and to learn from experience (Meredith, 2015). During these time windows, the neuronal system is most responsive for important developmental changes and neuroplasticity (Hudspeth & Pribram, 1990; Johnson, 2005; Kolb & Gibb, 2014). Hence, outcome of pediatric TBI depends on the state of neuro- and cognitive development with injury predominantly affecting those skills and processes that are emerging or undergoing rapid maturation at the time of injury, and/or altering future development of associated functions (Anderson, Spencer-Smith, et al., 2009; Anderson, Spencer-Smith, et al., 2011; Crowe, Catroppa, Babl, Rosenfeld, et al., 2012; Giza et al., 2007). Conversely, the impact of TBI on skills that are already in place may be transient and subsequent recovery more favourable in these areas (Anderson et al., 2005b; Anderson, Spencer-Smith, et al., 2009; Dennis, 1988; Dennis et al., 2014). Language abilities are one example of skills that are developmentally sensitive to the timing of TBI (Ewing-Cobbs & Barnes, 2002; Turkstra et al., 2015). For example, Ewing-Cobbs and colleagues (1987) showed that children (aged five to 10 years) and adolescents (aged 11 to 15 years) with TBI both show more impairments in terms of visual naming, expressive and written language skills as compared to receptive language skills. However, overall greater deficits were seen in terms of written language in children compared to adolescents. These results support the notion that the preschool and early school years are periods of intense development of expressive and written language development. In addition, studies have shown that children who sustain TBI during the preschool years are more likely to present with

lexical deficits such as sentence repetition or word fluency, while adolescents experience a differential vulnerability to TBI-induced impairments in higher-order language skills such as reading comprehension, pragmatics, and narrative discourse (Ewing-Cobbs & Barnes, 2002 for a review; Turkstra et al., 1996). Furthermore, compared to adolescent TBI, middle childhood TBI has been associated with persistent pragmatic language impairments up to two years post-injury (Ryan, Catroppa, Beare, et al., 2015). Lending further support to the sensitive periods model, Crowe and colleagues (2012) found that TBI during middle childhood (i.e., between 7-9 years of age) resulted in worse intellectual outcomes compared to TBI sustained during the preschool years or in late childhood, given that this period constitutes a critical time for cognitive development. These findings jointly show the developmental status at the time of the insult determines the pattern of difficulties after pediatric TBI. Importantly, TBI may also hinder the development and acquisition of new skills, thus increasing the developmental gap between children who sustain TBI and their non-injured peers (Babikian et al., 2015; Beauchamp, Séguin, et al., 2020).

The observation that both severity and injury age predict language recovery after pediatric TBI (Anderson et al., 1997) supports a "double hazard" model suggesting that earlier and more severe brain injuries lead to more severe consequences, and that outcome is generally worse if at least two risk factors can be identified (Anderson et al., 2005b; Escalona, 1982). Consequently, children who sustain TBI during early childhood may thus be the most vulnerable to unfavourable consequences, especially if the injury is severe and/or other risk factors are present (e.g., social disadvantage, poor family functioning). Supporting this model, moderate to severe TBI sustained before the age of seven has been associated with substantially poorer neurocognitive outcomes compared to those who sustain these injuries at an older age (Anderson et al., 1999; Dennis et al., 1995; Taylor & Alden, 1997).

Lesion characteristics. Clinical presentations of childhood TBI vary widely as a function of the extent and the location of neuropathology with more pronounced brain damage typically being linked to worse outcomes and higher morbidity (Anderson et al., 2005b; Bigler, 2013; Wilde, Hunter, et al., 2012). As described in more detail below, damage to certain regions of the brain has been associated with specific neuropsychological problems following pediatric TBI (e.g., Bigler, 2013; Ryan, van Bijnen, et al., 2016; Urban et al., 2017; Wilde et al., 2011). Overall worse outcomes can be observed in those with bilateral and more widespread injuries (Catroppa, Anderson, Ditchfield, et al., 2008), whereas smaller and more restricted lesions are generally

associated with better recovery (Levin et al., 2004). Using susceptibility weighted imaging (SWI), Beauchamp and colleagues (2013) found that number and volume of lesions in the acute stage (i.e., within one week of injury) after pediatric TBI were negatively associated with GCS and intellectual functioning six months later. Similarly, other studies found that a higher number and volume of lesions were related to a longer duration of coma and a lower GCS (Tong et al., 2004), as well as to poorer cognitive functioning (Babikian et al., 2005). However, given the diffuse nature of TBI, the extent of brain damage rather than lesion location alone may be a better predictor for outcome (Power et al., 2007). Indeed, diffuse axonal injury has been linked with poorer outcomes in a range of domains, supporting the idea that TBI causes brain damage at network-level by disrupting the connections between distributed brain regions implicated in cognitive functions (Caeyenberghs et al., 2013; Ryan et al., 2017). Importantly, over time, the impact of injury characteristics and neurological factors on recovery seem to fade, suggesting that in the long-term, other factors need to be considered that affect outcome after childhood TBI, such as environmental or psychosocial factors with which they may interact (Anderson et al., 2005b; van der Horn et al., 2019).

Family-environmental factors

Many family-environmental factors can influence post-TBI recovery, across all ages and severities. For example, social and economic disadvantage have been found to be a risk factor for sustaining TBI (Parslow et al., 2005) and for negative TBI outcomes (Yeates et al., 1997). Lower socioeconomic status (SES) in particular has been linked to more unfavourable consequences after pediatric TBI, including social (Yeates et al., 2004), cognitive (Taylor et al., 2002; Yeates et al., 2010) and language dysfunction (Catroppa & Anderson, 2004), as well as poor parent-child interactions (Lalonde et al., 2020). In addition, children who are socially disadvantaged may experience slowed recovery (Anderson, Spencer-Smith, et al., 2011; Breslau, 1990; Taylor & Alden, 1997).

Decades of developmental psychology research have demonstrated the importance of parental factors and early caregiving characteristics for child development. Given the critical role that parents naturally play in typical development, there is little doubt as to their importance in outcome and recovery following childhood TBI. Numerous studies support the notion that pre- and post-injury family-level and parent-related factors are associated with TBI recovery. For example, global family functioning can exert either a positive or negative influence on post-TBI outcomes (Beauchamp, Séguin, et al., 2020; Rivara et al., 1993; Ryan, van Bijnen, et al., 2016; Yeates et al.,

2012). As such, family dysfunction has been associated with greater intellectual and cognitive deficits after severe TBI (Keenan et al., 2018; Max et al., 1999; Rivara et al., 1993; Yeates et al., 2004). By contrast, positive family functioning, characterized by affective responsiveness, good problem-solving strategies and positive communication can positively impact psychosocial outcomes post-injury (i.e., behavioural adjustment, adaptive functioning, social competence; Keenan et al., 2018; Rivara et al., 1993; Wade et al., 2016; Yeates et al., 2007; Yeates et al., 2004; Yeates et al., 2010), as well as cognitive and academic functioning (Anderson et al., 2012; Durber et al., 2017).

Several studies have also reported links between parental mental health and the risk of sustaining a TBI (Lowery Wilson et al., 2019), as well as between parent psychological functioning and child behavioural post-injury outcomes (Peterson et al., 2013; Raj et al., 2014). For example, parenting stress (i.e., stress associated with the parenting role) and feelings of parental distress (i.e., parents' feelings of conflict and competence in their parental role) has been shown to negatively affect behavioural outcomes after early mTBI (Gagner et al., 2018), as well as emotional functioning after severe acquired brain injury (Labrell et al., 2018). This relation is likely to be bidirectional, in that parental distress can also increase a child's own stress following injury, and hence affect recovery. On the other hand, parents, independent of severity, may feel distressed as a result of their child's injury (Ganesalingam et al., 2008), due to concerns about how their child will recover and fear of the consequences of TBI for the future (Prigatano & Gray, 2007). In addition, parents' coping strategies and how they experience the family burden associated with their child's injury can affect subsequent recovery from pediatric TBI (Aitken et al., 2009; Stancin et al., 2008).

Furthermore, parent-child relationships, parental responsiveness and parenting practices have been shown to be important for behavioural recovery (Wade et al., 2011; Wade et al., 2008). For instance, parents' reduced affective responsiveness can contribute to unfavourable behavioural and social outcomes in their child after TBI (Ryan, Mihaljevic, et al., 2016; Wade et al., 2011) and the quality of pre-injury parent-child interactions has been shown to moderate social and behavioural consequences of severe TBI in children (Yeates et al., 2010). In addition, authoritative and warm parenting, characterized by high acceptance, warmth and autonomy development predict socially appropriate behaviours and better social adjustment and competence in the long-term, compared to a permissive parenting style (e.g., low expectations of appropriate behaviours, few

instructions), independent of severity (Wade et al., 2016; Yeates et al., 2010). Early childhood TBI can also affect the quality of parent-child interactions (Fairbanks et al., 2013; Lalonde et al., 2018; Wade et al., 2008), for example due to enhanced stress levels leading to less positive interactions (Crnic et al., 2005). Thus, there appears to be multiple interactive ways in which parents contribute to their child's recovery (Beauchamp, Séguin, et al., 2020).

In sum, pre- and post-injury family-environmental factors are associated with outcomes after pediatric TBI and an unfavourable family environment can constitute a risk factor for poor outcomes even in those with less severe injuries. While these factors are important at all ages, they may play an especially important and influential role in the context of early TBI, given that during the first years of life children spent most of their time with their parents (Beauchamp, Séguin, et al., 2020).

Child characteristics

Pre-injury functioning. Premorbid child functioning can also predict post-injury outcomes. For example, a higher intelligence quotient (IQ) and adaptive functioning levels (i.e., better cognitive reserve) prior to injury are associated with better long-term cognitive and intellectual functioning (Catroppa, Anderson, Morse, et al., 2008; Fay et al., 2010). By contrast, pre-injury attention problems are related to poorer attention post-injury (Yeates et al., 2005) and pre-existing social and cognitive difficulties predict poorer social participation after pediatric TBI (Ryan, Hughes, et al., 2015). A higher risk for sustaining TBI has also been reported in children that have learning and behavioural difficulties, for example through higher risk-taking activities associated with externalizing behavioural problems (Hawley, Ward, Long, et al., 2003; Parslow et al., 2005). These findings indicate that TBI-related consequences interact with pre-injury variables to create a cumulative effect on long-term outcomes (Fay et al., 2010).

Biological factors. Sex and genetic factors are associated with both the occurrence of and recovery from pediatric TBI. Sustaining a TBI is approximately twice as likely for boys than for girls (Arambula et al., 2019). In addition, there is some suggestion that there are sex differences in the response to and the recovery from injury, although results are conflicting. For instance, female adults who sustained childhood TBI present a higher rate of internalizing problems (e.g., depression, anxiety), while males report more externalizing behaviour problems (e.g., aggression, substance abuse or criminal behaviour), independent of severity (Despins et al., 2016; Scott et al., 2015). Another study found poorer sub-acute performance on neurocognitive tests of memory and

learning in boys compared to girls who sustained mild to severe TBI between six and 16 years old (Donders & Woodward, 2003). On the other hand, a recent review reports that girls are more likely to have persistent PCS and longer clinical recovery times, such as time taken to return to school and sports-related activities compared to boys after a concussion (Iverson et al., 2017). However, sex differences in pediatric TBI are still poorly understood. They might be related to biological origins such as sex hormones which could differentially affect the response to neuroinflammation and neural excitation of the brain, or to different biomechanical mechanisms such as differences in the strength of neck muscles (Arambula et al., 2019). Alternately, sex may rather differentially moderate outcome and depend on other injury and psychosocial variables (Zamani et al., 2019). The matter may be further complicated by methodological aspects such as fewer girls sustaining TBI than boys, and thus being underrepresented in clinical trials (Arambula et al., 2019). The link between sex and outcome is far from being simple and other variables including both biological (e.g., hormones) and gender need to be taken into account.

Genetic factors have recently come to the forefront of empirical endeavours to better understand TBI outcome and may be useful in explaining a portion of the variability in presentation and recovery. Genetic studies in the context of TBI have generally employed a candidate gene approach to study specific genes which may be involved in injury outcome (Kurowski et al., 2012). These studies focus on single nucleotide polymorphisms (SNP), genetic variants at a specific location in a deoxyribonucleic acid (DNA) sequence which may lead to changes in the expression of proteins implicated in the response to injury (Kurowski et al., 2012). To date, most research has focused the apolipoprotein E (ApoE) gene and the brain-derived neurotrophic factor (BDNF) gene.

ApoE is involved in neuronal repair, inflammatory response to injury, and protection of neuronal membranes (Blackman et al., 2005; Wang et al., 2013), and is the most widely studied genetic factor in the context of TBI research (Lawrence et al., 2015; Li et al., 2015). The presence of the ApoE ε4 allele has been associated with more unfavourable clinical and functional outcomes after pediatric TBI, as well as with slower recovery (Kassam et al., 2016; Treble-Barna et al., 2016). An age-dependent effect of genetic factors has been shown, indicating that the adverse effect of the ApoE ε4 allele is most strongly pronounced in pediatric TBI compared to adult TBI, likely through its role in neuroplasticity and neural repair which may be intrinsically different in the developing versus the adult brain (Kassam et al., 2016; Kurowski et al., 2012; Teasdale et al., 2005). Finally, there is evidence for genetic by environmental interactions, such that ApoE ε4 has

been found to interact with parenting styles. For example, in the context of positive parenting, poorer adaptive functioning has been found in ApoE ε4 carriers vs non-carriers who sustained moderate to severe pediatric TBI. By contrast, in a less favourable family environment, non-carriers of the allele had poorer adaptive functioning than carriers of the ApoE ε4 allele (Treble-Barna et al., 2016).

Another target gene in the context of pediatric TBI is BDNF, one of the most abundant neurotrophic factors in the central nervous system (CNS), involved in neurotransmitter synthesis, neuronal growth, differentiation, apoptosis, and synaptic plasticity (Casey et al., 2009; Snider, 1994; Thoenen, 1995). BNDF plays a key role in CNS reorganization and repair following neurological injury (Centonze et al., 2007; Di Filippo et al., 2008). Acutely after brain injury, BDNF is up-regulated in the CNS (CSF and plasma), followed by consistent reductions in BNDF levels, and eventually, cell death (Chiaretti et al., 2003; Clark et al., 1994; Griesbach et al., 2002; Mocchetti & Wrathall, 1995; Sofroniew et al., 2001). This upregulation has been interpreted as an early marker of injury and an endogenous neuroprotective mechanism against the negative impact of injury and biochemical and molecular alterations following TBI (Chiaretti et al., 2003; Mocchetti & Wrathall, 1995). A particular SNP of the BDNF gene called Val66Met, also known as G196A or rs6265, is found in 30-50% of the general population (Shimizu et al., 2004). The alteration of the amino acids from valine to methionine (Val66Met) reduces activity-dependent release of the BDNF protein and can thus interfere with brain plasticity mechanisms, thereby reducing the brain's capacity for functional recovery after brain injury (Chen et al., 2004; Egan et al., 2003). Studies investigating the role of the Val66Met polymorphism in TBI recovery have mainly been conducted in adults, and report associations with poorer cognitive performance (McAllister et al., 2012; Pearson-Fuhrhop & Cramer, 2010), as well as more emotional symptoms (Narayanan et al., 2016; Wang et al., 2018). These findings indicate that an increase in BDNF levels is associated with favourable recovery, while a decrease in BDNF release and therefore the diminished potential for plasticity associated with the Met-allele may constitute a risk factor for poor outcome (Siironen et al., 2007). Nonetheless, results are equivocal, with some studies suggesting a protective effect with better TBI-outcome in Met-allele carriers who sustain severe TBI (Barbey et al., 2014; Krueger et al., 2011). In pediatric TBI, there are few studies investigating the effects of this polymorphism on outcomes. Genetic effects in the context of pediatric TBI need to be considered with an appropriate developmental lens. Indeed, they may have a differential effect

in the context of rapid brain development compared to adults, given that BDNF levels naturally fluctuate across development and thus differentially affect phenotypes at different developmental stages (Casey et al., 2009; Giza et al., 2007).

In sum, a challenge in the field of pediatric TBI is to understand how the various injury-related, environmental, and child variables presented above jointly explain post-TBI outcome. While previous research has provided evidence for the importance of each of these factors (Babikian et al., 2015), they typically only explain up to 35% of variance in outcomes (Maas et al., 2015). To date, these factors have not been studied as part of larger, comprehensive biopsychosocial models combining multiple factors. Adding genetic factors to prognostic models of recovery could account for at least a portion of the unexplained and vast heterogeneity in recovery trajectories and outcomes.

Consequences of pediatric TBI

Pediatric TBI can result in a range of symptoms and consequences which differ in terms of intensity, duration and clinical manifestation, largely depending on injury severity. Immediately after injury (i.e., the acute phase, up to one week after injury), PCS are common, such as somatic (e.g., fatigue, dizziness or headaches), cognitive (e.g., inattention, forgetfulness or slowed speed of processing), physical (e.g., balance problems), and affective problems (e.g., irritiabiliy, Moran et al., 2011; Zemek et al., 2013). While most PCS disappear within the first three months post-injury (i.e., the sub-acute phase), some children experience persistent PCS that last for months or years post-injury (Novak et al., 2016; Yeates et al., 2012; Zemek et al., 2013).

In addition, acute and chronic neuropsychological problems, such as cognitive, behavioural, and emotional difficulties can occur following pediatric TBI, with poorest outcomes typically observed after severe injuries. While some of these occur in the context of PCS directly after the insult (Beauchamp & Anderson, 2013), many neuropsychological consequences are long-lasting (Anderson, Catroppa, et al., 2009; Babikian et al., 2015; Dégeilh et al., 2018; Ewing-Cobbs, Barnes, et al., 2004; Ewing-Cobbs et al., 2006; Gagner, Dégeilh, et al., 2020; Jones et al., 2019; Keenan et al., 2018; Ryan, Catroppa, Beare, et al., 2015; Yeates et al., 2005). Among these, cognitive deficits are frequently reported, such as difficulties in executive functioning (EF), memory, attention, and problem-solving (Anderson et al., 2001; Anderson et al., 2004; Babikian & Asarnow, 2009; Beauchamp, Catroppa, et al., 2011; Ewing-Cobbs, Prasad, et al., 2004; Yeates et al., 2005). Moreover, some children experience language and communication deficits (Catroppa

& Anderson, 2004; Ryan, Catroppa, Beare, et al., 2015; Turkstra et al., 2015). Pediatric TBI can also lead to poor adaptive functioning (Anderson et al., 2012; Dégeilh et al., 2018) and behavioural problems such as aggressive behaviours, externalizing and internalizing behavioural symptoms (Anderson et al., 2004; Cole, Gerring, et al., 2008; Gagner et al., 2018; Li & Liu, 2013; Ryan, Hughes, et al., 2015). In addition, emotional problems and mood disturbances such as anxious or depressive symptoms may occur (Di Battista et al., 2014; Luis & Mittenberg, 2002; Massagli et al., 2004; McKinlay et al., 2009; Sariaslan et al., 2016). Finally, academic problems, chronic behavioural difficulties, and in severe cases, conduct and justice problems can manifest after childhood TBI (Ewing-Cobbs, Barnes, et al., 2004; Hendryx & Verduyn, 1995; Williams et al., 2010).

While the consequences of TBI are fairly well documented in school-age children and adolescents, fewer evidence is available for children aged six years and younger. In addition, studies of early TBI have focused predominantly on cognitive outcomes, whereas issues in social or adaptive functioning are less well documented in this age group, especially after mild injuries. The limited literature suggests that although the majority of children who sustain early mTBI will recover entirely, some may experience long-term social (Bellerose et al., 2015; Kaldoja & Kolk, 2015; Keenan et al., 2018; Lalonde et al., 2018), emotion regulation, adaptive and behavioural difficulties (Dégeilh et al., 2018; Gagner et al., 2018; McKinlay et al., 2002; McKinlay et al., 2009; Pastore et al., 2013), though behavioural results are variable (Green et al., 2013; McKinlay, Grace, et al., 2010; McKinlay et al., 2014). These findings are incongruous with findings in school-age children and adolescents for whom negative socio-behavioural outcomes are seldom observed in the long-term following mild injuries. These inconsistencies are likely to be partly due to methodological differences across studies (i.e., definitions, timing and assessment of injury, measures used to document behaviour). A review of the cognitive, academic, behavioural, socio-affective and adaptive consequences of early TBI is included in Appendix II of the thesis. Overall, worse outcomes are identified after early TBI if injury is sustained at a younger age, is moderate to severe in nature, and non-accidental (see Appendix II for details).

While many of the physical, cognitive or emotional consequences frequently emerge in the acute or sub-acute phase post-injury, social consequences such as socially adaptive behaviour difficulties or reduced social participation may appear acutely or arise only later in the recovery process.

Social competence in typical development and after pediatric TBI

Development of social competence

In order to appreciate social difficulties after pediatric TBI, it is important to first understand social functioning in the context of typical development. TBI during childhood and adolescence occurs at a time of ongoing social and brain development, characterized by a protracted maturational course starting with the initial rudimentary social skills of early childhood (e.g., detection of biological motion, gaze following, first smile) to the high-level social competence of early adulthood (e.g., moral reasoning, social decision-making; Soto-Icaza et al., 2015). Social competence refers to the capacity to effectively function in society, as an individual, in dyadic relationships as well as in groups, and being able to establish lasting and meaningful social relationships (Beauchamp & Anderson, 2010; Blakemore, 2010; Frith & Frith, 2012). Successful social development is associated with positive developmental outcomes such as academic achievement (Caprara et al., 2000), peer acceptance and positive social relationships (Ladd, 1999), better conflict management (Green & Rechis, 2006), as well as good mental health (Huber et al., 2019; Jones et al., 2015). Socially competent children are able to successfully develop and maintain interpersonal relationships and are less likely to experience social exclusion and associated negative emotions (Bornstein et al., 2010). Conversely, disruptions to social development and its brain bases, for instance after an acquired injury such as TBI, can lead to psychological distress, reduced social participation, poor self-esteem, and poor QoL (Beauchamp & Anderson, 2010). In the following sections, social competence and social cognition will be discussed in the context of typical development and pediatric TBI.

A biopsychosocial model of social competence. Multiple models and frameworks have been put forward to represent the factors that shape an individual's social functioning (Beauchamp & Anderson, 2010; Cattaneo & Rizzolatti, 2009; Crick & Dodge, 1994; Iacoboni, 2009; Yeates et al., 2007). Inspired by neuroscientific and clinical neuropsychology perspectives, these models are useful for understanding social dysfunction after pediatric TBI. Compared to some other models of social functioning, Beauchamp & Anderson (2010) propose an integrative biopsychosocial SOcio-Cognitive Integration of Abilities modeL (SOCIAL; Figure 2) that describes the determinants of social competence in both typical development and clinical populations. Combining insights from neuropsychology, social neuroscience and developmental psychology, the model posits that external (e.g., environmental), internal (e.g., child-related) and cognitive

factors (e.g., attention-EF, communication and socio-emotional/socio-cognitive skills) interact dynamically in the context of ongoing brain maturation to determine a child's social competence (Beauchamp & Anderson, 2010). Cognitive functions are divided into three categories: 1) attention and executive skills such as selective and sustained attention, self-regulation, response inhibition, cognitive flexibility, goal setting and processing speed; 2) social communication skills, including verbal and non-verbal expressive and receptive language, pragmatics, and prosody; and 3) socio-cognitive abilities, including emotion recognition, intent attribution, theory of mind (ToM; inferring mental states such as desires, intentions, emotions and beliefs), empathy (understanding the affective state of others) and moral reasoning (Beauchamp & Anderson, 2010). These socio-cognitive abilities are involved in perceiving and processing social stimuli and situations by helping us understand others' behaviours, intentions and emotions (Adolphs, 2001; Beer & Ochsner, 2006; Frith & Frith, 2012; Soto-Icaza et al., 2015). They are necessary to make sense of the social world, to function in everyday situations, and to have meaningful social interactions and relationships (Diesendruck & Ben-Eliyahu, 2016; Mostow et al., 2002).

According to the model, socio-cognitive components interact with external and internal factors, as well as with ongoing brain development. External factors refer to both distal family factors such as socioeconomic factors, as well as proximal influences such as parent-child interactions, parental practices, or family functioning (Ackerman & Brown, 2006; Fernandes et al., 2019; Kvalevaag et al., 2015; McLoyd, 1998; Spinrad & Gal, 2018; Wade, Cann, et al., 2019). SOCIAL also takes into account the influence of an individual's ethnicity or culture through educational systems, social customs and norms as well as child-rearing practises (Kirmayer et al., 2007). Internal factors refer to child-related variables such as temperament, personality traits or physical attributes as well as demographic variables such as age or sex that may influence social interactions and participation (Crowe et al., 2011; Ozer & Benet-Martinez, 2006; Rothbart, 2019; Salley et al., 2013). Both internal and external factors interact with brain maturation and integrity (structural and functional). As such, any compromise to the integrity of the brain, whether through developmental, acquired or environmental processes could disrupt the delicate balance and course of socio-cognitive development with observable manifestations of maladaptive social skills down the line. Changes at any level of the model can induce alterations in social cognition and social competence more generally. Depending on the timing of the insult, contributing factors may be variably affected (Ryan, Hughes, et al., 2015).

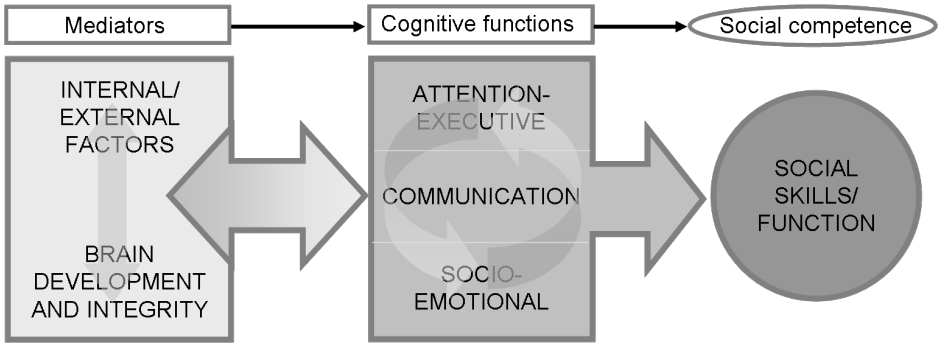

Figure 2. Socio-Cognitive Integration of Abilities model (SOCIAL).
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Development of social cognition and social competence. Socio-cognitive skills help us to perceive and process social cues, interpret and make sense of our own and others' emotions, beliefs and behaviours, and range from basic processes such as face perception, emotion recognition, attribution of intent, to more complex abilities such as ToM, empathy or moral reasoning (Adolphs, 2001; Beer & Ochsner, 2006; Frith & Frith, 2012). Social cognitive skills have a strong developmental basis, emerging in the first years of life and becoming more refined and consolidated throughout childhood and adolescence, in parallel with ongoing brain maturation and the increasing complexity of social behaviours (Adolphs, 2001; Beauchamp & Anderson, 2010; Blakemore, 2011; Paus, 2005; Stuss & Anderson, 2004).

Precursors of social cognition and competence are already present in the first few months of life starting with a baby's first smile, and are primarily associated with early visual capacities, such as biological motion discrimination, imitation, and gaze following (Emery, 2000; Happe & Frith, 2014; Hoehl et al., 2008; Soto-Icaza et al., 2015). These precursors are the building blocks for the development of more complex social skills such as face and emotion recognition, joint attention and social perspective-taking which emerge and evolve during the first two years of life (Carpenter et al., 1998; Charman et al., 2000; Happe & Frith, 2014; Moll & Kadipasaoglu, 2013; Mundy et al., 2000).

The preschool period is characterized by a progressive refinement of rudimentary motor and sensory skills through a dynamic interplay with the environment and ongoing neural development (Soto-Icaza et al., 2015). Children's social information processing skills evolve and initial egocentric perceptions of the environment develop into cooperative play and perspective-taking, accompanied by a rapid increase in language and communication skills (Rubin et al., 2006;

Yeates et al., 2007). The scope and duration of children's social interactions increase and play activities become more organized (Eckerman & Stein, 1990; Huber et al., 2019). Emotional processing and regulation increase in parallel with EF such as inhibitory control and working memory (Cowan, 2016; Dowsett & Livesey, 2000; Galyer & Evans, 2001).

In parallel, early aspects of ToM develop and mature rapidly (Sodian, 2011; Surian et al., 2007). Joint attention and social perspective-taking constitute precursors of false belief understanding (FBU), defined as an understanding that others have thoughts, desires or emotions that can differ from one's own (Charman et al., 2000). FBU surfaces between three and five years of age and represents the earliest appearance of ToM (Perner & Roessler, 2012; Premack & Woodruff, 1978). With the understanding of intention and false beliefs, milestones for social development are achieved (Frith & Frith, 2003; Wellman et al., 2001). The maturation of emotion processing and ToM further parallel the maturation of empathy (Bird & Viding, 2014).

Higher-order socio-cognitive abilities emerge during middle childhood in time for school entry. ToM abilities continue to evolve and children consolidate a sense that others' thoughts and emotions may be different from their own (Damon & Hart, 1982). In addition, children's communication skills continue to improve, incorporating more complex language skills, such as pragmatics and the understanding of irony (Bara & Bucciarelli, 1998; Dennis et al., 2001; Loukusa et al., 2007). School-age children spend increasing time with peers and these interactions become more independent of their parents. Friendships become more stable, building on children's increasing ability to perspective-taking (Poulin & Chan, 2010).

Adolescence, typically defined as the period from the onset of puberty until the end of the teenage years, is also an important period for brain development and social relationships (Blakemore, 2008, 2011). Through dynamic interactions with increasing general cognitive and affective skills (e.g., EF, motivation, language, emotions), socio-cognitive abilities mature further in adolescence (Beauchamp, 2017; Beauchamp & Anderson, 2010; Beaudoin & Beauchamp, 2020). In addition, adolescents spend a considerable amount of time with their peers and social interactions become more complex and hierarchical, occurring more and more independently of adult supervision (Steinberg & Moris, 2001). Given these pre-programmed maturational events, it is clear that sustaining TBI during childhood and adolescence can disrupt the expected progression of socio-cognitive skills.

Social problems after pediatric TBI

Social problems after pediatric TBI are common and increasingly recognized as one of the most debilitating sequelae among young survivors of pediatric TBI with a global impact on well-being and QoL. Social problems have been observed both in the early as well as later phases post-injury across all TBI severities (e.g., Anderson et al., 2013; Anderson et al., 2017; Catroppa et al., 2017; Keightley, Cote, et al., 2014; Ryan, Catroppa, Godfrey, et al., 2016; Ryan, van Bijnen, et al., 2016; Yeates et al., 2004; Zamani et al., 2019). For example, several studies show that children and adolescents who sustain TBI participate less in their social environments (e.g., home, school, recreation), frequently experience difficulties interacting with others, have fewer social relationships and friendships, and overall poor social competence (Anderson et al., 2013; Anderson et al., 2017; Bedell & Dumas, 2004; Ganesalingam et al., 2011; Prigatano & Gupta, 2006; Ryan, Catroppa, Beare, et al., 2015; Sirois et al., 2019). Following pediatric TBI, many survivors also exhibit poor social adjustment and socially maladaptive communication and behaviours (Anderson et al., 2013; Anderson et al., 2017; Catroppa et al., 2015; Li & Liu, 2013; Yeates et al., 2010).

Social problems may aggravate the risk for poor academic outcomes, mood problems, drug use, antisocial behaviours, or suicide (Beauchamp & Anderson, 2013; Catroppa et al., 2017; Kennedy et al., 2017). Among children with TBI, there is a higher incidence of clinically relevant socio-behavioural problems including antisocial and aggressive behaviours as well as a higher rate of social withdrawal compared to typically developing controls (TDC; Andrews et al., 1998; Chapman et al., 2010; Dooley et al., 2008; Max, Lindgren, et al., 1998). Although the majority of studies have focused on school-aged children and youth with TBI, social problems such as poor social adjustment, reduced social participation or delays in socio-emotional development are also reported in preschoolers with mild (Kaldoja & Kolk, 2015) and mild complicated to severe TBI (Yeates et al., 2010). Moreover, while social functioning deficits are more frequently encountered in the context of severe TBI and are often more pronounced (Rivara et al., 2011; Ryan, van Bijnen, et al., 2016), they are also common after mTBI (Kaldoja & Kolk, 2015; Keightley, Cote, et al., 2014; Sariaslan et al., 2016).

Of note, while some children initially seem to keep up with their peers developmentally, it may only be later that they fall behind, especially when social demands increase or when they reintegrate in their social environment, potentially because important developmental milestones are not met (Beauchamp & Anderson, 2013; Giza et al., 2009; Wells et al., 2009). Social problems

may result from a direct interruption of social function or could be due to an inability to acquire new skills, alongside difficulties in other domains such as attention or other cognitive deficits (Anderson & Moore, 1995; Anderson, Spencer-Smith, et al., 2009; Yeates et al., 2004). For example, impulsivity or poor inhibition can represent important challenges when navigating social situations (Wells et al., 2009). These social difficulties can have repercussions on well-being and QoL. QoL is a holistic construct including several dimensions of health such as physical, social and psychological functioning (World Health Organization, 2006). Indeed, several studies demonstrate that pediatric TBI affects QoL, even after mTBI for which recovery is generally more favourable (Brown et al., 2016; Centers for Disease Control and Prevention, 2015; Di Battista et al., 2014; Fineblit et al., 2016). Although many TBI-related consequences affect QoL, for many children and adolescents, social disturbances may in fact be the most debilitating symptoms. Social problems following pediatric TBI and their underlying mechanisms remain incompletely understood; however, they are posited to be associated with a disruption of underlying socio-cognitive skills and their neural substrates.

Social cognition after pediatric TBI

Social disturbances following pediatric TBI, including socialisation difficulties, maladaptive and aggressive behaviours, poorer quality of friendships, or social withdrawal, are common and multifaceted symptoms. It has been postulated that a disruption of socio-cognitive skills and their underlying neural circuitry may be at the core of socio-behavioural problems (Allain et al., 2018; Muscara et al., 2008; Tousignant et al., 2018; Zamani et al., 2019).

Several studies report poor socio-cognitive skills following moderate-severe childhood TBI, such as difficulties in emotion processing and recognition, empathy, ToM, intent attribution, or moral reasoning (Beauchamp, Dooley, et al., 2013; Dennis, Simic, et al., 2013; Dennis et al., 2012; Ryan et al., 2014; Ryan, Catroppa, Beare, et al., 2016; Schmidt et al., 2013; Tonks et al., 2009; Tousignant et al., 2018; Turkstra et al., 2008). Although severe pediatric TBI generally results in greater socio-cognitive deficits, they also occur after mTBI, and can be persistent for all injury groups (Kaldoja & Kolk, 2015; Ryan et al., 2018). For example, compared to TDC, children who sustained early mTBI were found to have poorer ToM (Bellerose et al., 2015), as well as deficits in facial affect processing (D'Hondt et al., 2017). In addition, poor social communication skills have been reported in children with mild to severe TBI, including deficits in turn-taking, comprehension of abstract language such as irony, sarcasm or humour, reading and understanding

social cues or understanding pragmatic language (Dennis et al., 2001; Dennis, Simic, et al., 2013). The longevity of these deficits has been demonstrated in young adults who sustained mild to severe childhood TBI and who experience chronic difficulties in social communication, emotion perception and ToM (Ryan et al., 2013). These socio-cognitive difficulties are associated with global aspects of social functioning, such as social participation, conflict management, social adjustment or socially adaptive behaviours (Beauchamp et al., 2018; Genova et al., 2019; Ryan et al., 2013; Ryan et al., 2020; Sirois et al., 2019; Spikman et al., 2013; Yeates et al., 2004).

Although social-behavioural dysfunction and socio-cognitive problems are known to occur after pediatric TBI, their underlying neural mechanisms are still incompletely understood. Given that socio-cognitive skills are underpinned by neural processes, it is possible that social problems following pediatric TBI are the result of either structural or functional disruption of the so-called social brain (Adolphs, 2001, 2009; Frith, 2007; Frith & Frith, 2012; Kennedy & Adolphs, 2012; Ryan et al., 2014; Ryan, Catroppa, Beare, et al., 2016).

TBI and brain development

The structure of the brain undergoes considerable maturational changes on its way to adult topological and functional organization (Batalle et al., 2018; Giedd et al., 1999; Mills et al., 2016; Shaw et al., 2008). Its overall size and regional GM increase rapidly in early childhood and then undergoes variable decline (i.e., through pruning in GM, that is, the elimination of superfluous neurons, synapses and axons). A change in the GM to WM ratio occurs throughout adolescence, alongside the maturation of large-scale neural networks (Gogtay et al., 2004; Matsuzawa et al., 2001; Mills et al., 2012; Pfefferbaum et al., 1994). In parallel, myelination continues to progress into young adulthood (Paus et al., 1999). Considering these rapid maturational processes occurring during childhood and adolescence, the developing brain is vulnerable to the consequences of brain injury. Indeed, brain injury sustained during these periods can interrupt the highly pre-programmed cascade of non-linear brain development, including the formation of neural connections between brain regions (Gogtay et al., 2004; Shaw et al., 2008). In turn, if connectivity is disrupted, the impact of the insult on brain development can be widespread, affecting parts of the brain that are remotely located from the initial site of injury (Yeates et al., 2007).

The social brain

Evidence from neuroimaging and lesion studies indicates that a set of brain regions, the so-called SBN, processes social cues and supports socio-cognitive skills (Adolphs, 2001, 2009; Kennedy & Adolphs, 2012). Social development and the maturation of social cognition is thus dependent on the integrity of the SBN (Beauchamp & Anderson, 2010). This brain circuit includes, among other regions, the superior temporal sulcus (STS), temporo-parietal junction (TPJ), temporal poles, medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC) anterior cingulate cortex (ACC), fusiform gyrus, amygdala, insula, and inferior parietal cortex (Figure 3; Adolphs, 2009; Beauchamp & Anderson, 2010; Johnson et al., 2005; Kennedy & Adolphs, 2012).

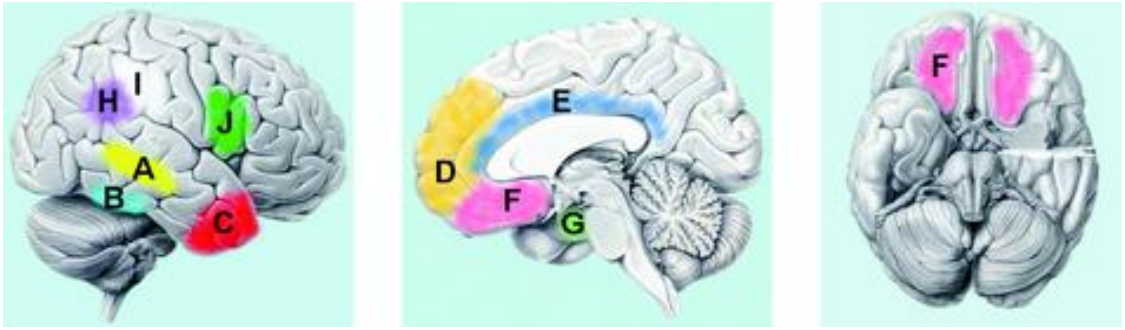

Figure 3. The social brain network.
(A) superior temporal sulcus; (B) fusiform gyrus; (C) temporal pole; (D) medial prefrontal cortex and frontal pole; (E) cingulate cortex; (F) orbitofrontal cortex; (G) amygdala; (H) temporoparietal junction; (I) inferior parietal cortex; (J) inferior frontal cortex; insula (not shown). From Beauchamp & Anderson, 2010. Copyright 2021 by the American Psychological Association. Reprinted with permission.

The SBN undergoes protracted maturation during childhood and adolescence, such as increasing myelinization and pruning, along with increasing specialization and interconnection occurring over the course of development (Giedd et al., 1999; Gogtay et al., 2004; Johnson, 2005; Menon, 2013; Sowell et al., 2004). Notably, the frontal and temporal lobes, which include key regions of the SBN, show the most protracted maturation of WM (Haynes et al., 2005; Kinney et al., 1988). These interconnected brain areas are at the core of human social interactions and their integrity is necessary to give rise to adaptive social functioning and building relationships (Adolphs, 2009; Frith, 2007). Given the distributed nature of the SBN, socio-cognitive skills rely on the integrity of these brain regions which in their synergy give rise to adequate social cognition.

As a consequence, disruption to any region of the SBN may lead to socio-cognitive deficits and ultimately, social dysfunction.

Structural brain alterations after pediatric TBI

Regional alterations in brain structure after pediatric TBI. Most studies describing morphological brain alterations following pediatric TBI have used MRI to identify changes in regional brain volumes or cortical thickness, thus providing objective markers of injury and allowing the investigation of neural mechanisms underlying socio-behavioural and neuropsychological outcomes (Bigler, 2013; Levin et al., 2008; Wintermark et al., 2015; Zamani et al., 2020). Intracranial lesions are seldom observed after mTBI; however, subtle abnormalities such as microhaemorrhages may be present in a minority of cases as revealed by sensitive techniques such as SWI (Beauchamp, Beare, et al., 2013; Rausa et al., 2020). Some reports exist of group-level GM changes, such as reduced regional volumes or cortical thickness (Beauchamp, Ditchfield, et al., 2011), which are likely to be transient in nature (Mac Donald et al., 2019), though others have failed to find any structural changes related to mTBI (Bigler et al., 2018). By contrast, multiple studies of moderate-severe pediatric TBI converge on the finding of morphological alterations, notably atrophic effects, such as global and local reductions in WM and GM volume or density, thinner cortices or alterations of gyrification patterns observable in the chronic stages post-injury (for reviews see Keightley, Sinopoli, et al., 2014; King et al., 2019; Zamani et al., 2020). Such changes are prevalent in frontal, temporal and parietal lobes (e.g., Bigler, 2013; Wilde, Hunter, et al., 2012; Wilde et al., 2005; Wilde, Merkley, et al., 2012; Wilde et al., 2020), as well as in subcortical regions including the hippocampus and the amygdala (e.g., Beauchamp, Ditchfield, et al., 2011; Fearing et al., 2008; McCauley et al., 2010).

A limited number of longitudinal MRI studies have been conducted after pediatric TBI sustained between five and 18 years (for reviews see King et al., 2019; Lindsey et al., 2019). Findings from these studies align with those of cross-sectional studies and show widespread morphological alterations, such as reductions in GM density and volume as well as cortical thinning when children with moderate-severe TBI are compared to age-matched TDC or children who sustained orthopedic injuries (OI) not involving the head (King et al., 2019; Lindsey et al., 2019). Between the acute and chronic phases, these alterations have been observed in the middle and superior frontal and temporal areas, lateral or middle occipital regions, posterior parietal and cingulate cortex, as well as in the amygdala, thalamus, and cerebellum (e.g., Dennis et al., 2017;

Dennis et al., 2016; Levin et al., 2000; Mayer et al., 2015; Wilde, Merkley, et al., 2012). These results indicate a different rate of change in volume or thickness between groups, meaning that reductions were greater in the TBI over the same time period when compared to the control group. Morphological alterations have also been associated with neuropsychological impairments (e.g., Dennis et al., 2017; Dennis et al., 2016; McCauley et al., 2010; Urban et al., 2017; Wilde et al., 2011).

Structural brain alterations and social skills after pediatric TBI. Regions of the SBN are particularly vulnerable to the acceleration-deceleration forces of TBI, thus increasing the putative risk for social problems post-injury (Bigler, 2013; Bigler, 2001; Wilde et al., 2005). As such, the heightened prevalence of socio-cognitive deficits among children with TBI may partly stem from the vulnerability of frontal, temporal and limbic structures that are part of the SBN to primary and secondary injuries associated with TBI (Zamani et al., 2020). Consistent with the early vulnerability hypothesis, it has been shown that brain injuries sustained during childhood disrupt SBN maturation more severely than injuries to the same regions during adulthood, resulting in more severe consequences for social outcomes (Eslinger et al., 2004). Some MRI studies have focussed specifically on documenting alterations to social brain regions and associated socio-functional correlates. They report associations between damage to fronto-temporal and limbic regions and poor ToM, impaired pragmatic language skills and overall poor social competence (e.g., Bigler et al., 2013; Dennis et al., 2016; Ryan et al., 2014; Ryan, Catroppa, Beare, et al., 2016; Ryan, Catroppa, Cooper, Beare, Ditchfield, Coleman, Silk, Crossley, Beauchamp, et al., 2015; Yeates et al., 2004). In a prospective longitudinal cohort study, Ryan and colleagues (2016) found that children with severe TBI had sub-acute volumetric reductions in several SBN regions such as the STS, fusiform gyrus, temporal pole, mPFC, OFC, temporo-parietal cortex, and cingulate gyrus. These alterations were correlated with impaired ToM six months post-injury, which mediated the link between altered SBN and the occurrence of socio-behavioural difficulties two years after pediatric TBI (Ryan, Catroppa, Beare, et al., 2016). In the same cohort, sub-acute neuropathology in frontal and temporal regions as well as the corpus callosum were associated with poorer social communication skills six months post-injury (Ryan, Catroppa, Beare, et al., 2015). Furthermore, when compared to uninjured controls, young adults who sustained severe childhood TBI have been found to have poorer emotion perception skills associated with volumetric reductions of the posterior corpus callosum and several frontal brain regions, further supporting the early

vulnerability of the SBN to long-lasting alterations (Ryan et al., 2014). Structural alterations have also been found in the amygdala which is critically involved in processing social and emotional cues, social recognition, social anxiety and social communication (Gupta et al., 2011; Wang et al., 2014). Results on how the amygdala is affected by pediatric TBI are, however, inconsistent, with one study reporting volumetric reductions post-injury several years after moderate-severe pediatric TBI (Wilde et al., 2007), while another reported increases ten years after severe injuries (Beauchamp, Ditchfield, et al., 2011). In sum, these studies suggest that morphologic alterations to the SBN are associated with long-term social problems, possibly through a disruption of socio-cognitive skills (Ryan, Catroppa, Godfrey, et al., 2016).

Brain network alterations after pediatric TBI

The brain is organized into networks of multiple regions which are structurally connected by WM fibers (WM microstructural organization), function together (functional brain connectivity), and share morphometric characteristics (structural covariance).

Alterations of the white matter microstructure. As briefly outlined above, the full complexity of social cognition is based on the interconnection between regions of the SBN. As such, the maturation of the WM organization is an essential part of SBN development (Wang & Olson, 2018; Yeates et al., 2007). Thus, although regional analyses of GM or WM are useful and have been related to socio-cognitive deficits, brain volume alone does not fully predict children's social skills after injury. Rather, given the diffuse nature of pediatric TBI and diffuse axonal injury that can occur as a result of the shearing mechanisms, unmyelinated WM tracts throughout the brain can be affected, in turn disrupting connections within the SBN (Adolphs, 2001; Ryan et al., 2014; Yeates et al., 2007).

Diffusion tensor imaging (DTI) measures the magnitude and directionality of water diffusion in brain tissues and in particular of WM. This technique has been used to explore how TBI affects WM microstructure (Ashwal et al., 2010; Wilde, Ayoub, et al., 2012). Cross-sectional studies show that children and adolescents with TBI have an altered WM organization in multiple WM tracts that are associated with the SBN, including the corpus callosum, inferior and superior frontal and supracallosal tracts, the internal capsule, superior cerebellar peduncle, orbitofrontal WM, cingulum, and uncinate fasciculus in the medium to long-term after injury and when compared to TDC (e.g., Caeyenberghs et al., 2011; Caeyenberghs et al., 2010; Levin et al., 2011; Roberts et al., 2014; Wilde, Ayoub, et al., 2012; Wilde et al., 2006; Wu, Wilde, Bigler, Li, et al.,

2010). These changes have been interpreted as reflecting WM disruptions, such as axonal disconnection or myelin damage (Zamani et al., 2020, for a review).

Less research has been conducted regarding longitudinal WM changes after pediatric TBI. The existing studies included children between five and 18 years of age and assessed WM alterations between the acute or sub-acute phase of injury and three to 24 months later, as well as associations between WM disruptions and long-term socio-cognitive deficits. They are overall consistent with cross-sectional findings of altered WM organization (for reviews see Lindsey et al., 2019; Zamani et al., 2020). For example, Wilde and colleagues (2012) explored changes in diffusion metrics over time (i.e., three to 18 months post-injury) in children and adolescents with moderate to severe TBI aged seven to 17 years. While in the control group WM organization was in line with ongoing and expected myelination processes, WM integrity continued to be compromised in the TBI group.

Links between diffusion metrics and neuropsychological outcomes have been reported for memory, EF, and processing speed (Babikian et al., 2010; Dennis et al., 2015; Ewing-Cobbs et al., 2008; Kurowski et al., 2009; Wilde et al., 2006; Wu, Wilde, Bigler, Yallampalli, et al., 2010). There is also evidence that disrupted WM pathways are associated with socio-cognitive deficits after pediatric TBI (Hanten et al., 2008; Levin et al., 2011; Ryan et al., 2018). For example, Levin et al. (2011) found links between altered WM organization in the left prefrontal WM and the cingulum fiber bundle and lower performance on a mental state attribution task. In addition, several studies report altered WM organization the corpus callosum, cingulum, cerebro-cerebellar and commissural tracts, uncinate fasciculus, as well as the inferior longitudinal and inferior fronto-occipital fasciculi, which were related to poor social problem-solving (Hanten et al., 2008), attention and speech deficits, as well as impaired ToM and pragmatic language skills in the chronic phase after pediatric TBI (Ryan et al., 2018). These findings suggest that disrupted WM tracts in SBN regions may underlie socio-cognitive and socio-behavioural outcomes after pediatric TBI.

Functional connectivity and pediatric TBI. At a functional level, brain development occurs gradually through ongoing activation and specialization of brain regions and their interactions between one another (Johnson et al., 2005). The SBN undergoes functional specialization through enhanced interaction between its sub-regions. This induces organizational changes at the neural network-level with certain regions responding primarily to certain types of cues or stimuli (Yeates et al., 2007). As such, “the response properties of a specific region are partly

determined by its patterns of connectivity to other regions, and their patterns of activity" (Johnson et al., 2005, p. 600). In typical development, a more distributed pattern of connectivity can be observed in early childhood compared to adulthood, indicating a gradual functional specialization (Casey et al., 2000; Menon, 2013). In addition, there is a shift from short-range connections to stronger and more specific long-range connections in adults, which is accompanied by a dynamic pruning process. This pruning limits over-connectivity and ensures a balance between excitation and inhibition to prevent aberrant brain connectivity in the developing brain (Menon, 2013). Damage to the GM and WM can in turn disrupt communication between brain regions and upset functional networks that underlie important cognitive and social processes (Sharp et al., 2014). Over the past two decades, multiple studies have investigated structural brain alterations following pediatric TBI, but much less is known about how these injuries affect the overall functional organization of the developing brain.

Resting-state functional magnetic resonance imaging (rsfMRI) is a non-invasive technique for assessing temporal correlations of changes in the blood-oxygen-level-dependent (BOLD) signal between brain regions at rest, that is, in the absence of a task (Fox & Raichle, 2007; Fox et al., 2005). It enables identification of brain regions showing increased or decreased neuronal activity and assesses temporal coherence between regions that form large-scale neural networks (Logothetis, 2003; Raichle & Mintun, 2006). These spatiotemporal correlations are referred to as resting-state functional connectivity (FC) between different regions of these networks (Rogers et al., 2007). RsfMRI can be used to examine associations between FC and cognitive and behavioural processes (Seeley et al., 2007), and can therefore provide important insights into the neural mechanisms involved in functional impairments after pediatric TBI (Ham & Sharp, 2012). Three main networks have been reliably identified using rsfMRI: The default mode network (DMN), central executive network (CEN) and the salience network (SN; Menon, 2011; Seeley et al., 2007; Uddin et al., 2011). The DMN is comprised of the posterior cingulate cortex (PCC), ventromedial prefrontal cortex (vmPFC) and the angular gyri, and is activated in the absence of a stimulus and thought to be involved in self-referential processing and social cognition (Andrews-Hanna et al., 2010; Buckner et al., 2008). The CEN is a network important for cognitive and executive control processes and represents connections between the dorsolateral prefrontal (dlPFC) and posterior parietal cortices, the thalamus and dorsal caudate (Menon, 2011; Menon & Uddin, 2010; Seeley et al., 2007). The SN includes the anterior insula, ACC and ventrolateral prefrontal cortex (vlPFC)

and is implicated in stimuli detection and goal-directed behaviour (Menon & Uddin, 2010; Seeley et al., 2007). The DMN, CEN and SN are of interest in the context of pediatric TBI, given their protracted development during childhood and adolescence (Buckner et al., 2008; Menon, 2011; Seeley et al., 2007). The interplay of these three networks is assumed to support cognitive (Dwyer et al., 2014; Menon, 2013) and social functions (Eggebrecht et al., 2017; Xiao et al., 2016).

Few studies have examined how pediatric TBI affects FC. Most studies have focused on mTBI and report *hyper*connectivity in the acute and sub-acute stages post-injury in networks implicated in EF and attention, as well as in visual and cerebellar networks, the DMN and in posterior brain areas for children and youth with mTBI compared to TDC (Borich et al., 2015; Manning et al., 2017; Murdaugh et al., 2018; Newsome et al., 2016). Yet, others report *hypo*connectivity in anterior brain areas (Murdaugh et al., 2018), or patterns of both increased and decreased FC (Lemme et al., 2020), such as decreases in DMN, visual and somatosensory networks, as well as higher FC in limbic circuits (Iyer, Barlow, et al., 2019).

Only a handful of studies examined FC after moderate-severe pediatric TBI (Newsome et al., 2013; Risen et al., 2015; Stephens et al., 2018; Stephens et al., 2017). These focused primarily on the DMN and FC between specific brain regions, indicating both increased and decreased patterns of intrinsic FC at different recovery stages. For example, altered FC was found in the DMN, motor networks, as well as the dorsal attention network in groups of children with chronic mild to moderate TBI (Risen et al., 2015; Stephens et al., 2018; Stephens et al., 2017). In adolescents with moderate-severe TBI, Newsome and colleagues (2013) found lower FC between right anterior cingulate cortex and amygdala as well as between these regions and frontal and temporal cortices two to three years post-injury, and concluded that altered connectivity may be involved in emotion recognition difficulties. Very little evidence exists as to how these patterns change over time in children with TBI (Lindsey et al., 2019). One study assessed FC using task-fMRI in adolescents with mild complicated to severe TBI at two time points between the sub-acute and one year post-injury (Cazalis et al., 2011). Results revealed that altered activation patterns normalized partially over time, ultimately resembling the pattern seen in healthy controls at the first assessment and corresponding to an improvement in cognitive performance (Cazalis et al., 2011).

In light of these diverging patterns of FC, the direction of the results is not clear. In addition, there is a lack of studies examining specific links between putative abnormal connectivity or brain

activation and social impairments. In addition, no work has systematically investigated FC changes (based on rsfMRI or task fMRI) within the SBN using a comprehensive network perspective of this circuit. Therefore, the underlying mechanisms of social dysfunction as a result of pediatric TBI are still poorly understood.

Structural covariance analysis. While the study of intrinsic FC has allowed important insights into the human brain network organization, the underlying structural basis of FC is unclear. Given the diffuse nature of TBI, disruption that occurs in one region may alter the overall topology of the brain, through loss of neurons as well as their interconnections (McKee et al., 2015; Mills et al., 2012). As such, assessing regional atrophy alone does not inform on global TBI-induced changes. By contrast, investigating morphological changes on the network-level may provide insight into how TBI perturbs normal development at the whole-brain level. Using structural MRI to investigate anatomical correlations of brain structural metrics (i.e., GM volume or cortical thickness) of distributed brain regions, so called structural covariance network (SCN) analyses, may be a promising approach (He et al., 2007; Lerch et al., 2006). SCN are based on the assumption that brain regions that increase or decrease at the same rate in terms of volume or thickness over time are anatomically and functionally connected across individuals (Alexander-Bloch, Giedd, et al., 2013; Alexander-Bloch, Raznahan, et al., 2013; Evans, 2013). SCN have been shown to underlie well-known anatomical (Gong et al., 2012) and FC networks, such as the DMN, CEN and SN. SCN have been linked to behavioural and cognitive functioning, and change in a systematic manner across the lifespan (Aboud et al., 2019; Alexander-Bloch, Raznahan, et al., 2013; Qi et al., 2019; Zielinski et al., 2010). SCN thus provide a unique measure of synchronized maturational changes in anatomically connected regions during development, and a way to investigate network integrity beyond classic DTI or rsfMR studies (Khundrakpam et al., 2013; Mechelli et al., 2005; Zielinski et al., 2010).

The SCN approach could provide a promising avenue for understanding the complex impact of TBI on brain structure, but has seldom been used. In adults with mTBI, one study found lower structural covariance in the CEN in the acute phase when compared to healthy controls, as well as both higher structural covariance in the DMN and SN, and lower structural covariance in the sensorimotor network in chronic mTBI, suggesting that some alterations persist (Song et al., 2020). In pediatric TBI, only one study has used SCN analyses and found divergent SCN in mild to severe TBI compared to TDC, which was related to poor EF (King et al., 2020). Previous studies

of pediatric TBI have also found morphological alterations in brain regions that are part of large-scale networks, such as sub-acute reduced volumes in regions of the DMN, CEN, SN or SBN (Ryan, Catroppa, Beare, et al., 2016; Ryan, Catroppa, Godfrey, et al., 2016; Ryan, van Bijnen, et al., 2016), and overall reduced volume of the DMN, CEN and SN (Ryan et al., 2017). However, these studies have not applied a network approach with a focus on how distributed brain regions operate together. Thus, other than that one study, almost nothing is known regarding synchronized morphological changes in these networks after pediatric TBI or about the long-term implications for the network architecture of the developing brain.

Gaps in the literature and thesis objectives

Although several models have been proposed to predict outcome and recovery after pediatric TBI, few comprehensive models exist using global outcomes such as QoL, and none include genetic factors. A better understanding of the factors that are critical for optimal recovery and adequate social competence are useful for developing targeted intervention and prevention strategies for pediatric TBI. In addition, there is currently a gap in the literature with respect to investigating neural mechanisms of social problems from a network perspective. Furthermore, the majority of existing research is cross-sectional and has been limited to specific socio-cognitive skills and links with individual brain regions, thus limiting our knowledge of the global impact of pediatric TBI at the network-level and from a longitudinal perspective. As such, no study has investigated alterations in FC in the SBN using a comprehensive neural systems approach. Similarly, little is known about how pediatric TBI affects the maturation of neural networks over time. This thesis focused both on early childhood and on school-age children and adolescents, and includes four empirical articles. The first two articles present data drawn from a prospective longitudinal project (LION study) on the effects of early mTBI on cognitive and social outcomes. Article 3 and 4 use data from a longitudinal cohort study exploring the impact of pediatric TBI on the brain and on social skills (Victoria Neurotrauma Initiative Study).

Article 1 aimed to empirically validate Beauchamp and Anderson's SOCIAL model (2010) in a sample of typically developing preschoolers (i.e., aged 18 to 60 months). Based on this theoretical model, it was assumed that all three broad categories (internal and external factors as well as socio-cognitive variables) would contribute to social competence in in the context of assumed normal brain development.

Article 2 aimed to examine which factors predict long-term QoL following early mTBI (i.e., sustained between 18 and 60 months of age). QoL was assessed six and 18 months post-injury and multiple potential candidate predictors from four domains (biological, family-environmental, injury and cognitive) were included in a statistical model. A novel aspect of the study is the inclusion of a genetic factor (BDNF) as a predictor. It was expected that a combination of the factors would contribute to QoL at both time points. It was further assumed that in the earlier recovery phase (i.e., six months post-injury), biological factors would contribute predominantly to post-mTBI QoL, and at later stages (i.e., 18 months post-injury), environmental and psychological factors would play a more important role in explaining the variance in children's QoL.

Article 3 aimed to investigate FC alterations within the SBN in children and adolescents who sustained moderate to severe TBI between nine and 15 years of age. Participants underwent rsfMRI 24 months post-injury. For the analyses, an exploration-replication approach was applied using an independent second sample of participants with similar demographic and injury characteristics. The hypotheses were that compared to non-injured control participants, children and adolescents with TBI would exhibit alterations in FC between nodes of the SBN (i.e., reduced FC) and that these differences would be related to behavioural outcomes.

Article 4 aimed to explore long-term changes in the brain's SCN following pediatric moderate to severe TBI in order to characterize the developmental impact of TBI on the immature brain and the long-term global impact of pediatric TBI on brain topology. The specific aims of this article were to investigate differences in structural covariance pattern within three core cognitive networks (i.e., DMN, CEN, and SN) between children with TBI and TDC (aged nine to 14 years) within three months of injury and two years later. In light of the exploratory nature of this study and limited literature using structural covariance in pediatric TBI, no *a piori* hypotheses were specified.

Finally, two additional articles are presented in Appendices I and II because they are closely related to the main thesis articles and were conducted in parallel to the main thesis work (one on the role of a genetic factor on internalizing behavioural problems following early mTBI and a review on preschool mTBI). The thesis concludes with a discussion of the main results, the theoretical, methodological and clinical implications, as well as a presentation of the limitations and avenues for future research.

Article 1

Social competence in early childhood: An empirical validation of the SOCIAL model

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Abstract

Social skills are the basis of human interactions and functioning in society. Social competence (SC) is thought to evolve gradually during childhood and adolescence via the interplay of multiple factors. In particular, the early years of life are marked by the emergence of basic social abilities and constitute the foundation for successful social development. The biopsychosocial SOcio-Cognitive Integration of Abilities modeL (SOCIAL) posits that internal (child-based), external (environment), and cognitive factors are critical to SC in the context of normal brain maturation; but this has yet to be shown empirically and comprehensively. This study tested the SOCIAL model in a sample of typically developing preschool children. Parents of 103 children (M = 67.59 months, SD = 11.65) completed questionnaires and children underwent neuropsychological assessment of executive functioning (EF), communication skills and social cognition. Three-step hierarchical regression analyses (1) Internal factors, 2) External factors, 3) Cognitive factors) confirmed that each step of the regression model significantly predicted SC. In the final model, general cognitive and socio-cognitive factors significantly predicted SC above and beyond internal and external factors: children with lower temperamental negative affect and less parent-reported executive dysfunction, as well as better non-verbal communication and theory of mind had better SC. Our findings support the conceptual SOCIAL model, and highlight the importance of internal, external, and cognitive factors for SC in the preschool years. Identification of factors associated with early social development can inform both normative and clinical approaches to identifying intervention loci and optimizing SC in those at risk for maladaptive social functioning.

Keywords: Social competence, preschoolers, social development, social cognition, validation.

Introduction

Social competence (SC) is the foundation of human behaviour, action, and thought. SC is crucial to creating and maintaining relationships, communicating with others, participating in social interactions and functioning in society (Cacioppo, 2002). These skills develop gradually throughout childhood and adolescence and reflect a complex interaction between cognitive, behavioural, neural, and environmental factors required for adequate SC (Frith & Frith, 2012; Soto-Icaza, Aboitiz, & Billeke, 2015). Given their established importance for academic success, life satisfaction, mental health, and emotional well-being across the lifespan, it is imperative that social skills develop soundly in early childhood (Ackerman & Brown, 2006).

Since the advent of social neuroscience and comprehensive models incorporating brain-based substrates of social cognition, there is increasing interest in understanding social development from a neurodevelopmental perspective (Beauchamp, 2017). Social problems can occur through disruptions to typical development, such as in developmental and neurological disorders, chronic illness, and mental health conditions. Social difficulties associated with these conditions can either stem from direct insult to underlying brain bases of social cognition, or environmentally, for example, as a consequence of stigmatization, paucity of social opportunities, restrictions in social participation, or family factors such as parenting style, parent–child interactions or parent mental health (e.g., Besag & Vasey, 2019; Catroppa, Anderson, Morse, Haritou, & Rosenfeld, 2008). Social problems increase the risk for adverse developmental outcomes in terms of poor academic achievement, dysfunctional social relationships, peer rejection, and mental health problems (Beauchamp & Anderson, 2010). Understanding the causes of social impairment depends on acquiring sound knowledge of how social skills develop in optimal environments and what contributes to variations in SC across typical development.

A number of studies highlight the importance of socio-cognitive skills for adequate SC (e.g., Adolphs, 2001; Besag &Vasey, 2019). Social cognition refers to cognitive processes, such as emotion recognition, theory of mind ([ToM]; understanding others' mental states), empathy (understanding the affective state of others), intent attribution or moral reasoning, which are crucial to process, interpret, and respond to social cues and situations by helping individuals understand others' behaviours, intentions, and emotions (Adolphs, 2001; Soto-Icaza et al., 2015). These socio-cognitive abilities are underpinned by the concerted activity of a complex network of brain regions (the "social brain"), which undergo protracted maturation during childhood and adolescence

(Adolphs, 2009; Frith & Frith, 2012). In addition, research in the field of developmental psychology has underscored the importance and central role of family factors and functioning for children's cognitive and social development, such as, for example, parent–child interactions and attachment security (Aksan, Kochanska, & Ortmann, 2006).

Models seeking to explain SC provide a conceptual framework to embody the various factors that shape social functioning in both typical and atypical development (Beauchamp & Anderson, 2010; Cassel, McDonald, Kelly, & Togher, 2019; Cattaneo & Rizzolatti, 2009; Crick &Dodge, 1994; Iacoboni, 2009; Izard, 2009; Soto-Icaza et al., 2015; Yeates et al., 2007). Such models allow for testing predictions and investigating links between SC and its determinants. However, most social models are only theoretically driven and seldom empirically tested in a comprehensive manner. While some empirical studies establish associations between SC and a limited number of specific factors, such as socio-cognitive (e.g., Devine, White, Ensor, & Hughes, 2016) or parental variables (e.g., Fernandes et al., 2019), the relative contribution of these constructs (environmental, cognitive, biological) to SC remains unclear.

Beauchamp and Anderson (2010) proposed a comprehensive and integrative model of social function accounting for domains and factors of influence in both healthy development and clinical conditions, the SOcio-Cognitive Integration of Abilities modeL ("SOCIAL"; Figure 1). SOCIAL integrates notions related to the biological basis (brain maturation and integrity), as well as the external (environment), internal (child-based), and cognitive factors associated with SC (biopsychosocial approach). SOCIAL posits that external factors, including distal factors (e.g., socioeconomic status [SES], ethnicity or culture), and proximal influences (e.g., parent–child interactions, parental practices, or family functioning), play a particularly important role during the early years of social development. Internal factors, for their part, refer to self-related variables such as temperament or personality traits or physical attributes that may influence social interactions and participation. Brain maturation and integrity mediate social development, providing a basis for the emergence of socio-cognitive skills. External and internal child attributes as well as brain development interact dynamically to support cognitive functions that determine SC: (1) attention and executive functioning (EF), (2) communication skills, and (3) socio-emotional functioning (or 'social cognition'). These skills are crucial for functioning in everyday situations and establishing meaningful social interactions and relationships.

During the preschool years, social skills become progressively refined via increasing brain specialization and environmental interactions. Children move from egocentric perceptions of their environment to cooperative play and perspective-taking, paralleled by an increase in social communication. The increased complexity of social behaviour becomes apparent in the discrimination of social agents and inference of others' intentions and beliefs (ToM; Soto-Icaza et al., 2015). In sum, the early years of life lay the cornerstone for adequate SC, and shedding light on its determinants is critical to enhance our understanding of the mechanisms involved in both typical and deviating paths of social development.

The original conception of SOCIAL posits that internal, external, and cognitive factors are critical to SC; however, the model has never been tested empirically. As a first step, this study aimed to test the comprehensive scope of the SOCIAL model in typically developing preschool children (TDC) and to explore factors associated with SC in the preschool years. As such, multiple predictors and aspects of functioning were included in the analyses, covering all domains described in the original model.

Method

Participants

The present study uses a convenience sample drawn from a prospective, longitudinal research project, which was approved by the local institutional review board and conducted in accordance with the declaration of Helsinki. Informed written consent from parents of participants was obtained prior to study inclusion. The original study aimed to document cognitive and social outcomes of early childhood traumatic brain injuries (TBI). Participants were followed at 6 (time point 1 [T1]), 18 (time point 2 [T2]), and 30 (time point 3 [T3]) months post-injury.

For the purposes of the current paper, only data from T2 and T3 for the two typically developing comparison groups (TDC, children with orthopedic injuries [OI]) were used to explore predictors of SC. Data from comparison groups were collapsed for analyses given previous findings in the same sample demonstrating no differences between OI and TDC participants on multiple environmental, familial, affective, and cognitive factors (Beauchamp, Landry-Roy, Gravel, Beaudoin, & Bernier, 2017).

Children with OI (defined as a limb trauma leading to a final diagnosis of simple fracture, sprain, contusion or unspecified trauma to an extremity) were recruited in a single, tertiary care,

paediatric emergency department between 2011 and 2015. TDC participants were recruited via advertisements and pamphlets distributed in urban daycare centres. At T1, all participants were between 24 and 66 months old.

Exclusion criteria were as follows: (1) suspicion of abuse; (2) diagnosed congenital, neurological, developmental, psychiatric, or metabolic condition; (3) less than 36 weeks of gestation; (4) child and parent not fluent in French or English; and (4) prior TBI. Participants who had completed T3 assessments were included in analyses if parents had returned T2 questionnaires. Further details of the larger study are reported elsewhere (Bellerose, Bernier, Beaudoin, Gravel, & Beauchamp, 2015, 2017; Dégeilh, Bernier, Gravel, & Beauchamp, 2018; Gagner, Dégeilh, Bernier, & Beauchamp, 2019; Gagner, Landry-Roy, Bernier, Gravel, & Beauchamp, 2018; Lalonde, Bernier, Beaudoin, Gravel, & Beauchamp, 2018, 2020; Landry-Roy, Bernier, Gravel, & Beauchamp, 2017, 2018; Séguin, Dégeilh, Bernier, El-Jalbout, & Beauchamp, 2020).

Procedure and measures

At all three follow-up time points, parents filled out questionnaires and all children completed a direct assessment. Variables that best fit the SOCIAL model structure were considered as candidate predictors from parent-report questionnaires at T2 and neuropsychological variables concurrent to the main outcome (SC) at T3. More specifically, relevant, developmentally appropriate variables were selected to correspond with those presented in SOCIAL, which presents a broad range of factors relevant from early childhood through adolescence. Then, in order to reduce the number of predictors given the moderate sample size and to restrain the analyses to only the most relevant constructs in this preschool sample, zero-order correlations were performed (see below). Internal and external factors were assessed at T2 (or at enrolment for demographic variables), and cognitive variables and the main outcome at T3.

Variable selection

Variable selection was based on the design of the larger project in which measures were included as a function of (1) psychometric (i.e., satisfactory internal and external validity), (2) developmental (i.e., appropriate for the age of the participants), and (3) pragmatic (i.e., task and overall assessment duration) considerations. More details are provided below for each measure. For the present substudy, variables from the larger project were then selected based on availability and the following theoretical assumptions in accordance with the original model: First, for internal

factors, measures assessing intrinsic temperament as well as physical health were considered relevant to testing SC in early childhood. Temperament rather than personality was included since clear personality profiles do not emerge until later in development and temperament is a more developmentally appropriate construct in this age group. In the external domain, the original SOCIAL model describes family function and environment, as well as SES and culture as contributing to SC. Here, a general family functioning scale and SES were selected to represent these concepts. Given that all families came from Quebec and the majority identified as Caucasian (>90%) with largely similar cultural backgrounds, it was assumed that culture would not differentially affect SC in this sample. With respect to cognitive factors, selected measures assessed each of the three cognitive domains described in the original SOCIAL framework (Attention-EF, Communication, Social Cognition). Attention and EF were assessed using performance-based measures tapping into cognitive flexibility, working memory, planning, and speed of processing, as well as a parent report of executive dysfunction. In the communication domain, both vocabulary and a non-verbal communication score, as a measure of more subtle aspects of language, were included. Finally, in the social cognition domain, SOCIAL theoretically includes emotion perception, attribution, ToM and empathy, as well as moral reasoning as potential determinants of SC. Here, we chose the available measures tapping into as many subdomains of social cognition as possible, that is, ToM (measured using a false beliefs task), empathy (using a parent questionnaire) and affect recognition (based on a neuropsychological test battery). Finally, normal brain development was assumed in the sample based on the aforementioned inclusion and exclusion criteria.

Internal factors

Temperament. The Child Behavioral Questionnaire Very Short Form ([CBQ-VS]; Putnam & Rothbart, 2006) is a parent report of child temperament for children aged 3–7 years (e.g., Chmait et al., 2020; Hughes & Shewchuk, 2012). Thirty-six items were rated by the primary caregiver on a 7-point Likert scale (≈ 15 min completion time). Three subscores are derived: Surgency/Extraversion (positive emotion, high activity level, rapid approach to potential rewards), Negative Affect (predisposition to frustration, discomfort, fear, anxiety and sadness), and Effortful Control (ability to inhibit or suppress dominant responses). The CBQ-VS has good psychometric

properties (Putnam, Gartstein, & Rothbart, 2006; Putnam, Jacobs, Gartstein, & Rothbart, 2010; Putnam & Rothbart, 2006).

Physical health. The physical health summary score (PedsQL-Physical) from the parent-proxy report of the Pediatric Quality of Life Inventory 4.0 ([PedsQL 4.0]; Varni, Seid, & Kurtin, 2001) for children aged 2–7 years was used to assess physical health, as in previous studies (Eadie et al., 2018; Hedgecock, Dannemiller, Shui, Rapport, & Katz, 2018). The primary caregiver rated each of the eight items on a 5-point scale (≈ 5 min completion time). Scores range from 0 to 100 with higher scores indicating better functioning. Good psychometric properties have been reported (Desai et al., 2014; Varni et al., 2001).

External factors

Socioeconomic status. Parents completed an in-house demographic questionnaire. Parental education, as a proxy for SES, was obtained by averaging parents' educational qualifications on an 8-level scale ranging from 1 (doctoral degree) to 8 (<7 years of school). In cases where information on highest educational attainment was available for only one parent, or if the child lived with one parent, an individual score was calculated.

Family functioning. The General Family Functioning scale from the Family Assessment Device ([FAD]; Epstein, Baldwin, & Bishop, 1983) assesses parental satisfaction with general family functioning and has been widely used in studies of children under the age of 12 years (Leeman et al., 2016). Each of the 12 items is rated on a 4-point scale (≈ 10 min completion time) with higher scores indicating poorer family functioning. The FAD shows overall good reliability and validity (Byles, Byrne, Boyle, & Offord, 1988).

Cognitive factors – attention and executive functioning

Processing speed. The Wechsler Intelligence Scale for Children Version 4 ([WISC-IV]; Wechsler, 2014) was administered to children aged 6 years and older and the Wechsler Preschool and Primary Scale of Intelligence Version 3 ([WPPSI-III]; Wechsler, 2002) was used for children <6 years of age (≈ 10 min completion time). Coding/Animal Coding and Symbol Search (M = 10, SD = 3) were used to calculate the Processing Speed Index (M = 100, SD = 15).

Parent report of executive dysfunction. The Behavior Rating Inventory of Executive Function ([BRIEF]; Gioia, Espy, & Isquith, 2003; Gioia, Isquith, Guy, & Kenworthy, 2000) is a parent report of behavioural indicators of executive dysfunction over the last six months and has

been used in previous research including preschool children (Anderson, McNamara, Andridge, & Keim, 2015; Heijligers et al., 2018). Items are rated according to three response options indicating the degree to which a particular behaviour is problematic. Eight (for children <5 years) or 10 (for children >5 years) subscores can be derived (≈ 15 min completion time). In the present analyses, the global executive composite score was used as an overall index of executive dysfunction (M = 50, SD = 10). Higher scores indicate *poorer* EF or more dysfunction. The BRIEF has good psychometric properties (Gioia et al., 2000).

Performance-based measures of executive functions. Three performance-based measures of EF were administered representing common measures of EF in preschool children (Anderson & Reidy, 2012 for a review). The object classification task for children ([OCTC]; Smidts, Jacobs, & Anderson, 2004) measures concept generation and cognitive flexibility in young children (≈ 5 min completion time). Children are asked to group six plastic toys according to three predetermined categories (i.e., colour, size, and function). The test has three levels with increasing levels of structure. A total score is calculated with a maximum score of 12.

The Spatial Span Test is part of the Cambridge Neuropsychological Test Automated Battery ([CANTAB]; Cambridge Cognition, 2006) and assesses working memory capacity (≈ 5 min completion time). Increasing numbers of white squares (starting at two and ending at nine) are presented to the child, some of which change colour briefly in a random sequence. Children have to remember the sequence and, at the end of the presentation, touch each of the boxes that changed colour in the same order (the second part is done in the reversed order). An alternate sequence of the same length is presented for incorrect responses. The maximum score is 28.

The Tower of Hanoi task ([ToH]; Simon, 1975) is a planning task during which participants are asked to change the arrangement of discs into an alternative configuration in as few moves as possible, moving only one disc at a time and placing smaller discs over larger ones (≈ 15 min completion time). The ToH is repeated five times with each of the disc sets (three and four discs) and the task ends when both sets of problems have been administered. Three types of score can be obtained: mean performance time for each disc set, mean of movements performed, and total number of errors made (rule violations). A total score (maximum = 6) was calculated and used for analyses.

Cognitive factors – communication

Vocabulary. Vocabulary was measured using the Vocabulary subtest from the Wechsler Abbreviated Scale of Intelligence Version 2 ([WASI-II]; Wechsler, 1999) for children aged six and older and from the WPPSI-III (Wechsler, 2002) for children younger than six years (≈ 15 min completion time). Raw scores from the two scales were combined for analyses.

Non-verbal communication. The non-verbal communication scale from an adapted French version of the Children's Communication Checklist ([CCC-2]; Vézina, Morasse, Desgagné, Fossard, & Sylvestre, 2011) for children aged 4–16 years was used to assess pragmatic language skills. The original version of the CCC-2 is well established as a measure of pragmatic language skills in children and has previously been used in preschoolers (Geurts & Embrechts, 2010; Väisänen, Loukusa, Moilanen, & Yliherva, 2014). The primary caregiver rates each of the 7 items on a 4-point scale (≈ 5 min completion time). For the adapted short version of the CCC-2, scaled scores are not available; hence, raw scores were used with higher scores indicating *poorer* skills. General composite scores of the CCC-2 in the original version show excellent test-retest reliability (Adams et al., 2012).

Cognitive factors – social cognition

Theory of mind. The false belief understanding (FBU) task (Hughes, Ensor, & Marks, 2011) was used as a measure of ToM (≈ 5 min completion time). This measure is widely used to assess ToM abilities in preschoolers (Beaudoin, Leblanc, Gagner, & Beauchamp, 2019). Children are shown a peep-through picture book with a deceptive element and asked to recall their initial belief about their perception, and predict a puppet's belief via two forced-choice questions. For both scenarios, children receive credit (one point) only if they are able to answer the corresponding control question, for a maximum of two points.

Empathy. The Griffith Empathy Measure ([GEM]; Dadds et al., 2008) is a 23-item measure of empathy that has previously been used in young children (Deschamps, Verhulp, de Castro, & Matthys, 2018; Vera-Estay, Seni, Champagne, & Beauchamp, 2016). The primary caregiver answers each item on a 9-point Likert scale ranging from strongly disagree (-4) to strongly agree (+4) (≈ 10 min completion time). The total score was used with higher scores indicating higher empathy. Adequate validity and reliability have been reported (Dadds et al., 2008).

Social perception. The Developmental NEuroPSYchological Assessment Version 2 ([NEPSY-II]; Korkman, Kirk, & Kemp, 2007) is a comprehensive test battery assessing neuropsychological development across six different cognitive domains in preschool and school-age children. The Affect Recognition subtest from the Social Perception domain was used to assess the ability to recognize facial affective states (≈ 10 min completion time).

Main outcome

Social competence. The Paediatric Evaluation of Emotions, Relationships, and Socialisation Questionnaire ([PEERS-Q]; Thompson et al., 2018) formerly known as The Developmental Assessment of Social Competence ([DASC]; Muscara, Catroppa, Beauchamp, & Anderson, 2010) was used to measure general SC. PEERS-Q is a comprehensive parent questionnaire rating children's SC and provides information on a range of components of SC, such as friendships (e.g., 'my child has a very close relationship with his/her friends') and social participation (e.g., 'my child participates actively in groups/sports'), thus tapping into social functioning and behavioural manifestations. The 55 items describe child behaviour and social skills in everyday situations when interacting with others and are rated on a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree) (≈ 20 min completion time). PEERS-Q is based on scientific and clinical evidence and integrates multidisciplinary perspectives on social development, including social neuroscience, psychology, neuropsychology, occupational and speech therapy, as well as qualitative information based on teacher and parent reports (Muscara et al., 2010). Items are based on constructs found to be linked with SC as reported in the literature on social development, including monitoring of behaviours, impulsivity, and problem-solving skills. A total social skills score is provided and ratings across six subdomains can be derived. Higher scores indicate *lower* SC, and the total raw score was used as a general measure of SC. PEERS-Q shows excellent psychometric properties in terms of validity and reliability (Hearps et al., unpublished data; Thompson et al., 2018).

Statistical analyses

Preliminary analyses

Analyses were carried out in SPSS version 25. Given that some parents or children did not complete some measures, there were missing data across participants and measures (1–8%). The

pattern of missing data was analysed using Little's MCAR test, which indicated that data were missing completely at random (χ^2 (1) = 383.83, p = .54). However, since Little's test lacks power (Enders, 2010), complete and incomplete cases were compared to investigate whether they differed on any of the study variables (for variables revealing 5% or more of missing data). Compared to those with available data (all ts between -2.5 and 3.3, ps < .05), participants who did not have data on the BRIEF (n = 7) had higher GEM scores; participants with missing data on the Spatial Span test (n = 7) had lower scores on NEPSY-Affect Recognition, WPPSI/WISC-Processing Speed, and on WPPSI/WISC-Vocabulary; participants with missing data on WPPSI/WISC-Processing Speed (n = 8) had lower GEM scores than participants with available data on this measure and were more often boys (χ^2 (1) = 4.75; p = .03). Missing values were imputed using the multiple imputation procedure available in SPSS. Twenty imputations were applied as per recommendations, and missing data estimated from all other data available including demographic information to correct for bias and maximize precision of the algorithm (Enders, 2010). Analyses were run on each imputed data set and results averaged. Descriptive statistics were calculated to examine variable distributions.

Zero-order correlations were then performed to check for multi-collinearity and to select potential predictors of SC (PEERS-Q) among relevant variables including internal factors (Sex, Age, CBQ-Surgency/Extraversion, CBQ-Negative Affect, CBQ-Effortful Control, PedsQL-Physical), external factors (Family living arrangement, Parental Education, FAD-General Family Functioning), and cognitive functioning (WPPSI/WISC-Processing Speed, BRIEF, OCTC, Spatial Span, ToH, WPPSI/WASI-Vocabulary, CCC-Nonverbal Communication, FBU, GEM, NEPSY-Affect Recognition). In order to guard against type II error given the modest sample size, only variables correlated with PEERS-Q at a p-level <.20 were included in further analyses. The higher p-level of .20 compared to the conventional level of .05 was chosen in order to also include potential suppressor effects. This approach allowed for the inclusion of more potential significant predictors in the subsequent regression analysis and thus to validate the SOCIAL model as closely and comprehensively as possible to its original conceptualization. If not otherwise indicated and where available, raw scores were used in all analyses as they provide a larger range of values compared to standard scores. All analyses were adjusted for sex and age.

Main analyses

Hierarchical regression analysis was conducted to examine factors associated with global SC (PEERS-Q). Potential predictors were entered in three steps, based on the SOCIAL model, and their potential for change: First, child and socio-demographic variables (sex, age) that are inherent to the individual were entered. Then, external factors pertaining to the child's environment were added, which, together with internal factors, are thought to mediate cognitive functions. Cognitive factors (Attention-EF, Communication, Social Cognition), which change over time both naturally and due to external influences, were added in step 3 to test the unique association of cognitive variables with SC, above and beyond internal and external factors. In the regression model, a *p*-level of <.05 was chosen to determine statistical significance.

Results

Participant characteristics and selection of predictor variables

The sample consisted of 103 children (52 boys, 51 girls). Participant characteristics for the main variables are summarized in Table 1. At T2, 91% of questionnaires were completed by mothers and three of the 103 (3%) families did not return the questionnaires. At T3, 90% of questionnaires were completed by mothers, and one family did not return the questionnaires (1%).

Table 2 presents the zero-order correlations among all relevant study variables as well as with the main outcome, PEERS-Q. Among the internal child factors, CBQ-Negative Affect, CBQ-Effortful Control, and PedsQL-Physical were significantly correlated with PEERS-Q. In order to limit the number of predictor variables, the CBQ-Negative Affect score was selected given its stronger correlation with PEERS-Q and to avoid including multiple subscales from the same measure in the regression model. Sex and Age were correlated with PEERS-Q at a p-level <.20. Therefore, Age, Sex, PedsQL-Physical, and CBQ-Negative Affect were included together in step 1 of the model to represent internal child factors. With respect to the external factors, Parental Education and FAD-General Family Functioning were both significantly associated with PEERS-Q and were included in the second step of the regression model. Among the cognitive factors (step 3), BRIEF, OCTC (Attention-EF), CCC-Nonverbal Communication (Communication), as well as FBU and GEM (Social Cognition) were included in the model.

Hierarchical regression

Results of the hierarchical regression analyses are shown in Table 3 and Figure 2. Internal factors (Sex, Age, CBQ-Negative Affect, PedsQL-Physical) were entered in the model in the first step and together explained a significant 22 % of the variance in PEERS-Q ($F(4,98) = 7.08$, $p < .001$). All four factors were significant independent predictors of PEERS-Q (all $p < .05$), indicating that children who were female, older, had better physical health and lower temperamental negative affect showed better social competence.

In step 2, Parental Education and FAD-General Family Functioning explained an additional 9 % of variance in PEERS-Q ($\Delta F(2,96) = 6.12$, $p = .004$). After this step, Age ($p = .002$), CBQ-Negative Affect ($p = .006$) and FAD-General Family Functioning ($p = .004$) remained significant independent predicting factors, with older age, lower temperamental negative affect and better family functioning predicting better SC.

Finally, cognitive factors (BRIEF, OCTC, CCC-Nonverbal Communication, FBU, GEM) were entered at step 3 and explained an additional 32 % of the variance above and beyond internal and external factors ($\Delta F(6,91)= 15.94$ $p < .001$). CBQ-Negative Affect ($p = .005$), BRIEF ($p < .001$), CCC-Nonverbal Communication ($p < .001$) and FBU ($p = .007$) were significant independent predictors of PEERS-Q, indicating that children who had lower negative affect, less executive dysfunction as reported by parents, better non-verbal communication, and better ToM showed better SC. The final model explained 63 % of the total variance in PEERS-Q and was significant ($F(12,91) = 14.31$, $p < .001$).

Discussion

SOCIAL is a conceptual framework of social development and its determinants (Beauchamp & Anderson, 2010). In this study, the model was empirically tested in typically developing preschoolers, given that early childhood is a sensitive period for social development. In keeping with SOCIAL, and in the context of assumed healthy brain development, the current results show that internal, external, and cognitive factors were all related to SC, and highlight the relative importance of cognitive factors. For internal factors, female sex, older age, better physical health, and lower temperamental negative affect predicted better SC. When external influences were included, better family functioning, older age, and lower temperamental negative affect

significantly predicted better SC. Further, cognitive factors (parent-reported executive dysfunction, non-verbal communication, and ToM) significantly predicted SC above and beyond internal and external factors. For the full model, lower negative affect and less parent-reported executive dysfunction, as well as better non-verbal communication and ToM were predictive of higher SC.

With regard to the role of internal, or 'child-related' influences, sex differences in SC have been the subject of extensive research, the bulk of which suggests that girls generally outperform boys in terms of social problem-solving and understanding others' intentions (e.g., Abdi, 2010; Fabes & Eisenberg, 1998). Studies also suggest that girls are better than boys in terms of processing and knowledge of emotions during infancy and the preschool years (McClure, 2000, for a meta-analysis). In addition, there is evidence of more rapid development of social information processing skills in girls, in turn fostering faster interpretation of social situations and heightened social learning at an earlier age compared to boys (Bennett, Farrington, & Huesmann, 2005). Such differences may be related to cultural preconceptions and gender roles (e.g., Brown & Leaper, 2010), as well as differential parenting styles for boys and girls (Rutter, Caspi, & Moffitt, 2003). The observation that older age is linked with better social skills supports the logical conclusion that social understanding generally increases with age (e.g., Franco, Beja, Candeias, & Santos, 2017), along with ongoing maturation of the social brain network (Adolphs, 2001). This result also supports the crucial function of healthy brain development for SC (Beauchamp & Anderson, 2010). With respect to the role of physical health, fewer health problems and better motor coordination likely enhance opportunities for social interactions and participation (Cummins, Piek, & Dyck, 2005).

The consistent significance of temperamental negative affect highlights the importance of children's innate temperament for social functioning. Temperamental characteristics are a core element in establishing the first positive social interactions during early and middle childhood (Rothbart, 2019), as well as for the development of prosocial skills (Laible, Carlo, Murphy, Augustine, & Roesch, 2014). Children with low temperamental negative affect may experience fewer feelings of anger, disgust, guilt, sadness, discomfort or fear. Conversely, negative feelings may prevent children from actively joining activities due to anxiety, anger, or poor social problem-solving, leading to reduced social interactions and isolation (Greco & Morris, 2001).

With respect to external factors, positive family functioning, reflected in few marital conflicts, positive communication, adaptive problem-solving strategies, affective involvement and

responsiveness, was associated with better SC, in line with previous research (e.g., Spinrad & Gal, 2018). Family factors are particularly important in the early years of life as children spend most of their time with their parents. Indeed, parents play a predominant role in shaping their children's first interpersonal interactions and their developmental course during early childhood, and early caregiving characteristics influence the way children acquire, affective coping strategies and adequate social behaviours (Aksan et al., 2006; Spinrad & Gal, 2018).

Cognitive development is also related to how social skills evolve. This is reflected in the current findings showing that elements (behavioural indicators of executive dysfunction, non-verbal communication, and ToM) from each of SOCIAL's three cognitive domains (Attention-EF, Communication, Social Cognition) predicted SC above and beyond internal and external factors. EF are critical to everyday functioning and provide a basis for successful social interactions and relationships by allowing children to integrate feedback, react flexibly to changes in routine, respect turn-taking, or inhibit negative reactions (Ganesalingam et al., 2011). These skills are directly linked to establishing socially appropriate behaviours and meaningful social relationships (Ganesalingam et al., 2011; Ryan et al., 2019).

With respect to the role of communication in the development of SC, previous work has identified non-verbal communication skills (gestures, facial expressions, tone of voice, eye contact, body language, posture) as key to SC (e.g., Hall, Horgan, & Murphy, 2019). Non-verbal communication is particularly important during the preschool years when expressive language skills and vocabulary are emerging. Such subtle aspects of social communication are linked to establishing social relationships by providing cues on context, turn-taking, and monitoring the appropriateness of words and utterances (Landa, 2005). In addition, understanding irony or the subtlety of deceptive messages is critical to responding appropriately and establishing positive peer relationships (Angeleri&Airenti, 2014).

Finally, among the socio-cognitive factors, ToM, assessed using a false belief understanding task, was associated with SC. Understanding and inferring the mental states of others, that is, their beliefs, intents, desires, and emotions, develops in a stepwise fashion, starting with an egocentric view of the world in early childhood (Brune & Brune-Cohrs, 2006). Specific ToM abilities that emerge during the preschool period include understanding of intentions and false beliefs (Beaudoin et al., 2019). In keeping with our findings, the importance of false belief understanding for early social development has previously been underscored (Soto-Icaza et al.,

2015, for review). ToM has been shown to have a direct impact on social relationships and is positively associated with good social problem-solving, judgment, and behaviour (e.g., Sokol, Chandler, & Jones, 2004). ToM thus plays a key role in children's everyday social functioning.

Among all potential predictors of SC, some were not correlated with SC (PEERS-Q), which may be due to limited statistical power. Other explanations may include the young age of the participants. For example, aspects of EF and communication mature with age and may thus become more important to SC during middle childhood (Best & Miller, 2010). In the case of temperament, surgency/extraversion refers to a high activity level, a tendency for positive emotions and seeking pleasurable activities, and high sociability (Rothbart, 2011). It is possible that the other two temperament subscores (negative affect and effortful control) are more important to social skills early in life. By contrast, a child's activity level and choice of 'pleasurable' activities is largely determined by parents during this stage of life and may thus not be as strong a predictor of child SC.

In sum, the findings empirically support the theoretical assumptions put forward in SOCIAL (Beauchamp & Anderson, 2010). This integrative biopsychosocial approach can be useful for capturing the building blocks of healthy social development and could provide a basis for translating research findings into clinical and educational approaches. Previous work in the area of social development has investigated individual predictors of SC and specific aspects of social behaviour in healthy (Hughes & Ensor, 2011) and clinical populations, such as autism spectrum disorders ([ASD]; Haigh, Walsh, Mazefsky, Minshew, & Eack, 2018). SOCIAL has also been used to shape the investigation of social functioning in paediatric traumatic brain injury (Ryan et al., 2019), though not comprehensively. The present study thus represents the first effort to empirically test all domains of the model jointly. A sound theoretical understanding of factors that are associated with appropriate social development is useful, but empirical validation of the model provides an additional step, which lends credibility and facilitates applications to clinical populations and remediation initiatives. The current findings also have the potential to stimulate the development of valid and reliable social measures tapping into each aspect of the model.

Limitations and future directions

This study is the first to test the SOCIAL model empirically and adds to the literature by investigating links between SC and a range of predictors in each of the proposed domains using both parent reports and direct child measures. Nonetheless, some limitations have to be considered.

First, results may not generalize to older children and adolescents. For instance, different variables might play a role in school-aged children or adolescents given the relative complexity of the social situations they are likely to encounter, including the increasing importance of peer relationships, as well as the reduced salience of parental influences during adolescence. Hence, conclusions about SC have to be drawn with an appropriate consideration of the unique characteristics of each developmental age group. Additional measures of family factors or other measures of socio-cognitive and communication skills were not included given the modest small sample size and limited statistical power. Given that some constructs were measured via parent questionnaires, the associations between parent-reported constructs may be inflated due to common source and parental bias. In the EF domain, performance-based measures of EF and a parent report of executive dysfunction (BRIEF) were not significantly correlated, suggesting that the BRIEF and performance-based measures of EF assess different aspects of child functioning, as reported elsewhere (Soto et al., 2020; Toplak, West, & Stanovich, 2013). Behavioural indicators of executive dysfunction as measured by the BRIEF significantly predicted SC, but may reflect more general functioning that is critical to social interactions, such as self-control, inhibition, and adapting to changes in routine, as perceived by parents. By including both specific performance-based measures of EF and parent-reported behavioural indicators of executive dysfunction, we opted to capture a broader range of child functioning indices, in light of the young age of the participants. In addition, while the original model suggests that the factors interact dynamically, the present analyses and sample did not allow for testing interactive effects. Furthermore, due to using a convenience sample, some measures were assessed at different time points, and age-related changes on specific measures were not adjusted for. In particular, given the constraints related to the sample size, we did not include additional age variables or a 'time between assessments' factor in the model. Hence, the present findings need to be interpreted cautiously and cannot be considered from a longitudinal perspective. However, all direct child factors, which may be more sensitive to developmental change, were assessed concurrently with the outcome measure. In addition, age at assessment was included in all analyses. Finally, the present findings are correlational in nature and do not inform on causal relationships between the factors examined here and SC. Longitudinal and experimental studies are needed to further explore the putative causal nature of the associations.

Future studies using larger samples would be useful for testing a wider range of variables, beyond those selected here. Additional measures that tap into other subdomains of the SC umbrella, such as social adaptive functioning or prosociality, may provide additional information on social functioning and should be used to enhance generalizability of the model to different contexts and populations. On the clinical end, this also includes tools sensitive to social behaviour problems. Future empirical validation of the model should also take into account genetic factors aswell as a longitudinal perspective in terms of brain maturation and behavioural changes throughout childhood. Including structural and functional neuroimaging markers in future models could allow for assessing brain integrity, in particular in the social brain, and examining links between SC and brain development. This would further enhance applicability to clinical populations with social problems, such as children with brain injury or altered neurodevelopment. Finally, while this study explored simple associations between SC and the domains put forward in the SOCIAL model, future studies using larger samples and multiple time points are needed to test specific interactive effects in order to validate the dynamic aspects of the model and the assumption that SC is the result of complex interactions between internal, external and cognitive factors.

Conclusions

SOCIAL is a theoretical framework capturing the dynamic and interrelated associations between cognitive, biological, and environmental factors that together shape SC. This first empirical investigation of the model confirms the importance of three global domains (internal, external, and cognitive factors) associated with SC in the preschool years: Children who have lower negative affect, less parent-reported executive dysfunction, better non-verbal communication and better ToM have better SC. Future research should seek to test the model in other age groups using larger samples and in the context of altered neurodevelopment, such as after brain injury or in ASD. Understand what factors are associated with social functioning in typical development provides a normative basis for diagnosis, assessment and treatment in conditions associated with a social impairment phenotype.

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Conflicts of interest

All authors declare no conflict of interest.

Author contributions

Carola Tuerk (Conceptualization; Formal analysis; Methodology; Visualization; Writing – original draft; Writing – review & editing) Vicki Anderson (Conceptualization; Methodology; Validation; Writing – review & editing) Annie Bernier (Methodology; Validation; Writing – review & editing) Miriam H. Beauchamp (Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing).

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. They are not publicly available because they contain information that could compromise research participant privacy and consent.

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Table 1. Descriptive Statistics for Main Study Variables

Variable	N original	M (SD)	Range
Internal factors			
Sex, males (%)	52 (50.50)		
Age at T2 (months)	103	54.15 (11.67)	36 – 76
Age at T3 (months)	103	67.59 (11.65)	47 – 90
CBQ-Surgency/Extraversion	100	4.77 (.68)	2.83 – 6.33
CBQ-Negative Affect	100	3.99 (.81)	1.42 – 6.25
CBQ-Effortful Control	100	5.53 (.57)	4.09 – 6.50
PedsQL-Physical	99	89.92 (9.97)	43.75 – 100
External factors			
Family living arrangement (%)			
Child lives with both parents	96 (93.20)		
Child lives with mother only	4 (3.90)		
Child lives with father only	1 (1)		
Shared custody	2 (1.90)		
Parental Education	103	2.85 (.85)	1.5 – 6
FAD-General Family Functioning	99	1.62 (.42)	1.00 – 2.75
Cognitive factors			
WPPSI/WISC-Processing Speed	95	105.55 (13.58)	80 – 144
BRIEF	96	49.99 (7.66)	33 – 68
OCTC	103	7.93 (2.22)	2 – 12
Spatial Span	96	7.83 (3.46)	1 – 18
Tower of Hanoi	103	4.40 (1.55)	.50 – 6
WPPSI/WASI-Vocabulary	103	23.04 (7.44)	7 - 61
CCC-Nonverbal Communication	99	1.25 (1.13)	0 – 5.60
FBU	102	3.16 (1.28)	1 – 5
GEM	102	29.55 (17.42)	-14 – 81
NEPSY-Affect Recognition	102	16.03 (4.93)	5 – 31
Outcome			
PEERS-Q	98	106.63 (19.90)	65 – 159

Note. Values are based on the imputed data set. Parental education was obtained by averaging both parents' educational qualifications on an eight-level scale ranging from 'Doctoral degree' to 'Less than 7 years of school'. BRIEF = Behavior Rating Inventory of Executive Function; CBQ = Child Behavioral Questionnaire; CCC = Children's Communication Checklist; FAD = Family Assessment Device; FBU = False Belief Understanding; GEM = Griffith Empathy Measure; NEPSY = Developmental NEuroPSYchological Assessment; OCTC = Object Classification Task for Children; PedsQL = Pediatric Quality of Life Inventory; PEERS-Q = Paediatric Evaluation of

Emotions, Relationships, and Socialisation Questionnaire; WASI = Wechsler Abbreviated Scale of Intelligence; WISC = Wechsler Intelligence Scale for Children; WPPSI = Wechsler Preschool and Primary Scale of Intelligence.

Table 2. Zero-order Correlations among Main Study Variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. Age at T3	---																		
2. Sex	.06	---																	
3. CBQ-S/E	.06	.17	---																
4. CBQ-NA	.28**	-.04	-.19	---															
5. CBQ-EC	.33**	-.33**	-.17	.14	---														
6. PedsQL-Physical	-.02	.09	.26**	-.06	-.10	---													
7. Family living arrangement	.25*	-.05	-.05	-.03	-.08	-.07	---												
8. Parental Education	-.06	.09	-.20*	-.03	-.14	-.09	.06	---											
9. FAD-GFF	.13	.05	-.06	.35***	-.01	-.13	.11	.13	---										
10. WPPSI/WISC -Processing Speed	.08	-.30**	-.14	.08	.28**	-.11	.15	-.16	.10	---									
11. BRIEF	.003	.12	.10	.19	-.29**	-.18	-.05	.20*	.33**	.03	---								
12. OCTC	.52***	-.09	-.04	.01	.18	-.17	.21*	-.13	-.05	.28**	-.03	---							
13. Spatial Span	.69***	-.06	-.02	.18	.29**	-.08	.14	-.20*	.07	.31**	-.08	.52***	---						
14. ToH	.42***	-.08	-.10	.28**	.19	-.09	.11	-.07	.10	.1	-.01	.24*	.41***	---					
15. WPPSI/ WASI-V	.43***	-.02	.12	.28**	.08	.04	-.01	-.22*	.11	.09	.10	.24*	.42***	.33**	---				
16. CCC-NVC	-.14	.12	-.10	.16	-.10	-.13	-.12	.14	.30**	.23*	.38***	-.04	-.04	.06	-.09	---			
17. FBU	.37***	-.12	-.04	.34**	.20*	-.14	.08	-.17	.24*	.17	-.04	.17	.31**	.39***	.48***	.07	---		
18. GEM	.18	-.24*	-.03	.23*	.32**	-.03	-.07	-.07	.02	.11	-.23*	-.01	.15	.11	-.001	-.23*	.19	---	
19. NEPSY-AR	.76***	.10	.05	.26**	.28**	-.02	.20*	-.11	-.01	.17	.11	.47***	.58***	.35***	.39***	-.12	.29**	.09	---

20. PEERS-Q	**-.16**	**.15**	-.09	**.28****	**-.20***	**-.22***	-.06	**.21***	**.38*****	.13	**.63*****	**-.14**	-.01	-.11	-.06	**.58*****	**-.14**	**-.21***	-.01

Note. Variables correlated at a *p*-level < .20 (bolded) were included in the regression model. BRIEF = Behavior Rating Inventory of Executive Function; CBQ = Child Behavioral Questionnaire (S/E = Surgency/Extraversion; NA = Negative Affect; EC = Effortful Control); CCC = Children's Communication Checklist; FAD = Family Assessment Device; FBU = False Belief Understanding; GEM = Griffith Empathy Measure; GFF = General Family Functioning; NEPSY = Developmental NEuroPSYchological Assessment; NVC = Nonverbal Communication; OCTC = Object Classification Task for Children; PedsQL = Pediatric Quality of Life Inventory; PEERS-Q = Paediatric Evaluation of Emotions, Relationships, and Socialisation Questionnaire; ToH = Tower of Hanoi; V = Vocabulary; WASI = Wechsler Abbreviated Scale of Intelligence; WISC= Wechsler Intelligence Scale for Children; WPPSI = Wechsler Preschool and Primary Scale of Intelligence.

* $p < .05$, ** $p < .01$, *** $p < .001$.

Table 3. Hierarchical Regression Analyses Predicting Social Competence (PEERS-Q)

Predicting factors	R2	ΔR2	β	F
PEERS-Q				
Step 1: Internal child factors	.22***	.22***		7.08***
Sex			.20*	
Age			-.28**	
CBQ-Negative Affect			.36***	
PedsQL-Physical			-.22*	
Step 2: External factors	.31***	.09**		7.28***
Sex			.17	
Age			-.28**	
CBQ-Negative Affect			.27**	
PedsQL-Physical			-.17	
Parental Education			.14	
FAD-General Family Functioning			.27**	
Step 3: Cognitive factors	.63***	.32***		14.31***
Sex			.05	
Age			-.09	
CBQ-Negative Affect			.22**	
PedsQL-Physical			-.11	
Parental Education			.01	
FAD-General Family Functioning			.12	
BRIEF			.38***	
OCTC			-.04	
CCC-Nonverbal Communication			.35***	
FBU			-.21**	
GEM			-.03	

Note. BRIEF = Behavior Rating Inventory of Executive Function; CBQ = Child Behavioral Questionnaire; CCC = Children's Communication Checklist; FAD = Family Assessment Device; FBU = False Belief Understanding; GEM = Griffith Empathy Measure; OCTC = Object Classification Task for Children; PedsQL = Pediatric Quality of Life Inventory; PEERS-Q = Paediatric Evaluation of Emotions, Relationships, and Socialisation Questionnaire. Results are based on the imputed dataset. Sex 1 = Girl, 2 = Boy. Lower PEERS-Q (Paediatric Evaluation of Emotions, Relationships, and Socialisation Questionnaire) scores indicate better social competence. Parental education was obtained by averaging both parents' educational qualifications on an eight-level scale ranging from 'Doctoral degree' to 'Less than 7 years of school'.
* $p < .05$, ** $p < .01$, *** $p < .001$.

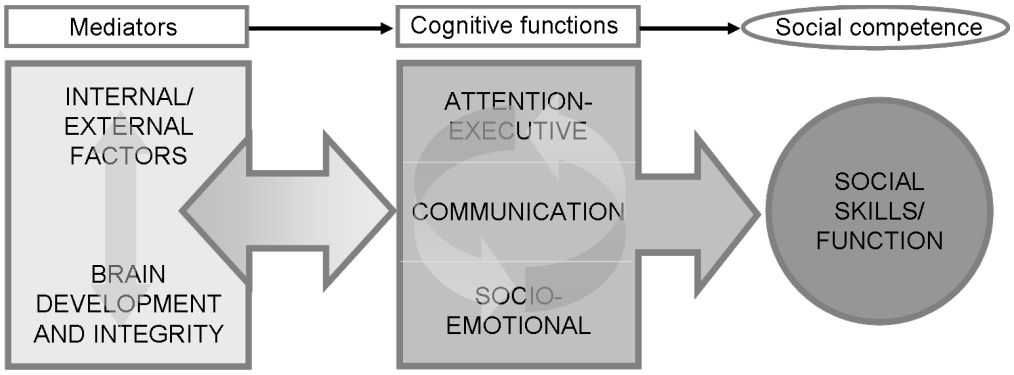

Figure 1. Socio-Cognitive Integration of Abilities modeL.
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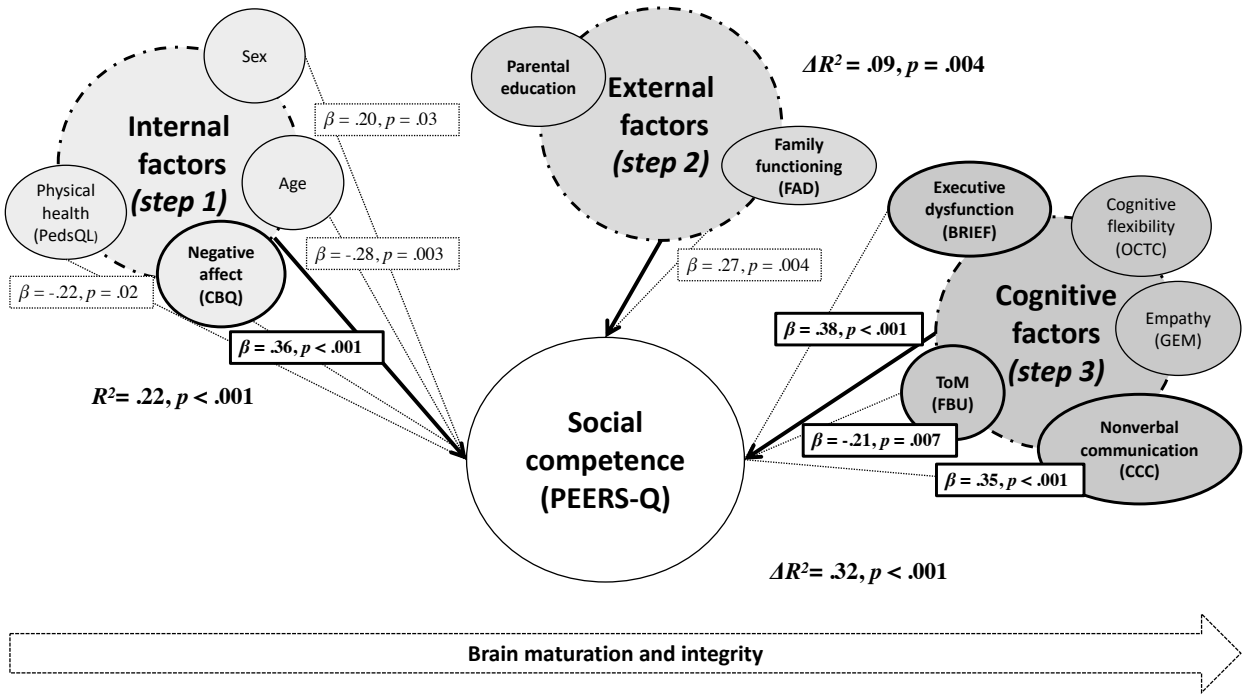

Figure 2. The SOCIAL model as validated in the present preschool sample.
Model validation was performed using 3-step hierarchical regression analyses: Step 1: Internal factors; Step 2: External factors; Step 3: Cognitive factors. Standardized β-values are shown for significant predictors at each step. Significant independent predictors in the final model are highlighted in bold. BRIEF = Behavior Rating Inventory of Executive Function; CBQ = Child Behavioral Questionnaire; CCC = Children's Communication Checklist; FAD = Family Assessment Device; FBU = False Belief Understanding; GEM = Griffith Empathy Measure; NEPSY = Developmental NEuroPSYchological Assessment; OCTC = Object Classification Task for Children; PedsQL = Pediatric Quality of Life Inventory; PEERS-Q = Paediatric Evaluation of Emotions, Relationships, and Socialisation Questionnaire, ToM = Theory of mind.

Article 2

Quality of life 6 and 18 months after mild traumatic brain injury in early childhood: An exploratory study of the role of genetic, environmental, injury, and child factors

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Abstract

Mild traumatic brain injury (mTBI) in early childhood is prevalent, and some children may be at risk for short- and long-term difficulties that could affect quality of life (QoL). Despite growing efforts to understand association between potential risk factors and outcomes after injury, prognosis is elusive and lacks the inclusion of genetic variables which may convey additional predictive power. This study assessed which factors contribute to pediatric QoL 6 and 18 months post-recruitment in 159 participants (mTBI = 52; orthopedic injury [OI] = 43; typically developing controls [TDC] = 64) aged 18 to 60 months at the time of injury (M = 37.50, SD = 11.69). Family environment, injury characteristics, and child cognitive-behavioral functioning were assessed at 6 months via parent questionnaires and socio-cognitive assessment. QoL was determined using the Pediatric Quality of Life Inventory at both time points. Genetic information (Brain-derived neurotrophic factor [BDNF] genotype) was collected using saliva samples. Hierarchical regression analyses testing biological, family-environmental, injury and cognitive-behavioral factors revealed that the BDNF Val66Met polymorphism was a significant independent predictor of better QoL 6 months post-injury in the mTBI group. Lower parental distress significantly and independently predicted higher QoL 18 months after mTBI, and 6 months post-recruitment in the TDC group. At 18 months, models were non-significant for both control groups. Genetic factors involved in neuroplasticity may play an important role in recovery 6 months after mTBI and contribute to outcome via their interplay with environmental factors. Over time, family factors appear to become the primary determinants of post-mTBI outcome.

Keywords: Mild traumatic brain injury**,** quality of life**,** BDNF**,** genetics**,** early childhood.

Introduction

Pediatric traumatic brain injury (TBI) is a frequent cause of disability in children and adolescents, even in its mild form (mTBI or concussion). It is especially prevalent in children five years and under (McKinlay et al., 2008; Trenchard et al., 2013). Early childhood constitutes a particularly important developmental period considering major and rapid brain maturation (Haartsen et al., 2016), rendering it vulnerable to injury. Across all pediatric age groups, a non-negligible minority of children with mTBI exhibit short- and long-term difficulties in neurocognitive, physical, emotional or behavioral functioning (Anderson et al., 2011a; Green et al., 2012; Taylor et al., 2010; Yeates et al., 2009, 2019; Zemek et al., 2013). Impairments in any of these domains can affect day-to-day functioning, individual well-being and overall satisfaction with life; in other words, they can impact a child's quality of life ([QoL]; Anderson et al., 2010; Fineblit et al., 2016). QoL is a broad ranging construct that includes school performance, physical, emotional, social as well as health outcomes, and thus captures the effects of mTBI on children's global functioning and well-being (Brown et al., 2016; McCarthy et al., 2005; Varni et al., 2007). A child's QoL can be negatively impacted if any of the multiple contributing factors such as family environment, cognitive abilities or biological determinants are disrupted (Beauchamp et al., 2019).

Despite generally favourable outcomes and improvements over time after pediatric mTBI (McCarthy et al., 2006; Tilford et al., 2007), some children appear to be more vulnerable, experiencing poor QoL several years post-injury (Brown et al., 2016; Fineblit et al., 2016; McCarthy et al., 2006; Zemek et al., 2016). Previous research has sought to identify risk factors associated with poor outcome after pediatric mTBI (Iverson et al., 2017; Yeates, 2010); however, reliable prognosis is difficult to establish. Heterogeneous recovery trajectories are likely due to complex interactions between multiple variables, such as injury characteristics (e.g., severity, age at injury, post-concussive symptoms [PCS]), child-related factors (e.g., sex, pre-morbid cognitive and behavioral functioning, temperament), as well as factors pertaining to the family environment (e.g., socioeconomic status [SES], quality of parent-child interactions, parent mental health). For example, previous studies indicate that elevated PCS (Boake et al., 2004; Moran et al., 2012; Novak et al., 2016; Stancin et al., 2002), higher parental distress (Rivara et al., 2011), as well as lower SES or family dysfunction (Anderson et al., 2010; McCarthy et al., 2006) contribute to poor outcome after childhood mTBI.

Even when considering multiple variables such as injury, child-related, or family-environmental factors, individuals with seemingly comparable profiles may have different recovery trajectories. Some suggest that genetic factors that are involved in neuroplasticity and modulate neural response to brain injury may offer additional predictive ability in explaining post-TBI outcomes (Kurowski et al., 2019; McAllister, 2010; McAllister et al., 2012; Pearson-Fuhrhop et al., 2012). However, few studies have looked at the role of genetics in recovery after childhood TBI (Kassam et al., 2016; Kurowski et al., 2012, 2019; Treble-Barna et al., 2020).

In the context of acquired brain injury, neuroplasticity refers to changes and reorganization processes at the molecular, synaptic, and cellular level, as well as alterations of neural networks (Su et al., 2016). The brain-derived neurotrophic factor (BDNF), encoded by the gene of the same name, is one of the most commonly studied genetic factors in recovery from neurotrauma in both adults and children, given its critical role in lesion-induced plasticity and outcome after injury. BDNF is a member of the nerve growth family of proteins critically involved in neuronal survival, synaptic plasticity and neurogenesis, thus rendering it a promising target for studying post-TBI outcomes (Casey et al., 2009; Gorski et al., 2003; Snider, 1994; Thoenen, 1995). Indeed, BDNF has been shown to be crucial for central nervous system (CNS) reorganization and repair following neurological injury (Centonze et al., 2007; Di Filippo et al., 2008; Hagemann et al., 1998). Following injury, BDNF is upregulated in the CNS (Chiaretti et al., 2003; Mocchetti and Wrathall, 1995), which is assumed to reflect a neuroprotective mechanism against injury-induced biochemical and molecular alterations and a contribution to synaptic reorganization (Chiaretti et al., 2003). A single nucleotide polymorphism of the BDNF gene named Val66Met (G196A or rs6265) is present in 30 – 50% of the general population (Shimizu et al., 2004). It significantly reduces activity-dependent BDNF release, and therefore has been linked to interference with naturally occurring mechanisms of brain plasticity, diminishing the capacity of the brain for functional recovery after injury (Chen et al., 2004; Egan et al., 2003). Consequently, the Val66Met polymorphism has typically been associated with poorer outcomes post-TBI in adults (McAllister et al., 2012; Pearson-Fuhrhop and Cramer, 2010; Vilkki et al., 2008). However, results are inconsistent (Krueger et al., 2011) and there is a paucity of studies on the role of the BDNF polymorphisms in pediatric TBI. In contrast to the aforementioned findings demonstrating that the presence of the Met allele constitutes a risk factor for poor post-injury outcome in adults, our group

was the first to report a protective effect of the Val66Met polymorphism for behavioral symptoms 6 months after early mTBI (Gagner et al., 2020b).

In sum, despite growing efforts to clarify the role of potential predictors and functional outcomes after pediatric mTBI, results are equivocal and lack the inclusion of genetic predispositions in a biopsychosocial framework, which may confer additional predictive power. Furthermore, longitudinal models considering a range of predictor variables and domains and their association with global outcomes such as QoL are scarce, as are prediction models following early childhood mTBI.

The objective of the present study was therefore to examine the degree to which a range of biological, family-environmental, injury and child cognitive-behavioral factors contribute to pediatric QoL 6 and 18 months following early mTBI (i.e., sustained between 18 and 60 months). It was hypothesized that a combination of the aforementioned factors contributes to QoL post-injury. More specifically, based on previous literature suggesting the importance of physiological factors in the earlier phases post-mTBI and the predominant role of environmental and psychological factors in the later stages of recovery (McNally et al., 2013; van der Horn et al., 2019), we hypothesized that biological factors would especially contribute to QoL 6 months postinjury, and family-environmental and cognitive-behavioral factors would predict QoL 18 months post-injury.

Experimental procedure

Participants

A prospective cohort study on cognitive and social outcomes following early TBI was approved by the local institutional review board and conducted in accordance with the declaration of Helsinki. Informed written consent from the parent was obtained prior to study inclusion. Here, we report on the genetic data collected from a subsample of the larger study as well as behavioral data pertaining to the 6- and 18-months post-injury assessments. More study details as well as previous results on the full sample are reported elsewhere (Bellerose et al., 2015, 2017; Dégeilh et al., 2018; Gagner et al., 2018, 2020a; Lalonde et al., 2018, 2020; Landry-Roy et al., 2017, 2018; Séguin et al., 2020). The present sample includes 159 children recruited to one of three groups: mTBI (n = 52), orthopedic injury ([OI]; n = 43) and typically developing children ([TDC]; n = 64).

In the larger parent study, inclusion criteria for mTBI participants were (i) injury age between 18 and 60 months, (ii) closed accidental head injury with a score between 13 and 15 at admission on the Glasgow Coma Scale ([GCS]; Teasdale and Jennett, 1974), (iii) at least one of the following symptoms: loss of consciousness, excessive irritability, persistent vomiting (more than two times), confusion, amnesia, worsening headaches, drowsiness, dizziness, motor or balance problems, blurred vision, hypersensitivity to light, and/or the presence of seizures. Participants with a diagnosis of mild complicated TBI (score between 13 and 15 on the GCS with evidence of an intracranial lesion on clinical computerized tomography or magnetic resonance imaging) were also included (n = 8). For the OI group, participants were included if they met the following inclusion criteria: (i) age at injury between 18 and 60 months, (ii) accidental limb trauma leading to a final diagnosis of simple fracture, sprain, contusion, or unspecified trauma to an extremity. Inclusion criteria for the TDC group were: (i) aged between 24 and 66 months (to ensure that the group was age-matched to the TBI and OI groups at the first assessment time point, i.e., six months post-injury for the injury groups). Exclusion criteria for all participants were the following: (i) non-accidental injury (for the TBI and OI groups), (ii) diagnosed congenital, neurological, developmental, psychiatric, or metabolic condition, (iii) < 36 weeks of gestation, (iv) child and parent not fluent in French or English, and (iv) history of prior TBI.

Procedure

Children from the mTBI and OI groups were recruited in a single, tertiary care, pediatric emergency department between 2011 and 2015 and screened by a research nurse. TDC were recruited consecutively via advertisements and pamphlets distributed in urban daycare centers. Participants fulfilling inclusion/exclusion criteria were invited to participate in the study.

For the two injury groups, families who agreed to participate were mailed a consent form and questionnaires within one week of injury in order to obtain information about the family environment (family living arrangement, SES, etc.) as well as their child's injury characteristics (time point 0 [T0]). Approximately 6 months post-injury (time point 1 [T1]), parents completed questionnaires with respect to the family environment, and their child's behavior. At this time point, children also participated in a direct socio-cognitive assessment. Given the absence of injury, the children in the TDC group completed T1 as soon as possible after recruitment, using the same socio-cognitive battery and parental questionnaires. Approximately twelve months later,

i.e., 18 months post-injury (time point 2 [T2]), QoL was again assessed via a parent questionnaire. To collect child genetic information, participants were invited to provide a saliva sample, either in person or via mail at any time point during the course of the study. This was optional for all participants. For the present analyses, only those participants who met all inclusion and exclusion criteria, who had completed the T1 and T2 assessments and who had available genetic data were included (Figs. 1 and 2).

Materials and measures

Biological factors

Brain-Derived Neurotrophic Factor (BDNF). Saliva samples (0.75 ml) were collected using Oragene OG-575 kits (DNA Genotek, Ottawa, Canada) which allows to collect saliva with the use of sponges, moved along the child's gums and inner cheeks, and then squeezed into a collection tube when saturated with saliva. To detect the presence of the BDNF polymorphism Val66Met, the amplification was performed using a thermal cycler (Biometra Tprofessional) using a PCR approach, with the following oligonucleotide primer pairs: 5′-biotin before GGACTCTGGAGAGCGTGAAT-3 and 5′-reverse CCGAACTTTCTGGTCCTCATC-3′. In addition to buffers, nucleotide components and a dose of 0.01 U of Taq polymerase supplier of PCR Master Mix (Qiagen), the amplification reactions contained 1 μg of DNA derived from saliva, 1 μM each primer, 0.4 mM of dNTP, 1.0 mM MgCl2, in a final volume of 50 μL. The PCR conditions included 35 cycles: 30 seconds at 95°C; 30 seconds at 61.2°C; and 1 minute at 72°C. These 35 cycles of amplification were preceded by an initial heating step of 3 minutes at 95°C and followed by a final extension of 4 minutes at 72°C. The PCR products were visualized on a 1.2% agarose gel. BDNF polymorphisms were then determined using a well-established pyrosequencing protocol (Petersen et al., 2005) using the following DNA sequencer: 5'-GCTGACACTTTCGAACA -3'. The sequence analyzed was: CA / GTGATAGAAGAG.

Family-environmental factors

Socio-demographic information. At enrolment, the primary caregiver (the mother in 89% of cases) completed an in-house questionnaire to collect demographic information (e.g., sex, ethnicity, parents' occupation, family living arrangement). SES was calculated using parents' scores on the Blishen Socioeconomic Index (Blishen et al., 1987), which provides a score based

on occupations in Canada. Scores range between 0 and 100 with higher numbers representing higher SES. For double-earner families, the highest socioeconomic score was used.

Family functioning. The General Family Functioning subscale of the Family Assessment Device ([FAD]; Epstein et al., 1983) was filled out by the primary caregiver in order to assess parental satisfaction with general family functioning. Each of the 12 items is rated on a 4-point scale, and a higher score indicates poorer family functioning.

Parenting stress. The Parenting Stress Index – BRIEF ([PSI]; Abidin, 1995) was filled out by the primary caregiver and measures the level of distress experienced in their relationship with their child and with regards to their parental role (e.g., perceived competence). The two 12-item subscales Parental Distress and Parent–Child Dysfunctional Interaction were used in the present analyses. Each item is rated on a 5-point scale, and a higher score indicates a higher level of parental distress or parent–child dysfunctional interaction.

Quality of parent–child interactions. An adaptation of the Mutually Responsive Orientation scale ([MRO]; Aksan et al., 2006; Kochanska et al., 2008), which focuses on the dyadic nature of parent–child exchanges, was used to assess the quality of parent–child interactions. Here, two 10-min sequences of parent–child interactions in two different contexts (snack time [MRO-Snack] and toy-centered activity [MRO-Play]) were videotaped during the assessment session. For each interactive context, three subscores (Harmonious Communication, Mutual Cooperation, and Emotional Ambiance) were averaged to create a total MRO score ranging from 1 to 5. Higher scores suggest mutually responsive, cooperative, harmonious, and/or emotionally positive interactions between parent and child, whereas lower scores indicate a disconnected, unresponsive, hostile, and/or affectively negative interaction. In the present study, randomly selected video sequences (23% for MRO snack and 22% for MRO play) were coded independently by two raters and interrater reliability was satisfactory for both subscales (ICC MRO-Snack = 0.80 and ICC MRO-Play = 0.87).

Injury factors

Injury characteristics. For the mTBI and the OI groups, a research nurse completed a standardized case report form immediately after recruitment for descriptive purposes (e.g., nature and severity of the injury, age at injury, neurological signs and symptoms, GCS) and to confirm inclusion/exclusion criteria. Injury severity in the OI group was assessed using the Abbreviated

Injury Scale (AIS; Committee on Medical Aspects of Automotive Safety, 1971) which measures anatomical injury severity on a 5-point ordinal scale (1 = minor, 2 = moderate, 3 = serious, 4 = severe, 5 = critical).

Postconcussive symptoms. The Postconcussive Symptom Interview ([PCS-I]; Mittenberg et al., 1997; Yeates et al., 2012) assesses 15 symptoms from the following domains: Physical, Cognitive, Affective and Sleep. A score out of 15 was calculated for symptoms observed in the past 6 months by the primary caregiver as a measure of long-term PCS.

Cognitive-behavioral factors

Cognitive functioning. The Bayley Scales of Infant Development-Third Edition (Bayley, 2005) cognitive subscale was used as an indicator of general cognitive functioning for children aged 24 to 30 months. The Global Index of the Wechsler Preschool and Primary Scale of Intelligence-Third Edition ([WPPSI-III]; Wechsler, 2002) was used as a measure of general intellectual functioning for children aged 30 months and older. Percentile ranks were used to facilitate direct comparisons between assessment tools. Scores from the Bayley's and WPPSI were combined for analyses.

Temperament. The Early Childhood Behavior Questionnaire-Very Short Form ([ECBQ-VS]; Putnam et al., 2010) for children between 18 and 36 months, or the Child Behavioral Questionnaire-Very Short Form ([CBQ-VS]; Putnam and Rothbart, 2006) for children between three and seven years of age, was filled out by the primary caregiver. The ECBQ-VS and CBQ-VS are 36-item parent-report instruments assessing child temperament with items rated on a 7-point Likert scale. Three subscores are derived: Surgency/Extraversion, Negative Affectivity, and Effortful Control.

Executive functioning. Spin the pots (Hughes and Ensor, 2005) is a working memory task during which children are shown 8 to 12 visually distinct boxes placed on a tray and 6 to 10 stickers (depending on the age). The assessor places the stickers in the boxes and tells children that they will have to find them once the boxes are closed. Each opening of the box is followed by a rotation (360°) of the boxes covered with a fabric and a new search trial begins. The task ends when children found all hidden stickers or when the maximum number of spins is reached A final score is obtained by calculating the proportion of stickers found out of the total number of rotations

needed to find all the stickers (or the maximum number of spins allowed). Higher scores indicate poorer working memory.

The Conflict Scale (Zelazo, 2006) is a cognitive flexibility task which consists of four levels of increasing difficulty. Children are asked to categorize items, either plastic animals or cards, according to a rule, and if they succeed on five trials out of six, the rule is changed in a post-switch phase. For example, children are first instructed to sort cards depicting trucks and stars according to color (blue or red). Then, the experimenter announces that they will stop playing the "color game" and now play the "shape game". Children must then sort cards according to shape (truck or star), regardless of color. There are 12 trials per level, for a maximum of 48 points, and a higher score indicates higher cognitive flexibility.

Shape Stroop (Carlson, 2005; Kochanska et al., 2000): In this inhibition and cognitive flexibility task, children are first shown six cards depicting three fruits (three large and three small fruits) and asked to identify each fruit for a maximum of six points (fruit identification part), as a measure of general preschool abilities. Then, children are shown cards depicting a small fruit embedded in a large fruit (e.g., small banana embedded in a large orange), and asked to point to each small fruit (e.g., "show me the small banana"). A total of three cards are presented, for a maximum of three points, and a higher score indicates better performance (inhibition part). The latter constitutes a conflict task, as children must inhibit the preponderant response (large fruit), to provide an alternative and less automatic response (small fruit).

Theory of mind. Theory of mind (ToM) was assessed using emotion and desires reasoning, and false belief understanding (FBU) tasks. The discrepant desires task (Bellerose et al., 2015; Repacholi and Gopnik, 1997) was administered to children 24 to 35 months of age. This task involves giving children the choice between two foods, one typically liked by children (e.g., cookies) and one that is generally less preferred (e.g., broccoli). Children are first given the chance to express their preference. Then the experimenter expresses a preference for children's nonpreferred food and then asks them to give her another food item because she is still hungry. The goal of the task is to assess whether children will answer egocentrically or will consider the experimenter's preferred food, even if it differs from their own. A total of four food combinations are presented, for a maximum of four points. For older children (> 36 months), a more advanced task in the form of stories was administered, assessing children's understanding of how fulfilled and unfulfilled desires might affect a character's feelings (Desires task; Bellerose et al., 2015;

Pears and Moses, 2003). The stories describe a character's search for a desired object in a particular location with three possible endings to the story: (a) the character finds the desired object, (b) he finds nothing, or (c) he finds a different object, not initially sought after. Children are asked to speculate on the character's feelings (happy or sad) in these three scenarios. Each possible ending is presented twice, for a total of six different stories. A score out of a possible six points is calculated. For both desires tasks, *z*-scores were calculated and the scores from the two tasks were combined for analyses.

During a false belief understanding (FBU) task (Bellerose et al., 2015; Hughes et al., 2011), children are presented with a peep-through picture book which incorporates a deceptive element and are then asked to recall their own initial belief about what they saw, as well as predict a puppet's belief via two forced-choice questions. For example, children are made to believe that they see an eye through the peep-through hole, but they find out at the end of the story that it is a spot on a snake. They are then asked: "Before we turned the page, what did you think it was, an eye or a snake?" and [Turn back to initial page, before the child saw it was a spot and not an eye] "This is Leo [puppet], he has never read this book, what does he think it is, an eye or a snake?" A control question is also included "What is it really, an eye or a snake?". For both scenarios, children receive credit (one point) only if they are able to answer the corresponding control question, for a maximum of two points.

Quality of life

The Pediatric Quality of Life Inventory 4.0 ([PedsQL 4.0]; Varni et al., 2001, 2007) is a generic measure of health-related QoL in children that assesses physical, mental, and social health as well as school functioning. The parent proxy-report for children aged between two and seven years was completed by the primary caregiver and consists of 23 items (21 items for children aged between two and four years) that are rated on a 5-point scale. Items are then transformed into a total healthy summary score (range 0 to 100) with higher scores indicating better QoL.

Statistical analyses

Preliminary analyses

Analyses were carried out in SPSS version 25. There were missing data across participants and measures owing to some parents' or children's failure to complete measures or assessment

time points. Rates of missing data varied from 1% to 21% across measures and groups and were hence below the recommended maximum threshold of 50% for multiple imputation (Collins et al., 2001; Graham, 2009). One of the recommended best practices for handling missing data is to estimate missing values with multiple imputation methods (Enders, 2010). The pattern of missing data was analyzed using Little's MCAR test, which tests the null hypothesis that data are missing completely are random. The test indicated that data were missing completely at random ($\chi 2(1) = 162.02$, $p = .99$). However, since Little's test has low statistical power (Enders, 2010), complete and incomplete cases (for variables revealing 5% or more of missing data) were also compared to investigate whether they differed on any of the sociodemographic variables or on the main outcome. Participants who had missing data on the Spin The Pots (n = 13), the Conflict Scale (n = 16), FBU (n = 22) and the Desires tasks (n = 12) were younger at both time points (all *t*s between 2.4 and 7.2, *p*s < .05). In addition, those who had missing data on the Conflict Scale task (n = 16) had lower SES ($t(153) = 2.3$, p = .04). In cases of missing data on the MRO-Play situation (n = 30), participants had lower PedsQL scores at T2 ($t(118) = 2.1$, $p = .04$). Last, participants with missing PedsQL data at T2 (n = 12) were girls in 91% of cases (p = .001), and had lower SES ($t(142) = 7.3$, $p < .001$). Missing data are considered missing at random (MAR) when a systematic association exists between the probability of missing data and one or more measured variables (Enders, 2010). Therefore, the data were MAR in the current study, which allows for optimal use of multiple imputation. To correct for bias and maximize the precision of imputed data, demographic information was included in the imputation model (Enders, 2010).

Missing values were imputed using the Markov Chain Monte Carlo procedure in SPSS (Geyer, 1992). Twenty imputations were applied according to recommendations, and missing data estimated from all other data available (including sociodemographic information, MRO and PedsQL as per the analyses above) to maximize algorithm precision (Enders, 2010; Graham, 2009). Analyses were then run on each imputed data set and results averaged (Schafer, 1997). Descriptive statistics were calculated to examine variable distributions.

Selection of predictors

Zero-order correlations were performed in the mTBI group to identify multi-collinearity and to select potential contributing factors of QoL (PedsQL) among candidate predictor variables including child biological factors (Sex, BDNF genotype), family-environmental factors (SES,

FAD-General Family Functioning, PSI-Parental Distress, PSI-Parent-Child Dysfunctional Interaction, MRO-Snack, MRO-Play), injury variables (Age at Injury, Lowest GCS, PCS-I) as well as cognitive-behavioral factors (Bayley/WPPSI-Cognitive functioning, ECBQ/CBQ-Surgency/Extraversion, ECBQ/CBQ-Negative Affectivity, ECBQ/CBQ-Effortful Control, Spin The Pots, Conflict Scale, Shape Stroop-Identification, Shape Stroop-Inhibition, Desires Tasks, FBU). Variables found to be correlated with PedsQL at T1 or T2 at a *p*-level < .20 were included in the regression models. In cases where two subscores of the same task or questionnaire were correlated with PedsQL at the $p < .20$ level, only the subscore that met the threshold at both T1 and T2 was considered for inclusion in order to limit the number of predictors in light of a modest mTBI sample size (n = 52). SES was included in all models independent of its correlation with PedsQL to control for potential effects of socioeconomic backgrounds.

Main analyses

First, a 2 x 3 mixed analysis of variance (ANOVA) with Time (T1, T2) as a within-subject factor and Group (mTBI, OI, TDC) as a between-subject factor was performed to investigate group differences on PedsQL and to determine whether there was a change in PedsQL over time. Two hierarchical regression analyses were run to examine which factors contribute to QoL (PedsQL) 6 months following early mTBI, and to explore the predictive value of those factors for long-term QoL, 18 months after early mTBI. Potential contributing factors were entered in four steps: 1) variables representing unchangeable biological factors; 2) family-environment factors; 3) injury characteristics; and 4) cognitive-behavioral variables. The latter were added to determine whether child-related variables that might be affected by TBI more directly contribute to QoL above and beyond biological, family and injury characteristics. Note that no interaction terms were included in these models in order to preserve degrees of freedom, given the relatively small sample size and the number of predictors. Identical models (without TBI-specific variables) were run for the two control groups.

Results

Preliminary analyses

Information on recruitment and follow-up details of participants are presented in Figs. 1 and 2. There were no differences in terms of age at recruitment (mTBI: $t(1,253) = 1.04$, $p = .30$,

OI: $t(1,256) = .42$, $p = .67$, TDC: $t(1,116) = 1.09$, $p = .28$) and sex (mTBI: $\chi 2\,(1) = .07$, $p = .79$, OI: $\chi 2(1) = .01$, $p = .95$, TDC: $\chi 2\,(1) = 1.85$, $p = .17$) between those who participated in the larger research project and those who refused to participate. Concerning attrition, 13 mTBI (11%), 17 OI (17%) and 1 TDC (1%) initially agreed to participate in the larger project but dropped out before T0 (T1 for the TDC participants). More families from the injury groups than the TDC group dropped out before T1 likely because 6 months elapsed between recruitment and T1 for the injury groups, whereas for the uninjured TDC group, T1 was completed immediately after recruitment. Among those who completed both the T1 and the T2 assessments, there were 21 mTBI (17%), 11 OI (11%) and 14 TDC (16%) with missing BDNF genotype. The main reasons for missing genetic data were: the parent did not want to participate in the genetic substudy, the parent was no longer reachable or had abandoned the project before genetic data could be collected, the parent did not return the sample that had been sent by mail with instructions for collection. The proportion of children with missing BDNF genotype was similar across groups ($\chi 2(2) = 2.72$, $p = .26$). There were no differences between families who agreed to participate in the genetic substudy and those who refused, in terms of child age ($p = .21$), SES ($p = .63$), PedsQL at T1 ($p = .08$), or PedsQL at T2 ($p = .09$). However, there was a difference in child sex ($\chi 2(1) = 4.06$, $p = .04$); the sex distribution was different for those that did not participate (28 girls vs 18 boys) compared to those that did participate in the genetic substudy (70 girls vs 89 boys).

In the final sample, 98 participants carried the wild-type Val66Val polymorphism (Val/Val homozygotes) and 61 participants carried at least one copy of the Met allele (Val66Met or Met66Met), thus 38% of the overall sample. Participants with Val/Met and Met/Met genotypes were combined for statistical analyses into a Met-allele carriers group. The proportion of Val/Val vs. Met-allele carriers was similar for each participant group: mTBI (60% Val/Val vs. 40% Met carriers), OI (63% Val/Val vs. 37% Met carriers) and TDC (63% Val/Val vs. 38% Met carriers). Participants' characteristics as well as injury details for the mTBI and OI groups are summarized in Table 1. All variables showed satisfactory variability and screening of variable distributions revealed normal or near-normal distributions. There were no between-group differences for the following demographic variables: child age at each assessment, age at injury, sex, ethnicity and family living arrangement.

Correlations and selection of predictor variables

Table 2 presents the zero-order correlations among all relevant study variables as well as with the outcome measure (PedsQL) in the mTBI group. For the PSI and ECBQ/CBQ, two subscores correlated with PedsQL at the $p < .20$ level, thus only the subscale that correlated with PedsQL at both time points was included in the model, i.e., PSI-Parental Distress and ECBQ/CBQ-Negative Affectivity. Given the number of age variables that were significantly intercorrelated, which is inherent to the longitudinal study design, only Age at Injury was included in subsequent analyses. Consequently, the first step of the regression models for PedSQL at T1 and T2 included nonmodifiable biological factors (Sex, BDNF genotype). Then, in step 2, family factors (SES, PSI-Parental Distress, MRO-Snack) were entered. The third step included injury variables (Age at Injury, Lowest GCS, PCS-I). In the fourth and last step, child cognitive-behavioral variables were added as predictors (ECBQ/CBQ-Negative Affectivity, Shape Stroop – Identification, FBU) to determine whether cognitive-behavioral variables would explain QoL over and above biological, family-environmental and injury factors. For the OI group, injury severity was included in the injury block (in addition to Age at Injury and PCS-I). Given the absence of injury in the TDC group, Age at assessment (T1) and PCS-I were included in the third (injury) block. Fig. 3 illustrates the regression model with all predictors.

Main analyses

A 2 x 3 mixed model ANOVA showed neither a significant main effect of Group ($F(2,156) = .69$, $p = .52$), nor a significant main effect of Time ($F(1,156) = .28$, $p = .62$) or a Group X Time interaction ($F(2,156) = 2.17$, $p = .12$), indicating that there were no overall PedsQL differences between groups, nor did the scores change over time. Two hierarchical regression analyses were conducted to identify which variables contribute to QoL 6 and 18 months after early mTBI (Table 3).

At 6 months post-injury, biological factors (Sex, BDNF genotype) were entered in the first step and did not explain a significant portion of variance in PedsQL ($F(2,49) = 2.27$, $p = .12$). In step 2, family-environmental factors (SES, PSI-Parental Distress, MRO-Snack) were added, but did not contribute significantly to the model ($\Delta F(3,46) = 2.19$, $p = .12$). Adding injury characteristics (Age at Injury, Lowest GCS, PCS-I) in step 3 explained an additional 18% of the variance in PedsQL and this change was significant ($\Delta F(3,43) = 4.29$, $p = .01$). At this stage, BDNF

genotype (β = 0.28, p = .02), MRO-Snack (β = 0.32, p = .03), Age at injury (β = 0.26, p = .04) and PCS-I (β = -0.33, p = .03) were all significant independent predictors of PedsQL. Specifically, children who were Met-allele carriers, and who had better parent–child interactions, sustained injury at an older age and presented fewer PCS, were reported to have better QoL 6 months postinjury. In step 4, cognitive-behavioral factors were added (ECBQ/CBQ-Negative Affectivity, Shape Stroop-Identification, FBU), but did not explain significantly more of the variance in PedsQL than did biological, family-environmental and injury factors (ΔF(3,40) = 0.91, p = .41). The final model with all independent variables, i.e. biological, family-environmental, injury and cognitive-behavioral factors, was significant (F(11,40) = 2.79, p = .01) and explained 41% of the total variance in PedsQL. BDNF genotype was the only significant independent predictor of PedsQL in the final model (β = 0.26, p = .05), indicating that children who were Met-allele carriers had better QoL.

A second regression analysis was also performed to predict PedsQL 18 months post-injury. In step 1, biological factors (Sex, BDNF genotype) were entered into the model and did not explain a significant portion of variance in PedsQL (F(2,49) = 1.15, p = .30). Then, in step 2, family-environmental factors (SES, PSI-Parental Distress, MRO-Snack) were added and explained a significant additional 16% of variance in PedsQL (ΔF(3,46) = 3.07, p = .04). Parental Distress was an independent significant predictor of PedsQL at this stage (β = -0.40, p = .004), with lower parental distress predicting better QoL. When injury factors (Age at injury, Lowest GCS, PCS-I) were introduced in step 3, the overall model remained significant (F(8,43) = 2.74, p = .02), but this step did not explain additional significant variance in PedsQL (ΔF(3,43) = 2.59, p = .06). At this stage, PSI-Parental Distress (β = -0.40, p = .01) and Age at Injury (β = 0.31, p = .02) were significant independent predictors of PedsQL, indicating that lower parental distress and older injury age contributed to better QoL. In step 4, cognitive-behavioral factors (ECBQ/CBQ-Negative Affectivity, Shape Stroop-Identification, FBU) did not significantly explain PedsQL above and beyond biological, family-environmental and injury factors (ΔF(3,40) = 1.54, p = .22). The final model with all independent variables was significant and all variables jointly accounted for 39% of the variance in PedsQL (F(11,40) = 2.52, p = .02). PSI-Parental Distress was the only significant independent predictor of PedsQL (β = -0.31, p = .04), with lower parental distress predicting better QoL.

Neither biological (R^2 = 0.03, F(2,40) = 0.66, p = .52), family-environmental (ΔR^2 = 0.07, F(5,37) = 0.89, p = .50), injury (ΔR^2 = 0.01, F(8,34) = 0.57, p = .79) nor cognitive-behavioral factors (ΔR^2 = 0.08, F(11,31) = 0.72, p = .70) significantly contributed to PedsQL at 6 months post-injury in the OI group. Similarly, at 18 months post-injury, neither biological (R^2 = 0.10, F(2,40) = 2.37, p = .10), family-environmental (ΔR^2 = 0.05, F(5,37) = 1.45, p = .24), injury (ΔR^2 = 0.004, F(7,35) = 0.85, p = .57) nor cognitive-behavioral factors contributed to PedsQL 18 months post-injury in the OI group (ΔR^2 = 0.01, F(11,31) = 0.63, p = .78).

In the TDC group at T1, biological factors did not explain significant variance in PedsQL (R^2 = 0.01, F(2,61) = 0.22, p = .80). In step 2, family-environmental factors explained an additional significant 32% of total PedsQL variance (ΔR^2 = 0.32, p < .0001, F(5,58) = 5.79, p = .001) with PSI-Parental Distress emerging as a significant independent predictor of PedsQL (β = -0.57, p < .0001). Neither the addition of Age nor PCS-I in step 3 (ΔR^2 = 0.07, p = .06, F(7,56) = 5.36, p < .0001), nor cognitive-behavioral factors in step 4 (ΔR^2 = 0.02, p = .64, F(10,53) = 3.90, p = .001) significantly explained additional variance in PedsQL. PSI-Parental Distress remained a significant independent predictor in all steps of the model (p < .001), with lower parental distress predicting better QoL. In the TDC group at T2, neither biological (R^2 = 0.02, F(2,61) = 0.66, p = .54), family-environmental (ΔR^2 = 0.11, F(5,58) = 1.81, p = .14), injury (i.e., Age and PCS-I; ΔR^2 = 0.04, F(7,56) = 1.69, p = .16) nor cognitive-behavioral factors (ΔR^2 = 0.03, F(10,53) = 1.36, p = .26) significantly contributed to PedsQL.

Of note, these results need to be considered in their exploratory context, given the number of predictors in relation to the small sample size.

Discussion

This study explored what biological, family-environmental, injury and cognitive-behavioral factors contribute to QoL 6 and 18 months after early mTBI (i.e., sustained between 18 and 60 months of age). The comprehensive range of potential predictors included a genetic factor (BDNF genotype), a variable rarely included in prognostic TBI models, much less in the context of early brain injuries, and thus represents an innovative strength of the study. Overall, groups did not differ in terms of QoL at either time point, with scores remaining in the normal range, echoing reports that, at least at the group-level, the majority of children with mTBI recover well (Beauchamp et al., 2018; Zemek et al., 2016). Nonetheless, understanding what contributes to

good QoL after early mTBI provides insight on both risk and protective factors that can be useful for identifying children who may need additional services and resources post-injury and for optimizing factors that will ensure favorable recovery.

Quality of life 6 months post-injury

Biological, family-environmental and injury factors jointly contributed to QoL 6 months after mTBI. That is, children with mTBI who were Met-allele carriers, had better parent–child interactions, were older at the time of the injury and experienced fewer PCS were reported to have better QoL. When cognitive-behavioral factors were additionally considered, genetic aspects, in the form of BDNF genotype, were the only significant predictor of QoL, in line with the initial hypothesis assuming an important role for biological factors in the earlier phases post-mTBI. Although the current results are conjectural given the limited sample size, and require replication in larger samples in order to be generalizable, they suggest that genetic factors, at least those related to BDNF, may be useful in explaining outcome after mTBI in young children. Carrying the Met allele predicted better QoL 6 months post-injury. This is contrary to some findings in adults with TBI reporting that the Met allele is often associated with poorer outcome, such as in cognitive (McAllister et al., 2012; Pearson-Fuhrhop and Cramer, 2010) and affective domains (Narayanan et al., 2016; Wang et al., 2018). This has been interpreted as being due to the association of the Val66Met polymorphism with a decrease in activity-dependent BDNF release (Chen et al., 2004) and a diminished potential for neuroplasticity, which may interfere with TBI recovery (Siironen et al., 2007). Other studies, however, indicate a protective effect for the Val66Met polymorphism in terms of long-term cognitive outcomes after severe TBI in adults (Krueger et al., 2011).

In previous work, our group also detected a protective effect of the Val66Met polymorphism on behavior in the current sample (Gagner et al., 2020b): children with early mTBI who were Met-allele carriers displayed less internalizing behavior problems compared to Val/Val carriers 6 months post-injury. Importantly, in typical development, alterations in BDNF levels differentially affect behavioral phenotypes across childhood (Casey et al., 2009). While naturally occurring plasticity is beneficial for healthy development during early childhood as the brain undergoes rapid maturational changes (Ivanova and Beyer, 2001; Silhol et al., 2005), mechanisms of brain plasticity in the young brain as a response to brain injury, i.e., a higher potential for plasticity in Val/Val homozygotes (via greater BDNF release), may be detrimental in the context

of significant, TBI-induced BDNF overexpression (Chiaretti et al., 2003). Indeed, increased plasticity may lead to poorer functional outcomes through faulty neurotransmissions and perturbations in neural connections (Giza and Prins, 2006). The enhanced potential for plasticity in the young developing brain may translate into poorer functional outcomes (Anderson et al., 2011b). Of note, BDNF genotype was a significant predictor of QoL only when injury factors were considered and remained the sole significant predictor in the full model. Given the known associations between BDNF and cognitive (e.g., Barbey et al., 2014; McAllister et al., 2012) and emotional symptoms after mTBI (e.g., Narayanan et al., 2016; Wang et al., 2018), BDNF may affect these domains, which then translates into reduced everyday functioning and thus poorer QoL. The link between BDNF and QoL may therefore be explained by a genetically determined better or worse response to TBI on a neural level (Treble-Barna et al., 2020), which could then possibly affect neurobehavioral outcomes, in turn impacting overall recovery, well-being, and QoL. Importantly, BDNF emerged as a significant predictor of QoL in the mTBI group only, suggesting a specific negative effect of an overexpression of BDNF on outcome following brain injury.

Quality of life 18 months post-injury

Family factors significantly contributed to QoL 18 months post-injury, with lower parental distress associated with better QoL. Furthermore, when injury characteristics were considered in the model, older injury age was, as in the 6-month model, associated with better QoL in addition to lower parental distress. Parental distress was the only significant independent predictor of QoL when all factors were considered together. BDNF genotype did not significantly contribute to QoL at this later stage post-injury.

These findings highlight the importance of considering family factors when predicting post-TBI outcome. For example, parents of children with mTBI tend to report higher levels of parental distress (i.e., their perceived level of competence, and feelings of conflict, support and depression associated with their role as a parent; Abidin, 1995) as demonstrated in previous studies (Bendikas et al., 2011; Clark et al., 2008). Reasons for parental distress include for example concerns about school performance, lack of friendships, and feelings of anger and apathy in their child following TBI, independent of injury severity (Prigatano and Gray, 2007). In addition, recovery and fear of the consequences of TBI for the future represent major parental worries

(Ganesalingam et al., 2011; Prigatano and Gray, 2007). In the current cohort, parental distress was related to both increased externalizing behaviors and poorer quality parent–child interactions (Gagner et al., 2018; Lalonde et al., 2020). Parental distress has also been shown to affect child stress after pediatric TBI, with secondary effects on the quality of parent–child interactions (Biringen et al., 2000; Cowan and Cowan, 2003), child emotional functioning (Labrell et al., 2018), and well-being (De Young et al., 2014). The present findings together with previous evidence underscore the importance of parental factors for a child's long-term QoL.

Interplay of genetic and environmental factors in determining QoL

Overall, in this preliminary study on a small sample, the findings suggest that genetic factors (i.e., BDNF genotype) may play an important role in earlier stages of the recovery process and up to 6 months post-injury, thus closer to the time when the brain undergoes restructuring following brain insult. It can be speculated that the effects of a sudden up-regulation of BDNF in the acute phase post-injury (i.e., as a protective mechanism) are still noticeable 6 months post-injury. When BDNF- levels return to normal at later stages of the recovery process, i.e., 18 months post-injury, the effect of BDNF weakens, and other factors become primary determinants of QoL.

The finding that both BDNF genotype and parent–child interactions are predictive of QoL when considered jointly with injury variables (step 3), and that BDNF genotype is the only predictor in the full model, tentatively suggests that QoL at 6 months post-injury may be the result of complex interplays between the neural response to injury (as conferred through changing BDNF levels), family-environmental (i.e., parent–child interactions) and injury factors (i.e., injury age, PCS). This assumption is also supported by evidence that BDNF interacts with environmental variables to predict neuroanatomical and behavioral phenotypes (Hosang et al., 2014; Zhao et al., 2018). Although speculative in light of the sample size and limited statistical power of the present study, it is possible that over time the neural effect fades. At 18 months post-injury, non-injury factors, i.e., family-environmental factors, may become the primary determinants of post-mTBI outcome, supporting the critical role of environmental factors including intact family functioning for healthy development, in line with previous TBI research (McNally et al., 2013; van der Horn et al., 2019). This is also supported by a similar finding in typically developing children in the present sample, where lower parental distress predicted better QoL at the first follow-up time point.

Strengths, limitations and future directions

This is the first study to investigate QoL in a sample of children who sustained early mTBI (that is, before the age of five years), a developmental subgroup in which prevalence of mTBI is high (Trenchard et al., 2013). The study is also novel in that it tests an inclusive model with multiple predictors of QoL using diverse sources and modalities such as observational data, parent reports and direct child assessments, allowing for a comprehensive evaluation of several domains of functioning. Another strength of the work involves the longitudinal aspect of the study, as very few prospective prediction models exist for early mTBI. In addition, a genetic variable (BDNF) was included in the analyses, which is rarely the case in mTBI research, even less so in studies of early mTBI. Including OI participants constitutes a rigorous manner to control for the effects of pre-injury differences and general injury effects such as fatigue or pain (Mathias et al., 2013; McKinlay et al., 2010), allowing for mTBI-specific conclusions. Including typically developing children additionally allowed for comparisons between children with mTBI and the peers they are compared to in everyday life.

Nonetheless, some limitations need to be considered. First, the sample size was modest for a genetic study and the magnitude of the genetic effects is small. As such, the associations between BDNF and QoL may be underestimated. In addition, the inclusion of several predictor variables may have inflated type I error. Therefore, the current results are preliminary and conclusions about the role of BDNF in determining outcome after early mTBI should be made cautiously. A common limitation in the existing literature on genetic effects on outcome after pediatric TBI is the observation that effects are typically small. Thus, multi-center studies are key in order to recruit larger samples which will allow for better generalizability and increased statistical power to detect potentially small effects. Second, due to the longitudinal nature of the study, some participants had incomplete follow-up data. However, multiple imputation was used to address this, following recommended best practices for handling missing data (Enders, 2010). Third, a parent questionnaire (PedsQL) was used to measure QoL, possibly introducing reporter bias. However, given the very young age of participants, self-report or direct child assessments of QoL would have been difficult if not impossible to obtain. Fourth, PCS were assessed using the PCS-I (Mittenberg et al., 1997) which was initially designed for use in children aged 5 to 18 years and may thus not capture the characteristics and symptoms of early childhood mTBI. This tool was chosen given that there is currently no validated measure for tracking PCS in children five years

and under. Future efforts need to consider the limited verbal and introspective skills young children are likely to have in relation to their PCS (Beaudoin et al., 2017). Fifth, only those who agreed to participate in the genetic substudy were included, which may have introduced bias in relation to the larger study population. However, there were no sociodemographic (age, SES) or PedsQL differences at either time point between those who participated in the genetic substudy and those who did not. Finally, Caucasians were overrepresented in the present sample. Importantly, there is evidence showing that genotype prevalence differs according to ethnicity and is associated with different phenotypes depending on ethnic group (Tsai, 2018). Unfortunately, given the modest number of participants, we were not able to test Hardy-Weinberg equilibrium to examine whether there was an under- or overestimation of participants with mTBI who were Met-allele carriers. Thus, future efforts should aim to address these limitations and use larger and more ethnically diverse samples in order to investigate whether results differ as a function of ethnic differences. In addition, in order to enhance generalizability and to better characterize the role of genetics in recovery after early mTBI, future work could also include additional gene candidates and polymorphisms that may play a role in pediatric mTBI outcome, such as those involved in response to brain injury, repair and neuroplasticity as well as cognitive capacity and reserve, for example, TP53, Apolipoprotein E, or DAT (see McAllister, 2010 for a review). In addition, other candidate genes could be those associated more directly with cognitive and behavioral capacity and outcomes, such as catecholamine genes or those involved in neurotransmitter signaling, such as dopaminergic system genes (Bennett et al., 2016; McAllister, 2010). A recent study by Kurowski and colleagues (2019) shows promise in investigating polygenetic effects using a systems biology-informed approach to explore a combination of genetic factors that are associated with distinct biological processes involved in TBI. Further efforts towards polygenetic approaches will be important in order to disentangle the distinct role of specific genetic markers for different aspects of outcome after pediatric TBI, such as cognitive functioning or clinical outcomes (McAllister, 2010). Parent genotype could be assessed to control for interactions between parent report and genotype. Future studies could also detail findings with regard to subdomains of QoL (i.e., physical, social, intellectual, emotional).

Conclusion

This is the first study to comprehensively examine the associations between mTBI sustained in early childhood and long-term QoL. The results provide preliminary evidence for the importance of considering genetic factors in predicting mTBI outcome. BDNF may contribute to QoL via its interplay with non-neurological, i.e., family environments and injury factors. In the long term, these effects seem to fade, with levels of parental distress instead becoming the determining factor for child QoL, suggesting a need for monitoring the health and emotional well-being of parents. This study provides the proof-of-concept for future efforts using larger samples to investigate the role of genetic factors in early mTBI outcome. Tracking QoL after early mTBI can be useful for monitoring global recovery and identifying functional disability across domains.

CRediT authorship contribution statement

Carola Tuerk: Conceptualization, Formal analysis, Methodology, Visualization, Writing - original draft. Charlotte Gagner: Conceptualization, Investigation, Writing - review & editing. Fanny Dégeilh: Data curation, Writing - review & editing. Jenny Bellerose: Investigation, Writing - review & editing. Gabrielle Lalonde: Investigation, Writing - review & editing. Catherine Landry-Roy: Investigation, Writing - review & editing. Marilou Séguin: Investigation, Writing - review & editing. Louis de Beaumont: Resources, Writing - review & editing. Jocelyn Gravel: Resources, Writing - review & editing. Annie Bernier: Methodology, Validation, Writing - review & editing. Miriam H. Beauchamp: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. Participants' Characteristics For The Mild Traumatic Brain Injury, Orthopedic Injury, And Typically Developing Control Groups

	mTBI (N = 52)	OI (N = 43)	TDC (N = 64)	*F / t / χ2*	*p*
Biological factors					
Sex, n (%) males	32 (61.54)	21 (48.84)	36 (56.25)	1.54	0.46
BDNF genotype, n (%) Val/Met or Met/Met	21 (40.39)	16 (37.21)	24 (37.50)	0.13	0.94
Age at T1 (months), *M (SD)*	44.17 (11.69)	41.50 (11.43)	43.78 (11.69)	0.71	0.49
Age at T2 (months), *M (SD)*	56.32 (11.70)	53.32 (11.95)	55.72 (11.75)	0.84	0.43
Family-environmental factors at T1					
SES, *M (SD)*	54.80 (15.58)	59.64 (12.52)	59.07 (10.98)	2.16	0.13
Ethnicity (Caucasian), n (%)	47 (90.38)	34 (79.07)	56 (88.89)	14.9	0.061
Family living arrangement, n (%)	--	--	--	6.33	0.39
Child lives with both parents	45 (88.24)	42 (97.67)	58 (92.06)	--	--
Child lives with mother only	6 (11.76)	1 (2.33)	5 (7.94)	--	--
Shared custody	1(1.92)	--	--	--	--
General Family Functioning (FAD), *M (SD)*	1.54 (0.41)	1.65 (0.48)	1.53 (0.37)	1.20	0.30
Parental Distress (PSI), *M (SD)*	2.09 (0.62)	1.96 (0.58)	2.01 (0.66)	0.54	0.59
Parent-Child Dysfunctional Interaction (PSI), *M (SD)*	1.54 (0.36)	1.50 (0.38)	1.43 (0.41)	1.24	0.29
Parent-child interaction (MRO-Snack), *M (SD)*	3.22 (0.66)	3.08 (0.62)	3.23 (0.64)	0.98	0.41
Parent-child interaction (MRO-Play), *M (SD)*	2.93 (0.58)	3.07 (0.55)	3.19 (0.63)	2.94	0.09
Injury factors					
Age at injury (months), *M (SD)*	37.50 (11.69)	34.60 (11.67)	--	1.20	0.23
TBI injury severity (Lowest GCS), *M (SD)*	14.78 (0.54)	--	--	--	--
OI injury severity (AIS), *M (SD)*	--	1.70 (0.51)	--	--	--
Long-term PCS (past 6 months, PCS-I), *M (SD)*	2.31 (3.01)	.51 (0.96)	0.60 (1.61)	12.54	< 0.001
Child behavioral and cognitive measures at T1					
Cognitive functioning (Bayley, WPPSI), %ile rank	57.88 (25.81)	62.19 (22.54)	61.42 (22.82)	0.48	0.62

Temperament (ECBQ, CBQ)					
Surgency/Extraversion, *M (SD)*	4.33 (1.26)	3.94 (1.32)	3.92 (1.37)	1.60	0.21
Negative Affectivity, *M (SD)*	4.33 (1.18)	4.52 (.84)	4.40 (1.02)	0.42	0.66
Effortful Control, *M (SD)*	5.28 (1.02)	5.38 (.62)	5.38 (0.89)	0.24	0.79
Executive functioning					
Spin The Pots, *M (SD)*	0.74 (0.17)	0.71 (0.23)	.70 (.18)	0.60	0.57
Conflict Scale, *M (SD)*	31.64 (16.05)	29.52 (17.28)	28.56 (16.82)	0.53	0.61
Shape Stroop-Identification, *M (SD)*	5.33 (1.36)	5.55 (1.05)	5.75 (.64)	2.39	0.10
Shape Stroop-Inhibition, *M (SD)*	2.42 (0.95)	2.48 (0.90)	2.58 (.72)	0.55	0.59
Theory of mind					
Desires tasks, *z*-score, *M (SD)*	-0.20 (1.07)	-0.07 (1.07)	0.18 (0.90)	2.22	0.13
False Belief Understanding, *M (SD)*	0.55 (0.69)	0.76 (0.78)	0.98 (0.75)	4.99	0.01
Quality of life					
PedsQL at T1, *M (SD)*	83.80 (9.76)	85.85 (8.77)	85.74 (10.11)	0.75	0.48
PedsQL at T2, *M (SD)*	84.90 (8.48)	83.21 (9.90)	86.15 (9.03)	1.40	0.27

Note. Values are based on the imputed data set (not imputed: family living arrangement, ethnicity).
AIS = Abbreviated Injury Scale, CBQ-VS = Child Behavioral Questionnaire Very Short Form, ECBQ-VS = Early Childhood Behavior Questionnaire Very Short Form, FAD = Family Assessment Device, GCS = Glasgow Coma Scale, IQ = Intelligence Quotient, MRO = Mutually Responsive Orientation, PedsQL = Pediatric Quality of Life Inventory, PCS = Postconcussive symptoms, PCS-I = Postconcussive symptom interview, PSI = Parenting Stress Index, SES = socioeconomic status, T1 = first assessment time point, T2 = second assessment time point, WPPSI = Wechsler Preschool and Primary Scale of Intelligence.

Table 2. Zero-order Correlations Among Relevant Study Variables In The mTBI Group

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1. PedsQL at T1	---																							
2. PedsQL at T2	**.55****	---																						
3. Sex	**-.19**	-.05	---																					
4. BDNF genotype	**.23**	**.21**	-.07	---																				
5. Age at T1	**.27**	**.29***	.02	.10	---																			
6. Age at T2	**.27**	**.31***	.03	.09	.995**	---																		
7. SES	.03	-.03	-.13	.04	-.01	.00	---																	
8. FAD-GFF	-.09	-.08	.10	-.08	.15	.13	-.05	---																
9. PSI-PD	**-.18**	**-.34***	-.03	.10	.12	.09	-.25	.48**	---															
10. PSI-PCDI	**-.20**	-.08	.26	-.04	-.05	-.06	-.48**	.33*	.38	---														
11. MRO-Snack	**.27**	-.01	-.05	.06	.11	.11	.12	.02	.01	-.24	---													
12. MRO-Play	.09	-.01	-.09	.02	-.05	-.04	.36*	.16	-.17	-.33*	.47**	---												
13. Age at injury	**.26**	**.29***	.02	.10	.997**	.997**	.00	.15	.11	-.06	.09	-.06	---											
14. Lowest GCS	**.24**	-.14	-.18	-.13	-.09	-.08	.31*	.02	-.03	-.25	.23	.29	-.08	---										
15. PCS-I	**-.21**	-.14	.01	.16	.06	.06	-.23	.30*	.31*	.09	.34*	.24	.06	-.22	---									
16. Bayley-WPPSI-CF	-.11	-.19	-.20	.02	-.07	-.05	.45**	-.06	.16	-.23	-.04	.16	-.05	.33*	-.12	---								
17. ECBQ/CBQ-S/E	.16	**.37****	.20	.11	.52**	.51**	.08	.06	-.14	-.13	-.10	-.07	.51**	-.09	-.11	-.09	---							
18. ECBQ/CBQ-NA	**-.40****	**-.33***	.02	-.11	-.31*	-.31*	-.08	.23	.18	.13	-.09	-.08	-.30*	-.02	.23	-.09	-.22	---						
19. ECBQ/CBQ-EC	.00	.09	-.08	.15	.26	.26	.15	-.01	-.08	-.23	-.20	.05	.26	.05	-.04	.03	.34*	.33*	---					
20. Spin The Pots	-.07	-.08	-.08	-.03	.26	.24	.15	-.18	-.03	-.03	-.12	-.16	.26	.10	-.23	.07	.21	-.25	.15	---				
21. Conflict Scale	.09	.14	.09	.14	.72**	.70**	.14	.10	.16	-.10	.12	.00	.71**	-.08	.14	-.04	.68**	-.30*	.21	.26	---			
22. Shape Stroop-ID	**.19**	.12	-.07	-.01	.58**	.58**	.02	.07	.11	-.23*	.19	.02	.58**	.02	.15	.10	.37**	-.18	.12	.20	.55**	---		
23. Shape Stroop-I	.16	.07	.12	.11	.61**	.59**	.05	.04	.16	-.04	.15	.00	.59**	-.04	.07	.07	.44**	-.48**	.03	.40**	.70**	.72**	---	
24. Desires tasks	.13	.05	-.40**	-.09	.29*	.32*	.28	-.06	-.01	-.32*	.26	.18	.31*	.22	-.02	.35*	.02	-.17	-.04	.17	.11	.36*	.17	---

25. FBU	**.21**	**.35***	-.03	.18	.21	.22	.13	-.06	-.19	-.21	.10	.15	.21	.22	-.04	-.04	.29	-.09	.21	.01	.22	.01	.05	.19

Note. Variables correlated at a *p*-level < .20 (bolded) were included in the regression models.
BDNF = brain-derived neurotrophic factor, CBQ = Child Behavioral Questionnaire (S/E = Surgency/Extraversion; NA = Negative Affect; EC = Effortful Control), CF = Cognitive Functioning, ECBQ = Early Child Behavioral Questionnaire, FAD = Family Assessment Device, FBU = False Belief Understanding, GCS = Glasgow Coma Scale, GFF = General Family Functioning, ID = Identification, I = Inhibition, MRO = Mutually Responsive Orientation, mTBI = mild traumatic brain injury, PedsQL = Pediatric Quality of Life Inventory, PCS = Postconcussive symptoms, PCS-I = Postconcussive symptom interview, PSI = Parenting Stress Index (PD = Parental Distress; PCDI = Parent-Child Dysfunctional Interaction), SES = Socioeconomic Status, WPPSI = Wechsler Preschool and Primary Scale of Intelligence.
*$p < .05$, ** $p < .01$.

Table 3. Hierarchical Regression Analyses Predicting Quality Of Life 6 And 18 Months After Early mTBI

	PedsQL 6 months				PedsQL 18 months			
Contributing factors	R^2	ΔR^2	β	F	R^2	ΔR^2	β	F
PedsQL								
Step 1: Biological	0.08	0.08		2.27	0.05	0.05		1.21
Sex			-0.18				-0.03	
BDNF genotype			0.22				0.21	
Step 2: Family-environmental	0.19	0.11		2.36	0.20	0.16*		2.48
Sex			-0.18				-0.07	
BDNF genotype			0.23				0.26	
SES			-0.09				-0.15	
PSI-Parental Distress			-0.23				-0.40**	
MRO-Snack			0.26				-0.01	
Step 3: Injury	0.37	0.18*		3.50**	0.32	0.12		2.74*
Sex			-0.16				-0.09	
BDNF genotype			0.28*				0.23	
SES			-0.22				-0.16	
PSI-Parental Distress			-0.19				-0.40**	
MRO-Snack			0.32*				0.04	
Age at Injury			0.26*				0.31*	
Lowest GCS			0.18				-0.11	
PCS-I			-0.33*				-0.15	
Step 4: Cognitive-behavioral	0.41	0.04		2.79**	0.39	0.07		2.52*
Sex			-0.15				-0.09	
BDNF genotype			0.26*				0.16	
SES			-0.21				-0.15	
PSI-Parental Distress			-0.16				-0.31*	
MRO-Snack			0.28				0.01	
Age at Injury			0.15				0.18	
Lowest GCS			0.18				-0.17	
PCS-I			-0.28				-0.12	
ECBQ/CBQ-NA			-0.21				-0.16	
Shape Stroop-ID			0.07				0.04	
FBU			0.03				0.26	

Note. Results are based on the imputed dataset. BDNF: 1 = Val/Val, 2 = Val/Met.
BDNF = Brain-derived neurotrophic factor, CBQ = Child Behavioral Questionnaire, ECBQ = Early Child Behavioral Questionnaire, FBU = False Beliefs Understanding, GCS = Glasgow Coma Scale, ID = Identification, MRO = Mutually Responsive Orientation, mTBI = mild traumatic brain injury, NA = Negative Affectivity, PedsQL = Pediatric Quality of Life Inventory, PCS-I = Postconcussive symptom interview, PSI = Parenting Stress Index, SES = Socioeconomic Status.
*$p < .05$, **$p < .01$.

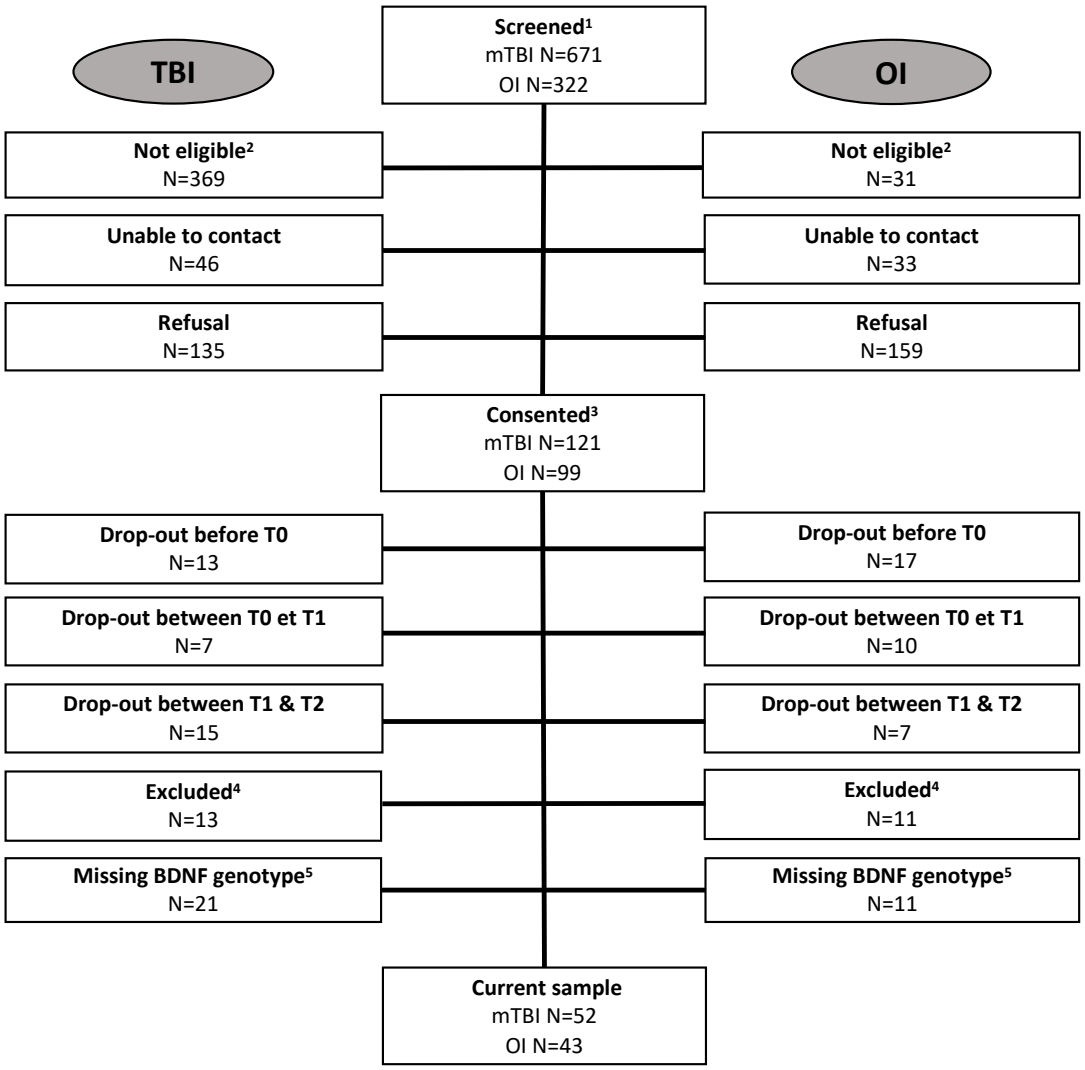

Fig. 1. Recruitment and follow-up chart of participants of mTBI and OI participants.
(1) The following emergency department (ED) diagnoses were screened for the study: mTBI group: traumatic brain injury, head fracture, concussion, intracranial bleeding/haemorrhage, polytrauma; OI group: limb trauma leading to a final diagnosis of simple fracture, sprain, contusion or unspecified trauma to an extremity. (2) Potential participants were not eligible because they did not satisfy an inclusion and/or exclusion criterion. (3) Consented refers to those participants whose parents signed a consent form. (4) These participants were excluded a posteriori, even if one or more measurement times had been completed, because they did not satisfy an inclusion and/or exclusion criterion that had not been detected at recruitment. (5) Missing BDNF genotype (e.g., parents did not agree to participate in the "genetic substudy", child was unable to provide enough saliva).

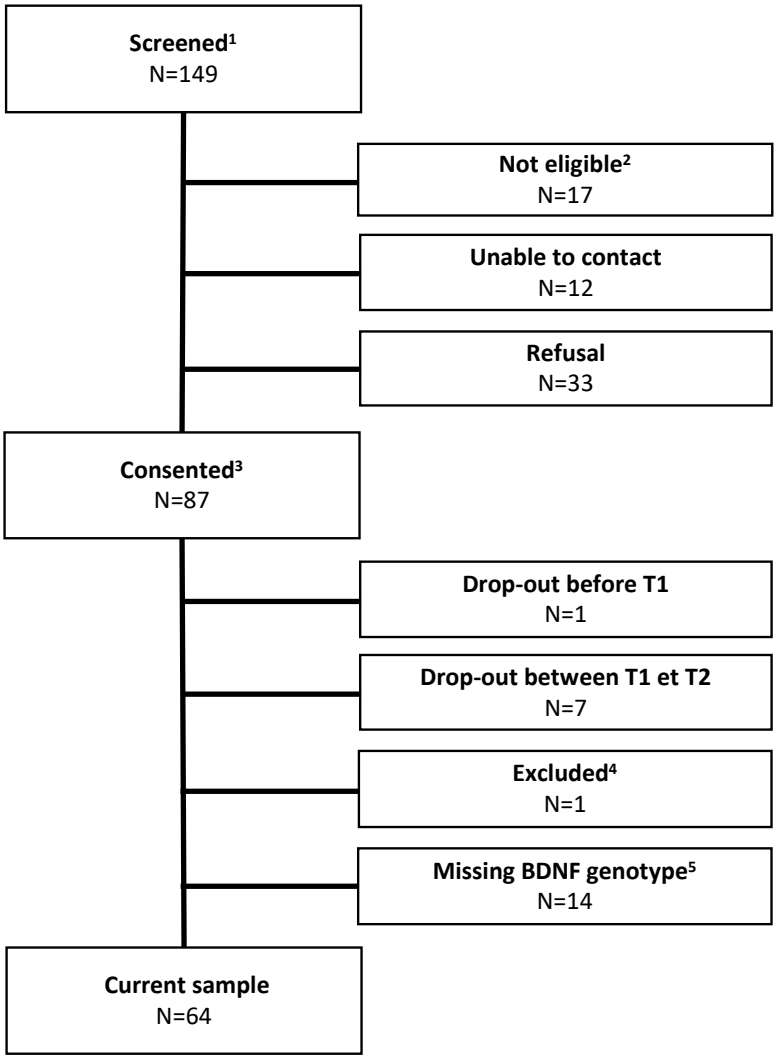

Fig. 2. Recruitment and follow-up chart for TDC participants.
(1) Screened refers to participants whose parents were given a study pamphlet at the local daycare and who gave their verbal consent to be contacted by the research coordinator. (2) Potential participants were not eligible because they did not satisfy an inclusion and/or exclusion criteria. (3) Consented refers to those participants whose parents signed a consent form. (4) These participants were excluded a posteriori, even if one or more measurement times had been completed, because they did not satisfy an inclusion and/or exclusion criteria that had not been detected at recruitment. (5) Missing BDNF genotype (e.g., parents did not agree to participate in the "genetic substudy", child was unable to provide enough saliva).

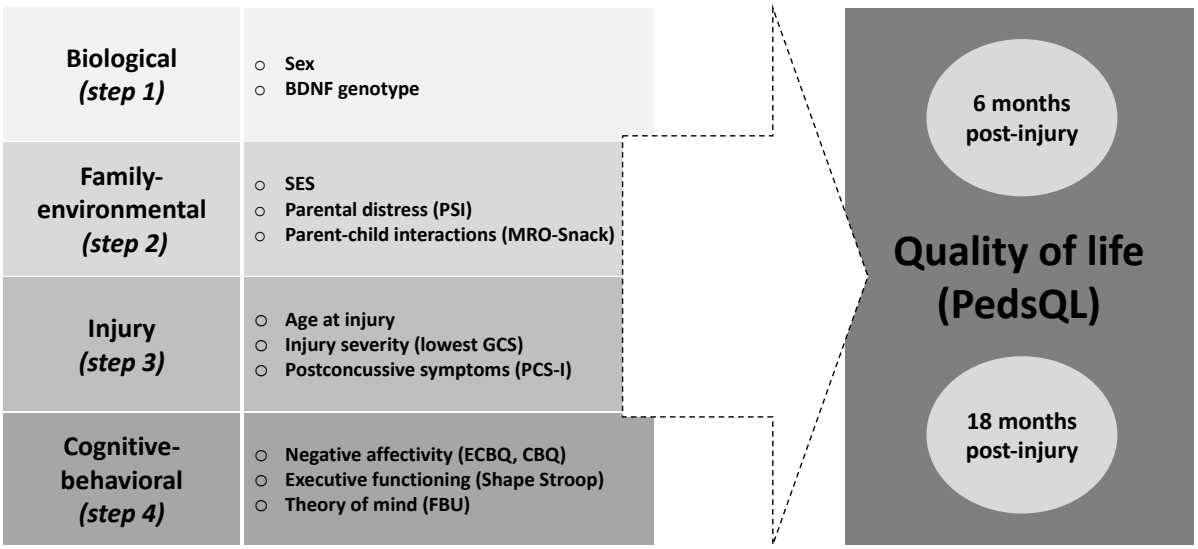

Fig. 3. Illustration of the 4-step hierarchical regression model predicting quality of life at 6 and 18 months post-injury.

Article 3

Altered resting-state functional connectivity within the developing social brain after pediatric traumatic brain injury

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Abstract

Traumatic brain injury (TBI) in childhood and adolescence can interrupt expected development, compromise the integrity of the social brain network (SBN) and impact social skills. Yet, no study has investigated functional alterations of the SBN following pediatric TBI. This study explored functional connectivity within the SBN following TBI in two independent adolescent samples. First, 14 adolescents with mild complex, moderate or severe TBI and 16 typically developing controls (TDC) underwent resting-state functional magnetic resonance imaging 12–24 months post-injury. Region of interest analyses were conducted to compare the groups' functional connectivity using selected SBN seeds. Then, replicative analysis was performed in an independent sample of adolescents with similar characteristics (9 TBI, 9 TDC). Results were adjusted for age, sex, socioeconomic status and total gray matter volume, and corrected for multiple comparisons. Significant between-group differences were detected for functional connectivity in the dorsomedial prefrontal cortex and left fusiform gyrus, and between the left fusiform gyrus and left superior frontal gyrus, indicating positive functional connectivity for the TBI group (negative for TDC). The replication study revealed group differences in the same direction between the left superior frontal gyrus and right fusiform gyrus. This study indicates that pediatric TBI may alter functional connectivity of the social brain. Frontal-fusiform connectivity has previously been shown to support affect recognition and changes in the function of this network could relate to more effortful processing and broad social impairments.'

Keywords: Functional connectivity, neurodevelopment, resting-state fMRI, RRID: SCR_009550, RRID: SCR_001622, RRID: SCR_007037, social brain, traumatic brain injury.

Introduction

Traumatic brain injury (TBI) sustained early in life has long-term consequences for development and ranks among the most common causes of death and disability in children and adolescents (Araki, Yokota, & Morita, 2017). Pediatric TBI represents a particular risk for long-term impairments and interruption of normal development given the vulnerability of the developing brain to structural and functional disruption (Anderson, Spencer-Smith, & Wood, 2011; Crowe, Catroppa, Babl, & Anderson, 2012). Behavioral and social problems may be particularly debilitating for everyday functioning and interpersonal relations (Anderson et al., 2013; Beauchamp, Dooley, & Anderson, 2010; Beauchamp & Anderson, 2013). The extent of such difficulties has been shown to correlate with injury severity (Anderson et al., 2013; McDonald, 2013). Indeed, adolescents who sustain moderate to severe TBI may present elevated rates of clinically significant behavioral and social dysfunction, including aggressive (Dooley, Anderson, Hemphill, & Ohan, 2008) and socially inappropriate behaviors (Cole et al., 2008; Hicks et al., 2017), as well as sociocognitive impairments such as affect recognition deficits (e.g., impaired facial affect recognition) and reduced empathy (Tousignant et al., 2018). These problems can appear both in the acute and chronic stages post-injury, and may aggravate with time resulting in adverse adult outcomes, such as reduced social participation, social isolation and maladaptive behaviors (Beauchamp et al., 2010; Catroppa et al., 2017).

The observation that TBI results in heterogeneous clinical outcomes supports the notion that long-term impairments, such as social problems, may be due to disruption of large-scale functional and anatomical neural networks (Ham & Sharp, 2012). Moderate to severe TBI is characterized by damage to white matter microstructure and diffuse axonal injury (Sharp, Scott, & Leech, 2014), resulting in disruption of large neural networks (Sharp et al., 2014). One such network is the social brain network (SBN), which has been shown to underlie social cognitive functions and may thus be implicated in social dysfunction following TBI (Johnson et al., 2005; Ryan, Catroppa, Beare, et al., 2016). It comprises the superior temporal sulcus (STS), fusiform gyrus, temporal pole, medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), amygdala, temporo-parietal junction (TPJ), and inferior parietal cortex ([IPC]; Beauchamp & Anderson, 2010; Johnson et al., 2005; Kennedy & Adolphs, 2012). Adolescence is a crucial time for social development during which the SBN undergoes profound changes and maturation (Blakemore,

2012). Thus, adolescents may be at particular risk for adverse social outcomes following TBI as they are in a developmental period where social skills are central to adequate social competence. There is evidence from neuroimaging studies suggesting links between structural SBN disruptions and social impairments after TBI in children (Bigler et al., 2013; Levan, Baxter, Kirwan, Black, & Gale, 2015) and adolescents (Ryan, Catroppa, Beare, et al., 2016; Ryan, Catroppa, Cooper, Beare, Ditchfield, Coleman, Silk, Crossley, Beauchamp, et al., 2015; Ryan et al., 2018; Ryan, van Bijnen, et al., 2016). Such structural alterations may be linked to changes in functional connectivity between different nodes of the SBN through a disruption of neuronal function (Ansari, Oghabian, & Hossein-Zadeh, 2011).

Resting-state functional magnetic resonance imaging (rsfMRI) is a powerful tool to explore the integrity of functional brain networks in both healthy and clinical populations (Fox & Raichle, 2007). By assessing correlations of fluctuations in the blood oxygen level-dependent (BOLD) signal between different nodes of the brain, rsfMRI allows for the investigation of largescale functionally connected brain networks (Fox et al., 2005). A line of research has begun to investigate the integrity of other well-established large-scale functional neural networks post-TBI. In adults with moderate to severe TBI, abnormal functional connectivity (including both hypo- and hyper-connectivity) has been observed in resting-state networks subserving motor, memory, cognitive, and visual processing (Guo et al., 2019; Hillary et al., 2014; Hillary et al., 2011; Rigon, Duff, McAuley, Kramer, & Voss, 2016; Rigon, Voss, Turkstra, Mutlu, & Duff, 2016, 2017; Shumskaya, van Gerven, Norris, Vos, & Kessels, 2017; Threlkeld et al., 2018). The most common findings points to functional connectivity abnormalities in the brain's default mode network (DMN) and salience network after adult TBI (Guo et al., 2019; Hillary et al., 2011; Threlkeld et al., 2018; Zhou et al., 2012).

Few studies have investigated altered functional connectivity following TBI in pediatric populations, especially in those with more severe injuries. Altered functional connectivity within the DMN, the dorsal attention network and motor networks have been found in three studies including children or adolescents with a range of TBI severities (Risen, Barber, Mostofsky, & Suskauer, 2015; Stephens et al., 2018; Stephens et al., 2017). Closer to the current topic, one study in adolescents with moderate to severe TBI found reduced functional connectivity between the right anterior cingulate cortex (ACC) and amygdala, as well as between these regions, the medial prefrontal cortices and right temporal areas (Newsome et al., 2013). Given that the differences

correlated with empathy ratings, the authors concluded that altered connectivity in these networks may be implicated in altered affective processing (Newsome et al., 2013). Together, these studies suggest that pediatric TBI may result in functional disruptions in functional networks related to behavioral and cognitive performance, with results indicating both stronger and lower connectivity when compared to typically developing peers.

Despite efforts to understand network reconfigurations following TBI, the consequences of moderate to severe TBI and its impact on functional connectivity during development remain unclear. Investigation of the underlying neural mechanisms of social dysfunction after pediatric TBI is largely limited to structural methods, studies focusing on single brain regions, and a handful of task-related fMRI approaches (e.g., Newsome et al., 2010; Scheibel et al., 2011), none of which have yet focused on the SBN using a network-vision of social functioning. The present study aimed to investigate functional alterations within the SBN in adolescents with moderate to severe TBI using an exploration-replication approach. It was hypothesized that (a) adolescents with TBI would show alterations in functional connectivity between regions of the SBN when compared with typically developing controls (TDC), and (b) that alterations in functional connectivity would be related to impairments in social skills in the TBI group. No hypothesis concerning the direction of differences in connectivity was established a priori given the lack of previous literature supporting directionality.

Materials and methods

Exploration study

Participants

Participants (n = 30, 11–16 years) were recruited between 2007 and 2010 as part of a larger prospective, longitudinal study of pediatric TBI and social skills (Anderson et al., 2013). Here, we report data from a subgroup of adolescent participants with mild complex, moderate or severe TBI and TDC participants who underwent rsfMRI within 12–24 months post-injury. The study was approved by the Royal Children's Hospital Human Research Ethics Committee, and the Victorian Department of Education Ethics Committee. All procedures were conducted in accordance with the Declaration of Helsinki. Parents gave their written, informed consent for children to participate in the study. Adolescents with TBI were identified via admission records at the emergency department, screened for eligibility and recruited immediately post-admission. Age-matched TDC

participants were recruited via local schools ensuring diversity in terms of socioeconomic backgrounds. Inclusion criteria were those of the original parent study: (a) age between 5 and 16 years at the time of injury; (b) closed head injury, including a period of altered consciousness or presence of at least two postconcussive symptoms; (c) medical reports of injury severity, including the Glasgow Coma Scale ([GCS]; Teasdale & Jennett, 1974), neurological and radiological findings; and (d) English speaking. The TDC group was required to meet criteria (a) and (d). Exclusion criteria were: (a) history of preinjury neurological or developmental disorder, nonaccidental injury, or previous TBI, and (b) prior intervention for social impairment.

TBI severity was determined based on medical records detailing GCS, as well as clinical neurological (i.e., presence of nausea, vomiting, drowsiness, memory or vision problems, confusion, impairment of proprioception, vertigo) and radiological findings (i.e., abnormalities on computed tomography [CT]/clinical MRI). Thus, classification was made as follows: (a) mild TBI: Lowest GCS 13–15, no evidence of mass lesion on CT/clinical MRI, no neurological deficits; (b) mild complex TBI: Lowest GCS 13–15, evidence of mass lesion on CT/clinical MRI; (c) moderate TBI: Lowest GCS 9–12, and/or mass lesion or other evidence of specific injury on CT/MRI, and/or neurological impairment; and (d) severe TBI: Lowest GCS 3–8, and/or mass lesion or other evidence of specific injury on CT/MRI, and/or neurological impairment.

About 12–24 months postinjury (mean [*M*] = 15.75 months, [*SD*] = 5.21 months), a subgroup of participants from the larger study completed a full MRI session including rsfMRI. The follow-up time frame of >1 year is based on reports that most social and behavioral difficulties after injury in individuals with TBI appear only in later stages of recovery (Anderson, Morse, Catroppa, Haritou, & Rosenfeld, 2004; Yeates et al., 2005). Participants were included in the present rsfMRI analyses if they met the following additional inclusion criteria: (a) mild complex, moderate or severe TBI, (b) useable rsfMRI imaging data (i.e., no excessive motion, see below), and (c) age 11–16 years at the time of the neuroimaging assessment. TDC participants were required to meet criteria (b) and (c). Participants with mild complex TBI were included in the analyses, as mild complex TBI is generally considered a more severe form of mild TBI given the presence of abnormalities on MRI/CT (Williams, Levin, & Eisenberg, 1990) and due to reports showing worse functional recovery that is similar to moderate–severe TBI (Temkin, Machamer, & Dikmen, 2003; Williams et al., 1990). After applying these inclusion criteria, 10 participants (5 TBI, 5 TDC) had to be excluded and 30 participants constituted the final sample (14 TBI, 16 TDC).

Behavior

Demographic and injury characteristics. Socioeconomic status (SES) was determined at the time of recruitment using the Australian and New Zealand Socioeconomic Classification of Occupations ([ANZSCO]; McMillan, Beavis, & Jones, 2009). The scale ranges from 0 to 100 with high scores reflecting higher occupational status for the primary caregiver. Cognitive abilities were measured using the Wechsler Abbreviated Scale of Intelligence 2nd version ([WASI-2]; Wechsler, 1999) at 24 months post-injury. Full Scale Intelligence Quotient ([FSIQ]; $M = 100$, $SD = 15$) is reported for descriptive purposes. For participants with TBI, the following details were collected at the time of recruitment via standard clinical report forms: GCS (injury severity), duration of loss of consciousness, neurological symptoms, surgical intervention, and cause of injury.

Child behavior. The Child Behavior Checklist for ages 6–18 ([CBCL]/6–18) is a standardized parent report questionnaire with good psychometric properties and which documents behavioral and social problems over the previous six months (Achenbach & Rescorla, 2001). Items are rated by the primary caregiver and behaviors are reported according to two main scales: (a) Internalizing problems including Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints subscales; (b) Externalizing problems including Rule-Breaking and Aggressive Behavior subscales. Parents filled out the questionnaire at the time of the rsfMRI assessment. Given the social focus of the study, scores are also reported for subscales specifically related to social functioning (Aggressive Behavior, Rule-Breaking, Social Problems). Higher scores (T-scores, $M = 50$, $SD = 10$) on any of the scales indicate more behavioral or emotional problems (Achenbach & Rescorla, 2001).

Magnetic resonance imaging

Image acquisition and pre-processing. MR images were acquired on a 3 Tesla Siemens Trio scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-channel matrix head coil. For each participant, a high-resolution T1-weighted structural MR image was acquired using a three-dimensional T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (repetition time [TR] = 1,900 ms, echo time [TE] = 2.52 ms, flip angle [FA] = 9°, slice thickness = 1.0 mm, voxel-size: 1.0 x 1.0 x 1.0 mm, field of view [FoV] = 250 mm, 192 slices, GRAPPA = 2, duration = 4.24 min).

RsfMRI images were acquired with a 2D T2-star echo planar image (EPI) sequence (TR = 2,200 ms, TE = 30 ms, FA = 90°, 32 slices, slice thickness = 3 mm, voxel-size 1.9 x 1.9 x 3.0 mm, FoV = 240 mm, 280 volumes, GRAPPA = 2, duration = 10.24 min). The time-frame of 10 min is recommended for resting-state image acquisition in pediatric populations, as it reduces risk of motion artifacts and the participant falling asleep (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012). All participants were instructed to focus on a central white cross presented on a black screen, not to move and to rest during this sequence.

T1 and rsfMRI images were subjected to quality control by visual inspection (C.T., F.D.) for motion artifacts and image quality. Then, SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK; https://www.fil.ion.ucl.ac.uk/spm, RRID: SCR_007037) and the CONN Functional Connectivity Toolbox version 17f (http://www.nitrc.org/projects/conn, RRID: SCR_009550, Whitfield-Gabrieli & Nieto-Castanon, 2012) running on MATLAB version R2017b (MathWorks, Inc., Natick, MA, USA; http://www.mathworks.com/products/matlab/, RRID: SCR_001622) were used for pre-processing and subsequent statistical analyses. Pre-processing steps in SPM12 included (a) slice timing correction of the EPI volumes and realignment to the first volume of the fMRI time series; (b) co-registration of the mean EPI (calculated during realignment) and the T1 images; (c) segmentation of tissues (gray matter [GM], white matter [WM] and cerebrospinal fluid [CSF]) and normalization using the T1 and an age-appropriate stereotaxic template (NIHPD 4.5–18.5 asymmetric: www.bic.mni.mcgill.ca/ServicesAtlases/NIHPDobj1; Fonov et al., 2011); (d) spatial normalization of the coregistered T1 image and EPI volumes with a voxel size of 2 x 2 x 2 mm; and (e) smoothing of the normalized EPI images at 6 mm full width at half-maximum (FWHM).

The CONN toolbox was then used to run the noise reduction step ("denoising") in order to remove unwanted motion, as well as physiological and other artefactual effects from the BOLD signal. This final step applies linear regression of nuisance variables using the anatomical principal component-based noise-correction "aCompCor" method (Behzadi, Restom, Liau, & Liu, 2007; Whitfield-Gabrieli & Nieto-Castanon, 2012) along with six movement parameters that were estimated during realignment. This was followed by band-pass filtering between 0.008 and 0.09 Hz in order to remove high-frequency noise. A threshold of 3 mm was applied for the six motion parameters, which none of the final sample surpassed. Mean frame-wise displacement was

calculated according to Power et al. (2012). There was no difference between the two groups (p = .784).

Data analyses

ROI-to-ROI resting-state fMRI analyses. Analyses steps are illustrated in **Figure 1**. Using the CONN toolbox and 16 regions of interest (ROI) from the SBN, ROI-to-ROI functional connectivity analyses were performed. ROIs were defined as 6 mm radius spheres around MNI coordinates derived from the social brain atlas described by Alcalá-López et al. (2018). This atlas is based on meta-analyses of neural activity related to social-cognitive processing involving almost 4,000 neuroimaging studies (Alcalá-López et al., 2018). The following ROIs were selected: Bilateral left posterior STS, fusiform gyrus, temporal pole, inferior frontal gyrus, TPJ, amygdala, as well as the dorsomedial PFC (dmPFC), the ventromedial PFC (vmPFC), the rostral ACC and the medial frontal pole. These brain regions have consistently been related to morphological abnormalities and to social difficulties following TBI (Ryan, Catroppa, Beare, et al., 2015; Ryan, Catroppa, Beare, et al., 2016; Ryan et al., 2017; Ryan, Catroppa, Cooper, Beare, Ditchfield, Coleman, Silk, Crossley, Rogers, et al., 2015; Ryan, Catroppa, Godfrey, et al., 2016; Ryan et al., 2018; see **Table 1** for details on ROIs and MNI coordinates).

Bivariate Pearson's correlations between the mean BOLD signal time-courses of each pair of ROIs were calculated at the first level of analysis. This resulted in individual ROI-to-ROI functional connectivity maps for each participant (16 x 16) with positive correlation coefficients describing positive functional connectivity, and negative correlation coefficients describing negative functional connectivity (anticorrelation). The six motion parameters (three rotations, three translations) calculated during pre-processing were included as nuisance regressors. Finally, correlation coefficients were converted into normally distributed z-scores using Fisher's transformation for parametric testing.

At the second-level analysis, two-sample t-tests were performed to assess between-group differences in ROI-to-ROI functional connectivity for each ROI, controlling for age at rsfMRI acquisition, sex, SES, and total GM volume to account for the global presence of structural lesions. In addition, all analyses were masked using a GM mask based on both TDC and TBI participants and involving GM, WM and CSF means from the normalized images. This was done in order to control for local effects of brain lesions. By also including TBI participants in the mask, the presence of focal atrophies was controlled for and analyses restricted only to those regions where

it was expected to measure brain activation, that is, in brain regions with GM. This mask was calculated using the following formula: GM mask = (meanGM > meanWM) ⋂ (meanGM > meanCSF) ⋂ (meanGM > 0.3). A false discovery rate ([FDR]; Chumbley, Worsley, Flandin, & Friston, 2010) was used at a threshold of $p < .05$ (two-tailed) at seed-level in order to control for Type I error.

Seed-to-voxel resting-state fMRI analyses. In a second step, the findings of the ROI-to-ROI analyses were tested in a less restrictive a priori analysis. Seed-to-voxel analyses were performed using bilateral seeds from the first ROI-to-ROI analyses that showed significant differences in resting-state functional connectivity between groups. This was done in order to explore whether the seeds from the first analyses would be connected with other regions of the social brain that were not initially selected. In order to constrain analyses to the social brain and to further reduce Type I error given the number of comparisons, a social brain mask was applied which was based on anatomical areas from the Harvard-Oxford atlas included in CONN (Desikan et al., 2006; Fox et al., 2005). This social brain mask included bilateral STS, fusiform gyrus, temporal pole, mPFC, frontal pole, ACC, OFC, amygdala, TPJ, IPC, inferior frontal cortex, and insula.

For each participant, individual correlation maps throughout the social brain were created by extracting the mean resting-state BOLD time course from each of the selected seeds and by calculating correlation coefficients with the BOLD time course of each voxel throughout the social brain. The resulting Pearson's correlation coefficients between the time series of each seed and the individual voxels were Fisher's *z*-transformed in order to estimate maps of voxel-wise functional connectivity for each seed in the social brain for each participant. The resulting maps were then included in second-level analyses to evaluate between-group differences in seed-to-voxel connectivity using two-sample *t*-tests implemented in CONN, covarying for age, sex, SES and total GM volume. In addition, the GM mask calculated in the previous step was applied to account for local effects of brain lesions. Voxel-wise statistics within the social brain mask were performed at a threshold of $p < .05$ (two-tailed) and corrected for multiple comparisons at cluster-level using the family-wise error ([FWE]; Nichols & Hayasaka, 2003), following the standard procedure as described in Whitfield-Gabrieli and Nieto-Castanon (2012). The more conservative FWE-correction was chosen as analyzing functional connectivity between each seed with a large number of voxels leads to an increased number of comparisons (Benjamini & Hochberg, 1995).

Behavioral data analyses. All data were first screened for violations of normality using SPSS statistical software (Version 25.0, Chicago, IL; http://www-01.ibm.com/software/uk/analytics/spss/, https://www.ibm.com, RRID:SCR_002865). Group comparisons were performed using independent samples *t*-tests for data that were normally distributed and Mann–Whitney *U* tests for those that were non-normally distributed. An α-level of $p < .05$ was employed in order to determine significance. Correlation analyses were performed to examine whether differences in functional connectivity between groups were related to social-behavioral functioning (CBCL scores) and to injury severity (GCS scores) in the TBI group. We extracted individual Fisher's *z*-transformed correlation coefficients: (a) indicating significant group differences in ROI-to-ROI functional connectivity; and (b) for clusters of voxels indicating significant group differences in connectivity with SBN structures in seed-to-voxel analyses.

Two-tailed partial Pearson's correlation analyses were then performed between extracted functional connectivity scores and CBCL scores, covarying for SES (as CBCL T-scores already account for age and sex). GCS scores were correlated with functional connectivity scores covarying for age, sex and SES. Given the high number of comparisons (n = 6), the threshold was lowered from $p < .05$ to $p < .01$ by applying Bonferroni correction (α-value divided by number of comparisons).

Replication study

Participants

A replication analysis was conducted using a second independent sample of nine individuals with moderate to severe TBI (seven females) and nine TDC participants (three females) with available rsfMRI and behavioral (CBCL) data as described above. Participants were ascertained as part of a separate cross-sectional research project on social reasoning in adolescents with TBI. TBI participants were retrospectively recruited one to six years after brain injury and were aged between 13 and 18 years. TDC participants were recruited through local schools using a random sampling strategy in order to include a broad range of socioeconomic backgrounds. Inclusion and exclusion criteria for both groups of participants were the same as those in the exploration study. The Mayo Classification System was used to determine injury severity retrospectively based on available positive clinical evidence (Malec et al., 2007).

Behavior

Demographics and injury characteristics. In order to match the measures as closely as possible to those used in the exploration sample, the primary caregiver's education was used as a proxy for SES. Education was rated on a scale from one to eight according to the following categories: 1 = primary school, 2 = Year 10 or lower high school, 3 = Year 11, 4 = Year 12, 5 = technical and further education, 6 = university bachelor degree, 7 = university postgraduate, 8 = other diploma. Similar to the exploration study, cognitive abilities were measured for descriptive purposes using the FSIQ from the WASI-2. For participants with TBI, standardized clinical report forms were used to collect the data on injury severity (GCS) and cause of injury.

Child behavior. CBCL data were also available for the replication sample and the same subscores as in the exploration study were used for analyses.

Magnetic resonance imaging

Image acquisition and pre-processing. MR images for this study were acquired on the same scanner as the exploration sample. Similarly, high-resolution structural T1 images were acquired following the same protocol. RsfMRI images were acquired with a 2D T2-star echo planar image sequence (TR = 2,000 ms, TE = 30 ms, FA = 90_, 32 slices, slice thickness = 3 mm, voxel-size 2.6 x 2.6 x 4.0 mm, FoV = 250 mm, 200 volumes, GRAPPA = 2, duration = 6.48 min). All participants had to focus on a central white cross presented on a black screen, were asked not to move and to rest during the sequence. Subsequent image pre-processing was conducted identical to the procedures described above. None of the participants surpassed the motion threshold of 3 mm, and no group difference was found for mean FD (p = .890).

Data analyses

ROI-to-ROI resting-state fMRI analyses. Following the analyses in the exploration study, which served to define more specific ROIs, ROI-to-ROI analyses were applied to the replication sample to test the results in an independent sample of adolescents. The ROI-to-ROI approach was chosen to replicate the results from the exploration study as closely as possible, therefore limiting the number of seeds and target regions and maintaining adequate statistical power given the smaller sample size. ROIs were chosen based on seeds and clusters showing significant group differences in the exploration sample. If not otherwise indicated, ROIs were selected bilaterally. At the first level of analysis, individual ROI-to-ROI functional connectivity

maps (4 x 4) were calculated for each participant including the six motion parameters calculated during the realignment step as nuisance regressors. Correlation coefficients were converted into Fisher's *z*-scores. Then, two-sample *t*-tests was applied to evaluate between-group differences in ROI-to-ROI functional connectivity for each seed, controlling for age at rsfMRI testing, sex, years of parental education, and total GM volume. Results were thresholded at $p < .05$ using FDR-correction method (two-tailed) to control for multiple comparisons and a GM mask was applied to all analyses following the same procedure as in the exploration sample to control for the presence of focal lesions.

Behavioral data analyses. As for the exploration sample, data were screened for violations of normality and group comparisons were performed using independent samples *t*-tests for data that were normally distributed and Mann–Whitney *U* tests for nonnormally distributed data. Significance was determined using an α-level of $p < .05$. Given the small sample size, partial correlation analyses of functional connectivity scores and CBCL scores or injury severity were not performed in this sample which is not recommended as it significantly reduces statistical power (Cohen, 1988).

Results

Exploration study

Participant characteristics

Participant demographic and injury characteristics including neuroradiological reports are summarized in **Tables 2** and **3**. There were no group differences for sex or age at the 24-month follow-up assessment. However, the two groups differed significantly with respect to SES, indicating higher SES for the TDC group ($p = .002$). Consequently, SES was included as a covariate in all analyses. In addition, a significant difference was found for IQ between the two groups ($p = .02$). Of note, a repeated-measures ANOVA showed that IQ remained stable over time from 6 to 24 months for both groups ($F[1,24] = 26.19$, $p = .52$). Group differences were found on the CBCL Internalizing subscale, indicating higher scores and thus more internalizing problems for the TBI compared to the TDC group ($p = .02$), as well as for the Rule-Breaking subscale indicating more problems for the TBI group ($p = .01$; **Table 2**). No other significant group differences were found on any other CBCL subscale.

ROI-to-ROI functional connectivity

We evaluated whether functional connectivity between selected ROIs from the SBN differed between the TBI and TDC groups. The results revealed positive connectivity between the dmPFC and left fusiform gyrus in participants with TBI as compared to TDC participants who showed negative connectivity between these two regions ($t[24] = 4.05$, $p = .004$, FDR-corrected; **Figure 2**).

Seed-to-voxel functional connectivity

The aim of these seed-to-voxel analyses was to highlight regions that showed group differences in the ROI-to-ROI analyses and to test the connectivity of these seeds with other regions that were not initially selected in a less restrictive a priori analyses. Based on the results of the ROI-to-ROI analyses, the bilateral fusiform gyrus and dmPFC were used as seeds in seed-to-voxel analyses. Significant differences between the two groups were found between the left fusiform gyrus and left superior frontal gyrus ($k = 483$, $x = -6$, $y = 60$, $z = 22$; $p = .001$, FWE-corrected at cluster-level), indicating positive connectivity for the TBI group and negative connectivity for the TDC group. No differences were found for the dmPFC seed or for the right fusiform gyrus seed. Results are summarized in **Figure 3**.

Correlations with CBCL and injury severity

Partial correlation analyses between functional connectivity and CBCL scores and injury severity revealed no significant associations in the TBI group after correction for multiple comparisons.

Replication study

Participant characteristics

Table 4 presents participant demographic and injury characteristics for the replication study. There were no group differences on any of the demographic variables. Nevertheless, in order to replicate the analyses performed on the exploration sample as closely as possible, parent education (as a proxy for SES) in addition to age and sex were included as covariates in all analyses. Information on injury and neuropathology based on CT and clinical MRI in the TBI participants is summarized in **Table 5**. No significant group differences were found on any of the CBCL scores (**Table 4**). The two TBI groups did not show any difference in IQ ($p = .09$), sex ($p = .96$), SES (p

= .23), or GCS (p = .93). All age-related variables showed significant differences, including age at rsfMRI acquisition (p < .001), injury age (p = .049), and time since injury (p < .001). In particular, the TBI group in the replication sample was older (difference score [years] = 3.73), had an overall older age at injury (difference score [years] = 1.56), and underwent brain imaging a longer time after injury (difference score [years] = 2.17) than the exploration sample.

A comparison of demographical variables between the two TDC groups (exploration and replication) showed no difference in IQ (p = .37), sex (p = .27), or SES (p = .15), but the two TDC groups differed for age, with those in the replication study being older than those in the exploration study (difference score [years] = 2.16, p = .003).

ROI-to-ROI functional connectivity

In the replicative ROI-to-ROI analyses, the left and right fusiform gyrus, dmPFC and left superior frontal gyrus were used as seed regions, based on the results of the exploration study. For the left superior frontal gyrus, an additional 6 mm spherical ROI was defined using peak coordinates from the significant cluster from the exploration study. Given that the bilateral fusiform gyrus showed differences in seed-based functional connectivity between groups in both analyses, the right fusiform gyrus was also included in the analyses in order to explore functional connectivity within and across hemispheres. Consistent with the analyses in the exploration sample, results revealed positive connectivity between the left superior frontal gyrus and right fusiform gyrus in participants with TBI, compared to TDC participants who showed negative connectivity between those two ROIs (t[12] = 2.86, p = .04, FDR-corrected; **Figure 4**). None of the other ROIs showed significant functional connectivity differences.

Discussion

This study aimed to investigate alterations of functional connectivity within the SBN following TBI associated with skull fracture and/or intracranial lesions in two independent adolescent samples. Given the inconsistencies across existing studies of functional connectivity in terms of methodology and sample constitution, and the lack of replication in previous studies, we applied an exploratory exploration-replication approach and two different types of ROI-analyses. Analyses in the two samples revealed similar patterns of altered functional connectivity within the SBN: Positive frontal-fusiform functional connectivity in adolescents with TBI compared to their non-injured peers. More specifically, in the exploration sample, group differences in ROI-to-ROI

functional connectivity within the SBN were found, indicating positive connectivity between the dmPFC and left fusiform gyrus in those with TBI compared to negative connectivity between these two regions in controls. Then, consistent with the findings of the ROI-to-ROI analyses, seed-to-voxel analyses revealed differences in functional connectivity, indicating positive connectivity in the TBI group and negative connectivity in the TDC group between the left fusiform and left superior frontal gyri. This confirmed altered frontal-fusiform connectivity in the TBI group. No significant associations between functional connectivity scores and behavior were found. The replication study revealed a similar pattern of altered connectivity between the right fusiform gyrus and left superior frontal gyrus, indicating positive functional connectivity in adolescents with TBI, and negative functional connectivity in non-injured adolescents.

Increased functional connectivity patterns have also been found in other rsfMRI studies of moderate to severe TBI in children and adults, indicating higher resting-state functional connectivity in the DMN (Bonnelle et al., 2011; Xiao, Yang, Xi, & Chen, 2015) and task-fMRI studies in adolescents with TBI revealing increased activation in the fusiform gyrus and PFC in relation to social cognition tasks involving theory of mind and affect recognition (Newsome et al., 2010; Rigon, Voss, Turkstra, Mutlu, & Duff, 2018; Scheibel et al., 2011). Increased functional connectivity could possibility be explained using the "cortical inefficiency model", developed in the field of schizophrenia research (Manoach, 2003), according to which additional resource allocation is required in order to maintain task performance. Consistent with this hypothesis, previous TBI studies report alterations in brain activity, whereby more extensive cerebral activation patterns have been observed in relation to task performance, suggesting neuroplastic mechanisms following TBI (see Levin, 2003 for a review). For example, in an fMRI study involving participants with moderate–severe TBI, Christodoulou and colleagues found higher and more widespread activation in the frontal lobes during a working memory task in participants with TBI compared to non-injured controls (Christodoulou et al., 2001). Such recruitment of the frontal lobes is in line with the present finding and may indicate changes in functional activity as a result of TBI. Importantly, higher functional connectivity has also been linked to neuropathology after moderate to severe TBI in adults (e.g., Scheibel et al., 2009). Conversely, Rigon et al. (2017) found lower functional connectivity between bilateral fusiform gyri and frontal brain regions, in particular in the mPFC, in a sample of adults with moderate to severe TBI, compared to TDC. However, the contrasting findings may be due to the age of the participants, as this study included adolescents

and the study by Rigon et al. (2017) was conducted in an adult sample. In sum, higher levels of functional connectivity in the TBI group as observed in our study (i.e., positive connectivity involving frontal brain regions), may reflect a failure in decoupling anterior brain areas indicative of more effortful processing (Price & Friston, 2002; Sharp et al., 2011).

From a developmental perspective, SBN regions, including prefrontal brain regions and the fusiform gyri, have been shown to undergo protracted structural and functional changes and specialization throughout infancy and into late childhood and adolescence (Blakemore, den Ouden, Choudhury, & Frith, 2007; Burnett, Bird, Moll, Frith, & Blakemore, 2009). In addition, such developmental changes are often paralleled by a valence switch of functional connectivity patterns, from positive to negative connectivity in brain areas involved in regulatory functions, including the PFC (Gabard-Durnam et al., 2014; Gee et al., 2013). Such changes in functional connectivity valence have been interpreted as a neurobiological mechanism for the development of regulatory functions, including inhibition and emotion regulation (Gabard-Durnam et al., 2014; Gee et al., 2013). This assumption finds further support in a study by Stephens et al. (2018) who found that children with TBI had less negative (i.e., anti-correlated) functional connectivity between the DMN and right Brodmann Area 40, associated with poorer response inhibition. Negative functional connectivity may be required for an optimal level of cognitive functioning, similarly to the present findings. It may thus be hypothesized that similar mechanisms might be at play with respect to frontal-fusiform connectivity patterns, and adolescents with TBI show more immature (positive) functional connectivity, whereas their uninjured counterparts may display more adult-like (negative) functional connectivity.

The fusiform gyrus, as well as several brain regions in the frontal lobe, have previously been shown to play a crucial role in affect recognition and processing, in particular facial affect recognition (Ganel, Valyear, Goshen-Gottstein, & Goodale, 2005). Socio-cognitive functions such as affect recognition have been shown to be impaired following moderate to severe TBI (McDonald, 2013; Ryan, Catroppa, Cooper, Beare, Ditchfield, Coleman, Silk, Crossley, Beauchamp, et al., 2015) and may therefore contribute to more general social dysfunction after TBI (Neumann, McDonald, West, Keiski, & Wang, 2016; Rosenberg, Dethier, Kessels, Westbrook, & McDonald, 2015). However, given no socio-cognitive tasks were included in the present study, any association between the resting-state fusiform findings and altered affect recognition remains speculative. While this study suggests that abnormal functional connectivity

within the SBN, and specifically frontal-fusiform connectivity, is present after TBI, future studies are needed to investigate any postulated associations with social functioning by using combined neuroimaging and behavioral designs.

Strengths and limitations

The present study is the first to examine resting-state functional connectivity alterations within the SBN after moderate to severe pediatric TBI and contributes to our understanding of social impairment after TBI, a problem that is increasingly recognized but for which the neural mechanisms remain obscure. This research is novel in that it focused specifically on the social brain and used two ROI-based analyses in two different samples of adolescents with TBI. Largely consistent results in both samples illustrate the robustness of the findings. Using two different samples enhances the generalizability of the findings and all data were acquired on the same scanner, excluding scanner bias. We further controlled for age, sex, total GM volume and SES in both samples, in addition to selecting only few ROIs for the analyses, thus applying a conservative approach. Nonetheless, some limitations need to be considered.

Using different samples introduced some heterogeneity and potential bias. RsfMRI did not take place in the same time span post-injury and the TBI replication sample was slightly older. It is possible that different neural reorganization mechanisms were underway in the two samples and conclusions regarding functional connectivity at different injury stages are not possible. However, consistent frontal-fusiform associations in both groups support the observation that similar aberrant functional connectivity within the SBN is present independent of these age variables. Age was included as a covariate in all analyses to control for possible age effects on the results. The lack of significant associations between functional connectivity and behavior may be a result of the small sample sizes and therefore the lack of statistical power to detect potential brain-behavior correlations. The absence of such associations may also be due to the general measure of behavior/social skills that was used (parent questionnaire, CBCL). Using direct child-measures would facilitate testing of specific social impairments. Last, the two groups differed significantly in terms of SES. While SES was controlled for in all analyses, it is possible that preexisting differences may partly explained functional connectivity differences. Longitudinal studies are needed to explore such a link more specifically and how functional connectivity evolves over time. Future research could expand on the present findings using more systematic studies on SBN alterations following TBI and larger, more homogeneous samples in longitudinal studies to

determine how functional connectivity evolves over time and to explore putative associations with social skills.

Conclusion

The study brings to light alterations in both intra- and interhemispheric connections within the SBN after TBI involving the fusiform gyrus bilaterally. Failure to deactivate frontal areas may be associated with more effortful and inefficient processing after TBI. In addition, differences in functional connectivity could point to altered developmental mechanisms following TBI. Despite the lack of association between altered functional connectivity and behavior in this study, the present findings suggest that abnormal frontal-fusiform connectivity after moderate to severe TBI in adolescence may reflect differences in facial affect recognition, emotion dysregulation and more global social difficulties as reported in other studies. The findings provide a basis for future efforts to establish the utility of resting-state functional connectivity as a potential marker of social dysfunction following TBI and to disentangle the complex mechanisms involved in adverse social functioning using combined neuroimaging-behavioral designs that investigate associations with social skills.

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Table 1. Selected Regions Of Interest (ROI) For The Connectivity Analyses

Social Brain ROI	Abbreviation	MNI coordinates		
		X	Y	Z
Left posterior superior temporal sulcus	pSTS_L	-56	-39	2
Right posterior superior temporal sulcus	pSTS_R	54	-39	0
Left temporal pole	TP_L	-48	8	-36
Right temporal pole	TP_R	53	7	-26
Left temporo-parietal junction	TPJ_L	-49	-61	27
Right temporo-parietal junction	TPJ_R	54	-55	20
Rostral anterior cingulate cortex	rACC	-3	41	4
Left fusiform gyrus	FG_L	-42	-62	-16
Right fusiform gyrus	FG_R	43	-57	-19
Dorsomedial prefrontal cortex	dmPFC	-4	53	31
Ventromedial prefrontal cortex	vmPFC	2	45	-15
Medial frontal pole	FP	1	58	10
Left inferior frontal gyrus	IFG_L	-45	27	-3
Right inferior frontal gyrus	IFG_R	48	24	2
Left amygdala	AM_L	-21	-4	-18
Right amygdala	AM_R	23	-3	-18

Note. 6mm- ROIs selected from Alcalá-López et al., 2018.

Table 2. Participant Characteristics (Exploration Sample)

	TBI, n=14	TDC, n=16	*Statistic*	*p*
	M (SD)	*M (SD)*		
Demographics				
Sex male (n, %)	11 (78.57)	9 (56.25)	χ^2 (1) = 1.67	.20
Age (years)	13.09 (1.42)	13.59 (1.68)	*t*(28) = .87	.39
SES (ANZSCO)	49.94 (21.30)	74.21 (18.21)	*t*(28) = 3.37	.002*
FSIQ (WASI-2)	96 (11.11), n = 11	106.07 (9.74), n = 15	*t(24)* = 2.45	.02*
Injury characteristics				
Age at injury (years)	11.77 (1.57)	--	--	--
Time since injury (months)	15.75 (5.21)	--	--	--
GCS (lowest)	10.86 (3.44)	--	--	--
Neurological symptoms (n, %)	4 (28.57)	--	--	--
Surgical intervention (n, %)	3 (21.43)	--	--	--
LOC (n, %)	n = 13			
no LOC	3 (21.43)	--	--	--
< 5 min	9 (64.29)	--	--	--
> 5 min, <24h	1 (7.14)	--	--	--
Cause (n, %)				
MVA	4 (28.57)	--	--	--
Fall/Blow	9 (64.29)	--	--	--
Kicked/struck by object	1 (7.14)	--	--	--
CBCL subscales				
Aggressive†	56.64 (10.08)	51.38 (1.82)	*U* = 81.50	.19
Social†	55.79 (8.14)	52.00 (3.86)	*U* = 84.50	.22
Internalizing	56.43 (6.63)	49.44 (8.12)	*t*(28) = 2.60	.02
Externalizing†	53.21 (8.47)	49.44 (6.89)	*U* = 70.50	.08
Rule-Breaking	56.21 (7.28)	50.69 (1.08)	*t*(28) = 2.82	.01

Notes: p-values are calculated using independent samples *t*-tests for continuous variables and chi-square (χ^2) tests for categorical variables between groups. For non-normally distributed data (†), Mann-Whitney *U* tests were used. For group comparisons on CBCL scores, the significance level was adjusted to *p*=.01. CBCL scores represent *T*-scores.

Abbreviations: ANZSCO, Australian and New Zealand Socioeconomic Classification of Occupations; CBCL, Child Behavior Checklist; FSIQ, Full-Scale Intelligence Quotient; GCS, Glasgow Coma Score; LOC, loss of consciousness; M, mean; MVA, motor vehicle accident; SD, standard deviation; SES, socio-economic status; TBI, traumatic brain injury; TDC, typically developing controls; WASI-2, Wechsler Abbreviated Intelligence Scale-2.
*Significant at $p < .05$.

Table 3. Neuropathology On Clinical CT/MRI For TBI Participants (Exploration Sample)

	Sex	Injury type	Age at injury	GCS	CT/MRI findings	Skull fracture
TBI_E1	M	Fall	10.5	8	L frontal extradural hematoma; L multifocal frontal GM/WM haemorrhage and gliosis	
TBI_E2	M	Kicked/ struck by object	14.0	15	R posterior frontal WM gliosis	
TBI_E3	M	Fall	11.0	13	R frontal parenchymal and cortical haemorrhagic contusions; L occipito-parietal cortical contusion; B frontal GM/WM haemorrhage and gliosis; B temporal, occipital, parietal GM gliosis; R temporal haemorrhage; multifocal GM/WM haemorrhage and gliosis	
TBI_E4	F	Fall	11.8	15	B multifocal anterior frontal WM gliosis; scalp edema in L occipital region	
TBI_E5	M	Fall	10.9	11	R inferior frontal extradural haemorrhage contusion; R inferior frontal GM/WM gliosis; B encephalomalacia	Complex fracture R frontal lobe, ethmoid and spheroid bones, superior and medial orbital walls
TBI_E6	M	MVA	10.5	10	Small L haemorrhagic cortical contusion and small extra axial hematoma; L anterior frontal haemorrhage; B multifocal frontal WM petechial haemorrhage and gliosis; L temporal multifocal	Undisplaced linear fracture L fronto-parietal bone

					WM haemorrhage and gliosis + anterior callosal haemorrhage	
TBI_E7	M	MVA	9.2	8	NA	
TBI_E8	F	Fall	12.3	15	Intra-axial bleeding; B petechial frontal haemorrhage	
TBI_E9	M	Fall	11.4	11	R occipital GM/WM haemorrhage	
TBI_E10	M	MVA	11.7	3	Scalp edema in L frontal region; subarachnoid haemorrhage	
TBI_E11	M	Fall	14.8	8	Scalp edema in L parietal region; L temporal and L frontal GM/WM haemorrhage; diffuse axonal injury; edema; mass effect	Undisplaced linear facture L parietal bone
TBI_E12	F	MVA	10.6	10	Scalp edema in R frontal region; globus pallidus calcification	
TBI_E13	M	Fall	12.3	14	Subdural bleed	
TBI_E14	M	Fall	13.9	11	NA	

Abbreviations: B, bilateral; CT, computed tomography; F, female; GCS, Glasgow Coma Score (lowest); GM, gray matter; L, left; M, male; MRI, magnetic resonance imaging; MVA, motor vehicle accident; NA, not available; R, right; TBI, traumatic brain injury; WM, white matter.

Table 4. Participant Characteristics (Replication Sample)

	TBI, n=9	TDC, n=9	*Statistic*	*p*
	M (SD)	*M (SD)*		
Demographics				
Sex male (n, %)	7 (77.78)	3 (33.33)	$\chi^2(1) = 3.60$	.06
Age (years)	16.82 (.81)	15.75 (1.29)	$t(16) = 2.10$	.05
SES	5.56 (1.74)	5.00 (2.00)	$t(16) = .63$	.54
FSIQ (WASI-2)	106.22 (14.57)	100.50 (15.31), n = 8	$t(15) = .79$	.44
Injury characteristics				
Age at injury (years)	13.33 (2.00)	--	--	--
Time since injury (years)	3.48 (1.69), 1.35 – 6.28	--	--	--
GCS (lowest)	11.00 (2.83)	--	--	--
Cause (n, %)				
MVA	4 (44.44)	--	--	--
Fall/Blow	5 (55.56)	--	--	--
CBCL subscales				
Aggressive†	54.22 (5.40)	54.11 (4.81)	$U = 39.50$	.93
Social†	53.67 (6.34)	51.11 (2.62)	$U = 29.50$	.28
Internalizing	49.44 (14.02)	48.11 (10.34)	$t(16) = .23$	.82
Externalizing	50.33 (9.15)	51.89 (5.44)	$t(16) = .44$	.67
Rule-Breaking	55.56 (6.65)	53.56 (2.51)	$t(16) = .84$	.42

Notes: *p*-values are calculated using independent samples *t*-tests for continuous variables and chi-square (χ^2) tests for categorical variables between groups. For non-normally distributed data (†), Mann-Whitney *U* tests were used. For group comparisons on CBCL scores, the significance level was adjusted to $p = .01$. CBCL scores represent *T*-scores.

Abbreviations: CBCL, Child Behavior Checklist; FSIQ, Full-Scale Intelligence Quotient; GCS, Glasgow Coma Score; M, mean; SD, standard deviation; SES, socio-economic status; TBI, traumatic brain injury; TDC, typically developing controls; WASI-2, Wechsler Abbreviated Intelligence Scale-2.

*Significant at $p < .05$.

Table 5. Neuropathology On Clinical CT/MRI for TBI participants (Replication Sample)

	Sex	Injury type	Age at injury	GCS	CT/MRI findings	Skull fracture
TBI_R1	F	MVA	15.27	NA	Parietal hematoma; subdural hematoma; generalized edema	Undisplaced parietal
TBI_R2	M	MVA	14.70	12	NA	Frontal bone (craniotomy)
TBI_R3	M	Fall	14.95	13	B temporal haemorrhage; small extradural collection over the lateral aspect of the L occipital lobe	
TBI_R4	F	Fall	14.32	NA	R temporo-occipital hematoma; B fronto-tempoeral haemorrhagic contusions	
TBI_R5	M	MVA	9.70	12	NA	NA
TBI_R6	M	MVA	13.62	6	NA	NA
TBI_R7	M	Fall	11.75	12	R frontal and anterior temporal contusion; intraparenchymal haemorrhage; small R frontal traumatic subarachnoid haemorrhage	R parietal
TBI_R8	M	Fall	14.63	13	L frontal cortical contusion	B occipital
TBI_R9	M	Fall	11.05	13	R frontal cortical contusion; L occipito-parietal cortical contusion	R frontal

Abbreviations: B, bilateral; CT, computed tomography; F, female; GCS, Glasgow Coma Score (lowest); L, left; M, male; MRI, magnetic resonance imaging; MVA, motor vehicle accident; NA, not available; R, right; TBI, traumatic brain injury.

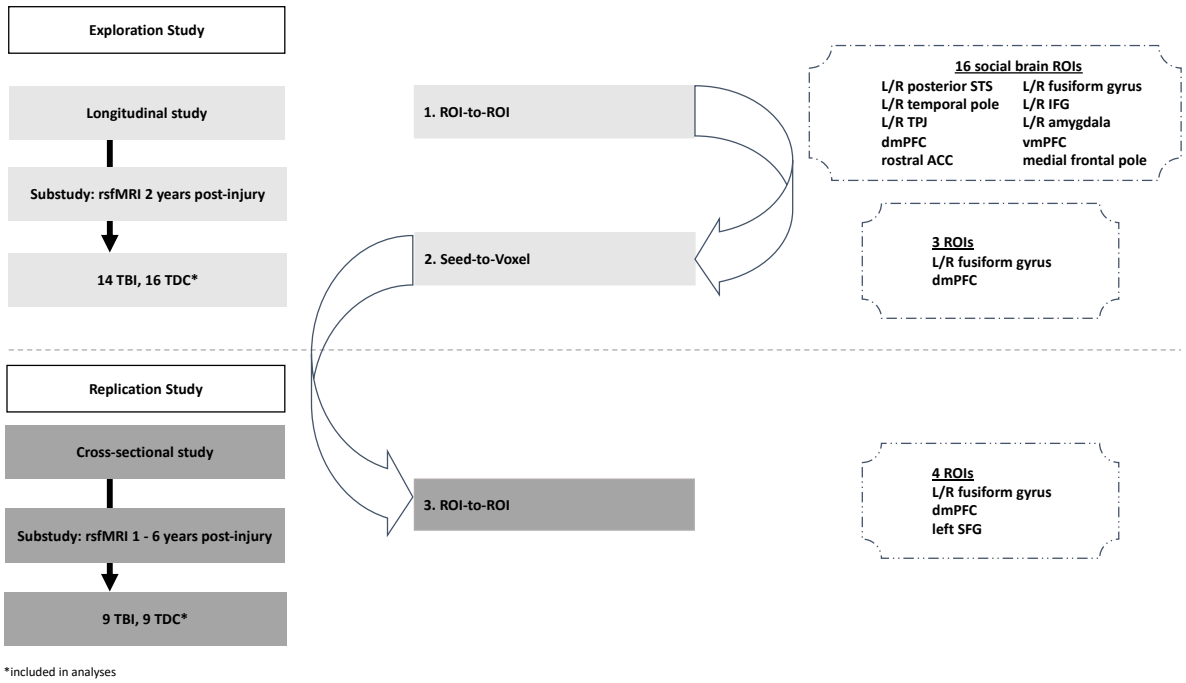

Figure 1. Overview of analyses steps.
Analyses were conducted in a stepwise manner: First, ROI-to-ROI analyses were performed between 16 ROIs of the social brain in a first sample that was part of larger longitudinal project (exploration study). Then, seed-to-voxel analyses were conducted to explore functional connectivity within the whole social brain in the same sample. Here, only significant seeds (bilateral) from the ROI-to-ROI analyses were selected to test whether these seeds may be connected with other regions within the social brain that were not initially selected. These analyses served to define more specific ROIs to be tested in an independent replication sample: A ROI-to-ROI approach was applied to test whether the results obtained in the exploration study would hold in an independent sample of participants that were recruited as part of a larger cross-sectional study (replication study).
Abbreviations: rsfMRI = resting-state functional magnetic resonance imaging; TBI = traumatic brain injury; TDC = typically developing controls; ROI = region of interest; L = left; R = right; STS = superior temporal sulcus; TPJ = temporo-parietal junction; dmPFC = dorsomedial prefrontal cortex; ACC = anterior cingulate cortex; IFG = inferior frontal gyrus; vmPFC = ventromedial prefrontal cortex; SFG = superior frontal gyrus.

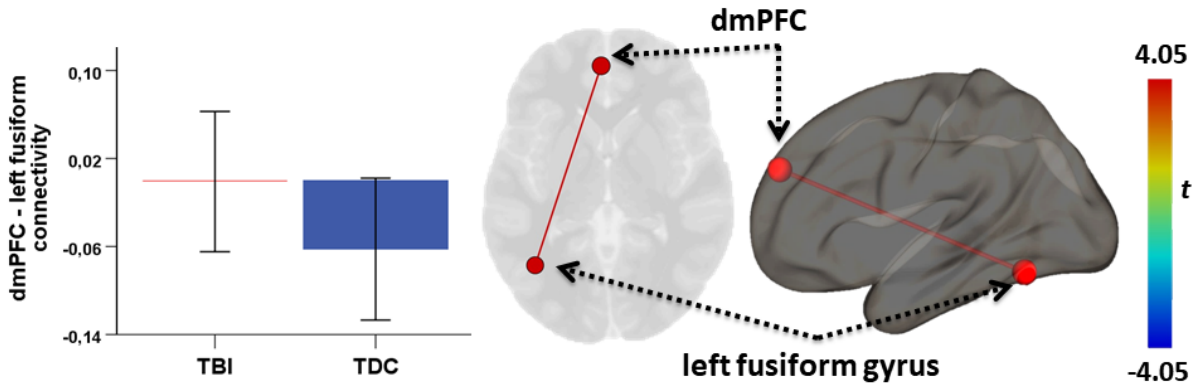

Figure 2. ROI-to-ROI functional connectivity analyses in the exploration sample.
A significant group difference in ROI-to-ROI functional connectivity between the TBI and the TDC group was found between dmPFC and left fusiform gyrus indicating positive connectivity in the TBI as compared to the TDC group which showed negative dmPFC-left fusiform connectivity. Error bars represent standard errors.
Abbreviations : dmPFC = dorsomedial prefrontal cortex; TBI = traumatic brain injury; TDC=typically developing controls.

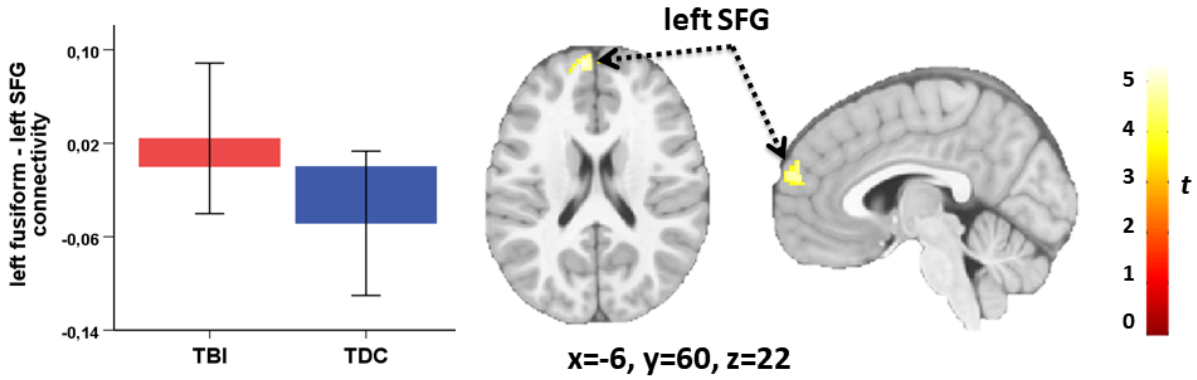

Figure 3. Seed-to-voxel functional connectivity analyses in the exploration sample.
A significant group difference in seed-to-voxel functional connectivity between the TBI and the TDC group was found between left fusiform gyrus and left SFG showing positive connectivity for participants with TBI and negative connectivity for TDC participants. Error bars represent standard errors.
Abbreviations: SFG = superior frontal gyrus; TBI = traumatic brain injury; TDC = typically developing controls.

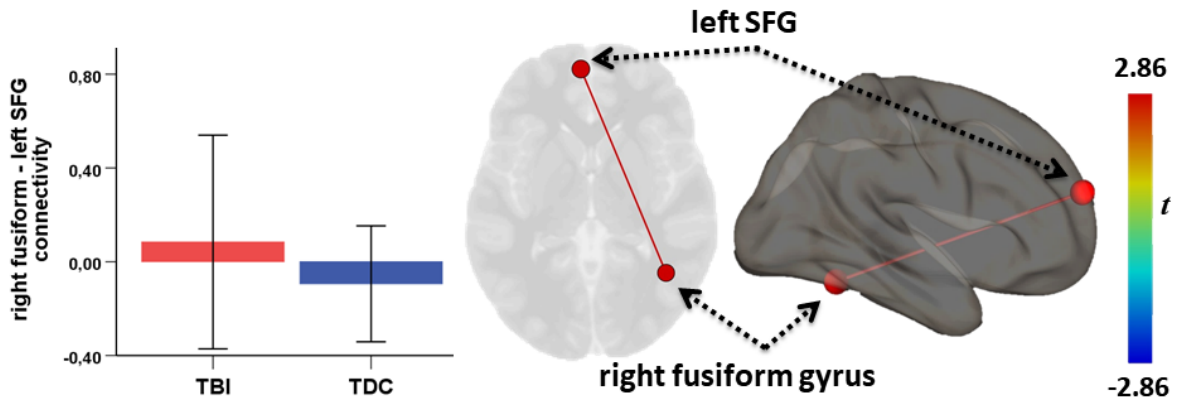

Figure 4. ROI-to-ROI functional connectivity analyses in the replication sample.
A significant group difference in ROI-to-ROI functional connectivity between the TBI and the TDC group was found between right fusiform gyrus and left SFG showing positive connectivity for the TBI group and negative connectivity for the TDC group. Error bars represent standard errors.
Abbreviations: SFG = superior frontal gyrus; TBI = traumatic brain injury; TDC = typically developing controls.

Article 4

Pediatric Moderate-Severe Traumatic Brain Injury And Gray Matter Structural Covariance Networks: A Preliminary Longitudinal Investigation

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Abstract

Pediatric traumatic brain injury (TBI) is prevalent and can disrupt ongoing brain maturation. However, the long-term consequences of pediatric TBI on the brain's network architecture are poorly understood. Structural covariance networks (SCN), based on anatomical correlations between brain regions, may provide important insights into brain topology following TBI.

Changes in global SCNs (default-mode [DMN], central executive [CEN] and salience networks) were compared sub-acutely (<90 days) and in the long-term (approximately 12 to 24 months) after pediatric moderate-severe TBI (n = 16), and compared to typically developing controls assessed concurrently (n = 15). Gray matter (GM) volumes from selected seeds (DMN: right angular gyrus [rAG], CEN: right dorso-lateral prefrontal cortex [DLPFC], salience network: right anterior insula) were extracted from T1-weighted images at both timepoints. No group differences were found sub-acutely; at the second timepoint, the TBI group showed significantly reduced structural covariance within the DMN seeded from the rAG and the 1) right middle frontal gyrus, 2) left superior frontal gyrus, and 3) left fusiform gyrus. Reduced structural covariance was also found within the CEN, that is, between the right DLPFC and the 1) calcarine sulcus, and 2) right occipital gyrus. In addition, injury severity was positively associated with GM volumes in the identified CEN regions. Over time, there were no significant differences in SCN in either group. The findings, albeit preliminary, suggest for the first time a long-term effect of pediatric TBI on SCN. SCN may be a complementary approach to characterize the global effect of TBI on the developing brain. Future work needs to further examine how disruptions of these networks relate to behavioral and cognitive difficulties.

Keywords: Traumatic brain injury, pediatric, structural covariance, magnetic resonance imaging, longitudinal.

Introduction

Worldwide, pediatric traumatic brain injury (TBI) is highly prevalent, affecting over three million children and adolescents each year (Dewan et al., 2016). TBI can lead to acute and chronic cognitive, emotional or behavioral sequelae which can affect academic and social functioning as well as quality of life (Beauchamp & Anderson, 2013; Brown et al., 2016; Catroppa et al., 2017), with more severe consequences reported after moderate to severe injury (Anderson et al., 2013; McDonald, 2013). The exact mechanisms and factors associated with unfavorable functional outcomes are difficult to pinpoint given heterogeneity in both clinical presentation and outcome; however, given that any insult to the developing brain is likely to disrupt brain maturation and associated processes (Gogtay et al., 2004), understanding the nature and extent of changes to brain structure after pediatric TBI is key.

During childhood and adolescence, the structure of the brain changes profoundly en route to mature neural architecture (Gogtay et al., 2004; Raznahan, Shaw, et al., 2011; Shaw et al., 2008). Pediatric TBI has the potential to interrupt this pre-programmed brain development cascade (Giza et al., 2007; Giza & Prins, 2006). In particular, TBI can result in cellular and tissue damage or loss which can induce long-lasting functional impairment (Bigler, 2013; Bigler, 2007; Bigler, 2016; Maxwell, 2012). Such damage is largely a function of age at injury, severity and pathology (Bigler, 2013).

Over the past decades, neuroimaging studies have quantified and characterized the impact of pediatric TBI on brain structure (e.g., Beauchamp et al., 2011; Ewing-Cobbs et al., 2008; Wilde et al., 2005; Wilde et al., 2020). Structural magnetic resonance imaging (MRI) studies have demonstrated morphometric differences, in particular an atrophic effect of TBI on the brain, when comparing children who sustain moderate to severe TBI to typically developing children (TDC) at both the early and chronic stages post-injury. For example, multiple cross-sectional studies converge on the finding of reduced gray (GM) and white matter (WM) volumes and cortical thickness, in particular in frontal, temporal and parietal regions (for reviews see Keightley et al., 2014; King et al., 2019; Zamani et al., 2020). Over time, primary and secondary injuries such as cerebral contusions in GM, myelin damage or neurometabolic changes (Araki et al., 2017) may progress and induce further anatomical and functional brain changes such as loss of neurons and altered brain connectivity (Königs et al., 2017; McKee et al., 2015). The few existing longitudinal

studies investigating TBI-related morphological changes over time echo findings from cross-sectional studies showing greater atrophy or reductions in regional brain volume and cortical thickness in children with TBI when compared to TDC within a given time period (e.g., Dennis et al., 2017; Wilde, Merkley, et al., 2012). Based on these findings, pediatric moderate-severe TBI appears to have long-lasting impacts on brain structure and may lead to divergent brain development trajectories (King et al., 2019).

While the aforementioned studies are useful in characterizing focal effects of TBI on the brain, they may not adequately represent the diffuse impact of TBI at the level of brain networks (Bullmore & Sporns, 2009; Pagani, Bifone, & Gozzi, 2016). Surprisingly few studies have examined how serious TBI affects the developing brain from a network perspective. The few existing studies have used resting-state functional MRI or diffusion tensor imaging (DTI) to explore brain network connectivity, and reveal acute and persistent alterations in functional connectivity (Risen et al., 2015; Stephens et al., 2018) and in WM microstructure (Genc et al., 2017; Ryan et al., 2018; Van Beek et al., 2015; Wilde et al., 2006). However, no one neuroimaging marker can fully characterized the impact of TBI on the developing brain, and complementary measures are therefore necessary to provide the most accurate assessment of how TBI affects brain network architecture.

Recent structural imaging advances provide new insights into anatomical connectivity in typical and atypical development. For instance, structural covariance network (SCN) analysis is a complementary approach for exploring the brain's topological organisation as well as network development (Mechelli et al., 2005; Zielinski et al., 2010). SCN analyses assess anatomical correlations of structural metrics (i.e., cortical thickness or GM volume) of distributed and related brain regions across individuals. The assumption underlying the study of SCN is that brain regions that increase or decrease at the same rate over time (in terms of volume or thickness) covary structurally and are thus anatomically and functionally connected (Alexander-Bloch, Giedd et al., 2013; Alexander-Bloch, Raznahan et al., 2013; Evans, 2013). SCN have been shown to reflect existing anatomical (Gong et al., 2012) and intrinsic functional connectivity networks (Alexander-Bloch, Giedd, et al., 2013; Alexander-Bloch, Raznahan, et al., 2013; Evans, 2013; Lerch et al., 2006; Zielinski et al., 2010). Given their systematic change across the lifespan, it is hypothesized that SCN provide a unique measure of synchronized maturational changes during development, which underlie higher-order cognitive functions (Mechelli et al., 2005; Raznahan, Lerch, et al.,

2011; Váša et al., 2017; Zielinski et al., 2010). By looking at brain changes in a network framework, this approach has the potential to capture developmental divergence in brain structure following pediatric TBI.

The default-mode (DMN), salience (SN) and central executive (CEN) networks are core neurocognitive networks that can reliably be identified using functional MRI (Fox & Raichle, 2007; Greicius et al., 2003; Seeley et al., 2007). The DMN, comprised of the posterior cingulate cortex (PCC), ventromedial prefrontal cortex (VMPFC) and the angular gyri, is involved in self-referential processing and social cognition (Andrews-Hanna et al., 2010; Buckner et al., 2008; Kim, 2012). The SN includes the anterior insula and dorsal anterior cingulate cortex (dACC) and plays an important role in stimuli detection and goal-directed behavior (Menon, 2011; Seeley et al., 2007). The CEN, anchored in the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) is involved in executive functioning (Koechlin & Summerfield, 2007; Menon, 2011; Seeley et al., 2007). These three networks are of particular interest in the context of pediatric TBI given their protracted maturation during childhood and adolescence (Uddin et al., 2011), broad involvement in cognitive and affective functioning, and vulnerability to pediatric TBI (Buckner et al., 2008; Menon, 2011; Seeley et al., 2007).

To date, SCN methods and longitudinal neuroimaging assessments have rarely been used to understand the developmental and long-term impact of pediatric TBI. Only one recent study using the SCN approach found divergent SCN three months post-injury in children who sustained mild to severe TBI when compared to TDC, with greater distance from the typical network being related to poorer executive functioning (King et al., 2020). The aim of the present study was to explore global SCN in children and adolescents with mild complex to severe TBI assessed within three months post-injury and again 12 to 24 months later with a focus on the DMN, SN, and CEN. In order to allow for comparisons with previous studies in children and adolescents, we used the same network hubs to construct the SCN as Zielinski and colleagues (2010). Finally, given the exploratory nature of the study, limited existing literature pertaining to SCN in TBI, and diverging results in previous studies investigating brain connectivity after pediatric TBI, we expected to find group differences in structural covariance at both timepoints, but did not specify *a priori* hypotheses as to the direction of the results.

Material and methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, and all measures in the study.

Participants

Data used in the present study were acquired between 2007 and 2010 as part of a prospective longitudinal cohort study on the psychosocial consequences of pediatric TBI sustained between the ages of five and 16 years. Further details of the parent study are provided elsewhere (Anderson et al., 2013; Catroppa et al., 2017). The study was approved by the Human Research Ethics Committee of The Royal Children's Hospital and the Victorian Department of Education Ethics Committee. All study procedures were conducted in compliance with the Declaration of Helsinki. All parents gave written, informed consent for their children to participate in the study and for extraction of clinical data from medical records. No part of the study procedures and analyses was pre-registered prior to the research being conducted.

Children and adolescents with TBI were recruited upon presentation to the emergency department. Inclusion criteria of the larger project for the TBI group were: (i) age 5 – 16 years at recruitment; (ii) documented evidence of a closed head injury including a period of altered consciousness and evidence of at least two post-concussive symptoms (i.e. headaches, irritability, nausea, poor concentration); (iii) medical records sufficiently detailed to determine injury severity including the Glasgow Coma Scale ([GCS]; Teasdale & Jennett, 1974), neurological (i.e., drowsiness, memory or vision problems, confusion, impairment of proprioception, vertigo) and radiological (i.e., abnormalities on computed tomography (CT)/clinical MRI) findings; (iv) no documented history of preinjury neurological or developmental disorder, nonaccidental injury or previous TBI; (v) no prior intervention for social impairment; (vi) English speaking. TDC participants were recruited from the community via local schools across different neighborhoods in order to ensure diversity of socioeconomic backgrounds, and matched to the TBI group on demographic variables (age, sex, socioeconomic status [SES]). They were required to meet inclusion criteria (i), (iv), (v), and (vi) above.

TBI severity was categorized using the following classification scheme: (i) mild TBI: GCS 13 – 15 on admission, no mass lesion on CT/clinical MRI, no neurological symptoms (in case of

evidence of intra-cranial pathology, these were classified as mild complex); (ii) mild complex TBI: Lowest GCS 13 – 15, mass lesion on CT/clinical MRI; (iii) moderate TBI: Lowest GCS 9 – 12, and/or mass lesion or other evidence of specific injury on CT/clinical MRI, and/or neurological impairment; (iv) severe TBI: Lowest GCS 3 – 8, and/or mass lesion or other evidence of specific injury on CT/clinical MRI, and/or neurological impairment.

The current study reports data from a subset of participants with mild complex, moderate and severe TBI and TDC who underwent repeat MRI scanning, sub-acutely (≤ 90 days post-injury for the TBI group) and in the long term (12 to 24 months later, mean [M] = 12.12, standard deviation [SD] = 7.24). MRI images were also obtained from the TDC subgroup at the same two timepoints. For the current substudy, a number of additional inclusion criteria were applied: (i) available structural MRI data at both assessments; (ii) quality control criteria applied to their MRI images during preprocessing (see below); and (iii) at least 8 years of age at the first assessment to limit the age range (M = 12.27, SD = 1.95, range 8.08 – 15.42). This resulted in a final sample of 31 participants (TBI n = 16, TDC n = 15). Among all participants that completed the substudy (n = 40), one mTBI participant was excluded to ensure a more heterogenous sample in terms of injury severity. Four participants (1 TBI, 3 TDC) had insufficient image quality at either the first or second MRI assessment (see below for more details), one control participant was aged less than eight years, and in the case of three participants (1 TBI, 2 TDC), one of the two T1 images was not available due to technical issues. This resulted in a final sample of 31 participants (TBI n = 16, TDC n = 15).

MRI acquisition

MR images were acquired on a 3 Tesla (3T) Siemens Trio scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-channel matrix head coil. For each participant, a high-resolution T1-weighted structural MR image was obtained using a sagittal three-dimensional (3D) T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (repetition time (TR) = 1900 ms; echo time (TE) = 2.15 ms; flip angle (FA) = 9º; field of view (FOV) = 256 mm; 176 slices; slice thickness = 1 mm; GRAPPA = 2; voxel-size = 1 x 1 x 1 mm).

Approximately 12 to 24 months later, a second MRI session took place and another high-resolution T1-weighted structural MR image was acquired on the same scanner (TR = 1900 ms; TE = 2.52 ms; FA = 9º; FOV = 250 mm; 192 slices; slice thickness = 1 mm; GRAPPA = 2; voxel-size = 1 x 1 x 1 mm). During the data collection period, no major scanner upgrades occurred.

Data analyses

All analyses including image processing and subsequent statistical analyses were performed using the Computational Anatomy Toolbox 12 (CAT12; http://www.neuro.uni-jena.de/cat/; RRID:SCR_019184) implemented in the Statistical Parametric Mapping 12 software (SPM12, Institute of Neurology, London, United Kingdom; RRID:SCR_007037) and running on MATLAB version R2017b (MathWorks, Inc., Natick, MA, USA).

Image processing

First, all raw MR images were subjected to quality control via visual inspection during which images were rated for issues of image quality such as motion artifacts, noise, ringing artifacts, ghosting, variations in slice intensity or incomplete brain coverage. A second quantitative data quality check was done after the segmentation step to control for inter-subject homogeneity and overall image quality (quality assurance ([QA] function in CAT12). Only subjects with a QA index higher than C+ were included. After these quality control steps, six TDC and three participants with TBI were excluded, resulting in a final sample of 16 TBI and 15 TDC participants.

Using the CAT12 longitudinal processing stream for voxel-based morphometry (VBM) data, each subject's structural T1-weighted images from both timepoints were first co-registered, and then bias-corrected using the average image based on each participants' images from the first and second timepoint as reference. This was followed by realignment of images across all subjects. For each participant, images from both timepoints as well as the average image were subsequently segmented into GM, WM and cerebrospinal fluid using age-appropriate stereotaxic tissue probability maps (NIHPD 4.5–18.5 asymmetric: www.bic.mni.mcgill.ca/ServicesAtlases/NIHPDobj1; Fonov et al., 2011). Then, spatial normalization to Montreal Neurological Institute (MNI) space with a voxel size of 1.5 mm x 1.5 mm x 1.5 mm was applied to the segmented GM and WM images. Finally, images were modulated nonlinearly (to account for brain size differences) and subsequently smoothed with an 8-mm full-width at half-maximum (FWHM) Gaussian kernel. An absolute threshold mask of 0.1 was used for the GM images to adjust for incorrect voxel classification.

Structural covariance analyses

SCN analyses focused on three core neurocognitive networks, notably the DMN, SN and CEN (Fox & Raichle, 2007; Greicius, Krasnow, Reiss, & Menon, 2003; Seeley et al., 2007). The

DMN is involved in self-referential processing and social cognition (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Buckner, Andrews-Hanna, & Schacter, 2008; Kim, 2012), the SN in stimuli detection and goal-directed behavior (Menon, 2011; Seeley et al., 2007), and the CEN in executive functioning (Koechlin & Summerfield, 2007; Menon, 2011; Seeley et al., 2007). These three networks were selected given their protracted maturation during childhood and adolescence (Uddin, Supekar, Ryali, & Menon, 2011), broad involvement in cognitive and affective functioning, and vulnerability to pediatric TBI (Buckner et al., 2008; Menon, 2011; Seeley et al., 2007).

For statistical analyses, three regions of interest (ROI) were selected, based on a pioneering study of structural covariance in the context of brain development (Zielinski et al., 2010). Specifically, the right angular gyrus was selected as a hub of the DMN (MNI coordinates: 46, -59, 23), the right dorso-lateral prefrontal cortex for the CEN ([rDLPFC]; MNI coordinates: 44, 36, 20), and the right anterior insula for the SN (MNI coordinates: 38, 26, -10). Analyses on contralateral seeds were not performed in order to limit the number of independent analyses, given the small sample size. ROIs were defined as 4-mm radius spheres as done previously (Zielinski et al., 2010) around the respective coordinates and regional GM volumes were extracted from the modulated normalized GM images of all 31 participants.

Subsequent SCN analyses on the smoothed and modulated GM images were performed separately for each seed by entering the extracted GM volumes from each seed and group as a regressor, and age at the MRI scan (i.e., first or second timepoint) and sex of participants as covariates. For each seed, differences between TBI and TDC in the regression slope (i.e., differences in structural association) were tested by modeling seed-GM volume by group interactions. Analyses were performed for each timepoint separately. Then, differences in regression slopes between the first and second timepoint within each group were investigated in order to assess how structural association patterns change over time (here, we modelled seed-GM volume by time interactions). T contrasts were used to test for voxels expressing a significantly stronger structural association in TDC compared with TBI, and the inverse, as well as between the first and second timepoint and vice versa within each group.

The resulting correlation maps were thresholded at a voxel-wise p-level of $p \leq 0.001$ (uncorrected) and then a cluster-level of threshold of $p \leq 0.05$ (uncorrected) was used to determine statistical significance. This approach was chosen given the modest sample size and the preliminary

and exploratory context of the study. However, all contrast maps were thresholded by applying a cluster extent threshold of $k \geq 100$ voxels and analyses were masked using an explicit inclusive mask of normalized GM images from the TDC group (using the first or second timepoint, respectively) in order to restrict analyses to GM areas. The following formula was used: mean GM > mean WM) $\cap$ (mean GM > mean CSF) $\cap$ (mean GM > 0.3). Regions were labelled using the SPM12 Neuropmorphometric atlas (http://www.neuromorphometrics.com/). Mean cortical volumes of significant clusters were extracted and correlated with seed volumes in order to display results.

Correlations with injury and cognitive variables

To investigate clinical significance of identified cluster peaks, correlation analyses were performed between identified clusters and intellectual functioning and injury variables within the TBI group. Specifically, GM volume was extracted from 4-mm radius spheres around MNI coordinates from peak voxels that showed significant between-group differences in structural covariance. Bivariate Pearson correlation analyses were then used to explore associations between the peak voxel volume and full-scale intelligence quotient (FSIQ) as measured using the Wechsler Abbreviated Intelligence Scale (WASI; Wechsler, 1999), lowest GCS score (as an indicator of injury severity), and age at injury. FSIQ was chosen given previous reports showing links between CEN and DMN connectivity and IQ in children and adolescents (Li & Tian, 2014; Sherman et al., 2014). A threshold of $p < 0.05$ was applied for these analyses.

Results

Sample characteristics

Participant demographics and injury characteristics (for the TBI group) including age, sex and socio-economic status (SES) based on the Australian and New Zealand Socioeconomic Classification of Occupations ([ANZSCO]; McMillan et al., 2009) are provided in Tables 1 and 2. There were no statistically significant group difference on any of the demographic variables. However, the two groups differed significantly in terms of FSIQ. There was no statistically significant difference between those who were included in the present analyses and those who were excluded from the larger cohort in terms of age at the first timepoint (p =.065), age at the second timepoint (p = .065), SES (p = .767) or sex (p = .142).

Differences in SCN topology between the TBI and TDC groups

Results of the SCN analysis are shown in Table 3 and illustrated in Figures 1 and 2. Within the DMN, anchored in the right angular gyrus, the patterns of structural association did not show any significant differences between the two groups at the first timepoint. By contrast, at the second timepoint, a significant group difference was observed, indicating reduced structural association between the right angular gyrus and three clusters centered in the right middle frontal gyrus (p = .001, k = 1026), left superior frontal gyrus (p =.002, k = 905) and left fusiform gyrus (p =.048, k = 305) in the TBI compared to the TDC group.

At the first timepoint, no difference in the pattern of structural associations was observed for the CEN (rDLPFC). However, approximately 24 months later, there was a significant group difference in structural association between the rDLPFC and two clusters centered in the left calcarine sulcus (p = .029, k = 361) and the right occipital gyrus (p = .050, k = 283), again indicating reduced structural association in the TBI compared to the TDC group.

Within the SN network anchored in the right anterior insula, there were no significant group differences in SC at either timepoint.

Changes in SCN topology over time within the TBI and TDC groups

Within the DMN, CEN and SN networks, there were no significant differences in structural association patterns over time in either group.

Associations of peak cluster volumes with injury variables and cognitive functioning

Follow-up correlation analyses were performed based on the findings from the second timepoint. For the DMN, bivariate Pearson correlations revealed no significant associations between FSIQ and the peak volume of the right middle frontal gyrus, left superior frontal gyrus or left fusiform gyrus. Similarly, no associations were found between these regions and either GCS score or injury age. With respect to the CEN, neither FSIQ nor injury age were significantly correlated with either the peak volume of the left calcarine sulcus or the right occipital gyrus. However, the peak volumes of the left calcarine sulcus (r = .501, p = .048) and the right inferior occipital gyrus (r = .617, p = .011) were significantly and positively correlated with the GCS score, indicating that higher volumes in these regions were associated with milder injury severity.

Discussion

This exploratory study investigated longitudinal patterns of GM structural covariance after moderate to severe pediatric TBI within three core networks, namely the DMN, SN and CEN. Results indicate overall reduced structural covariance in the DMN and CEN 12 to 24 months post-injury in the TBI group when compared to TDC. Taken in the context of a preliminary and exploratory study, these results may indicate a non-transient effect of pediatric TBI on brain development, and support previous findings of long-term alterations in brain structure after pediatric TBI (e.g., Dennis et al., 2017; King et al., 2019; Wilde, Merkley, et al., 2012) as well as findings of lower structural covariance in the DMN and CEN after adult TBI (Song et al., 2020). In addition, the results suggest that these alterations may be related to injury severity.

Reduced structural associations at approximately 24 months post-injury were observed within the DMN for the TBI group (compared with TDC), notably between the right angular gyrus and bilateral middle and superior frontal regions, which are considered part of the posterior DMN (Li et al., 2013; Uddin et al., 2009; Xu et al., 2016), as well as between the right angular and left fusiform gyrus. Very few studies have examined intrinsic functional connectivity within the DMN and other regions after pediatric TBI and show both increased and decreased connectivity patterns in children with TBI of different severities and at different recovery stages (e.g., Iyer et al., 2019; Newsome et al., 2013; Risen et al., 2015; Stephens et al., 2018). It is thus unclear whether changes in DMN connectivity are compensatory mechanisms against the effects of injury or a direct effect of injury. Although the exact correspondence between functional connectivity and SCN is still unclear, the present finding of reduced structural covariance between the right angular gyrus and middle-superior frontal regions are consistent with a previous study showing lower functional connectivity within DMN regions four weeks after pediatric mild TBI and decreased GM volume in these regions (Iyer et al., 2019). Considering that synchronous neuronal firing patterns mediate synaptogenesis (Katz & Shatz, 1996), the decreased structural correlations may be indicative of a disruption of this process and subsequent dysconnectivity. Furthermore, given documented interactions between the angular gyri and several large-scale networks (Zhao et al., 2019), reduced structural association between the angular and fusiform gyrus may reflect a disruption of inter-network communication. Finally, given the role of the fusiform gyrus in facial and visuo-cognitive processing (Kanwisher et al., 1997; Wang et al., 2013), as well as evidence that the DMN is connected with brain regions implicated in perceptual cognitive processes (Buckner & Krienen,

2013), reduced angular-fusiform covariance may underlie some of the observed cognitive difficulties after pediatric TBI (e.g., Rigon et al., 2019), though in the context of the current study, this interpretation is speculative and warrants further investigation using functional correlates.

Reduced structural covariance was also observed within the CEN, though these results did. Not survive FWE-correction at the cluster-level and interpretations thus remain tentative. The CEN and associated frontal regions are critically involved in executive control processes (Menon, 2011), which are frequently disrupted by pediatric TBI (Sesma et al., 2008; Wilde et al., 2005; Yu et al., 2018). Indeed, regional structural MRI studies show reduced cortical thickness and GM volume in the DLPFC in the acute phase post-injury (McCauley et al., 2010; Urban et al., 2017), which were related to poorer EF in one study (Wilde, Hunter, et al., 2012). Damage to frontal areas, such as to the DLPFC, could over time affect the CEN, and underlie persistent executive difficulties. Altered structural association in the CEN also supports previous findings showing divergent structural covariance in the CEN after pediatric TBI and in relation to executive dysfunction (King et al., 2020). Moreover, reduced structural association between anterior and posterior regions suggests that pediatric TBI can disrupt the formation of long-range connections and cross-networks links. For example, fronto-occipital WM tracts such as the fronto-occipital fasciculus, typically associated with attention and visual processing (Catani & Thiebaut de Schotten, 2008), have been found to be vulnerable to disruption by TBI (Palacios et al., 2012). The finding of lower DLPFC-occipital structural covariance observed here in the TBI group thus supports the finding of frontal-occipital disruption following pediatric TBI. Finally, the association of the identified clusters with injury severity suggests that structural association patterns may be more strongly affected after more severe forms of TBI.

In previous publications from the same cohort, Ryan and colleagues found reduced volumes in regions of the DMN, CEN and SN (Ryan, Catroppa, Beare, et al., 2016; Ryan et al., 2017; Ryan, Catroppa, Godfrey, et al., 2016; Ryan, van Bijnen, et al., 2016). However, none of these studies used a comprehensive network approach in their analyses. Here, the observation of reduced SCNs and more localized topology after pediatric TBI may reflect both atypical cortical development or decoupling between brain regions and disruption of cross-hemisphere communication (Voss & Zatorre, 2015). In typical development, SCN follow a specific maturational trajectory (Alexander-Bloch, Raznahan, et al., 2013; Fan et al., 2011; Khundrakpam et al., 2013), with a progressive shift of covariance from a local to a more distributed pattern throughout childhood, reflecting an age-

related increase in cross-network links observed until early adolescence (Fair et al., 2009; Zielinski et al., 2010), and subsequent pruning (i.e., age-related decreases in structural covariance) during adolescence (Arain et al., 2013; Zielinski et al., 2010). Furthermore, increased correlations between left and right hemispheres can be observed during adolescence (Aboud et al., 2019). Thus, in the context of early adolescence in the present study, it is possible that TBI sustained during development disrupts the expanding network formation in its first phase, that is, an increase in cross-network and cross-hemispheric links, leading to overall reduced associations within and between nodes of large-scale networks, as well as interrupted cross-hemisphere communication. Overall, the developmental wiring process may be disrupted as a result of pediatric TBI, resulting in a more immature pattern of structural covariance.

Reduced structural covariance could also reflect underlying disconnection as a result of diffuse axonal damage, as reported in previous studies using DTI in the sub-acute (Genc et al., 2017; Ryan et al., 2018) and long-term phase (Genc et al., 2017) after pediatric TBI (Zamani et al., 2020, for a review). For example, in a substudy of the current cohort, compromised WM integrity was found both at the sub-acute and two years after moderate-severe pediatric TBI (Genc et al., 2017). The observation of reduced structural associations at two years post-injury, but not in the sub-acute phase, suggests that with the progression of TBI-related neural reorganization, acute regional damage (i.e., reductions in GM and WM) as a direct effect of injury may interfere with ongoing maturational and wiring processes. Over time, this may then translate into alterations at the global network-level, i.e., an increased pattern of disconnection within and between nodes of large-scale networks, consistent with previous findings of altered functional connectivity and WM approximately two years after pediatric TBI (Genc et al., 2017; Tuerk et al., 2020). The results also indirectly support findings that some difficulties only emerge in the long-term post-injury (Li & Liu, 2013) and provide a potential neural mechanism.

Strengths, limitations and future directions

Given the exploratory nature of this study, results are to be considered preliminary and interpreted with caution. Overall, however, the present findings indicate that there are long-term changes at the level of the network topology after pediatric moderate to severe TBI, echoing previous findings of altered brain structure and integrating these findings from a network perspective. A novelty and strength of the present study consists in the use of SCN analysis which has rarely been applied to TBI, and, to the best of our knowledge, only once in a cross-sectional

design of pediatric TBI (King et al., 2020). Longitudinal neuroimaging studies are scarce in the context of pediatric TBI, and therefore exploring SCN over time offers new insights into the development of structural covariance patterns following pediatric TBI and the long-term impact of pediatric TBI on brain topology.

However, the sample size was modest for structural covariance analyses and while statistically strong effects were found, other more subtle effects may have been masked, such as with respect to the SN, in which no group or time differences were observed. Because of the modest sample size, generalizability of the findings is limited. In addition, existing analytic tools did not allow us to concurrently compare these structural association patterns between the two groups over time. Furthermore, we were not able to investigate structural covariance patterns across different age bands given the modest sample size. Future advances in terms of statistical analyses and software could focus on how to perform three-way interactions in (i.e., seed X group X time) in structural covariance to disentangle normative developmental from injury-related changes. Although we found links between altered structural covariance patterns and injury severity for the CEN, no significant associations were found with FSIQ and other cognitive-behavioral associations were not tested given the limited sample size and lack of a priori information to guide hypothesis testing. The conclusions with respect to the functional significance of the findings remain to be determined. Finally, we did not correct for multiple comparisons and instead opted to report uncorrected results given the exploratory nature of the study. Nonetheless, a conservative approach was applied by restricting analyses to voxels with a GM mask based on the TDC participants as well as by adjusting for covariates in all analyses.

Future studies should use larger and more homogeneous samples to increase the robustness of these preliminary findings and to extend analyses to the contralateral hemisphere as well as to other stable SCN, such as those proposed by Zielinski and colleagues (2010) in the developing brain, including primary visual, auditory, motor, speech and semantic networks. This will be important for characterizing the global effect of TBI on the developing brain and its neural network architecture. In addition, combining SCN analysis with other neuroimaging approaches would help to identify the mechanisms underlying structural covariance and their associations with functional connectivity. Future studies should also assess how altered patterns of structural covariance relate to other injury characteristics (i.e., extent and location of neuropathology, injury age and severity etc.) and behavioral variables (e.g., socio-cognitive variables, executive functions). A better

understanding of how pediatric TBI affects development at the neural network level may help determine early markers of unfavorable recovery and identify children at risk for poor outcomes. This study provides a proof-of-concept for future research using SCN to investigate the developmental impact of TBI on the maturation of large-scale structural brain networks.

Conclusions

This study provides preliminary evidence for a non-transient effect of pediatric TBI on brain structural covariance networks, as shown by the findings of reduced structural associations in two core brain networks (DMN and CEN) two years post-injury. This work supports SCN as a useful approach to comprehensively investigate brain networks after pediatric TBI, and to characterize the global effect of TBI on the developing brain in the context of large-scale networks. Combining this approach with other neuroimaging techniques as well as behavioral data will be critical to enhance (i) our understanding of how disruptions of these networks relate to behavioral and cognitive functioning in the short- and long-term, and (ii) how TBI affects the maturation of brain structural and functional networks during sensitive developmental periods.

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Declarations of interest

None.

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Table 1. Demographic Characteristics Of All Participants

	TBI	TDC	t/χ^2	*p*
Demographics				
Total (n)	16	15	--	--
Sex (male), *n (%)*	12 (75)	10 (67)	.609	.261
SES, *M (SD)*	56.87 (21.88)	69.88 (14.94)	-1.94	.063
FSIQ (WASI), *M (SD)*	97.29 (2.92)	105.50 (9.69)	-2.10	.045
Age at first MRI (years), *M (SD)*	11.96 (1.57)	12.61 (2.31)	-.91	.370
Age at second MRI (years), *M (SD)*	13.07 (1.45)	13.51 (1.83)	-.73	.469
Time: Injury – First MRI (days), *M (SD)*	54.19 (58.27)	--	--	--
Time: Injury - Second MRI (months), *M (SD)*	15.01 (4.81)	--	--	--
Time : First – Second MRI (months), *M (SD)*	13.38 (5.52)	10.78 (8.71)	.99	.334

SES was calculated using the ANZSCO (scores range from 0 to 100 with higher scores reflecting higher occupational status for the primary caregiver). Significance-level: $p < .05$.
MRI = magnetic resonance imaging; FSIQ = full-scale intelligence quotient; SES = socioeconomic status; TBI = traumatic brain injury; TDC = typically developing controls; WASI = Wechsler Abbreviated Intelligence Scale.

Table 2. Injury Characteristics Of The TBI Group

	M	*SD*	*range*
General injury characteristics			
Age at injury (years)	11.81	1.57	9.17 – 14.75
Lowest GCS	11.19	3.49	3 - 15
Neurological symptoms, n (%)	4 (25)	--	--
Surgical intervention, n (%)	5 (31.25)	--	--
Loss of consciousness			
None, n (%)	4 (25)	--	--
< 5 min, n (%)	10 (62.5)	--	--
> 5 min, n (%)	1 (6.25)	--	--
Unknown, n (%)	1 (6.25)	--	--
Cause of injury			
MVA (car, pedestrian/bike), n (%)	4 (25)	--	--
Fall (stationary or moving), n (%)	11 (68.75)	--	--
Kicked/struck by object, n (%)	1 (6.25)	--	--
CT/clinical MRI pathology (acute)			
No pathology, n (%)	2 (12.5)	--	--
Frontal, n (%)	13 (81.25)	--	--
Extra-frontal, n (%)	5 (31.25)	--	--
Sub-cortical, n (%)	3 (18.75)	--	--

Participants with mild complex (n = 5), moderate (n = 7) and severe (n = 4) TBI were combined into one group.
CT = computed tomography; GCS = Glasgow Coma Score; MRI = magnetic resonance imaging; MVA = motor vehicle accident; TBI = traumatic brain injury.

Table 3. Group Differences In SCN Topology (TDC > TBI) For Seed Regions At The Second Timepoint

	Cluster / Peak	Side	MNI coordinates			Extent (*k*)	Max *T*	p^a	*p*(FWE)
			x	y	z				
DMN (R angular gyrus)	**Middle frontal gyrus**	**R**	**33**	**34**	**45**	**1026**	**4.74**	**.001**	**.008**
	Superior frontal gyrus/Frontal pole	R	14	56	33		4.70		
		R	24	46	38		4.42		
	Superior frontal gyrus/ Frontal pole	**L**	**-27**	**51**	**30**	**905**	**4.61**	**.002**	**.014**
		L	-15	51	40		4.55		
	Frontal pole/ Middle frontal gyrus	L	-40	46	24		4.47		
	Fusiform gyrus	**L**	**-33**	**-18**	**-36**	**305**	**4.24**	**.048**	**.306**
	Fusiform gyrus/ Inferior temporal gyrus	L	-27	-4	-44		4.18		
	Temporal pole	L	-24	6	-40		3.72		
Executive control network (R DLPFC)	**Calcarine sulcus**	**L**	**-10**	**-78**	**6**	**361**	**4.22**	**.029**	**.209**
		L	-9	-81	14	s.c.	4.03		
	Inferior occipital gyrus	**R**	**38**	**-78**	**4**	**283**	**4.71**	**.050**	**.329**
		R	27	-86	6	s.c.	4.40		
	Occipital pole	R	22	-96	8	s.c.	3.85		

[a] = uncorrected at cluster-level. $p < .001$ (voxel-wise, uncorrected), *p*(FWE) = corrected at cluster-level,
FWE = family wise error, s.c. = same cluster.

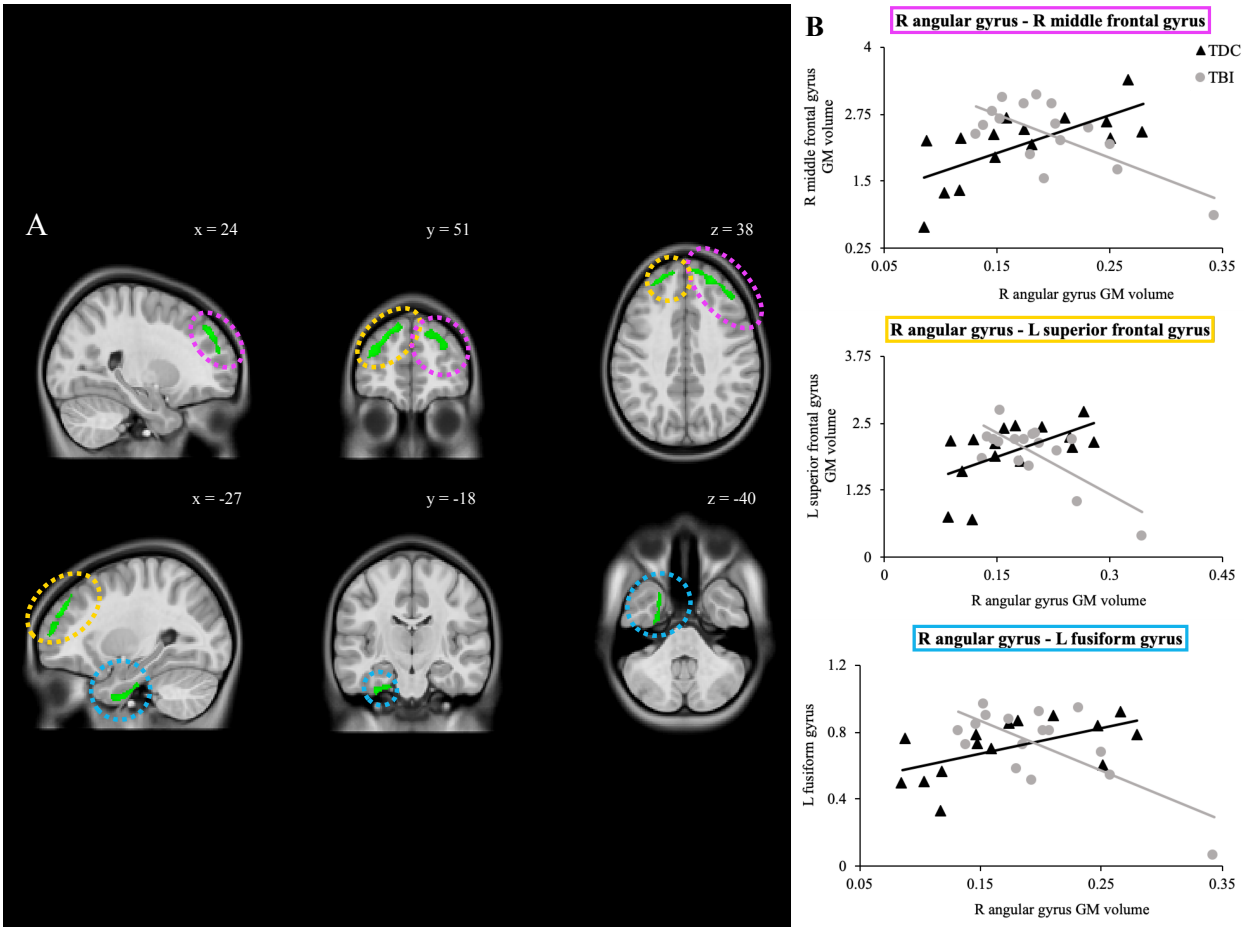

Figure 1. Differences in GM structural covariance networks between TBI and TDC groups at the sceond timepoint (structural associations between network seeds and 4-mm radius spheres centered on the peak voxel expressing differences in structural association between groups).

A) For the default-mode network (right angular gyrus), the TBI group showed a reduced structural association between the right angular gyrus and right middle frontal gyrus (pink), left superior frontal gyrus (yellow), as well as with the left fusiform gyrus (light blue). B) Scatterplots depicting significant differences in structural association patterns between the TBI and TDC group.

Abbreviations: GM = gray matter; L = left; R = right; TBI = traumatic brain injury; TDC = typically developing controls. Results are displayed on a normalized pediatric template (Fonov et al., 2011).

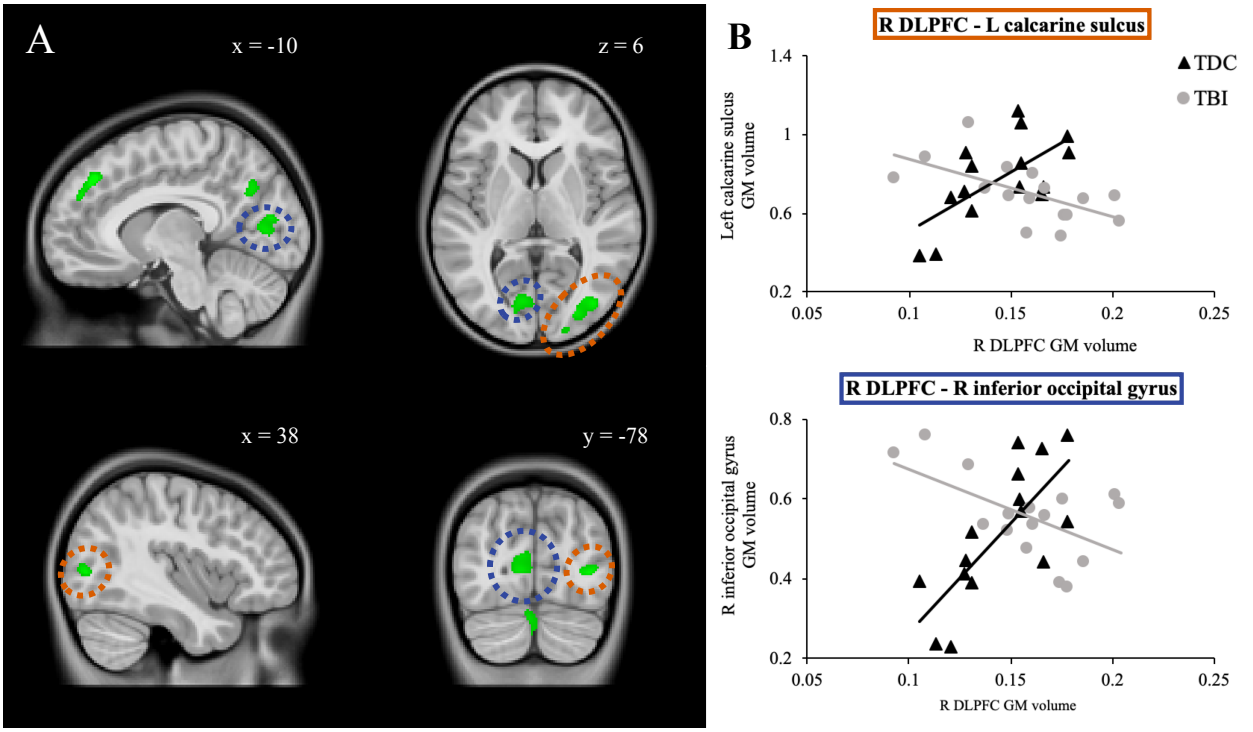

Figure 2. Differences in GM structural covariance networks between TBI and TDC groups at the second timepoint (structural associations between network seeds and 4-mm radius spheres centered on the peak voxel expressing differences in structural association between groups).

A) For the central executive network (right DLPFC seed), the TBI group showed a reduced structural association between the right DLPF and the left calcarine sulcus (brown) as well as with the right inferior occipital gyrus (blue). Gray dots represent TBI and black triangles represent TDC. **B)** Scatterplots depicting significant differences in structural association patterns between the TBI and TDC group.

Abbreviations: DLPFC = dorsolateral prefrontal cortex; GM = gray matter; L = left; R = right; TBI = traumatic brain injury; TDC = typically developing controls. Results are displayed on a normalized pediatric template (Fonov et al., 2011).

Discussion

Disturbances of social functioning are a common consequence of pediatric TBI across all injury severities. For many, they constitute the most debilitating symptoms, impacting well-being and long-term QoL (e.g., Catroppa et al., 2012; Li & Liu, 2013). To understand the origin of such problems, prediction models are key for determining what factors place children at risk for poor social outcomes as well as to develop efficient prognostic and diagnostic tools. A first step towards this aim is to understand social functioning in the context of expected development. Theoretical models that depict social development and how social competence emerges can be helpful for conceptualizing the multifaceted factors that contribute to social functioning; however, many such models lack empirical validation and hence, clinical applicability. In addition, while prognostic models in the field of TBI abound, most focus only on a subset of potential domains of influence with limited predictive ability. As such, there is currently a dearth of comprehensive approaches and, in particular, a paucity of studies that consider the role of genetic factors in explaining variability in outcomes after pediatric TBI.

Further to these issues surrounding outcome prediction, the brain basis of the social problems that arise after pediatric TBI remain incompletely understood. Given that brain development occurs in a protracted, non-linear fashion across childhood and adolescence, and includes the formation of large-scale neural networks, pediatric TBI can interfere with the pre-programmed sequence of maturational events and disrupt these complex networks, including those sub-serving social skills. To date, most studies seeking to describe structural or functional neural substrates of social functioning after pediatric TBI have focused on individual brain regions and used cross-sectional designs. These studies, though valuable, provide only an incomplete picture of the neural processes underlying social problems after pediatric TBI and lack a neural network perspective of social functioning. Similarly, the developmental impact of pediatric TBI on brain and behavioural outcomes over time remains elusive and requires a longitudinal viewpoint.

Using a multi-modal approach including a comprehensive set of child- and family-related data, genetic variables as well as structural and functional neuroimaging techniques, the overall goal of this thesis was to identify what contributes to social competence in typical development, test a predictive model of QoL after pediatric TBI, and assess how pediatric TBI affects the developing brain using a neural network perspective. The thesis is based on two distinct data sets

from prospective longitudinal cohort studies of early mTBI (LION study) and moderate to severe TBI sustained during childhood and adolescence (Victoria Neurotrauma Initiative Study). First, the aim was to empirically validate the SOCIAL model which provides a theoretical framework of factors that play a role in determining an individual's social competence both in typical development and after brain injury (Article 1). Second, a comprehensive biopsychosocial model including a range of genetic, family injury and cognitive factors was tested to examine predictors of long-term QoL after early mTBI (Article 2). The third objective was to evaluate how pediatric moderate-severe TBI impacts large-scale structural and functional brain networks, in particular the social brain and three main neurocognitive networks (i.e., DMN, CEN and SN; Articles 3 and 4). In the discussion that follows, results obtained across the four empirical articles will be discussed and embedded into the existing literature. Methodological, theoretical and clinical implications as well as study limitations and future research avenues will be presented.

Summary of findings

The first article supports the SOCIAL model as a valid framework for conceptualizing social competence and its contributing factors. The results highlight that all domains of the model (i.e., internal, external and cognitive factors) contribute to a child's social competence level. Analyses of a sample of preschoolers revealed that internal, cognitive and socio-cognitive factors play a particularly important role in predicting social competence such that children with lower negative affect and better abilities in terms of EF, non-verbal communication and ToM had a higher level of social competence. Testing this model empirically and comprehensively provides validation for understanding typical development and supports its applicability to the study of brain insult, such as after pediatric TBI.

The second article applied a biopsychosocial approach to evaluate which of a comprehensive range of biological, family-environmental, injury and child cognitive-behavioural factors contribute to child QoL six and 18 months after early mTBI (i.e, sustained between 18 and 60 months of age). The hypothesis that biological factors would play a significant role in the earlier phase post-injury was supported by the results: At six months post-injury, a genetic factor (BDNF genotype) was the only significant predictor of QoL in the final model. More specifically, the Val66Met polymorphism was associated with better QoL, suggesting that the presence of this genotype may act as a protective factor against poor post-TBI outcome. At 18 months post-injury,

family-environmental factors contributed to QoL, in line with the *a priori* hypothesis: Lower parental distress was related to better QoL in the final model. Contrary to what was expected, cognitive-behavioural factors did not contribute to QoL above and beyond family-environmental factors at 18 months post-injury. The same models applied to the data of two controls group (TDC and children with OI) were non-significant, except for parental distress which also predicted QoL at 6 months post-recruitment in the TDC group.

The aim of the third thesis article was to investigate whether FC within the social brain is altered after more severe forms of pediatric TBI (i.e., mild complex, moderate and severe TBI). Building on previous work investigating neural correlates of social difficulties after pediatric TBI, this study aimed to apply a comprehensive network perspective of the social brain by including several nodes of the network in the analyses. Using two independent samples of children and adolescents with mild complex to severe TBI who underwent rsfMRI 24 months post-injury, two region of interest (ROI) analyses were performed based on main SBN nodes. Results indicate that FC was altered in the TBI group between the dorsomedial prefrontal cortex (dmPFC) and left fusiform gyrus, as well as between the left fusiform gyrus and left superior frontal gyrus. Between these regions, positive connectivity was found for the TBI group, contrasting with a negative FC pattern for the TDC group. In the second sample, these results were largely replicated, with altered (i.e., positive) FC observed between the left superior frontal gyrus and right fusiform gyrus for the TBI group (i.e., negative connectivity for TDC). These results show, for the first time, altered FC within the SBN after pediatric TBI using a network perspective of social functioning. The exploration-replication approach supports the robustness of altered frontal-fusiform connectivity, though the modest sample sizes warrant further replication and study in larger cohorts.

Finally, the fourth article applied SCN analyses to a sample of children and adolescents with mild complex, moderate or severe TBI across two time points (three and 24 months post-injury). Changes in the DMN, SN and CEN were compared between the TBI and a TDC group. While no group differences were found after three months, significant differences were revealed two years later, with the TBI group showing reduced structural covariance within the DMN and the CEN. There were no changes over time in either group. This exploratory study reveals a chronic effect of pediatric TBI on the developing brain at the level of brain networks. It also supports the use of SCN analyses to evaluate the developmental impact of pediatric TBI on the brain's network topology and complement other approaches used to investigate brain connectivity

Interpretation of the thesis findings

Factors predicting social development in early childhood – implications for pediatric TBI

As highlighted throughout the thesis, many factors need to be considered for predicting outcome after pediatric TBI. Comprehensive biopsychosocial approaches such as those presented in Articles 1 and 2 are important because they capture several domains of functioning all of which may play a role in recovery. In the social realm, although several models have been proposed to integrate the different factors that play a role in social development, there is a lack of well-validated and comprehensive models which could be applied to clinical practice. While the findings of Article 1 highlight that all domains of the SOCIAL model are relevant to social competence in early childhood, they underscore the particular importance of child temperament, EF, and social cognition (i.e., non-verbal communication, ToM). There is evidence from the TBI literature that disruptions of these three domains (i.e., temperament, EF and social cognition) can occur, and together, the results of those previous studies and the current work could help to explain why social difficulties arise following pediatric TBI.

Temperament traits, referring to affective, motor and reactive tendencies (Rothbart & Derryberry, 1981) capture a child's ability to react and adapt to the environment (Goldsmith et al., 1987). Developmental changes in affective and behavioural traits, such as an age-related decrease in negative emotionality, an increase in positive emotions along with stronger emotional self-control, contribute to normative socio-emotional development and are shaped by experience and environmental factors (Kochanska et al., 2000; Rothbart et al., 2000; Saarni et al., 2006). Temperament can also be influenced by traumatic life experiences (Laceulle et al., 2012). In translating the present findings to pediatric TBI, sustaining a brain injury could slow the maturation of temperament, resulting in attenuated levels of negative affectivity and effortful control, as well as lower surgency, and consequently disrupt social functioning. A recent study using data from the LION cohort investigated the developmental trajectory of temperament six and 18 months after early mild to severe TBI (Séguin et al., 2020). In the absence of preinjury differences between TBI and OI groups, the findings show that the increase in the temperamental subdomain of surgency (i.e., a tendency towards positive emotions, seeking new information and a high energy/activation

level), was smaller over time after moderate-severe TBI compared to either the mTBI or the OI group. Although these results were not found for negative affectivity specifically, alterations in this aspect of child temperament may also occur and could contribute to social difficulties following childhood TBI (Ganesalingam et al., 2006). In Article 1 and in the context of typical development, temperamental negative affect was the most constant predictor in all steps of the regression model, supporting the critical role of temperament for social competence (Sanson et al., 2004). Positive as opposed to negative temperamental affect has previously been associated with a higher level of social competence in preschoolers, consistent with our findings (Farver & Branstetter, 1994; Youngblade & Mulvihill, 1998). There are also links between lower levels of negative affectivity/more positive emotionality and better resilience and coping styles (Shiner & Masten, 2012). On one hand, in the context of pediatric TBI, temperamental traits may influence how children react to TBI and associated symptoms. On the other hand, brain insult may directly induce changes in temperament, such as causing higher levels of negative affectivity or, could enhance pre-existing levels of negative emotions (i.e., irritability, discomfort, sadness, fear, anger). These changes may translate into behavioural consequences in young children, such as internalizing behaviours (i.e., withdrawal, anxiety, depression; Gagner et al., 2018), and in turn affect social interactions and participation (Bornstein et al., 2010; Verron & Teglasi, 2018).

EF and two socio-cognitive factors (i.e., non-verbal communication, ToM) predicted social competence in the preschool sample, above and beyond internal and external factors, thus emphasizing the cognitive core of the SOCIAL model. Social competence relies strongly on EF, in particular when individuals are required to interact and communicate with others (Wiseman-Hakes et al., 2020). For example, EF are required to maintain an idea, process what another person has said, prepare a response, or wait for one's turn to speak. Impairments in EF constitute one of the most widely acknowledged symptoms of pediatric TBI (Beauchamp, Catroppa, et al., 2011; Crowe et al., 2013; Ewing-Cobbs, Prasad, et al., 2004), and may thus contribute to social difficulties, as shown in previous studies (Ganesalingam et al., 2011; Muscara et al., 2008). In the socio-cognitive domain, non-verbal and pragmatic language refer to the use and comprehension of language in context, including planning and organization of discourse, topic maintenance and turn-taking, comprehension of irony, sarcasm or deceptive language, as well as prosody, eye contact, gestures and tone of language (Bucciarelli et al., 2003; Wiseman-Hakes et al., 2020). While pediatric TBI, specifically moderate and severe forms, can affect basic expressive and receptive

language skills (Ewing-Cobbs et al., 1997; Sullivan & Riccio, 2010), deficits in higher-order aspects such as pragmatics are also common (Dennis et al., 1998; Didus et al., 1999; Ryan et al., 2013; Sullivan & Riccio, 2010). In translating the present findings in typical development to TBI, disturbances in pragmatic language could contribute to poor social competence. In addition to pragmatic language difficulties, multiple studies report difficulties in ToM, both after mild (e.g., Bellerose et al., 2015) and moderate to severe pediatric TBI (e.g., Dennis et al., 2012; Ryan, Catroppa, Beare, et al., 2016), and these may contribute to global social difficulties. For example, a previous study in the LION cohort revealed poor ToM in children with early mTBI compared to TDC six months post-injury (Bellerose et al., 2015), and poorer ToM was associated with poorer adaptive and social functioning one year later (Bellerose et al., 2017). Socio-cognitive skills such as ToM are also associated with social problem-solving, judgment and social behaviour both in normative development (e.g., Sokol et al., 2004) and after pediatric TBI (Dennis et al., 2012). Thus, the present findings indirectly support the role of social cognition for predicting social outcomes after pediatric TBI.

ToM, pragmatic language and EF are necessary for social communication, a key element of social competence. Children's emerging communication skills rely on cognitive skills such as EF (e.g., working memory, cognitive flexibility), as well as on socio-cognitive skills (e.g., ToM, emotion recognition; Wiseman-Hakes et al., 2020). Both ToM and pragmatic language undergo protracted development throughout the early years of life, and continue to mature during middle childhood and well into adolescence, paralleled by improvements in EF (Blakemore, 2011; Dumontheil et al., 2010; Grantham-McGregor et al., 2007). The interplay of these three factors (i.e., ToM, pragmatics, EF) is vital to social communication (see Wiseman-Hakes et al., 2020 for a conceptual framework). A disruption in any of these skills can contribute to social communication difficulties following pediatric TBI, such as difficulties in judging appropriateness of topic, planning and organization of discourse, understanding irony or sarcasm or social and non-verbal cues (Ciccia et al., 2018; Dennis, Simic, et al., 2013; Ryan, Catroppa, Godfrey, et al., 2016; Sullivan & Riccio, 2010; Turkstra et al., 1996; Turkstra et al., 2015). Social communication deficits can in turn affect global indicators of social competence, such as social relationships, social participation, and integration into everyday activities (Dennis, Agostino, et al., 2013; Turkstra et al., 2001; Wiseman-Hakes et al., 2018).

The findings of Article 1 capture the factors that contribute to social competence in normative development, and offer indirect insight into what role they may play in social outcome after pediatric TBI. While many factors and models have been proposed to predict outcome after pediatric TBI, the SOCIAL model is unique in revealing possible pathways for fluctuations in social competence both in uninjured children and those who sustain TBI. As such, stimulating these factors could foster optimal social development.

The role of genetic factors: The Val66Met Polymorphism

In keeping with the biopsychosocial approach, the prediction model presented in Article 2 showed that BDNF genotype was an independent predictor of QoL six months after early mTBI: Children who were Met-allele carriers had better QoL six months post-injury. This is somewhat surprising given that the presence of the Val66Met polymorphism has typically been associated with poorer functioning in adults, including difficulties in (affective) episodic memory (Cathomas et al., 2010; Egan et al., 2003; Hariri et al., 2003), psychopathology such as major depressive disorder (Legge et al., 2015), and post-traumatic stress disorder (Felmingham et al., 2013), as well as morphological brain alterations such as reduced amygdala and hippocampal volumes (Egan et al., 2003; Pezawas et al., 2004). This evidence, together with findings that adult Met-allele carriers with TBI have poorer cognitive and emotional outcomes (McAllister et al., 2012; Pearson-Fuhrhop et al., 2012; Wang et al., 2018), would support the hypothesis that the Met allele should also be associated with poorer outcomes in children with TBI, due to decreased BDNF levels and a lower potential for neuroplasticity as conveyed by the Met compared to the Val allele.

There is currently little evidence as to how this polymorphism affects outcomes after pediatric TBI. The prognostic model testing in Article 2 builds on an initial study in the same cohort showing that six months after early mTBI, children carrying Met allele had *fewer* internalizing behaviours compared to those who were Val/Val homozygotes (Gagner, Tuerk, et al., 2020; see Appendix I). At 18 months post-injury, genotype had no differential effect on behavioural outcomes in the three groups (i.e., mTBI, OI, TDC), consistent with the present findings showing that over time, the predictive importance of the genetic factors seems to fade and other factors become more important in determining post-injury outcomes. It appears that in the context of early childhood mTBI, the Val66Met polymorphism may act as a protective mechanism against unfavourable outcomes.

Given the paucity of previous studies on the effect of the Val66Met polymorphism on functional outcomes after pediatric TBI, interpretations of the observed effects remain speculative. Considering the current results and those published in adults with TBI, a possible hypothesis is that favourable prognosis post-injury occurs in those presenting a genetic baggage allowing for an optimal potential for neuroplasticity, as a function of age and the developmental period. As mentioned in the thesis introduction, BDNF is critically implicated in neuroplasticity processes, with the Val66Met polymorphism significantly reducing BDNF release (Chen et al., 2004; Egan et al., 2003). In the context of TBI, a physiological response typically occurs during which BDNF is upregulated following brain insult (Chiaretti et al., 2003; Mocchetti & Wrathall, 1995). Hence, findings can be interpreted in the context of altered mechanisms of neuroplasticity following pediatric TBI. As suggested by Giza & Prins (2006), although plasticity is generally considered to be beneficial and necessary for brain maturation, in the context of brain injury, the pre-programmed developmental cascade and naturally occurring processes of neuroplasticity may be derailed. More specifically, plasticity allows for reorganization of the brain after injury (Su et al., 2016), yet may in fact have detrimental consequences in the context of a developing brain. A higher potential for plasticity (i.e., TBI-induced overexpression of BDNF conveyed by the Val allele) may actually lead to poorer outcomes due to altered and aberrant processes stimulated by increased excitatory responses (Chiaretti et al., 2003). Injury to the immature brain may trigger an unfavourable neurological response during a time that is characterized by the formation of dendritic arborizations and synaptic connections between brain regions. As shown in experimental studies of mild to severe brain injury, manifestations of such a response are an abnormal release of neurotransmitters, altered or aberrant communication between brain regions and abnormal cell death (Giza & Prins, 2006). Aberrant neuroplasticity may thus disturb the normally occurring developmental sequence of brain maturational processes, including processes of pruning or programmed cell death which are necessary for the increasing specialization of brain regions and functional systems (e.g., Giedd et al., 1999; Johnson, 2005). This may result in excessive connections between regions, giving rise to functional difficulties and repercussions on cognitive and behavioural development. Consequently, reduced BDNF release in children carrying the Met allele may serve as a protective mechanism against abnormal neuroplasticity, at least during the first months post-injury. At 18 months post-TBI, it can be assumed that neural restructuration elicited by the TBI has mitigated, if not ceased.

Ultimately, differential genetic effects in adults versus children are perhaps not surprising given the specific developmental context with intrinsic and distinct properties of the immature brain that need to be considered. For example, BDNF levels fluctuate naturally across development, and therefore affect phenotypes differentially at different stages of development. As such, one allele may be a risk factor for recovery during some periods, yet may be protective during other developmental periods (Casey et al., 2009). For example, during adolescence, BDNF levels reach their peak, and the presence of the Val66Met polymorphism could thus protect against poor outcomes, to counterbalance the effects of a TBI-related increase in BDNF (Casey et al., 2009; Katoh-Semba et al., 1997). In addition, the effect of Val66Met on brain morphology that has been reported in adults (i.e., reduced hippocampal volumes) seems to be reversed in children (Brouwer et al., 2014).

Although speculative, given the role of the BDNF protein in brain morphology and in forming, maintaining and strengthening neural connections (Gorski et al., 2003), it may also play a role in altered structural and functional brain connectivity such as revealed in Articles 3 and 4. More specifically, it is possible that restructuring takes places in particular at the level of long-range neural connections, the effects of which may only be noticeable later on. Further research is required to understand the specific neural and molecular process in relation to BDNF genotype, its effects on brain structure and function, and the temporal evolution of such effects in the context of pediatric TBI.

Finally, BDNF genotype alone does not explain QoL, yet likely exerts its effect on QoL via interactions with other variables. BDNF genotype predicted QoL when considered together with injury factors (i.e., PCS and injury age) and family-environmental factors (i.e., parent-child interactions). This suggests that complex interactions are at play, which ultimately can only be teased out using more complex and sophisticated statistical models in larger samples. For example, it is possible that BDNF conveys its effect on QoL via its influence on PCS. More specifically, BDNF genotype may differentially affect the number or the pattern of PCS, which have a neurological basis. In addition, given the important role of BDNF in learning and cognitive functions (Snider, 1994; Thoenen, 1995), the Val66Met polymorphism could also indirectly lead to better QoL via its effect on cognitive, behavioural or affective outcomes. This would align with our previous results demonstrating a protective effect of the Val66Met polymorphisms on internalizing behaviours after early mTBI (Gagner, Tuerk, et al., 2020). Genetic factors implicated

in neuroplasticity and the overall response to injury may interact with TBI to influence behavioural and cognitive outcomes, ultimately affecting QoL. This idea is consistent with some results in adults suggesting that Met-allele carriers have better cognitive recovery in terms of general intelligence and EF after severe TBI (Barbey et al., 2014; Krueger et al., 2011). Moreover, although in clinical populations the Val66Met polymorphism has often been associated with mood and anxiety disorders (Felmingham et al., 2013; Legge et al., 2015), contrasting views suggest that a moderate amount of BDNF might in fact have a mood-stabilizing effect in affective disorders (Govindarajan et al., 2006). Based on such evidence, a disposition to negative or positive emotions may affect other domains, such as social functioning, and, ultimately, QoL. Affective disposition can further have an impact on the family environment, such as the quality of parent-child interactions, contributing to better (or poorer) child QoL. Overall, if found in the current cohort, such complex interactions would support previous evidence showing that environmental factors such as stressful life events (i.e., TBI) may interact with genetic predispositions (i.e., BDNF genotype) to predict behavioural outcomes (Hosang et al., 2014; Zhao et al., 2018). Notably, the association between BDNF genotype and QoL was observed in children with mTBI only. This indicates that the findings are neither simply an effect of genotype on behavioural or cognitive phenotypes, nor related to a general stressful life event (i.e., having undergone procedures in the ED which are similar for the mTBI and OI groups). In addition, given that parents did not know their child's genotype, their response on the QoL questionnaire are, in that regard, unbiased. The results should therefore represent a brain-injury specific effect, such as a TBI-induced effect of BDNF-levels and not natural variations of BDNF as conveyed by the Val/Met versus Val/Val genotypes, as is the case for the two control groups. However, future research is necessary to elucidate the mechanisms through which the Val66Met polymorphism influences post-injury outcomes in children, in the context of ongoing brain maturation, and across different developmental stages. This could help explain heterogeneous outcomes following pediatric TBI.

At 18 months post-injury, when the direct effects of injury including secondary injuries have faded, it can be assumed that recovery, especially in the case of mTBI, is no longer determined by neurological factors, but rather by psychological and environmental factors (van der Horn et al., 2019). The current result indicating that parental distress predicts QoL at 18 months post-injury is consistent with this hypothesis and supports our previous findings showing no differential effect of BDNF genotype on behavioural outcomes in the very long-term (Gagner, Tuerk, et al., 2020).

This is also in line with a recent study by Kurowski and colleagues (2019) who found that links between genetic factors and behavioural outcomes differed at earlier and later recovery stages following early TBI: At six months post-injury, genetic influences on outcomes differed between TBI and OI groups when comparing "case" genes (genes implicated in biological pathways associated with the response to neurological injury, including BDNF) with "control" genes (genes not implicated in TBI recovery or the neurological response to injury). More case genes/polymorphisms were linked to behavioural outcomes than control genes and they were also more likely to be related to differential behavioural outcomes in the TBI *vs* the OI group. At seven years post-injury, genetic effects on behaviour were not different for the two groups. At this later stage, more case genes were related to behavioural outcomes independent of group (TBI *vs* OI), therefore putatively reflecting general behavioural variations.

Parental influences on outcomes after early mTBI

Article 2 highlights an important role for family-environmental factors in determining outcome after early mTBI, consistent with previous findings in pediatric TBI (e.g., Durber et al., 2017; McNally et al., 2013). Various parental factors have been extensively documented as contributing to a child's affective and behavioural development and well-being during typical development, such as affective responsiveness, attachment security, and sound parent mental health (Allen et al., 2002; Barnes & Theule, 2019; Fernandes et al., 2019; Mensah & Kiernan, 2010; Webb et al., 2018). Unsurprisingly, there is also evidence for family and parental factors contributing to outcome after pediatric TBI, both after moderate to severe injuries (e.g., Ryan, van Bijnen, et al., 2016) and after mTBI (e.g., Gagner et al., 2018). For example, the post-injury family environment has been shown to affect socio-cognitive and long-term social adjustment (Chapman et al., 2010; Ryan, Catroppa, Godfrey, et al., 2016; Wade et al., 2011; Yeates et al., 2010). In the youngest age group, the influence of family and parental factors may be amplified, given the amount of time toddlers and infants spend with their parents and their relatively stronger dependence on caregiver figures. The findings of Article 2 show that parental distress (i.e., parents' feelings of conflict and competence in their parental role) contributed to very long-term child QoL, that is, up to 18 months post-injury, with lower distress levels predicting better QoL. Parental distress has previously been shown to predict PCS in school-age children with mTBI (Ganesalingam et al., 2008; McNally et al., 2013) and behavioural problems after early mTBI (Gagner et al., 2018). In addition, given the known association between parent mental health and

social adjustment (Ryan, van Bijnen, et al., 2016), parenting styles (Chapman et al., 2010) and overall family functioning (Wade et al., 2011), parental distress may affect these other domains, with long-term impacts on child QoL.

Several potential mechanisms could underlie the association between parental distress and child QoL. In general, distress caused by their child's injury may affect how parents react and adjust to their child's injury, in turn influencing child recovery and QoL. This might be amplified for parents who present with pre-existing distress in their role as a parent, or feelings of anxiety or depression, which may be compounded by the burden of a traumatic experience. Regardless of pre-existing difficulties, childhood TBI can affect normal family functioning, and has been associated with increased family burden and parental distress (Ganesalingam et al., 2008; Max, Castillo, et al., 1998). Moreover, mood disorders and poor parent mental health have not only been associated with increased risk of children sustaining TBI (Lowery Wilson et al., 2019), they also contribute to poor child behavioural recovery, with more parent psychological problems being linked to more child externalizing (Raj et al., 2014) and internalizing behavioural problems (Peterson et al., 2013) after mild complicated to severe TBI. Although moderate-severe TBI is more likely to cause parental distress, even mTBI has been associated with higher parental stress levels (Hawley, Ward, Magnay, et al., 2003). Moreover, a previous study on the LION cohort also found an association between parental distress on externalizing behavioural problems after early mTBI (Gagner et al., 2018). Parents of young children may experience even higher levels of distress, concern and worry than those of school-age children given the increased dependence and vulnerability of their young charges. In addition, parents may experience feelings of guilt and blame themselves for their child's injury, such as previously documented in children who sustained TBI, independent of severity (Brown et al., 2013; Ganesalingam et al., 2008; Stancin et al., 2008).

Another potential mechanism explaining the link between parent distress and child QoL may lie both in how well parents are able to distinguish between injury-related and normal fluctuations of their child's behaviour and how they respond to their child. For example, in young children, some PCS may resemble behavioural fluctuations that are normal for early childhood, such as temper tantrums, irritability or inattentiveness. It may thus be difficult for parents to differentiate between naturally occurring behavioural changes and those that are related to TBI. (Dupont et al., submitted; Podolak et al., 2020; Suskauer et al., 2018). This may cause additional stress as parents may feel helpless or incompetent in terms of understanding the origins of their

child's behavioural difficulties. In turn, to counter-balance potential behavioural changes or TBI-related symptoms observed in their child, and due to distress as well as a lack of adequate coping strategies, parents may maladaptively adjust their parenting styles. This may manifest in overprotective or more punitive and authoritarian parenting behaviours (Woods et al., 2011) which may have negative effects on behavioural (Woods et al., 2011) and cognitive outcomes (Potter et al., 2011), and eventually affect QoL.

Increased stress levels, maladaptive parenting styles together with potentially persistent PCS can strain dyadic interactions between parents and their child, also contributing to poor child QoL. For example, parents who feel stressed tend to be less involved with their child and less responsive in their interactions with their child (Deater-Deckard, 1998). In the present study, although not in the final model, better parent-child interactions predicted better QoL at six months after early mTBI when injury factors were considered jointly with family factors (step 3 of the model, Article 2). Poorer quality parent-child interactions have previously been found to be affected after early TBI (Fairbanks et al., 2013; Lalonde et al., 2018; Wade et al., 2008). For example, a previous study in the LION cohort found that early mTBI is associated with poorer parent-child interactions and that *more* PCS predicted *better* quality relationships six months after early mTBI (Lalonde et al., 2020). Consistent with the above-mentioned interpretation, the authors suggest that correctly identifying PCS in their child may help parents to better respond to their child's needs, in turn fostering their dyadic relationships. The results of Article 2 and specifically the model at 18 month post-injury also align with previous reports of parents of children with mTBI indicating higher stress levels in their parenting role, in their interaction with their child and with respect to their child's behaviour (Hawley, Ward, Magnay, et al., 2003). Finally, parent distress may also impact their affective responsiveness to their child's needs. For example, in children with moderate to severe TBI, family affective responsiveness has been shown to prospectively modulate socio-cognitive outcomes (Ryan, Mihaljevic, et al., 2016).

Together, the present and previously published findings suggest that multiple complex and interactive factors co-occur through which a parent can influence outcomes and recovery after early childhood TBI, and these ideas have recently been conceptualized in the "Perception, Attribution, and Response after Early Non-inflicted Traumatic Brain Injury" (PARENT) model (Beauchamp, Séguin, et al., 2020; Figure 4). This model takes into account factors pertaining to the child (i. injury-related: severity, PCS; ii. biologically-determined: age, sex, genetics, temperament, sleep;

iii. functional outcomes: pre- and post-injury behaviour and cognition) and to the parent (pre- and post-injury parental psychological functioning, family variables: parenting styles, burden of injury, environmental: SES). Both child and parental factors contribute to three steps (i.e., Perception, Attribution, Response) through which parents influence their child's outcome and recovery post-TBI: Parents' *perception* of PCS and behavioural alterations (if present), whether they correctly *attribute* these changes to their child's TBI or to normal behavioural fluctuations, and their ability to adjust their *responses* in terms of parenting behaviours, affective responsiveness, interactions with their child, and coping strategies. Given that many predictors of outcome after early TBI, such as child temperament, behaviour and family-related variables, often rely on parent reports, it is imperative that parental factors such as mental health or parenting styles be considered. Based on the PARENT model, it can be hypothesized that, consistent with our findings, parents who are better at detecting their child's PCS, associating them with the occurrence of a brain injury, and adequately and affectively reacting to these changes, may have better interactions with their child, experience lower distress, ultimately contributing to their child's QoL after their injury.

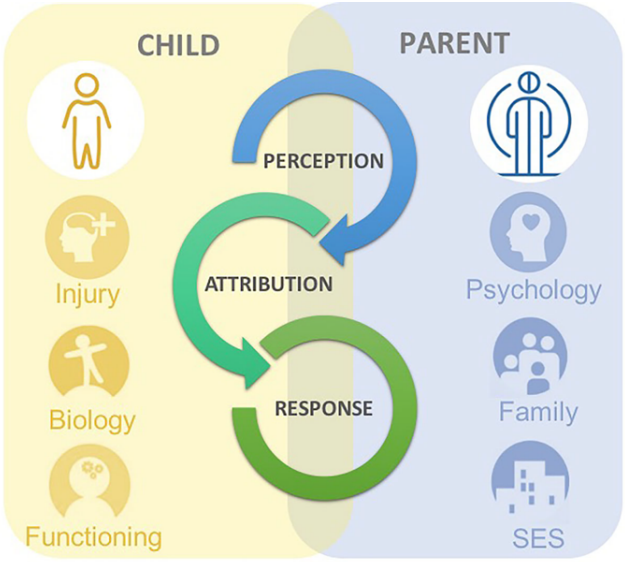

Figure 1. The "Perception, Attribution and Response after Early Non-inflicted Traumatic Brain Injury (PARENT) model.
From Beauchamp, M. H., Séguin, M., Gagner, C., Lalonde, G., & Bernier, A. (2020). Reprinted with permission from Taylor & Francis.

Finally, the importance of parental distress is also reflected by the findings of lower distress and better QoL in the TDC group at six months. This normative finding suggests that a family climate without parental distress and mood disturbances is beneficial for a child's QoL even in the

absence of injury and may even be protective against injury. In the OI group, none of the selected factors contributed to QoL, suggesting that the findings in the mTBI group are brain-injury specific. The observation that none of the variables contributed to long-term QoL in the two control groups indicates that long-term parental distress levels may be particularly heightened and important in the context of pediatric TBI and supports the enduring nature of the association between parental mental health and child outcomes. Future efforts are needed to differentiate between maternal and paternal distress, as they could have an additive negative effect on outcomes (Kvalevaag et al., 2015).

Applying neural network approaches to the study of pediatric TBI

There has been a paradigm shift during the past two decades of neuroscientific research from the study of isolated brain areas towards analyses of brain networks. Characterizing connectivity in the developing brain has been proposed as a powerful way to enhance our understanding of brain maturation and the emergence of large-scale networks that underlie cognitive and affective functioning (Behrens & Sporns, 2012; Bressler & Menon, 2010; Power et al., 2011). While many studies have shed light on the neural mechanisms of neurodevelopmental disorders by using network approaches (see Menon, 2013 for a review), the pediatric TBI literature considerably lags behind in this regard. To address this gap, we presented two network approaches to studying the impact of pediatric TBI on the developing brain.

In Article 3, a comprehensive network approach was employed to study the impact of pediatric TBI on the SBN from a network perspective. The results indicate altered FC in children with TBI (i.e., positive FC) when compared to TDC (i.e., negative FC) within selected regions of the social brain, notably between the left fusiform gyrus and two frontal areas in one sample (i.e., dmPFC, left superior frontal gyrus), and between the right fusiform and the left superior frontal gyrus in a second independent sample. Although this particular study did not reveal any links with the broad behavioural measure (i.e., CBCL) used, associations between alterations within the social brain and social difficulties may yet be identified. In the meantime, given the absence of brain-behaviour correlations in this sample, the following interpretations pertaining to putative links of the altered FC patterns in the TBI group with socio-behavioural outcomes remain speculative. The fusiform gyrus is a key region for processing faces, as well as facial affect and socio-cognitive skills including emotion recognition and ToM (Ganel et al., 2005; Kanwisher et al., 1997; Schultz et al., 2003). Deficits in emotion recognition are common after pediatric TBI (Newsome et al.,

2013; Ryan, Catroppa, Cooper, Beare, Ditchfield, Coleman, Silk, Crossley, Beauchamp, et al., 2015; Schmidt et al., 2013), and may play a critical role in social disturbances after pediatric TBI. More specifically, social interactions require the understanding of non-verbal cues, such as facial expressions, in order to appropriately interpret and react to other's emotions and actions (Nowicki & Mitchell, 1998). In adults with moderate to severe TBI, poor facial affect recognition has been associated with negative social outcomes, such as poor social integration (Knox & Douglas, 2009), and socially inappropriate behaviours (Pettersen, 1991). The present findings indirectly support previous neuroimaging studies in adults with TBI, showing the involvement of the fusiform gyrus in facial affect recognition deficits. For example, altered connectivity between frontal regions and the right fusiform gyrus has previously been shown in different fMRI designs investigating affect recognition deficits after adult moderate-severe TBI (Neumann et al., 2016; Rigon et al., 2017, 2019). The associations between poor emotion recognition and FC between visual and prefrontal regions as revealed in one of these studies (e.g., Rigon et al., 2017) suggest that altered frontal-fusiform FC might serve as one of the mechanisms underlying poor facial-affect recognition. The fusiform gyrus has also been shown to be implicated in socio-cognitive and face perception deficits in Autism Spectrum Disorders (ASD; Schultz et al., 2003; van Kooten et al., 2008), and specifically in ToM deficits following adolescent moderate-severe TBI (Scheibel et al., 2011), suggesting an important role in the neural mechanisms of socio-cognitive difficulties following pediatric TBI.

In the exploration sample, an association between dmPFC-left fusiform connectivity and CBCL-Aggressive Behaviour was revealed, albeit only when uncorrected for multiple comparisons. In addition, the TBI group had more internalizing and rule-breaking behaviours (CBCL), in line with reports of an association between pediatric TBI and behavioural problems (Cole, Gerring, et al., 2008; Finnanger et al., 2015; Hughes et al., 2015; Ryan, Hughes, et al., 2015). A disruption of connections involved in facial affect processing may lead not only to difficulties in social interactions, but subsequently results in negative emotions due to psychological distress through lower social effectiveness, though such a claim needs direct empirical testing and is only suggested here as a possible line of interpretation and further research.

Of note, there was a difference in FC valence (i.e., positive versus negative FC) between the two groups. The origin of negative FC as observed in the TDC group is still a subject of debate and incompletely understood (Fox et al., 2007). However, it is possible that negative connectivity is based on inhibitory interneuron networks which give rise to decoupling between distant brain

regions (Buzsáki et al., 2004). The negative FC in the TDC group is in line with previous studies showing that initial positive connectivity becomes increasingly negative over the course of development (Chai et al., 2014; Gee et al., 2013). The positive pattern observed here may reflect an imbalance in the excitatory-inhibitory balance following TBI which can affect properties of large-scale neural networks, resulting in aberrant connectivity as seen in many neurodevelopmental conditions (Menon, 2011, 2013).

Given the heterogeneous nature of pediatric TBI causing diffuse brain morphological and functional alterations, it is unlikely that its impact on complex cognitive and behavioural functions can be assessed by focusing on a single neuroimaging parameter (i.e., FC, WM fiber integrity, GM volumetric alterations). Therefore, using SCN may be a promising complementary approach to gain insight into how TBI affects brain topology during development. In adults with mTBI, there is some work relying on the SCN approach, with results showing lower structural covariance in the CEN in the acute phase, and lower structural covariance in the DMN in the chronic phase when compared to healthy controls (Song et al., 2020). In the pediatric TBI literature, only one recent study applied the SCN approach to a sample of children with TBI and found divergent SCN in TBI when compared to controls, which was related to EF deficits (King et al., 2020). Reduced structural association as revealed in Article 4 is consistent with morphological studies of reduced GM volume and thickness in pediatric TBI populations (King et al., 2019). Here, for the DMN, reduced association patterns were found between the right angular gyrus and two frontal areas (i.e., right middle frontal gyrus and left superior frontal gyrus) as well as the left fusiform gyrus. Abnormalities in the DMN have been shown in several neurodevelopmental and psychiatric disorders, including ASD (Jann et al., 2015), depression (Gaffrey et al., 2012), and Attention Deficit Hyperactivity Disorder (Choi et al., 2013), which are all characterized, to some degree, by deficits in socio-affective or socio-cognitive processes (Bora & Pantelis, 2016; Cole, Luby, et al., 2008; Leekam, 2016). Although the DMN is typically referred to as a task-negative network (i.e., it is activated at rest, in absence of a task), it is nonetheless implicated in socio-cognitive processes (Mars et al., 2012; Schilbach et al., 2008). In samples of mild to severe pediatric TBI, altered FC in the DMN has previously been reported, although patterns of result are equivocal (Iyer, Zalesky, et al., 2019; Risen et al., 2015; Stephens et al., 2018). In keeping with the role of the DMN for social processing, a recent study has shown that there is an overlap between the DMN and the SBN (Mars et al., 2012). The pattern of reduced SC between the angular and fusiform gyrus aligns with

such a presumed overlap of the DMN with the SBN. The involvement of the fusiform gyrus in both altered FC within the SBN (Article 3) and reduced structural covariance with the DMN (Article 4) supports its putative role in altered socio-cognitive functions after pediatric TBI and may thus provide a neural basis. In addition, although behavioural correlates were not confirmed, reduced structural covariance in the CEN in children and adolescents with TBI when compared to TDC may underlie frequently observed deficits in EF (Sesma et al., 2008; Wilde et al., 2005; Yu et al., 2018). Consistent with the vulnerability of fronto-temporal areas to pediatric TBI (Bigler, 2013; Wilde et al., 2005), the findings in Articles 3 and 4 highlight the important role of frontal areas within the SBN, DMN and CEN, suggesting that they constitute central nodes for the integrity of brain circuits involved in social, cognitive and behavioural functions. Given frontal neuropathology is common after pediatric TBI, this damage may over time induce large-scale changes at the level of these networks.

Overall, the present findings using both FC and SCN and showing altered anterior-posterior connections jointly demonstrate that pediatric TBI affects one of the hallmarks of brain connectivity development, that is, the emergence and strengthening of long-range connections, as well as inter-hemispheric communication (Fair et al., 2009; Menon, 2013; Supekar et al., 2009). Results from Articles 3 and 4 both suggest brain network alterations, specifically positive FC within the SBN on the one hand, and reduced structural covariance patterns in the DMN and CEN on the other hand, both approximately two years following moderate-severe pediatric TBI. Accordingly, while local brain changes may occur soon after the insult, over time, they may affect the brain at the network level. It is still unclear how FC relates to structural (WM) connectivity and to SCN. However, the seemingly opposite patterns in the TBI groups across the two studies (i.e., positive frontal-fusiform connectivity *and* reduced structural covariance patterns) might not be contradictory. Indeed, reduced GM volumes and subsequently weaker structural associations may give rise to increased FC patterns in the TBI group as a compensatory mechanism to rebalance the system. Although some overlap has been demonstrated between FC and anatomical connectivity as measured using DTI (Greicius et al., 2009; Koch et al., 2002), there might not necessarily be a one-to-one correspondence between anatomical and functional connections, in either GM or WM (Chen et al., 2011; Honey et al., 2009). SC may not precisely match FC, but may instead display broad associations with brain areas showing different degrees of associations between structure and function (Grandjean et al., 2017; Zimmermann et al., 2016). Future studies are needed to better

understand how FC relates to structural connectivity and how the SBN, DMN, CEN and SN interact to underpin socio-cognitive and behavioural difficulties following pediatric TBI.

Implications of the findings

The four articles each incorporate novel methodological and theoretical aspects in studying social and neural outcomes after pediatric TBI. Together, their results have the potential to inform and stimulate future work and ultimately inform clinical management of pediatric TBI.

Methodological contributions

A network perspective of pediatric TBI

This thesis supports the notion that the impact of TBI on the developing brain should be considered through a network perspective, rather than through simple associations between individual brain regions and behaviour. The past two decades have seen an increase in studies using structural brain imaging to investigate alterations in GM volume or cortical thickness in children with TBI. However, they do not always consider the role of brain connectivity which is the basis of many cognitive and behavioural problems observed in other domains and disorders, and which might also pertain to pediatric TBI (Menon, 2013). Nonetheless, in the context of TBI and specifically pediatric TBI, research on how brain injury affects brain networks is only beginning to emerge. Here, to our knowledge, we present the first study to examine FC within the SBN after moderate-severe TBI. By using a network perspective of the social brain and including several key SBN nodes, this study contributes to characterizing the neural mechanisms of social problems following pediatric TBI, which are to date poorly understood. The approach of using two independent samples constitutes a strength and supports the finding of altered frontal-fusiform connectivity. Although more research is needed, these findings may set the ground for future studies to find biomarkers of social impairment post-TBI and support rsfMRI as a promising tool to evaluate the global impact of TBI on the brain.

The thesis also presents and supports the use of SCN analysis in pediatric TBI. This approach, based on standard anatomical MRI images, has found multiple applications in various neurodevelopmental disorders. However, to date, only one cross-sectional study used the technique in pediatric TBI (King et al., 2020). While the current findings are in line with previous results from structural MRI studies showing reduced GM volumes both in the acute and chronic post-injury stages, they take it a step further by integrating them into a network perspective. Compared

to classic network approaches, the SCN technique offers insights into maturational changes in anatomically connected brain regions (Alexander-Bloch, Raznahan, et al., 2013; Zielinski et al., 2010). In addition, given that pediatric TBI is highly heterogeneous with diffuse impacts on the brain, it affects cognitive and behavioural development in ways that cannot solely be captured by studying the integrity of WM fiber pathways (Irimia et al., 2012). Additional network-based techniques can help to quantify the impact of pediatric TBI on brain topology. Eventually, these techniques may help improve prediction of post-TBI outcomes by providing biomarkers for socio-behavioural and cognitive outcomes of pediatric TBI.

Theoretical contributions

Genetic factors involved in neuroplasticity

From a theoretical point of view, this thesis suggests that even in the context of mild brain injuries and in the long-term, mechanisms of neuroplasticity may play a determining role in post-injury outcome. Mechanisms of neural plasticity at the molecular, cellular and neural level are critical processes and occur naturally during normal development. Through stimulating external events or cues, neuroplasticity allows for neural projections to be built, for increased dendritic arborization and cognitive development (Greenough et al., 1973; Rosenzweig & Bennett, 1996). As such, it shapes structural and functional brain development through experience and learning. In the context of brain injury during development, such plasticity may, however, not be beneficial (Giza & Prins, 2006). Indeed, after moderate-severe injury, several structural and functional alterations occur as a result of lesion-induced plasticity (Herbet et al., 2016). The present findings highlight that genetic factors involved in such processes (i.e., BDNF genotype) play an important role for post-injury recovery. This is somewhat surprising with respect to two aspects: First, given that mTBI is usually characterised by absence of visible structural neuropathology and overall better recovery compared to more severe forms of TBI, it could be expected that neural effects may play a less important role for outcome. Yet, the findings indirectly point towards some neurological injury effects even in the case of mTBI. Second, BDNF genotype contributes to post-injury outcome beyond the acute and sub-acute stages of recovery, possibly through ongoing neural restructuring and via interaction with environmental variables. The present findings provide a potential mechanism through which the young brain is more plastic than the adult brain, yet paradoxically this leads to poorer outcome after TBI (Anderson et al., 2005b; Giza & Prins, 2006). In relation to plasticity and vulnerability perspectives, the results of a differential effect of genes

involved in neuroplasticity processes on post-injury outcomes support the idea that plasticity is not universally beneficial, but rather critically depends on the developmental stage and genetic factors involved in such processes (Anderson, Spencer-Smith, et al., 2011; Dennis, Spiegler, et al., 2013). As Dennis and colleagues propose: "Plasticity is neutral with respect to outcome. Although the effects of plasticity are often beneficial, the outcome of plasticity may be adaptive or maladaptive." (Dennis, Spiegler, et al., 2013, p.2). Indeed, the current findings suggest that outcome of pediatric TBI depends on a more or less favourable response to brain injury based on individual genetic make-up in terms of neuroplasticity. Consequently, some children may be more vulnerable than others to unfavourable outcomes, depending on their developmental stage at the time of the injury and how TBI interferes with ongoing neuroplasticity processes.

Comprehensive models of prognosis

Another important contribution of the thesis is the focus on comprehensive prediction models including global outcomes (i.e., QoL, social competence) and a broad range of factors, and, in Article 2, a genetic factor. The role of genetics in particular has to date largely been neglected in prediction models of pediatric TBI outcome. The biopsychosocial models presented in this thesis include factors from several domains (i.e., biology, family environment, injury, child behaviour and cognition), as well as across a range of performance-based measures, observational data and parent-reported accounts of child functioning, providing a comprehensive view of prognosis. A global account of potential predictors of outcome is useful for capturing different recovery profiles and inter-individual variability with respect to how children react to TBI. This might be particularly useful in the case of mTBI, where the majority of children overall recover well in the mid- to long-term (Anderson et al., 2005a; Babikian et al., 2011; Carroll, Cassidy, Peloso, et al., 2004). These models may be of value in identifying factors that can be optimized to promote positive recovery or protect against poor cognitive or social outcomes. Similarly, the first empirical validation of the SOCIAL model employs a comprehensive view of what contributes to social competence in typical development, notably, during early childhood. This can inform future research as well as clinical approaches in targeting potential risk factors for poor social functioning after pediatric TBI. It also provides a basis to illustrate how brain injury can differentially affect social development, i.e. through a disruption of one or more of the several factors that are critical to successfully establish social competence.

Clinical implications

The results of this thesis have clinical relevance, in particular with respect to the factors that contribute to recovery based on the biopsychosocial approaches presented in Articles 1 and 2. First, the thesis findings support the inclusion of socio-cognitive assessments in clinical practice when working with children with TBI. Although this domain has been under-acknowledged in pediatric neuropsychological evaluations, it has become increasingly clear that it is important to assess potential impairments of socio-cognitive skills, especially given that ToM and pragmatic language skills are critical for social functioning (e.g., Beauchamp, 2017; Peterson et al., 2016; Ryan, Catroppa, Beare, et al., 2015; Ryan, Catroppa, Beare, et al., 2016). Assessing and monitoring socio-cognitive abilities together with general cognitive skills such as EF in children with TBI may help to detect potential future social problems early on and to orient early interventions where necessary.

Family dysfunction and poor parental mental health such as high parental stress levels have been shown to be linked to poor social outcomes after pediatric TBI (Ganesalingam et al., 2008; Ryan, Mihaljevic, et al., 2016; Ryan, van Bijnen, et al., 2016; Yeates et al., 2010), and might be amenable to family-centered therapeutic approaches. These approaches have been shown to be beneficial and improve behavioural outcomes in children with mild complicated to severe TBI (Wade, Fisher, et al., 2019; Wade, Oberjohn, et al., 2009; Wade, Walz, et al., 2009). While parents may naturally be stressed about their young child's injury, some might be more prone to experience such feelings and more intensely. Worried and stressed parents may be detrimental to a child's recovery and exacerbate social and behavioural difficulties in the long-term. For example, parents may apply a more permissive or authoritarian (e.g., high demands, low responsiveness) parenting style in response to their child's behavioural or social difficulties. However, this may be counterproductive and might negatively impact their relationship with their child. Clinicians should provide parents with information about how to identify and understand their child's injury and PCS, without adding more concern. Providing opportunities for parents to promote recovery of their child through teaching good parental practices may also reduce parents' feelings of helplessness. Clinicians could monitor such family-environmental factors and provide psychoeducation and special education interventions to foster positive child outcomes, family functioning, parenting practices as well as parent-child relationships (Kochanska, 1997; Woods, Catroppa, Godfrey, & Anderson, 2014; Woods, Catroppa, Godfrey, Giallo, et al., 2014).

The thesis highlights the need to consider all pediatric ages and severity groups, including early childhood during which TBI prevalence is high. The work also offers clues on what areas of functioning could be the focus of remediation or optimisation, such as parental mental health or socio-cognitive functioning. This thesis may inform clinical and public health guidelines in that recovery should be monitored long-term, as different factors might play a role at different stages of recovery. This is particularly relevant as many rehabilitation efforts are only pursued for one year post-injury, especially after mTBI. Identifying children at risk for poor (social) outcomes early on, following them closely and long-term, and providing affected children and their families with the appropriate support and resources is critical to foster optimal development and ensure they do not fall behind developmentally. The findings could guide clinicians with respect to which potential risk factors should be monitored and be included in prevention and intervention approaches.

The results of the SOCIAL model validation may also help identify intervention targets for children at risk, such as after TBI, and to create a profile of strengths and weaknesses across the SOCIAL domains. For example, given that pragmatic language skills show rapid maturation during middle childhood (Didus et al., 1999; Dumontheil et al., 2010), they may constitute a particular focus for interventions in this age group. Conversely, in adolescents, higher-order ToM skills may be most vulnerable to TBI (Blakemore, 2011; Giedd et al., 1999), and could thus be targeted. In light of the dynamic aspect of the model, these (socio-)cognitive factors should not be considered in isolation, as they likely contribute to social competence together with internal and external (environmental) factors. For example, a child's temperamental predisposition to positive emotions and to approach social activities in the context of intact family functioning and positive parent-child interactions may set the stage for developing adequate social communication and competence. The validation of this model has the potential to contribute to the design of assessment tools by targeting the specific domains of the model, in particular in the cognitive domain.

Strengths and limitations

Relatively few studies have used prospective longitudinal designs in pediatric TBI and an even smaller number of longitudinal neuroimaging studies. This is particularly problematic given the rapid maturational changes that occur throughout childhood and adolescence at both the brain and behavioural level (Batalle et al., 2018; Shaw et al., 2008). While cross-sectional designs are useful for capturing group differences between children with TBI and TDC at a given moment in

time, they cannot inform on how such differences progress, whether children with TBI eventually close the developmental gap with their peers, and/or whether new problems emerge later on. Longitudinal studies therefore allow to capture the developmental impact of TBI and to identify long-term problems. Moreover, they help to disentangle normative from injury-related changes and the dynamic evolution of neuropathology and TBI-induced brain alterations (Bigler, 2016). The present thesis thus makes an important contribution to the literature through the longitudinal designs presented, in particular in terms of identifying predictors of QoL in the long-term and tracking SCN changes over time.

The thesis is novel in its focus in Articles 1 and 2 on early childhood. Most research on pediatric TBI has focused on school-age children, adolescents and young adults and thus an important gap in the pediatric TBI literature is the under-representation of infants, toddlers and preschoolers in cohort studies, especially given the high prevalence of TBI during early childhood (McKinlay et al., 2008; Trenchard et al., 2013). Consequently, few prospective prediction models exist for early TBI, and the short- and long-term consequences are not fully described, despite early childhood being an important period of intense cognitive and social development (Grantham-McGregor et al., 2007). The thesis also provides insights into both mild (in terms of prediction models of outcome) and moderate-severe TBI (in terms of neural network alterations), with results therefore contributing to the pediatric TBI literature at a large scale.

The aforementioned strengths notwithstanding, a number of methodological limitations need to be considered. First, a limitation of all four studies presented in the thesis are the modest sample sizes and limited statistical power. The analyses were, however, as stringent and conservative as possible by controlling for relevant covariates (age, sex), using appropriate control groups (one in Articles 3 and 4, and two in Article 2), and/or adjusting for possible brain lesions in the neuroimaging studies (by using GM masks). Small samples are a particular issue with regard to genetic factors. In order to make more general claims about the role of genetic effects in pediatric TBI recovery, larger samples are needed for adequate power, but also to take into account ethnicity given genotype prevalence may differ according to ethnic group (Tsai, 2018). Nonetheless, given the novelty of including a genetic factor and the exploratory context, the findings of Article 2 (and the associated article in Appendix I) have the potential to serve as a proof-of-principle and a foundation for future research in larger samples.

Second, many constructs included in these studies, in particular the outcome measures in the prediction models (i.e., social competence and QoL), were assessed using parent questionnaires which may be subject to reporter bias and not accurately reflect actual child functioning. Along the same lines, some of the predictors in the regression models were also measured via parent questionnaires, potentially introducing common source bias. This is in part an inherent limitation of studying young children in whom some constructs, such as QoL or PCS, are difficult to assess directly. To balance potential effects of bias, and acquire a broader picture of child functioning, both parent-reported as well as direct child, i.e., performance-based, measures of several domains of functioning (i.e., social cognition, EF) were included.

Third, due to limitations with respect to the sample size, no statistical interactive effects were tested in either the SOCIAL or QoL model. Further research is needed to test the dynamic aspect of the SOCIAL model and to assess gene-environment interactions. For both models, specific variables were selected, largely based on the broader longitudinal designs from which the data were drawn. Consequently, some other potentially important variables were not included, for example family-environmental factors including family affective responsiveness or parenting styles, as well as other indicators of parent mental health, such as depression or anxiety, known to be risk factors for child socio-behavioural and cognitive developmental even in uninjured children (Kvalevaag et al., 2015; Mensah & Kiernan, 2010; Spruijt et al., 2018; Wade, Cann, et al., 2019).

Fourth, in Articles 3 and 4, there was some variability in terms of time since injury for TBI participants and thus, different age-dependent neural mechanisms might have been at play. Time since injury is a variable that should be considered in future studies to investigate how the specific changes and group differences evolve with increasing time. In addition, given rapid maturational processes occurring throughout childhood and adolescence, focusing on specific narrow age bands in the future would allow for better distinguishing injury from normative developmental processes. This is particularly important given that some functional deficits may only emerge later, when children reach the age at which specific skills typically develop (Anderson & Catroppa, 2005; Anderson et al., 2005b; Feldman et al., 1992).

Fifth, no associations were found between neuroimaging parameters and behavioural or cognitive correlates. In Article 4, we opted not to include specific behavioural correlates given the exploratory nature of the study and lack of literature allowing the elaboration of *a priori* hypotheses. In Article 3, the lack of significant findings may have been due to limited statistical

power or could have been due to the non-specific nature of the behavioural measures which were not initially designed to test associations with specific social skills (i.e., CBCL, ABAS). These limitations preclude any conclusions whether the observed group differences provide an underlying mechanism for socio-behavioral difficulties.

Further limitations with respect to the neuroimaging studies (rsfMRI and SCN) also need to be considered. For example, there remains a dearth of knowledge on how the BOLD signal is affected by internal factors, such as metabolic or molecular changes or changes related to an individual's mental state, as may be the case after TBI (Kety et al., 1948; Lang et al., 2014). Furthermore, given our clear *a priori* hypotheses involving the SBN, we opted for ROI-based analyses and against a more data-driven approach (i.e., independent component analyses). However, ROI identification may be limited when mass structural lesions are present, as some functional reorganization of structural and functional networks may have occurred since the TBI (Duffau, 2005; Goldmann & Golby, 2005). In Article 3, we controlled for both global and focal lesions by using GM volume as a covariate and a study-specific GM mask. As such, we only considered regions with GM for analyses (excluding those with lesions), as brain activation is generally detectable only in GM (Logothetis, 2003). Following the same principle, a GM mask was also applied in Article 4.

With respect to the SCN approach, GM volume was used as the basis for the SCN. While many studies have used a similar approach (Mechelli et al., 2005; Montembeault et al., 2016; Zielinski et al., 2010), others have instead relied on cortical thickness to construct SCN (Bernhardt et al., 2014; Sharda et al., 2017). While cortical thickness may have a more straightforward biological meaning, by using GM volume we were able to include subcortical structures in our analyses. However, GM volumes are based on both cortical thickness and surface area which follow different maturational trajectories (Herting et al., 2015). Thus, having combined two different maturational aspects may prevent us from drawing clear and unbiased conclusions as to the developmental interpretation of the SCN results. Future studies could use multiple morphological parameters (i.e., volume and cortical thickness) to disentangle questions regarding the maturation of SCN after TBI. Finally, we did not find changes in SCN over time in either group. This could reflect a true absence of time-related changes, or simply a lack of statistical power. A note on power and effect sizes is provided in the following section.

Effect sizes and power calculation

For the regression analyses in Articles 1 and 2, Cohen's f^2 can be calculated to estimate effect size *a posteriori* (where $f^2 = .02$ is considered a small, .15 a medium, and .35 a large effect size). In Article 1, 11 predictors were included in the hierarchical regression model on 103 participants. A medium effect size ($f^2 = .24$) was observed in the final model with 11 predictors. Given the sample size of $N = 103$, statistical power was .92 to find this effect to be significant ($\alpha = .05$). In Article 2, 11 predictors were included in the model on a sample of $N = 52$. For the final model at T1 including 11 predictors, the observed f^2 was .16 (medium effect size). Given the sample size of $N = 52$, we had a 37% probability of finding this effect to be significant ($\alpha = .05$), which is considered low statistical power. For the model at T2, f^2 was .11 which is a small effect and statistical power was again low (.24).

Traditional power calculations are less straightforward in neuroimaging studies given different definitions of power and modeling approaches as well as multiple comparisons among large amounts of voxels in the brain. For rsfMRI studies, it is recommended to have a group size of $N = 40$ (per group) to have sufficient power (at least 80% or higher) to detect group differences (Chen et al., 2018; Geuter et al., 2018). For structural covariance analyses, a sample size of $N = 30$ or higher per group is considered necessary for adequate power (Carmon et al., 2020). For both Articles 3 and 4 only half or less of the required sample sizes were achieved, and thus, statistical power was low.

Future research avenues

A key element of future studies will be to use larger samples in order to validate and replicate the present findings, as well as to build upon and extend the analyses included in this thesis. It is often difficult, if not impossible, for one laboratory alone to acquire datasets that are sufficiently large to address the various limitations of current pediatric TBI research. In that regard, multicenter studies are promising, as they allow for better statistical power as well as advanced statistical analyses based on larger samples. To address the complexity and heterogeneity of cases and outcomes of pediatric TBI, the field will benefit from multi-center initiatives such as illustrated by the Advancing Concussion Assessment in Pediatrics (A-CAP study; Yeates et al., 2017) or the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI study; www.ClinicalTrials.gov; NCT02119182) studies. In addition, sufficiently detailed description of

samples will be critical to combine results into meta-analyses which will enhance generalizability of the results. Such efforts could greatly accelerate our current understanding of prognosis, taking into account a large range of factors as well as the underlying brain correlates of cognitive and behavioural function after pediatric TBI.

Using larger samples is crucial when investigating genetic factors, as well as links between possible genetic markers and outcomes of pediatric TBI. To date, even when links between a polymorphism and a specific outcome are found, effects are typically small, explaining less than 5% of variance (Comings, 1998). It is unlikely that a single gene polymorphism can account for variability in outcomes. Genome-wide studies are needed to disentangle complex associations between specific genetic factors and outcomes, as well as interactions between genetic and environmental variables. Additional candidate genes and polymorphisms of interest in pediatric TBI may be genes involved in the neural response to injury, repair and mechanisms of neuroplasticity, cognitive capacity and reserve (McAllister, 2010). In addition, catecholamine genes and genes involved in neurotransmitter signaling such as those of the dopaminergic system are potential candidates, given their role in cognitive and behavioural functioning (Bennett et al., 2016; McAllister, 2010). Recent studies show promise in investigating polygenetic risk scores (Treble-Barna, Pilipenko, et al., 2020) and systems biology-informed approaches (Kurowski et al., 2019) to explore combinations of genetic factors associated with distinct biological processes involved in TBI, in particular genes involved in cell death, inflammatory response, neurotransmitter signaling and brain development.

In addition, research on epigenetic effects (i.e., a change in gene expression without changing the DNA sequence) is practically non-existent in the TBI literature, but could provide further insights into gene-environment interactions and how injury could potentially affect gene expression during development (Treble-Barna, Patronick, et al., 2020). Finally, future studies should also test the effect of BDNF on different age and injury severity groups. Age will be an important variable to consider, as the effect of the Val66Met polymorphism and associated BDNF levels may differentially affect phenotypes at different developmental periods (Casey et al., 2009).

There are increasing calls to consider sex and gender differences in outcome and recovery after pediatric TBI. To date, results are equivocal, and many studies have not put much emphasis on putative different recovery trajectories for girls versus boys, although some evidence suggests

that the response to injury may be different depending on sex (see Arambula et al., 2019 for a review).

To further improve prognostic models of outcome, studies should include structural and functional neuroimaging markers and other genetic factors along with other environmental and child factors, as well as premorbid variables. Pre-injury factors including pre-injury family function or premorbid learning or behavioural difficulties may add additional predictive power (e.g., Babikian et al., 2013; Yeates et al., 1997). Prognostic models should also be applied at different stages of recovery, and include moderate and severe pediatric TBI to account for the role of these factors at different stages of recovery and for different severity groups. Additionally, future studies using larger samples could explore interactive effects between the presented factors and identify possible moderators of outcome.

Future neuroimaging studies should replicate the findings presented in this thesis and extend analyses to brain networks within and across both hemispheres, and other well-established networks (i.e., auditory, motor, visual, speech, semantics, cerebellar, mentalizing networks), thus providing a better account of how pediatric TBI affects overall neural network organization during development. It will also be important to assess how altered patterns of FC and SCN relate to social, behavioural and cognitive outcomes. More homogeneous samples should be used to understand the role of site of injury and time variables, such as age at injury and time since injury which are often confounded or not accounted for. This will also be important to differentiate between developmental and TBI-induced alterations over time. Additional efforts should also be undertaken to examine putative alterations in brain connectivity in mild and early TBI, for which the existing literature is limited. Efforts are currently underway to acquire MRI in preschoolers without sedation (Beauchamp, Degeilh, et al., 2020), which could contribute to understanding the impact of TBI on the brain at an early stage of development.

SCN analysis is a promising approach to assess how TBI affects the developing network structure. Future work should explore how SCN are linked to FC, as well as to cognitive and behavioural outcomes. SCN may be a complementary approach to use in pediatric TBI, as it provides important new information on structural connectivity, beyond that obtained using DTI. Although DTI is commonly used in pediatric TBI to study effects of injury on the WM architecture, it has limitations pertaining to crossing fibers (Schilling et al., 2019) and SCN may thus be promising in getting further insights into brain structure, in particular the GM architecture post-

injury. Studies combining different approaches, each with their own focus and strengths, have the potential to provide the best and most comprehensive assessment of how pediatric TBI affects the brain's network organization during development. Future studies could combine the presented methods to study brain connectivity with approaches such as electro- (EEG) or magnetoencephalography (MEG) or graph theoretical methods to better understand brain connectivity in pediatric TBI.

Finally, using artificial intelligence in the form of machine learning approaches could be a promising way to contribute to prognostic models and to gather clinical, neuroimaging and demographic information to identify subgroups of children with TBI who have similar characteristics. An overall better understanding of how pediatric TBI affects development at the neural network level may help determine early markers of unfavourable recovery, identify children at risk for poor outcomes, and provide targeted interventions. In sum, combining neuroimaging with clinical indicators and the aforementioned risk factors might by promising in providing a comprehensive assessment of potential early risk factors to optimise recovery.

Conclusions

Pediatric TBI is characterized by vast heterogeneity in terms of etiology, clinical presentation, and recovery trajectories, resulting in poor prognostication. This challenge is captured in the Hippocratic aphorism: "No head injury is so serious that it should be despaired of, nor so trivial that it can be ignored." Establishing valid and empirically tested prognostic models is vital to understanding what influences outcome and recovery. Pediatric TBI warrants attention given that it occurs during times of rapid brain and social development, thus interfering with ongoing maturation of brain networks that underlie social and cognitive skills. The present thesis used a multi-modal approach relying on prospective longitudinal designs, as well as behavioural and neuroimaging data across a range of domains and measures to address several gaps in the literature.

This work supports the use of comprehensive biopsychosocial approaches for establishing prognosis and identifying both risk factors for poor recovery and variables that could protect against negative outcomes after pediatric TBI. These can aid in our understanding of post-injury outcomes, especially in the youngest developmental groups, which have received little attention to date. Supporting theoretical assumptions put forward in the SOCIAL model (Beauchamp & Anderson, 2010), the findings underscore the particular role of child temperament, EF and socio-

cognitive factors for social competence in typical development, and provide indirect insights into ways to stimulate social competence in children who sustain TBI. In addition, genetic factors involved in neuroplasticity may provide avenues for explaining the heterogeneity in outcome observed in children with seemingly comparable injuries. Parental factors are important in pediatric TBI recovery, notably, parent mental health.

In sum, the present findings contribute to efforts aimed at identifying early risk factors for adverse outcomes and suggest potential targets for prevention and intervention strategies. The thesis addresses the paucity of research on brain connectivity in the field of pediatric TBI and suggests that TBI affects the brain at the level of large-scale networks. The results provide a proof-of-principle for future work applying a network perspective to pediatric TBI research and encourage future endeavours to elucidate the impact of TBI on the numerous and complex interconnections between regions that form large-scale neural systems and underlie cognitive and behavioural functioning.

Determining which children will recover well after pediatric TBI and which will experience difficulties cannot simply be answered by theories of either early vulnerability or plasticity. Consideration of the complex interaction of neuroplasticity, age and developmental stage, cognitive-behavioural, family environmental, genetic and neuroimaging markers is indispensable for the best possible prognosis. No matter their presentation and severity, brain injuries need adequate consideration and management, both in the short- and long-term.

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Appendix I

Brain-Derived Neurotrophic Factor Val66Met Polymorphism and Internalizing Behaviors after Early Mild Traumatic Brain Injury

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Abstract

Pediatric traumatic brain injury (TBI) can lead to adverse emotional, social, and behavioral consequences. However, outcome is difficult to predict due to significant individual variability, likely reflecting a complex interaction between injury- and child-related variables. Among these variables are genetically determined individual differences, which can modulate TBI outcome through their influence on neuroplasticity mechanisms. In this study, we examined the effect ofVal66Met, a common polymorphism of the brain-derived neurotrophic factor gene known to be involved in neuroplasticity mechanisms, on behavioral symptoms of mild TBI (mTBI) sustained in early childhood. This work is part of a prospective, longitudinal cohort study of early TBI. The current sample consisted of 145 children between ages 18 and 60 months assigned to one of three participant groups: mild TBI, orthopedic injury, or typically developing children. Participants provided a saliva sample to detect the presence of the Val66Met polymorphism, and the Child Behavior Checklist was used to document the presence of behavioral symptoms at 6- and 18-months post-injury. Contrary to our initial hypothesis, at 6 months post-injury, non-carriers of the Val66Met polymorphism in the mTBI group presented significantly more internalizing symptoms (e.g., anxiety/depression and somatic complaints) than Val66Met carriers, whowere similar to orthopedically injured and typically developing children. However, at 18 months post-injury, all children with mTBI presented more internalizing symptoms, independent of genotype. The results of the study provide evidence for a protective effect of the Val66Met polymorphism on internalizing behavior symptoms 6 months after early childhood mTBI.

Keywords: Behaviors, children, concussions, genetic, traumatic brain injury

Introduction

Pediatric traumatic brain injury (TBI) can lead to impaired functioning in a range of neurocognitive and psychosocial domains,[1,2] and typically follows a dose–response relationship with regard to injury severity and the extent or chronicity of consequences.[3] In the case of milder forms of TBI (concussion or mild TBI [mTBI]), adverse consequences are transient and resolve within a few weeks formost children.[4,5] However, there is evidence that some children are more vulnerable to the effects of mTBI and display significant and persistent problems after injury, especially in social and behavioral domains.[6,7]

Differential recovery outcomes and trajectories are likely the result of a complex interplay between injury characteristics, child factors such as age at injury and pre-injury functioning,[8,9] and environmental factors such as socio-economic status and parenting practices.[10,11] In addition, some authors suggest that genetically determined individual differences may modulate TBI outcome through their influence on neuroplasticity mechanisms.[12-14] Neuroplasticity consists of the ability of the brain to change and adapt as a result of experience (i.e., experience-dependent plasticity), or to reorganize following an acquired brain injury (i.e., lesion-induced plasticity). These changes and reorganization processes occur at molecular, synaptic, and cellular levels, as well as through more global network changes.[15]

The brain-derived neurotrophic factor (BDNF), encoded by the BDNF gene, is of particular interest when studying neuroplasticity mechanisms and has received considerable attention with respect to lesion-induced plasticity and acquired brain injury outcome. BDNF is the most abundant neurotrophin present throughout the brain and plays a key role in neuronal survival, synaptic plasticity and neurogenesis.[16–19] Animal models of experimental brain injury reveal acute up-regulation of neurotrophic factors, such as BDNF, in the central nervous system.[20] In keeping with this, in a study of children age 3 months to 16 years with severe TBI, BDNF levels in cerebrospinal fluid and plasma showed a sharp peak acutely after injury.[21] This increase is thought to reflect an endogenous attempt of neuroprotection against biochemical and molecular changes induced by the brain insult, while contributing to synaptic reorganization processes, thus protecting against neurological damage and cognitive deficits.[21-23]

The BDNF gene has several polymorphisms, of which the Val66Met (also known as rs6265) variant is the most studied. BDNF Val66Met is common in humans, with an allele frequency of 20 to 30% in Caucasian populations.[21-23] Its prevalence makes it possible to study its

impact without requiring very large samples and this partly explains why it has been extensively studied in healthy controls, as well as in clinical populations. BDNF Val66Met is the result of a valine (Val) to methionine (Met) substitution at codon 66 of the gene. This substitution leads to alterations in intracellular trafficking of BDNF, which decrease protein regulated secretion by about 25%.[24,25] Taking these mechanisms into account, it is assumed that the Val66Met polymorphism (in other words, the presence of the Met allele) is associated with reduced potential for neuroplasticity, and thus a diminished capacity for functional recovery after neurological insult.[26]

Genetic association studies exploring the role of the BDNF Val66Met polymorphism in TBI functional recovery are rare and only target adults. Moreover, results of the few existing adult studies are conflicting and difficult to reconcile, in part because of methodological differences (e.g., injury severity level and type of outcome evaluated). For example, some studies report that after severe forms of TBI (i.e., focal penetrating head injuries), the Met allele (i.e., Val66Met polymorphism), but not the hypothesized Val allele, promotes recovery of executive functioning27 and general intelligence.[28] Conversely, the Met allele seems to be a risk factor for socio-emotional problems after milder forms of TBI. A recent study showed a strong association between the presence of the Val66Met polymorphism and depressive symptoms in the first week after mTBI in adults.[29] Similarly, another study found that in adults with a history of multiple concussions (defined as a head injury that resulted in post-concussive symptoms), increased brooding rumination and elevated symptoms of depression are reported among Met-allele carriers.[30]

Despite these emerging findings on the role of BDNF Val66Met in recovery after TBI, the results of studies conducted in adults have limited applicability to the pediatric population because of the distinctive neurobiology of the immature brain. Further, natural concentrations of BDNF throughout the brain vary across development, such that the reduced protein expression conferred by the Met allele may constitute a protective factor in some developmental periods (e.g., during adolescence when BDNF levels peak) while representing a risk factor during others.[31] Thus, to better understand the role of the BDNF Val66Met polymorphism on TBI outcome, studies targeting well-defined developmental periods are needed.

In sum, genetic predispositions are thought to play an important role in functional recovery after TBI. However, there is a paucity of genetic association studies specific to TBI in children.[32] In particular, there are no candidate gene studies that investigate the role of BDNF gene

polymorphisms on the functional outcome of pediatric TBI, even though BDNF is believed to play an important role in neuroplasticity after a brain insult. The current study aimed to explore the association between the presence of the Val66Met, a common polymorphism of the BDNF gene, and behavioral symptoms after mTBI sustained in early childhood (i.e., between 18 and 60 months), a period during which TBI is highly prevalent[33] and during which the brain undergoes major and rapid changes through brain plasticity mechanisms. In accordance with the results found in adults, it was hypothesized that Met-allele carriers would display more behavioral problems than Val/Val homozygotes.

Methods

The data presented here constitute a sub-study of a larger prospective longitudinal cohort study investigating cognitive, behavioral and social outcomes of preschool TBI[9,34–38] and approved by the local institutional ethics review board. The current analyses focus on BDNF Val66Met polymorphism and behavioral symptoms after early mTBI.

Participants and recruitment

The current sample constitutes a sub-group of participants from the larger aforementioned cohort study, who agreed to participate in an additional and optional genetic sub-study. This sub-group consisted of a total of 145 children assigned to one of three participant groups: mild TBI (mTBI; n = 47), orthopedic injury (OI; n = 42), and typically developing children (TDC; n = 56; see descriptive variables in Table 1). Children from the two injury groups were between ages 18 and 60 months at the time of the injury and were recruited in a single, tertiary care pediatric emergency department. The mTBI group comprises children who sustained a closed-head injury with a score between 13 and 15 at admission on the Glasgow Coma Scale (GCS). Children who had a diagnosis of complicated mTBI (score between 13 and 15 on the GCS with evidence of an intracranial lesion on clinical computed tomography or magnetic resonance imaging) were also included (n = 8). The OI group comprises children who sustained a limb trauma, leading to a final diagnosis of simple fracture, sprain, contusion or unspecified trauma to an extremity. To compose the TDC group, non-injured children of equivalent age were recruited via information pamphlets left for parents in urban daycare centers. To ensure that the three groups were of comparable age at the first assessment timepoint (i.e., 6 months post-injury for the two clinical groups), children in the TDC group were between ages 24-66 months at the time of recruitment.

Exclusion criteria for the three groups were: 1) diagnosed congenital, neurological, developmental, psychiatric, or metabolic condition; 2) gestational age <36 weeks; 3) child and parent not fluent in French or English; 4) history of prior TBI serious enough to warrant a visit to the ED; and 5) suspicion of a non-accidental injury (for the mTBI and OI groups). More detailed information on the recruitment procedure and inclusion criteria were provided previously.[9]

Measures and materials

Descriptive variables

For the mTBI and the OI groups, a research nurse completed a standardized case report form immediately after recruitment for descriptive purposes (e.g., nature and severity of the injury, neurological signs and symptoms, GCS) and to confirm inclusion/exclusion criteria. Parents of all three groups completed an in-house socio-demographic questionnaire to collect information regarding demographics (e.g., sex, ethnicity, parental education, family living arrangement).

Behavioral outcome

At 6-months (T1) and 18-months post-recruitment (T2), mothers were asked to complete the age-appropriate version (i.e., preschool version for ages 1.5-5.0 years or school-age version for age 6-18 years) of the Child Behavior Checklist (CBCL).39 For each version, items are rated using a 3-point scale (0 = not true; 1 = somewhat or sometimes true; 2 = very true or often true). There are 100 items in the preschool CBCL version and 113 items in the school-age version. Items are combined in empirically based syndrome subscales and these subscales are combined in two higher order factors: Internalizing Problems including four subscales (emotionally reactive, anxious/depressed, somatic complaints, and withdrawn), and Externalizing Problems including two subscales (attention problems and aggressive behavior). T scores were used in all analyses.

Saliva collection and analysis

Participants were invited to provide a saliva sample (0.75 ml) during the course of the study, either in person or via mail. The sample was collected using Oragene OG-575 kits (DNA Genotek, Ottawa, Canada) by collecting saliva with a sponge moved along the child's gums and inner cheeks, and then squeezed into a collection tube when saturated with saliva. To detect the presence of the polymorphism Val66Met, the amplification was performed using a thermal cycler (Biometra Tprofessional) using a polymerase chain reaction (PCR) approach, with the following

oligonucleotide primer pairs: 5'-biotin before GGACTCTGGAGAGCGTGAAT-3 and 5'-reverse CCGA ACTTTCTGGTCCTCATC-3'. In addition to buffers, nucleotide components and a dose of 0.01U of Taq polymerase supplier of PCR Master Mix (Qiagen), the amplification reactions contained 1 μg of DNA derived from saliva, 1 μg each primer, 0.4mM of dNTP, 1.0mM MgCl2, in a final volume of 50 μL. The PCR conditions included 35 cycles: 30 sec at 95°C; 30 sec at 61.2°C; and 1 min at 72°C. These 35 cycles of amplification were preceded by an initial heating step of 3 min at 95°C and followed by a final extension of 4 min at 72°C. The PCR products were visualized on a 1.2% agarose gel. The Val66Met polymorphism was sequenced with a pyrosequencing protocol[40] with a slight modification using the oligomer: 5'-GCTGACACTTTCGAACA -3'. The sequence analyzed was: CA / GTGATAGAAGAG.

Statistical analysis

All analyses were conducted using IBM SPSS Statistic (version 21.0). First, preliminary analyses were performed to ensure that groups were equivalent in terms of socio-demographic factors. Chi-squared analyses were conducted on categorical variables (i.e., sex, ethnicity, family living arrangement), and analyses of variance (ANOVAs) or Student's t-tests were conducted for continuous variables (i.e., age at assessment, age at injury, parental education). Where significant group differences were found for any of these socio-demographic variables (or even a statistical trend), the main analyses detailed below were conducted including the potentially confounding variable as a covariate.

In the main analyses, three-way mixed analyses of variance were performed for both the Internalizing Problems score and the Externalizing Problems score on the CBCL, with Group (mTBI, OI, TDC) and Genotype (Val/Val homozygotes, Met-Allele carriers) as between-subject factors and Time (T1, T2) as a within-subject factor. In the case of a significant interaction, planned follow-up analyses (ANOVAs or Student's *t*-tests) were conducted to determine simple main effects. An alpha level of $p \leq 0.05$ was considered significant. Effect sizes were calculated using Cohen's *d* (small effect $d = 0.2$, medium effect $d = 0.5$, large effect $d = 0.8$; Cohen, 2013).[41]

Results

Follow-up details and participant characteristics

Information on recruitment and follow-up details for all three groups are presented in Figures 1 and 2. There were no differences between families who agreed to participate in the overall study and those who refused participation, in terms of child age [mTBI: $t(217) = 0.81$, $p = 0.42$; OI : $t(216) = -0.39$, $p = 0.70$; TDC : $t(111) = 0.61$, $p = 0.55$] and sex [mTBI: $\chi^2(1) = 0.59$, $p = 0.44$; OI : $\chi^2(1) = 0.43$, $p = 0.51$; TDC : $\chi^2(1) = 2.28$, $p = 0.13$]. Concerning attrition, 19 mTBI (16%), 27 OI (27%), and 1 TDC (1%) initially agreed to participate in the study but dropped out before the first assessment time-point (T1). More families from the injury groups than the TDC group dropped out before T1 because 6 months elapsed between recruitment and T1 for the clinical groups, whereas for the uninjured TDC group, T1 was completed immediately after recruitment. Twenty-four mTBI (27%), 11 OI (18%), and 17 TDC (20%) were excluded from analyses because they had missing CBCL data for either T1 or T2 (e.g., parents never returned the questionnaire booklet).

Finally, among the children with complete CBCL data for both assessment time-points, there were 17 mTBI (27%), 7 OI (14%) and 11 TDC (16%) with missing BDNF genotype. The main reasons for missing genetic data were: 1) the parent did not want to participate in the genetic sub-part of the study (n = 13); 2) parent was no longer reachable or had abandoned the project at the time the data collection for the genetic sub-part of the study was in progress (n = 13); and 3) the parent did not return the sample that had been sent by mail with instructions for collection (n = 4). The proportion of children with missing BDNF genotype was similar across groups ($\chi^2(2) = 3.3$, $p = 0.19$). There were no differences between families who agreed to participate in the genetic sub-study and those who refused, in terms of child age $t(156) = 0.55$, $p = 0.55$) and sex ($\chi^2(1) = 2.85$, $p = 0.58$).

The final sample consisted of 145 children: 47 mTBI (29 boys, 62%), 42 OI (21 boys, 50%) and 56 TDC (30 boys, 54%). As detailed in Table 1, there were no between-group differences for the following demographic variables: child age at each assessment, age at injury (for the two clinical groups), sex ratio, ethnicity, and family living arrangement. However, a between-group difference was observed for parental education level ($p = 0.01$), with parents in the mTBI group

having significantly lower educational qualifications than parents in both the OI and the TDC group.

In the overall sample, 91 participants carried the wild-type Val66Val polymorphism (Val/Val homozygotes) and 54 participants carried at least one copy of the Met allele (Val66Met or Met66Met), representing 37% of the study sample. Participants with Val/Met and Met/Met genotypes were combined for statistical analyses into a Met-allele carriers group. The proportion of Val/Val versus Met-allele carriers was similar for each participant group: mTBI (62% Val/Val vs. 38% Met carriers), OI (62% Val/Val vs. 38% Met carriers) and TDC (64% Val/Val vs. 36% Met carriers).

Main analyses

Externalizing problems

For the Externalizing Problems score, there was a significant main effect of Group [$F(2, 139) = 4.71$; $p = 0.01$], regardless of Genotype or Time. Contrasts revealed that children with mTBI (mean [M]= 54.04; standard error [SE] = 1.21) had higher reported rates of externalizing symptoms than TDC [M = 49.04; SE = 1.12; $p = 0.003$, 95% CI (1.75 – 8.26)]. It is noteworthy that although there was a significant group difference, mean scores remained in the average range (i.e., below the clinical significance level cut-off) for all three groups. There was no main effect of Genotype or Time, nor was there a Group x Genotype x Time interaction.

Internalizing problems

Results for the Internalizing Problems score are presented in Figure 3. There was a significant main effect of Group, [$F(2, 139) = 4.39$; $p = 0.014$], with children in the mTBI group (M = 53.58; SE = 1.42) having higher reported rates of internalizing problems than children in both the OI [M = 49.13; SE = 1.50; $p = 0.033$, 95% CI (0.36 – 8.54)] and the TDC groups [M = 48.07; SE = 1.32; $p = 0.005$, 95% CI (1.68 – 9.34)]. However, there was no main effect of Time ($p = 0.13$) or Genotype ($p = 0.26$).

The Group x Genotype x Time interaction was significant [$F(2, 139) = 3.05$; $p = 0.05$]. Visual inspection of the means and interaction graph indicate that at T1, Val/Val participants who sustained mTBI presented more internalizing problems (M= 57.48, standard deviation [SD] = 10.08) compared with Met-allele carriers who sustained mTBI (M= 47.61, SD = 11.42), the latter being comparable to all others groups (Val/Val and Met-allele carriers in the OI and TDC groups).

Accordingly, a planned follow-up analysis indicated that at T1, the difference between Val/Val and Met-allele carriers in the mTBI group was significant [$t(50) = 3.19$; $p = 0.002$] and represented a large-sized effect $d = 0.90$. At T2, however, Val/Val and Met carriers who sustained mTBI had similar rates of internalizing problems [$t(45) = 0.99$; $p = 0.33$]. At T2, regardless of genotype, there was a significant Group difference [$F(2, 142) = 4.52$; $p = 0.01$], with mTBI children (M= 55.04; SE = 12.35) presenting more internalizing symptoms than children in both the OI [(M= 49.43; SE = 8.73; $p = 0.02$, 95% CI (0.99 - 10.24)] and the TDC groups [(M= 48.98; SE = 11.37; $p = 0.01$, 95% CI (1.75 – 10.37)].

Note that a more conservative model including parental education level as a covariate was conducted and yielded similar results; the Injury Group x Genotype x Time interaction was still significant [$F(2, 138) = 3.06$; $p = 0.05$].

Discussion

This prospective cohort study examined the role of BDNF Val66Met, a naturally occurring polymorphism in the BDNF gene, with respect to behavioral outcomes after early mTBI. This BDNF polymorphism is thought to represent a risk factor for poorer functional outcome after brain injury, given that the Met allele is associated with decreased activity-dependent BDNF release, and therefore less neurotrophic support for neuroplasticity. Contrary to our initial hypothesis, the results of the study provide evidence for a protective effect of the Met allele on internalizing behavior symptoms 6 months after mTBI sustained during early childhood. As such, in the mTBI group, Val/Val homozygotes presented significantly more internalizing symptoms than Met-allele carriers. The latter had similar levels of symptoms as orthopedically injured and non-injured control participants, for whom there was no differential effect of genotype. The protective effect of the Met allele in the mTBI group disappeared over the following 12-month period. That is, at 18 months post-injury, all children with mTBI continued to show more internalizing symptoms compared with orthopedically injured and non-injured peers, independent of genotype.

The results obtained at 6 months post-injury contrast with those of two prior adult mTBI studies showing greater internalizing behavior problems for Met-allele carriers.[29,30] Discrepancies between pediatric and adult findings are perhaps not surprising, given that the structure and function of the pediatric brain is rarely analogous to that of the adult brain,[42] but the current pattern of results contrasts with those typically found in adults. In typical development, gene- or

environment-related alterations in BDNF levels have different effects on behavioral phenotypes across development.[31] During the preschool period, the immature brain develops rapidly due to normal mechanisms of brain plasticity. This plasticity is considered beneficial in the context of healthy development because it drives brain growth through the creation of new neurons and synaptic connections, which are refined as new learning occurs. However, mechanisms of brain plasticity that occur in response to brain injury could instead be detrimental in the developing brain.

There is evidence of TBI-induced altered developmental plasticity mechanisms after pediatric TBI, including for example faulty neurotransmission, enhanced apoptotic injury-induced cell death, and perturbations in neuronal connectivity.[43] These types of maladaptive plasticity contribute to making the developing brain more vulnerable to the effects of injury and may explain why young children show poorer functional recovery compared with older children and adults, despite the fact that they have a higher potential for plasticity. This adds to the fact that sustaining brain injury during early childhood may disrupt the pre-determined sequence of brain maturation and the resulting developmental processes. In other words, an increased potential for TBI-induced plasticity allowed by greater availability of BDNF neurotrophins in Val/Val homozygotes can interfere with the normal developmental blueprint and thus may not translate into better functional recovery.[44] Together, these developmental factors may explain why Val/Val homozygotes are at greater risk for poor behavioral outcome in the first few months after sustaining a mTBI during early childhood.

Another hypothesis to explain the disparity between the results obtained in our study of early childhood compared with those observed in adults is that natural concentrations of BDNF in the central nervous system vary with age. Consequently, an allele that confers reduced release of BDNF may represent a risk factor at a particular age, while offering protection during another developmental period.[31] In a developmental period during which natural expression of BDNF protein is already abundant, the overabundance of BDNF in response to TBI could trigger biochemical reactions leading to neuronal death, thereby compromising post-TBI recovery. In line with these explanations, findings from a study of older TBI patients and with more severe injuries revealed Gene x Age interactions with BDNF in relation to TBI mortality.[45] The authors suggest that age-specific risk profiles may be related to differential expression patterns in the relative balance of pro-survival/pro-apoptotic BDNF target receptors across aging. It is not clear, however,

whether this explanation could apply to milder forms of TBI, or even within a developing, immature brain.

Prior studies in other clinical populations have demonstrated the maladaptive effect of an overexpression of BDNF, in particular with regard to the development of neuropathic pain46 and epileptogenesis.[47]

Impact of BDNF Val66Met on long-term recovery

All children with mTBI, independent of genotype, presented more internalizing symptoms than orthopedically injured and non-injured peers at 18 months post-injury. Compared with the 6 months post-injury time-point, this suggests a persistence of internalizing behavior symptoms in Val/Val homozygotes, and an increase in symptoms in Met-allele carriers, who were initially comparable to orthopedically injured and non-injured peers 6 months post-injury, as seen in Figure 3. This long-term persistence of symptoms is somewhat surprising after mTBI, which is usually associated with more transient effects.[4,5] The fact that there is no longer any differential effect of genotype 18-months post-injury suggests that the etiology of behavioral symptoms in the long-term may no longer be neurological.

For example, at 18-months post-injury, parents may perceive and report behavioral difficulties that are real, but that may be a result of environmental changes related to the accident (e.g., changes in parenting practices) that may affect all children with mTBI, independent of their genotype. It is possible that child behavior problems that have a neurological basis have a detrimental impact on parenting quality, impeding behavioral recovery.[37,48] In short, it can be assumed that at 6 months post-injury, children show internalizing symptoms related to a combination of neurological processes (mediated by BDNF genotype) and non-neurological factors, but that over time, symptoms crystallize due to family-related or other environmental factors, nonetheless related to TBI, but non-neurological.

Limitations and future studies

The main limitation of this work is the reliance on a sole informant (the mother) for providing post-injury behavioral ratings. As with any parent-report questionnaire, it is not possible to blind to group status and this could introduce personal bias and confounds related to parental perception and mental state, for example. However, with regard to the difference observed between Val/Val homozygotes and Met-allele carriers in the mTBI group, genotype is unknown to mothers

and therefore cannot be influenced by parental bias. Another limitation of the study is the absence of potential environmental risk factors (e.g., related to parenting sensitivity and socio-economic status) known to contribute to TBI outcome to assess their interplay with BDNF genotype. Indeed, in non-injured populations, it has been shown that BDNF interacts with environmental risk factors and adversity to predict neuroanatomical and behavioral phenotypes.[49-51]

An additional limitation of the study is the small sample size for a genetic study, as well as the candidate gene approach that was used. Results of candidate gene studies are not always replicated by follow-up studies or by genome-wide association studies and should be interpreted with caution. Future studies should reproduce the results of this study in independent cohorts, as well as consider genome-wide approaches. A study conducted by Kurowski and colleagues[52] shows promise using a genomic approach, informed by systems biology, to study combinations of genes underpinning an array of biologic processes involved in TBI. The current project nevertheless makes a novel contribution given the paucity of genetic association studies specific to pediatric TBI and especially in early childhood.[32] Finally, another limitation of the study is that Caucasians are over-represented in the cohort studied (i.e., almost 90% in the mTBI group). Given that it is possible that a particular genotype confers different cognitive and behavioral phenotypes depending on ethnicity,[53] future studies should seek to include a larger and more varied sample and to analyze the results according to ethnic differences.

Future studies could also investigate the role of other genes and polymorphisms that may influence pediatric TBI outcome. Promising gene candidates could be those potentially involved in preinjury risk factors for TBI, response to neurotrauma, repair, and plasticity processes, or pre- and post-injury cognitive capacity and reserve.[13] In fact, a recent study used a polygenic risk scores approach to examine the differential cumulative influence of candidate genes involved in the inflammatory response on pediatric TBI outcomes.[54] Finally, future studies should also explore the role of BDNF Val66Met on cognitive functions that could underlie behavioral problems after pediatric TBI, such as executive functions, decision-making and social cognition.

Conclusion

The current study provides support for a transient protective effect of the Val66Met polymorphism on internalizing symptoms after early mTBI. In the particular context of early childhood mTBI, it appears that enhanced potential for neural plasticity in Val/Val homozygotes

might be more deleterious than beneficial for internalizing behaviors in the first 6 months post-injury. Future studies of pediatric TBI should investigate combined and interactive effects of genetic variants and environmental risk factors, thus providing a better understanding of the wide variability in outcomes.

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The authors report no conflicts of interest.

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Table 1. Participants' Sociodemographic And Descriptive Charateristics

	mTBI n = 47	OI n = 42	TDC n = 56	*F / t / χ2*	*p*-Value
Age at assessment (months), M (SD)	-	-	-	-	-
At the first assessment time point (T1)	44.3 (11.9)	41.31 (11.4)	43.53 (11.9)	0.76	.47
At the second assessment time point (T2)	56.5 (11.9)	53.01 (12.1)	55.84 (12.0)	1.04	.36
Age at injury (months), M (SD)	37.8 (11.9)	34.41 (11.7)	-	1.34	.18
Sex, *n* (%) males	29 (61.7)	21 (50)	30 (53.6)	1.32	.52
Ethnicity (Caucasian), *n* (%)	42 (89.4)	33 (78.6)	49 (87.5)	14.04	.08
Family living arrangement, *n* (%)	-	-	-	6.19	.40
Child lives with both parents	41 (87.2)	41 (97.6)	51 (91.1)	-	-
Child lives with mother only	4 (8.5)	1 (2.4)	5 (8.9)	-	-
Shared custody	1 (2.1)	0 (0)	0 (0)	-	-
Parental education[1], M (SD)	3.36 (1.1)	2.85 (0.9)	2.82 (0.8)	5.07	.01*
BDNF Genotype, *n* (%)	-	-	-	0.09	.96
Val/Val	29 (61.7)	26 (61.9)	36 (64.3)	-	-
Met-allele carriers	18 (38.3)	16 (38.1)	20 (35.7)	-	-

(1) Parental education was obtained by averaging both parents' educational qualifications on an 8-level scale ranging from 'Doctoral degree' to 'Less than 7 years of school'. For participants for whom the value was available for only one of the two parents, the latter was used.

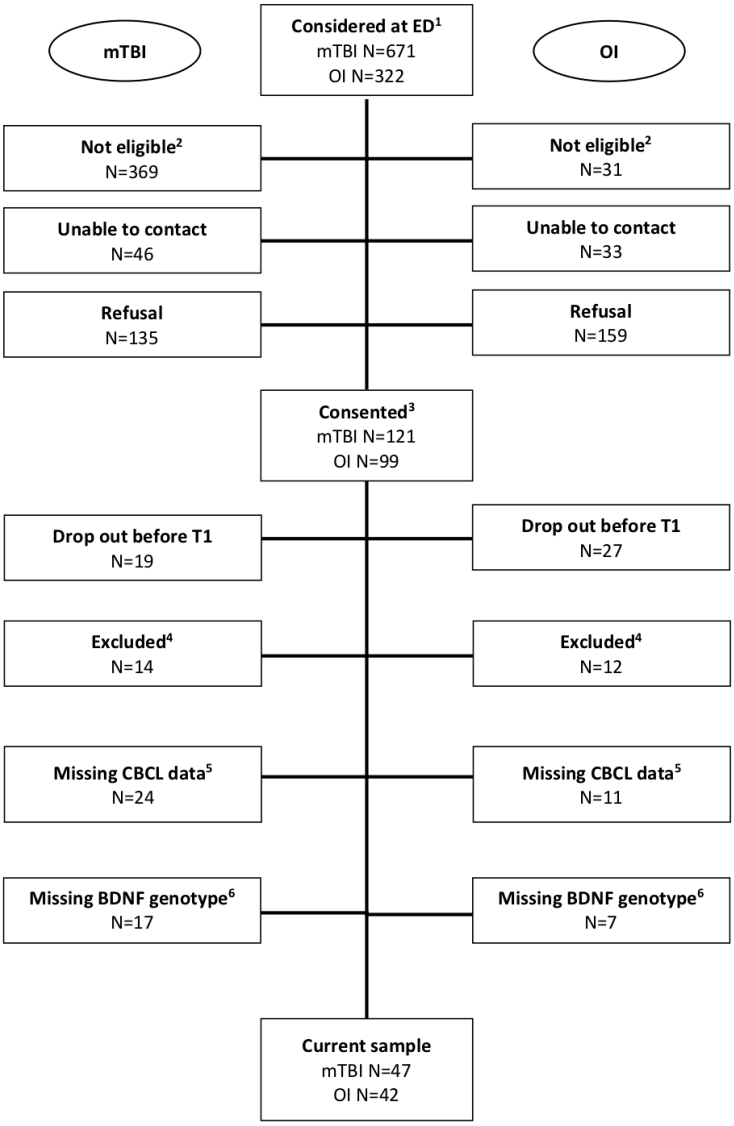


FIG. 1. Recruitment and follow-up flowchart of the mild traumatic brain injury (mTBI) and orthopedic injury (OI) groups.
(1) The following emergency department (ED) diagnoses were considered for participation in the study: mTBI group: traumatic brain injury, head fracture, concussion, intracranial. bleeding/hemorrhage, polytrauma; OI group: limb trauma leading to a final diagnosis of simple fracture, sprain, contusion, or unspecified trauma to an extremity. **(2)** Potential participants were not eligible because they did not satisfy an inclusion and/or exclusion criteria. **(3)** Consented refers to those participants whose parents signed a consent form. **(4)** These participants were excluded a posteriori, even if one or more timepoints had been completed, because they did not satisfy an inclusion and/or exclusion criteria that had not been detected at recruitment. **(5)** Missing Child Behavior Checklist data at T1, T2 or both (e.g., failure to return the questionnaire booklet). **(6)** Missing brain-derived neurotrophic factor genotype (e.g. parents did not agree to participate in the genetic sub-study, child was unable to provide enough saliva).

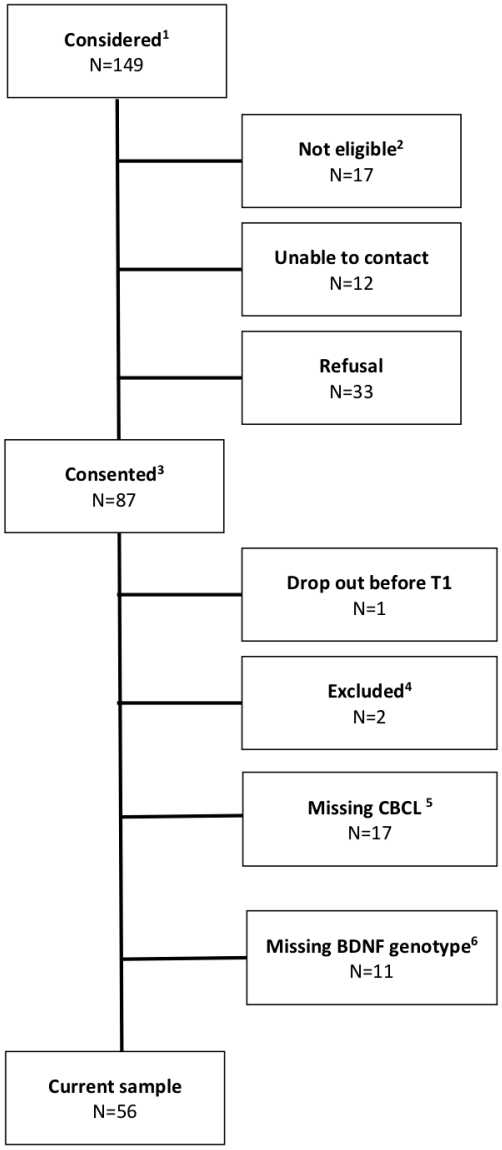
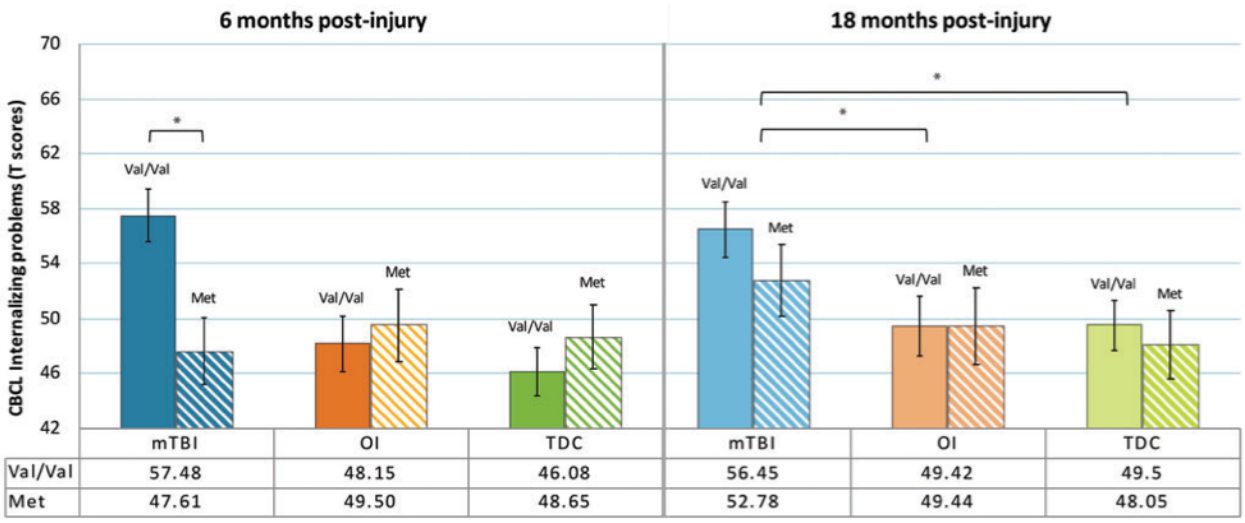


FIG. 2. Recruitment and follow-up chart for the typically developing children.
(1) Considered refers to participants whose parents were given a study pamphlet at the local daycare and who gave their verbal consent to be contacted by the research coordinator. **(2)** Potential participants were not eligible because they did not satisfy an inclusion and/or exclusion criteria. **(3)** Consented refers to those participants whose parents signed a consent form. **(4)** These participants were excluded a posteriori, even if one or more timepoints had been completed, because they did not satisfy an inclusion and/or exclusion criteria that had not been detected at recruitment. **(5)** Missing Child Behavior Checklist data at T1, T2 or both (e.g., failure to return the questionnaire booklet). **(6)** Missing brain-derived neurotrophic factor genotype (e.g., parents did not agree to participate in the genetic sub-study, child was unable to provide enough saliva).



	mTBI	OI	TDC	mTBI	OI	TDC
Val/Val	57.48	48.15	46.08	56.45	49.42	49.5
Met	47.61	49.50	48.65	52.78	49.44	48.05

FIG. 3. CBCL Internalizing problems 6 and 18 months post-injury.
At T1, the difference between Val/Val and Met-allele carriers in the mTBI group was significant. At T2, Val/Val and Met carriers who sustained mTBI had similar rates of internalizing problems. However, regardless of genotype, children with mTBI had significantly more internalizing symptoms than children in the OI and the TDC groups. Color image is available online.

Appendix II

What about the little ones? Systematic review of cognitive and behavioral outcomes following early TBI

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Abstract

There is increasing empirical focus on the effects of early traumatic brain injuries (TBI; i.e., before the age of 6 years) on child development, but this literature has never been synthetized comprehensively. This systematic review aimed to document the cognitive, academic, behavioral, socio-affective and adaptive consequences of early TBI. Four databases (Medline, PsycNET, CINAHL, PubMed) were systematically searched from 1990 to 2019 using key terms pertaining to TBI and early childhood. Of 12, 153 articles identified in the initial search, 43 were included. Children who sustain early TBI are at-risk for a range of difficulties, which are generally worse when injury is sustained at a younger age; injury severity is moderate-severe, and injury mechanisms are non-accidental. Early childhood is a sensitive period for the emergence and development of new skills and behaviors and brain disruption during this time is not benign. Research, clinical management, intervention and prevention efforts should be further developed with consideration for the unique characteristics of the early childhood period.

Keywords: Early TBI, preschoolers, cognition, behavior, systematic review.

Introduction

Sustaining pediatric traumatic brain injury (TBI) can disrupt the typical development of emerging cognitive and social skills and lead to adverse consequences and poor long-term outcomes (Anderson et al., 2005; Anderson et al., 2009; Verger et al., 2000). During early childhood (i.e., before the age of 6 years), a range of cognitive and socio-affective functions undergo intense development, including attention and executive functioning, as well as social cognition, emotion and behavior regulation and adaptive functioning (Grantham-McGregor et al., 2007). Birth cohort data indicate that "early TBI", defined as "an alteration in brain function caused by an external force and sustained during infancy, toddlerhood or the preschool period", is prevalent (McKinlay et al., 2008; Menon et al., 2010). As such, it is important to fully understand the consequences of early TBI on multiple functional domains. Yet, most empirical studies and reviews focus on school-age children, adolescents and adults rather than on the youngest, and potentially most vulnerable, developmental group.

The empirical literature focusing on the consequences of pediatric TBI in school-aged children and adolescents is exhaustive and shows a variety of consequences affecting diverse domains. Meta-analytic and systematic reviews in older pediatric age groups suggest the presence of attention, executive and social cognition impairments (Babikian et Asarnow, 2009; Babikian et al., 2015; Rosema et al., 2012), internalizing and externalizing behavior problems (Albicini et McKinlay, 2018; Durish et al., 2018; Kennedy et al., 2017; Li et Liu, 2013), psychiatric disorders (Albicini et al., 2017; Emery et al., 2016; Keightley et al., 2014; Max et al., 1997; Narad et al., 2018), academic difficulties (Mealings et al., 2012), and poorer quality of life (Di Battista et al., 2012).

There exist a number of reviews on neurocognitive outcomes after pediatric TBI (Albicini et al., 2017; Albicini et McKinlay, 2018; Babikian et Asarnow, 2009; Babikian et al., 2015; Di Battista et al., 2012; Durish et al., 2018; Emery et al., 2016; Keightley et al., 2014; Lloyd et al., 2015; Lopes et al., 2013; Roberts et al., 2016; Trenchard et al., 2013). Some reviews focus on a subsample of TBI (ex. mild TBI: Emery et al., 2016; Keightley et al., 2014; non accidental TBI: Lopes et al., 2013), on a specific domain (ex. social functioning: Rosema et al., 2012) or on a wide age range (ex. 0-18 years old: Babikian et Asarnow, 2009; Di Battista et al., 2012; 0-13 years old: Kennedy et al., 2017), but only two include information on the specific effects of early TBI (Garcia et al., 2015; Wetherington et Hooper, 2006). Garcia and colleagues (2015) report that children who

sustain TBI before the age of five years encounter difficulties such as externalizing behaviors, and attentional, language, and cognitive dysfunction (ex. Intellectual Quotient (IQ), executive functioning). Wetherington and colleagues (2006) suggest the presence of developmental changes and impairments in selected cognitive abilities, motor functions and socio-behavioral skills. However, neither review was conducted systematically and both also included children older than six years, precluding specific conclusions concerning the effects of early TBI. Moreover, the results mainly focussed on cognitive and behavioral outcomes, with limited information on socio-emotional functioning, and no coverage of adaptive functioning.

In sum, there is a growing literature concerning the effects of early TBI, but findings have not yet been presented in a synthetized and comprehensive manner. We undertook a systematic review of the literature in order to provide a broad view of the potential impact of sustaining TBI at a young age. The goal of this review was to investigate the cognitive, academic, behavioral, socio-affective and adaptive consequences of early TBI.

Methodology

Search strategy

A systematic review was carried out according to the PRISMA guidelines (Liberati et al. 2009). Four databases were searched: Medline (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) from 1946 to Present), PsycNET (PSYcInfo, PSYCARTICLES, APA Books), CINAHL (Plus with Full Text) and PubMed. Two groups of key terms pertaining to TBI and the early childhood period were used with appropriate truncations: (brain injur* or head injur* or concussion* or "head trauma*" or "brain trauma*") AND (preschool* or infan* or toddler* or neonat* or pediatric* or newborn* or child*). The fields of search for each database were:

- PsycNET : Keywords
- Medline : Title, Keyword Heading Word, Heading Word
- CINAHL : Subject Heading (keyword search on all subject fields in the record)
- PubMed : Text Word

Eligibility criteria

Inclusion criteria

All papers in which the main purpose of the study was to report original empirical data from early TBI (0 – 5 years; 11 months old) were retrieved according to the following criteria:

1) Peer-reviewed journal articles only (i.e. conference proceedings, books and book chapters were excluded);
2) Articles that reported empirical data from pediatric TBI (an alteration in brain function, or other evidence of brain pathology, caused by an external force; Menon et al. 2010);
3) Children were < 6 years of age at the time of the injury (i.e., birth to 5 years, 11 months, 29 days).
    a. For articles that included both children <6 years and >6 years old and presented results by age group (ex. preschoolers, middle school, etc.), outcomes were reported only for those who sustained early TBI, if available.
4) All TBI severity included (concussion or mTBI, moderate and severe TBI)
5) Any mechanism of TBI: accidental TBI (aTBI) or non-accidental TBI (naTBI; ex. infantile non-accidental trauma ("shaken baby"), inflicted TBI);
6) Closed head injury;
7) Reported outcomes known to measure at least one of the following domains: cognitive and academic outcomes (intelligence/development, attention, executive functioning, memory, language, social cognition, academic) and behavioral and socio-affective outcomes (emotion regulation and behavior, social skills and adaptative functioning);
8) Studies in humans (i.e., not animal or microcellular specimens).

Exclusion criteria

Papers that contained at least one of the following elements were excluded:

1) Nontraumatic mechanisms of injury, such as inflammation, infection, or autoimmunity;
2) Prenatal head injury or in utero head trauma;
3) Penetrating injury (ex. Garth et al. 1997);
4) Meta-analyses, reviews, opinion paper, editorials, commentaries, legal cases, single case studies;
5) Languages other than English or French;

6) Publication before 1990;
7) Outcomes:
    a. Exclusively biological, physiological, neurological, genetic, sensorimotor, biomarkers, sleep, neuroimaging occupational, global functional (ex. Activities of Daily Living, Quality of Life), disability or morbidity outcomes.
    b. Non-interpreted/descriptive
    c. Postconcussive symptoms (PCS).

Manuscript review process

During the first stage of screening, three reviewers independently performed preliminary screening of titles and abstracts to exclude any article that did not meet the inclusion and exclusion criteria. In the second stage of screening, all remaining articles were read in full to ensure the paper met the selection criteria. Disagreements about eligibility were resolved through discussion and consensus.

Data collection process

A structured database was created to extract the following pre-determined information from each selected article: Authors and year of publication, injury severity, age and type of injury, control group, design and timing of follow-up, cognitive and academic outcomes (intelligence/development, attention, executive functioning, memory, language, social cognition and academic) and behavioral and socio-affective outcomes (emotion regulation, behavior, social skills and adaptive functioning).

Risk of bias

The quality of selected studies was independently assessed by two reviewers based on a minor adaptation of the criteria proposed by Hayden (2006). The following risks of bias were evaluated: study participation (ex. there is adequate participation in the study by eligible individuals), study attrition (ex. response rate is adequate), outcomes (ex. the method and setting of measurement are the same for all study participants), confounding (ex. important potential confounders are accounted for in the study design) and analysis (ex. there is no selective reporting of results). Presence of bias was judged either as “Yes”, “Partly”, “No” or “Unsure”.

Results

Study selection

Details of the search results are presented in Figure 1. The initial search identified 17, 668 articles based on the keywords and search criteria used in the four databases. A total of 8967 articles were found in Ovid (Medline), 2553 in CINAHL, 2578 in PsycNET and 3570 in PubMed. After removal of 5515 duplicates, 12, 153 were screened to evaluate whether inclusion/exclusion criteria were met. After the first stage of screening (review of titles and abstracts), 9511 articles were excluded. After the second stage of screening (full-text review), 2599 were excluded, for a final total of 43 articles included in the systematic review. The majority of articles were rejected because they did not meet inclusion criteria 3 (early TBI).

[Insert Figure 1 here]

Table 1 summarizes the articles that were included for systematic review as a function of participant characteristics, assessment, time since injury, as well as main findings related to cognitive/academic and behavioral/socio-affective outcomes. For some articles, percentage/proportions of the population with deficits in the above mentioned domains are reported (Barlow et al., 2005; Bonnier et al., 2007; Ewing-Cobbs et al., 1998; Ewing-Cobbs et al., 2006; Keenan et al., 2019; Kieslich et al., 2001; Pastore et al., 2013; Prasad et al., 1999; Sonnenberg et al., 2010; Vassel-Hitier et al., 2019). Publication dates ranged from 1990 to 2019, and 11 articles were published in the last 5 years (2015-2019; Bellerose et al., 2015; Bellerose et al., 2017; D'Hondt et al., 2017; Dégeilh et al., 2018; Gagner et al., 2018; Kaldoja et Kolk, 2015; Keenan et al., 2018; Keenan et al., 2019; Lalonde et al., 2016; Landry-Roy et al., 2018; Vassel-Hitier et al., 2019). Abbreviations are used to reduce information burden and are defined below in the table.

[Insert Tables 1 and 2 here]

Risk of bias

Tables 2 and 3 present quality assessment according to five potential risks of bias (Participation, Attrition, Outcomes, Confounding and Analysis). Overall, 38 studies (88%) comprised at least one risk of potential bias. More specifically, 28 studies (65%) presented a potential risk of bias related to “study participation”. In the majority of the studies (n=28, 65%),

adequate participation in the study by eligible individuals was unspecified and/or TBI classification characteristics were vague. Twenty-seven studies (63%) had shortcomings related to "study attrition". One (2%) study had potential risks of bias related to "outcome measurement". Eight studies (19%) had shortcomings related to "confounding measurement and account" and 13 (30%) presented potential risk of bias regarding "analysis".

[Insert Tables 3 and 4 here]

Study characteristics

Design

Of the 43 studies identified, most (n=39, 91%) employed prospective designs and four (9%) employed a retrospective design (Bonnier et al., 2007; Kieslich et al., 2001; Papoutsis et al., 2014; Sonnenberg et al., 2010). Among the prospective studies (n=39), 19 (49%) were longitudinal (Coster et al., 1994; Dégeilh et al., 2018; Ewing-Cobbs et al., 1999; Ewing-Cobbs et al., 2006; Ewing-Cobbs et al., 2004; Ewing-Cobbs et al., 2013; Gagner et al., 2018; Green et al., 2013; Kaldoja et Kolk, 2015; Keenan et al., 2018; Keenan et al., 2007; Keenan et al., 2019; McKinlay, Corrigan, et al., 2014; McKinlay et al., 2002; McKinlay et al., 2009; McKinlay et al., 2010; Prasad et al., 1999; Tonks et al., 2011; Wrightson et al., 1995), 11 (28%) were cross-sectional (Beers et al., 2007; Crowe et al., 2014; L. M. Crowe et al., 2012; Crowe et al., 2013; Louise M. Crowe et al., 2012; Landry et al., 2004; Marsh et Whitehead, 2005; Pastore et al., 2013; Stipanicic et al., 2008; Walz et al., 2009; Wetherington et al., 2010), and nine (23%) used both longitudinal and cross-sectional designs (Barlow et al., 2005; Bellerose et al., 2015; Bellerose et al., 2017; D'Hondt et al., 2017; Ewing-Cobbs et al., 1998; Lalonde et al., 2016; Landry-Roy et al., 2018; Liu et Li, 2013; Vassel-Hitier et al., 2019).

Comparison groups

Thirty-four (79%) articles included a comparison group. Nine articles (21%) did not use any comparison groups impeding the possibly of drawing brain-injury specific conclusions (Barlow et al., 2005; Beers et al., 2007; Bonnier et al., 2007; Louise M. Crowe et al., 2012; Ewing-Cobbs et al., 1998; Kieslich et al., 2001; Prasad et al., 1999; Sonnenberg et al., 2010; Vassel-Hitier et al., 2019). For those that included a comparison group, seven (16%) included children with orthopedic injuries (OI; Coster et al., 1994; Dégeilh et al., 2018; Keenan et al., 2018; Keenan et al.,

2019; Marsh et Whitehead, 2005; Walz et al., 2009; Wrightson et al., 1995), one (2%) used an "other acquired brain injuries" comparison group (Pastore et al., 2013), 20 (47%) compared their sample to typically developing children (TDC) (Bellerose et al., 2015; Crowe et al., 2014; L. M. Crowe et al., 2012; Crowe et al., 2013; D'Hondt et al., 2017; Ewing-Cobbs et al., 1999; Ewing-Cobbs et al., 2006; Ewing-Cobbs et al., 2004; Ewing-Cobbs et al., 2013; Green et al., 2013; Kaldoja et Kolk, 2015; Keenan et al., 2007; Landry-Roy et al., 2018; Landry et al., 2004; Liu et Li, 2013; McKinlay, Corrigan, et al., 2014; Papoutsis et al., 2014; Stipanicic et al., 2008; Tonks et al., 2011; Wetherington et al., 2010), and six (14%) recruited both OI and TDC comparison groups (Bellerose et al., 2017; Gagner et al., 2018; Lalonde et al., 2016; McKinlay et al., 2002; McKinlay et al., 2009; McKinlay et al., 2010).

Sample Characteristics

Age

As per the review inclusion criteria, age at injury ranged from birth to 5 years, 11 months and 29 days. When considering mean age at injury for TBI groups, 14 studies (33%) focused on infants (0-18 months; Barlow et al., 2005; Beers et al., 2007; Bonnier et al., 2007; Crowe et al., 2014; Crowe et al., 2013; Ewing-Cobbs et al., 1999; Ewing-Cobbs et al., 2004; Ewing-Cobbs et al., 2013; Keenan et al., 2007; Keenan et al., 2019; Marsh et Whitehead, 2005; Stipanicic et al., 2008; Vassel-Hitier et al., 2019; Wetherington et al., 2010), 11 (26%) on toddlers (18-36 months; Bellerose et al., 2015; Bellerose et al., 2017; Coster et al., 1994; L. M. Crowe et al., 2012; Dégeilh et al., 2018; Ewing-Cobbs et al., 2006; Gagner et al., 2018; Landry-Roy et al., 2018; Papoutsis et al., 2014; Pastore et al., 2013; Prasad et al., 1999), two (5%) on preschoolers (36 to 72 months; D'Hondt et al., 2017; Walz et al., 2009); and two (5%) combined one of these early age groups with children older than 6 years (Keenan et al., 2018; Kieslich et al., 2001). Other articles (30%) did not present mean age at injury and instead presented interval ages at injury (minimum: 0, maximum: 15 years; Green et al., 2013; Kaldoja et Kolk, 2015; Keenan et al., 2018; Keenan et al., 2007; Kieslich et al., 2001; Lalonde et al., 2016; Liu et Li, 2013; McKinlay, Corrigan, et al., 2014; McKinlay et al., 2002; McKinlay et al., 2009; McKinlay et al., 2010; Tonks et al., 2011; Walz et al., 2009). Other studies covered more than one age group: one (2%) article examined both infants and toddlers (Landry et al., 2004). Three articles (7%) covered toddlers and preschoolers (18-72 months; Keenan et al., 2018; Kieslich et al., 2001; Lalonde et al., 2016; Wrightson et al., 1995),

and eleven articles (26%) covered all three developmental groups (0-72 months; Louise M. Crowe et al., 2012; Ewing-Cobbs et al., 1998; Green et al., 2013; Kaldoja et Kolk, 2015; Liu et Li, 2013; McKinlay, Corrigan, et al., 2014; McKinlay et al., 2002; McKinlay et al., 2009; McKinlay et al., 2010; Sonnenberg et al., 2010; Tonks et al., 2011). Overall, the majority of the studies included either infants and/or toddlers and few focused on preschoolers (36-60 months). In the articles that compared early childhood age groups among themselves, younger groups presented worse outcomes in comparison to older groups (Louise M. Crowe et al., 2012; Ewing-Cobbs et al., 2004; Keenan et al., 2018; Keenan et al., 2019; Kieslich et al., 2001; Sonnenberg et al., 2010). Of the studies that investigated both aTBI and naTBI, some articles reported a significant difference regarding age at injury between the two groups, with the naTBI group being younger than the aTBI group (Ewing-Cobbs et al., 1998; Ewing-Cobbs et al., 2006).

Age at assessment (post-injury delay)

Time post-injury for follow up ranged from 1 month to 20 years. Most of the studies (19; 44%) documented outcomes within 1-year post-injury (Beers et al., 2007; Bellerose et al., 2015; Bellerose et al., 2017; Coster et al., 1994; D'Hondt et al., 2017; Dégeilh et al., 2018; Ewing-Cobbs et al., 1998; Ewing-Cobbs et al., 1999; Ewing-Cobbs et al., 2013; Gagner et al., 2018; Kaldoja et Kolk, 2015; Keenan et al., 2018; Keenan et al., 2019; Lalonde et al., 2016; Landry-Roy et al., 2018; Landry et al., 2004; Prasad et al., 1999; Walz et al., 2009; Wrightson et al., 1995). Twelve (28%) explored follow up from 2 to 5 years (Barlow et al., 2005; Crowe et al., 2014; L. M. Crowe et al., 2012; Crowe et al., 2013; Louise M. Crowe et al., 2012; Ewing-Cobbs et al., 2006; Ewing-Cobbs et al., 2004; Keenan et al., 2007; Liu et Li, 2013; Marsh et Whitehead, 2005; Sonnenberg et al., 2010; Wetherington et al., 2010) and ten (23%) from 6 to 10 years (Bonnier et al., 2007; Kieslich et al., 2001; McKinlay et al., 2002; McKinlay et al., 2010; Papoutsis et al., 2014; Pastore et al., 2013; Sonnenberg et al., 2010; Stipanicic et al., 2008; Tonks et al., 2011; Vassel-Hitier et al., 2019). Only two (5%) reported outcomes 10-20 years (Green et al., 2013; McKinlay et al., 2009) post-injury and one study (2%) over 20 years post-injury (McKinlay, Corrigan, et al., 2014).

Pre-injury characteristics

Thirteen (30%) articles reported participant pre-injury characteristics (Bellerose et al., 2015; Bellerose et al., 2017; Dégeilh et al., 2018; Gagner et al., 2018; Kaldoja et Kolk, 2015; Keenan et al., 2018; Keenan et al., 2019; Lalonde et al., 2016; Landry-Roy et al., 2018; McKinlay,

Corrigan, et al., 2014; McKinlay et al., 2002; McKinlay et al., 2009; Wrightson et al., 1995). Studies that assessed pre-injury behavior did so retrospectively mainly with parental recall on questionnaires, usually within the first two weeks after injury. Of these, some studies found differences between TBI and control groups. First, toddlers who sustained mTBI presented significantly more externalizing behaviors (CBCL) compared to TDC (Bellerose et al., 2015; however, see also Gagner et al., 2018). Second, toddlers and preschoolers had comparable levels of behavior manifestations (SDQ, CBCL) to those with OI, regardless of mechanism and severity of injury (Keenan et al., 2018). In a third study, parent and teacher ratings of emotional regulation and behavior (Connors) of toddlers and preschoolers who sustained mTBI were comparable to those of the OI group (Wrightson et al., 1995). Fourth, in a group of toddlers and preschoolers who sustained either naTBI or aTBI (all severities), executive functions (BRIEF) were mostly comparable to OI, except working memory which was poorer in the uncomplicated mTBI group compared to all other groups (complicated mTBI, moderate TBI (modTBI), severe TBI (sTBI), OI) (Keenan et al., 2018). Fifth, in a combined group of infants with naTBI or aTBI (all severities), communication (ASQ-3), was poorer in infants who sustained sTBI compared to infants with OI (Keenan et al., 2019). Sixth, in children who sustained mTBI, adaptive functions (ABAS or Vineland) were comparable to OI (Dégeilh et al., 2018; Wrightson et al., 1995) and TDC (Bellerose et al., 2015; Bellerose et al., 2017; Dégeilh et al., 2018), while toddlers with mTBI and TDC showed higher leisure levels compared to OI (Lalonde et al., 2016). Seventh, in children (0-6 years) who sustained mTBI, boys with mTBI showed more self-regulation problems (ASQ-S-E) compared to girls with mTBI and typically developing (TD) boys, and girls who sustained mTBI presented more adaptive difficulties compared to TD girls. No difference in social difficulties, communication, compliance and affect (ASQ-S-E) where noted between these groups during the pre-injury period (Kaldoja et Kolk, 2015). Other articles (n=3; 7%) used pre-injury characteristics only as confounding variables for main statistical analyses (see McKinlay, Corrigan, et al., 2014; McKinlay et al., 2002; McKinlay et al., 2009) rather than in group comparisons.

TBI characteristics

Type of injury (accidental vs non accidental injury). Twenty-seven articles (63%; Albicini et al., 2017; Bellerose et al., 2015; Bellerose et al., 2017; Coster et al., 1994; Crowe et al., 2014; L. M. Crowe et al., 2012; Crowe et al., 2013; Louise M. Crowe et al., 2012; D'Hondt et al.,

2017; Dégeilh et al., 2018; Gagner et al., 2018; Green et al., 2013; Kaldoja et Kolk, 2015; Lalonde et al., 2016; Landry-Roy et al., 2018; Liu et Li, 2013; Marsh et Whitehead, 2005; McKinlay, Corrigan, et al., 2014; McKinlay et al., 2002; McKinlay et al., 2009; McKinlay et al., 2010; Papoutsis et al., 2014; Pastore et al., 2013; Prasad et al., 1999; Sonnenberg et al., 2010; Tonks et al., 2011; Walz et al., 2009; Wetherington et al., 2010) focused on aTBI, three (7%; Beers et al., 2007; Landry et al., 2004; Stipanicic et al., 2008) examined naTBI and 13 (30%; Barlow et al., 2005; Beers et al., 2007; Bonnier et al., 2007; Ewing-Cobbs et al., 1998; Ewing-Cobbs et al., 2006; Ewing-Cobbs et al., 2004; Ewing-Cobbs et al., 2013; Keenan et al., 2018; Keenan et al., 2007; Keenan et al., 2019; Kieslich et al., 2001; Vassel-Hitier et al., 2019; Wetherington et al., 2010) investigated both aTBI and naTBI. For those studies that investigated aTBI, 19 (44%) reported falls as the most frequent mechanism of injury.

TBI definition. *Accidental injury* was usually defined as "evidence of a TBI", without further operational criteria. There was little consensus regarding the definition of TBI in papers that included specific criteria. The most commonly used definitions were "blunt trauma or acceleration or deceleration forces" and "an injury to the head with observed or reported decreased level of consciousness, amnesia, and/or neuropsychological abnormality or diagnosed intracranial lesion" from the Centers for Disease Control (Marr et Coronado, 2004; ex. Keenan et al., 2018). Other authors used alternate definitions such as "crush head injury which is produced by static forces occurring when the head is stationary and pinned against a rigid structure" (Prasad et al., 1999). *Non accidental TBI* (naTBI) was typically defined through established confession of the perpetrator or by applying an algorithm for presumptive abuse (Duhaime et al., 1992; Goldstein et al., 1993), which relies on information about the type of cranial injury, history of the injury, and associated physical findings to classify an injury as presumptive or suspicious for abuse.

TBI severity classification. Ten studies (23%) performed comparisons across severity groups (Crowe et al., 2014; L. M. Crowe et al., 2012; Crowe et al., 2013; Louise M. Crowe et al., 2012; Green et al., 2013; Keenan et al., 2018; Keenan et al., 2019; Papoutsis et al., 2014; Walz et al., 2009; Wetherington et al., 2010) and used similar severity criteria (Alexander, 1995; CDO, 2004; Keith Owen et Taylor, 2005; Marr et Coronado, 2004; Osmond et al., 2010). These typically relied on a combination of Glasgow Coma Scale (GCS; Teasdale et Jennett, 1974), duration of loss of consciousness, post-traumatic amnesia and neuroimaging/radiology results.

Some authors did not use TBI severity classification (Wrightson et al., 1995) or used only GCS (mTBI 13-15, modTBI 8-12 and sTBI <8 or 3-8; Marsh et Whitehead, 2005). Others (Beers et al., 2007) used a modified version of the GCS adapted from the Advanced Trauma Life Support manual (Morgan, 1997) for children younger than two years of age. This version modifies the verbal scale by rating the child's interactions with the environment rather than verbal skills. Other studies used further GCS adaptations (Reilly et al., 1988), taking into account language abilities in children under three years of age; for example, by replacing verbal items with questions about crying and parent-child interactions (Papoutsis et al., 2014). Ewing-Cobbs and collaborators (Ewing-Cobbs et al., 1999; Ewing-Cobbs et al., 2004; Ewing-Cobbs et al., 2013) modified the GCS motor and verbal scales to accommodate the behavioral capabilities of children from birth to 35 months of age. Specifically, spontaneous movement in infants aged 0–6 months and goal-directed movements in children aged 7–35 months were considered comparable to following commands in older children (ex: "Cries" and "cries to indicate need" were regarded as equivalent to the verbal scale items "confused" and "oriented"). Others research groups have since applied this modified GCS to their own work (Bonnier et al., 2007). Some studies combined TBI severity groups (ex. modTBI and sTBI) or altered the original GCS cut-offs, for example defining moderate-severe TBI (msTBI) by a GCS of 4-13 (Pastore et al., 2013; Prasad et al., 1999). One group used the Pediatric Performance Category Scale at discharge for classifying disability (mild to severe disabilities; Stipanicic et al., 2008). Finally, some authors used other measures, such as the Injury Severity Scale (ISS; Coster et al., 1994), to categorize TBI severity. In some cases, due to limited availability of valid medical data, head injury could not be defined using medical diagnoses. For example, Liu and colleagues (2013) defined mTBI as no loss of consciousness and/or no hospitalization for treatment due to injury.

No firm consensus emerges regarding the use of neuroimaging findings to classify mTBI in the studies included. Likewise, the use of definitions related to the terms concussion, uncomplicated

mTBI (no visible brain lesions) or complicated mTBI (visible brain lesions on clinical imaging) was not uniform (Papoutsis et al., 2014).

Twenty-eight (65%) studies report a duration of alteration of consciousness (AOC) of less than 24 hours (Landry et al., 2004) or a duration of loss of consciousness (LOC) of either less than 5, 20 (McKinlay et al., 2010), 30 minutes (Keenan et al., 2018; Keenan et al., 2019; Liu et Li, 2013;

Papoutsis et al., 2014) or one hour (Crowe et al., 2013) for mTBI, and an AOC of < 24 hours for modTBI, an AOC of ≥ 24 hours for sTBI or duration of length of coma (Vassel-Hitier et al., 2019). Ewing-cobbs and colleagues (1999; 2006; 2013) describe duration of impaired consciousness as the number of days a child was unable to follow a one-stage command or engage in goal-directed movements, as indicated by the modified GCS motor scale (see above).

Few authors considered post-traumatic amnesia (PTA) to define severity of injury. When reported, PTA of two hours or less was associated with mTBI and more than two hours with msTBI (McKinlay, Corrigan, et al., 2014). Some authors included amnesia as a neurological sign (ex. Bellerose et al., 2015; Bellerose et al., 2017). Finally, 16 articles reported post-concussive symptom or neurological signs in relation to injury severity classification (Bellerose et al., 2015; Bellerose et al., 2017; Papoutsis et al., 2014).

In some cases, a range of TBI severities was combined into a single TBI group (Coster et al., 1994; Tonks et al., 2011), though, the majority of studies reported only a specific severity grouping, such as mTBI (Bellerose et al., 2015; Bellerose et al., 2017) or sTBI (Bonnier et al., 2007; Pastore et al., 2013). Some articles explored the impact of TBI in multiple severity groups, typically combining participants with modTBI and sTBI (McKinlay, Corrigan, et al., 2014).

Methodology

Sample size

Sample sizes varied considerably from fewer than 20 participants (Albicini et al., 2017; D'Hondt et al., 2017; Green et al., 2013; Marsh et Whitehead, 2005; Pastore et al., 2013; Prasad et al., 1999; Stipanicic et al., 2008) to more substantial sample sizes of 100 or more participants, (Albicini et al., 2017; Ewing-Cobbs et al., 2013; Keenan et al., 2018; Keenan et al., 2019; Kieslich et al., 2001; Liu et Li, 2013; McKinlay et al., 2002).

Measures and assessment tools

When reporting cognitive or academic outcomes, nine (21%) studies used direct assessments methods exclusively (Bonnier et al., 2007; Crowe et al., 2014; Louise M. Crowe et al., 2012; Ewing-Cobbs et al., 1998; Ewing-Cobbs et al., 2004; Landry-Roy et al., 2018; Papoutsis et al., 2014; Stipanicic et al., 2008; Walz et al., 2009). When reporting behavioral and socio-affective outcomes, 12 (28%) studies used indirect methods such as questionnaires completed by primary caregivers and teachers (Coster et al., 1994; Gagner et al., 2018; Green et al., 2013; Kaldoja et

Kolk, 2015; Keenan et al., 2018; Keenan et al., 2019; Liu et Li, 2013; McKinlay, Corrigan, et al., 2014; McKinlay et al., 2009; McKinlay et al., 2010; Pastore et al., 2013) or by physicians (Sonnenberg et al., 2010). The majority of publications combined both direct and indirect assessment methods to describe either cognitive and/or behavioral and socio-affective outcomes (n=15; 35%; Barlow et al., 2005; Beers et al., 2007; Bellerose et al., 2015; Bellerose et al., 2017; L. M. Crowe et al., 2012; Crowe et al., 2013; Dégeilh et al., 2018; Ewing-Cobbs et al., 1999; Keenan et al., 2007; Marsh et Whitehead, 2005; McKinlay et al., 2002; Prasad et al., 1999; Tonks et al., 2011; Wetherington et al., 2010; Wrightson et al., 1995). Two studies (5%; D'Hondt et al., 2017; Ewing-Cobbs et al., 2013) used direct observational measures exclusively, and two (5%) others used a combination of indirect assessment (i.e., questionnaires) and observational methods to measure behavioral and socio-affective consequences (5%; Albicini et al., 2017; Lalonde et al., 2016; Landry et al., 2004). Finally, three articles used a combination of direct assessment with school outcomes (7%; Ewing-Cobbs et al., 2006; Kieslich et al., 2001; Vassel-Hitier et al., 2019).

Study Outcomes

In Table 1, results of group comparisons are reported where possible (ex. TDC vs. TBI vs. OI). Otherwise, percentages (Barlow et al., 2005; Marsh et Whitehead, 2005; Pastore et al., 2013; Prasad et al., 1999; Sonnenberg et al., 2010; Vassel-Hitier et al., 2019), proportions (Bonnier et al., 2007), frequencies (Kieslich et al., 2001) and odds-ratios are documented (Ewing-Cobbs et al., 2006; Keenan et al., 2007). Of the 43 articles included in the review, 16 (37%) focused on cognitive or academic outcomes, eleven (26%) on behavioral and socio-affective outcomes and 16 (37%) investigated both domains.

To structure the presentation of study outcomes by domain, mechanism, injury severity and age at injury, each of the following sections presents the three types of injuries (aTBI, naTBI or both aTBI and naTBI), then, in each of these categories, outcomes are separated according to injury severity (mild, moderate, severe), and finally, in each of these subcategories, study findings are presented according to age at injury (infants, toddlers, preschoolers).

Cognitive/academic outcomes

Intelligence/Global Development. Twenty articles (46%) reported IQ or global developmental outcomes.

aTBI

mTBI. Children (0-6 years) who sustained mTBI presented IQ/global developmental functioning comparable to that of OI and TDC groups up to 10 years post-injury (L. M. Crowe et al., 2012; Crowe et al., 2013; Louise M. Crowe et al., 2012; McKinlay et al., 2002; Papoutsis et al., 2014; Wetherington et al., 2010; Wrightson et al., 1995).

msTBI. Children (0-6 years) who sustained msTBI had poorer IQ/global developmental functioning up to three (verbal IQ: Crowe et al., 2014; Global: Wetherington et al., 2010) and four (verbal and non-verbal IQ; L. M. Crowe et al., 2012; Louise M. Crowe et al., 2012) years post-injury, compared to TDC, and up to one month post-injury when compared to OI (Walz et al., 2009).

naTBI

Infants and toddlers who sustained naTBI had impaired (Barlow et al., 2005) or poorer developmental/intellectual functioning compared to those who sustained aTBI (Beers et al., 2007; Ewing-Cobbs et al., 1998) and TDC (Ewing-Cobbs et al., 1999; Ewing-Cobbs et al., 2006; Landry et al., 2004; Stipanicic et al., 2008), up to two years post-injury.

aTBI vs naTBI

Toddlers with naTBI also had poorer developmental outcomes (< 3 SDs) compared to those with aTBI up to one year post-injury (Keenan et al., 2007).

aTBI and naTBI

In a combined group of infants who sustained severe aTBI or naTBI, global development as well as verbal and non-verbal IQ were impaired up to 6.60 years post-injury (Bonnier et al. 2007). Similarly, in another study, verbal IQ was impaired up to 6.80 years post-injury (Vassel-Hitier et al. 2019). Toddlers with naTBI also had poorer developmental outcomes (< 3 SDs) compared to those with aTBI up to one year post-injury (Keenan et al. 2007). Finally, more than half of children (0-6 years) with moderate-severe naTBI or aTBI showed intellectual and/or academic delays up to 8.75 years post-injury (Kieslich et al. 2001).

Attention. Five studies (12%) reported on attention.

aTBI

mTBI and modTBI. In infants who sustained mTBI, auditory vigilance and selective attention were comparable to TDC up to 3.91 years post-injury (Crowe et al., 2013). In infants who sustained either complicated or uncomplicated mTBI, visual selective attention was comparable to TDC up to seven years post-injury (Papoutsis et al., 2014).

In a combined group of infants who sustained mTBI or modTBI, visual attention was poorer compared to OI up to 6.60 years post-injury (Marsh et Whitehead, 2005). In toddlers who sustained complicated mTBI, divided attention was poorer than in those with uncomplicated TBI or TDC, up to seven years post-injury (Papoutsis et al., 2014).

msTBI. In infants who sustained msTBI, auditory vigilance and selective attention were found to be comparable to TDC up to 3.91 years post-injury (Crowe et al., 2013).

naTBI

In infants who sustained naTBI, auditory attention was poorer, while visual attention was comparable to TDC up to 78 months post-injury (Stipanicic et al., 2008).

aTBI & naTBI

In a group of infants who sustained moderate-severe naTBI or aTBI, visual scanning was comparable to TDC up to one-year post-injury (Ewing-Cobbs et al., 2004). In a combined group of infants who sustained severe aTBI or naTBI, visual and auditory reaction times and selective attention were impaired up to 6.60 years post-injury (Bonnier et al., 2007).

Executive functioning. Fourteen studies (33%) reported on executive functioning.

aTBI

mTBI. In infants who sustained mTBI, inhibition was poorer while parent-rated executive functions were comparable to TDC up to 3.91 years post-injury (Crowe et al., 2013). In a combined group of infants who sustained either mTBI or modTBI, inhibition, planning and cognitive flexibility were comparable to OI up to five years post-injury (Marsh et Whitehead, 2005). In toddlers with uncomplicated or complicated mTBI, information processing, auditory working memory, goal setting, organization and parent-rated executive functions were comparable to TDC up to seven years post-injury (Papoutsis et al., 2014). Also, in toddlers and preschoolers who sustained mTBI, inhibition and cognitive flexibility were comparable to TDC up to six months

post-injury (Landry-Roy et al., 2018). Finally, in toddlers and preschoolers who sustained mTBI, information processing was comparable to OI up to 12 months post-injury (Wrightson et al., 1995)

msTBI. In infants who sustained msTBI, inhibition was poorer while parent-rated executive functions were comparable to TDC up to 3.91 years post-injury (Crowe et al., 2013). In infants who sustained sTBI, information processing was poorer compared to infants who sustained mTBI or modTBI up to 2.50 years post-injury (Louise M. Crowe et al., 2012).

In a study of children 0-6 years, regardless of TBI severity, verbal fluency, flexibility, and planning were comparable to those of TDC up to 10 years post-injury (Tonks et al., 2011). However, in the same cohort, children assessed when they were 10-16 years old presented poorer working memory compared to TDC, while those tested when they were 8-10 years showed comparable results (Tonks et al., 2011). Moreover, regardless of severity, information processing was comparable to TDC up to 3.91 years post-injury (L. M. Crowe et al., 2012; Crowe et al., 2013).

naTBI

In infants who sustained naTBI, auditory working memory, verbal fluency, planning (tower), motor and cognitive inhibition were poorer, while planning (mazes) and cognitive flexibility were comparable to TDC up to 78.90 months post-injury (Stipanicic et al., 2008).

aTBI & naTBI

In a combined group of infants with either moderate-severe naTBI or aTBI, visual working memory and inhibition were poorer while cognitive flexibility was comparable to TDC up to one year post-injury (Ewing-Cobbs et al., 2004). In a combined group of infants who sustained severe aTBI or naTBI, auditory working memory, inhibition, cognitive flexibility and planning were impaired compared to normative data up to 6.60 years post-injury (Bonnier et al., 2007). Also, in infants who sustained severe naTBI and aTBI, problem solving was impaired compared to OI one year post-injury (Keenan et al., 2019). In a combined group of toddlers with either moderate-severe naTBI or aTBI, visual working memory was comparable to TDC 5.70 years post-injury (Ewing-Cobbs et al., 2006).

In a group of toddlers and preschoolers with all severity types of naTBI or aTBI, inhibition, metacognition (all severities) and working memory (complicated mTBI & modTBI only) were poorer compared to OI at 3 and 12 months post-injury (Keenan et al., 2018).

Memory. Three articles (7%) reported on memory processes.

aTBI

mTBI and modTBI. In infants who sustained mTBI or modTBI, visual memory was poorer and auditory-verbal memory was comparable to OI up to five year post-injury (Marsh et Whitehead, 2005). In toddlers and preschoolers with mTBI, visual and auditory-verbal memory were comparable to OI after one month and up to 6.50 years post-injury (Wrightson et al., 1995).

naTBI

In infants who sustained naTBI, verbal and visual memory were comparable to TDC up to 78.90 months post-injury (Stipanicic et al., 2008).

Language. Nine articles (21%) reported on language outcomes.

aTBI

mTBI and modTBI. In toddlers and preschoolers who sustained mTBI, global developmental language scales were comparable to OI up to 12 months post-injury (Wrightson et al., 1995). In a combined group of infants who sustained either mTBI or modTBI, language skills such as speeded naming, comprehension of instructions, and verbal fluency were comparable to OI up to five years post-injury (Marsh et Whitehead, 2005).

msTBI. In infants who sustained moderate-severe aTBI, language skills, such as expressive vocabulary, sentence and word structure were poorer compared to mTBI and TDC up to 47 months post-injury (Crowe et al., 2014).

naTBI

In infants who sustained naTBI, abnormalities in speech and language skills were reported compared to normative data up to 90 months post-injury (Barlow et al., 2005), and poorer receptive language was found compared to TDC up to 78.90 months post-injury (Stipanicic et al., 2008).

aTBI & naTBI

In a combined group of infants who sustained severe aTBI or naTBI, expressive and receptive language, as well as, written language skills (i.e. receptive and expressive lexicon, lexical organization, sentence comprehension, syntactic expression and communication) were impaired compared to normative data up to a 6.80 years post-injury (Bonnier et al., 2007; Vassel-Hitier et

al., 2019). In a group of toddlers who sustained moderate-severe aTBI or naTBI, language (assessed via vocabulary, pattern analysis and memory for sentences) was poorer compared to TDC up to 5.70 years post-injury (Ewing-Cobbs et al., 2006).

Social cognition. Six articles (14%) reported social cognitive outcomes.

aTBI

mTBI. In toddlers who sustained mTBI, theory of mind (ToM) was poorer compared to TDC and OI, six and 18 months post-injury (Bellerose et al., 2015; Bellerose et al., 2017). In a subgroup of the same cohort, emotional facial expression processing (measured using event-related potentials) was impaired compared to TDC six months post-injury (D'Hondt et al., 2017).

msTBI. In preschoolers (3-6 years) who sustained severe aTBI, false content belief was poorer while false location belief and global ToM skills (i.e. sum score of appearance-reality tasks, false content/location tasks and control tasks) were comparable to modTBI and OI up to one month post-injury (Walz et al., 2009).

aTBI vs naTBI

In infants who sustained aTBI, regardless of severity, initiating social interactions was poorer compared to naTBI and TDC two months post-injury, and these difficulties resolved one year post-injury (Ewing-Cobbs et al., 2013).

aTBI & naTBI

In infants who sustained aTBI or naTBI, joint attention was poorer in sTBI compared to complicated mTBI and modTBI up to one year post-injury (Ewing-Cobbs et al., 2013).

Academic achievement. Five articles reported on academic outcomes (12%).

aTBI

mTBI and modTBI. In a combined group of children (0-6 years) who sustained either mTBI or modTBI, academic abilities (ex. mathematic reasoning and written language including letter knowledge, spelling, reading and writing) were comparable to OI up to 79 months post-injury (Marsh et Whitehead, 2005; McKinlay et al., 2002; Wrightson et al., 1995).

aTBI & naTBI

In infants who sustained either moderate-severe aTBI or naTBI, 38% were reported to be attending mainstream school with adaptations and/or to have repeated a school year, and 24% were attending specialized classrooms up to 6.80 years post-injury (Vassel-Hitier et al., 2019).

Toddlers who sustained moderate-severe aTBI or naTBI presented poorer mathematics, comprehension, reading and writing abilities and showed more unfavorable academic outcomes compared to TDC up to 5.70 year post-injury (Ewing-Cobbs et al., 2006).

More than half of children (0-6 years) who sustained moderate-severe naTBI or aTBI showed global intellectual and/or academic delays (ex. repeating a school year) up to 8 years and 9 months post-injury (Kieslich et al., 2001).

Behavior and socio-affective skills

Twenty-eight articles (65%) reported behavioral and/or socio-affective outcomes, with 19 (44%) documenting emotion regulation and behavior, six (14%) documenting social behavior, and 14 (33%) documenting adaptive skills.

Emotional regulation and behavior.

aTBI

mTBI and modTBI. In a combined group of infants who sustained either mTBI or modTBI, externalizing and internalizing behaviors were comparable to OI up to five years post-injury (Marsh et Whitehead, 2005). In toddlers who sustained mTBI, more externalizing behaviors were noted compared to TDC (Bellerose et al., 2015; Gagner et al., 2018) and OI (Gagner et al., 2018) six months post-injury (Bellerose et al., 2015; Gagner et al., 2018). More internalizing behaviors were also observed in toddlers who sustained mTBI compared to both OI and TDC six months post-injury (Gagner et al., 2018). Parent and teacher ratings of emotional regulation and behavior of toddlers and preschoolers who sustained mTBI were comparable to those of OI up to 6.50 years post-injury (Wrightson et al., 1995). Moreover, internalizing and externalizing behaviors were also observed in children with mTBI compared to TDC when investigated at six years of age (Liu et Li, 2013).

In children (0-6 years) who sustained mTBI, ADHD-type behaviors as well as conduct and hyperactivity/inattention problems were observed in inpatient (i.e. all children who had been admitted to hospital for less than 2 days) compared to outpatient (i.e. all of the children who had

been seen by a general practitioner or at an emergency department and sent home), OI, and TDC when children were assessed at seven (McKinlay et al., 2010) and up to 16 years of age (McKinlay et al., 2002; McKinlay et al., 2009). Moreover, more substance abuse and mood disorders were noted in inpatients compared to outpatients, OI, and TDC, while comparable levels of anxiety disorders were observed in these same groups when children were assessed between 14 and 16 years of age (McKinlay et al., 2009). Finally, more violent offenses in inpatients and outpatients were noted compared to TDC; more property offenses were noted in inpatients compared to outpatients and TDC, and greater drug dependence was observed in inpatients compared TDC when children were assessed 11-20 years post-injury (McKinlay, Corrigan, et al., 2014).

In children (0-6 years) who sustained mTBI, boys with mTBI showed more self-regulation problems compared to girls with mTBI and typically developing boys, nine months post-injury. Boys who sustained mTBI also presented poorer autonomy compared to typically developing boys and girls with mTBI, nine months post-injury. Finally, no compliance or affective difficulties were found in these groups for the same post-injury period (Kaldoja et Kolk, 2015).

msTBI. In toddlers with severe aTBI, internalizing and externalizing problems were present with reported increases in behaviors such as aggression, destructive behaviors, anxiety, depression, and somatic complaints up to 8.50 years post-injury (Pastore et al., 2013).

In toddlers with aTBI, regardless of TBI severity, behavior was comparable to that of toddlers with OI up to six months post-injury (Coster et al., 1994) and to TDC up to 3.90 years post-injury (L. M. Crowe et al., 2012). Finally, children (0-6 years; regardless of severity) presented more socio-emotional difficulties compared to TDC when assessed at 8 to 10 years and 10 to 16 years of age (Tonks et al., 2011).

naTBI

Regardless of injury severity, infants who sustained naTBI displayed behavior problems up to 90 months post-injury (Barlow et al., 2005). Moreover, in infants who sustained moderate-severe naTBI, emotion regulation, as well as others indices such as attention arousal (one month post-injury only) and orientation and engagement (measured by the Bayley Behavior Rating Scale, BBRS; Bailey, 1969) were impaired compared to TDC up to three months post injury (Ewing-Cobbs et al., 1999).

aTBI & naTBI

In a combined group of infants who sustained moderate-severe aTBI or naTBI, more internalizing behaviors (i.e., withdrawal) were noted while externalizing behaviors were comparable to mTBI and TDC up to three years post-injury (Wetherington et al., 2010).

In a combined group of infants and toddlers who sustained moderate-severe naTBI, levels of positive affect and compliance where poorer, while negative affect was comparable to TDC up to one year post-injury (Landry et al., 2004).

Infants and toddlers with severe aTBI or naTBI presented more socio-emotional difficulties (ex. self-regulation, affect, communication) compared to TDC up to one year post-injury (Keenan et al., 2019). In toddlers and preschoolers, regardless of mechanisms of injury, more behavioral difficulties were found in sTBI compared to OI at three months and up to 12 months post-injury (Keenan et al., 2018). Moreover, in the same groups, regardless of mechanism and severity of injury, most behaviors were comparable except affective, anxious and ADHD-type behaviors were more elevated in TBI compared to OI at three months and up to 12 months post-injury (Keenan et al., 2018).

Social skills. Six articles reported social skills outcomes (14%).

aTBI

mTBI. Toddlers who sustained mTBI presented poorer parent-child interaction quality compared to TDC and comparable parent-child dysfunctional interaction compared to OI and TDC six months post-injury (Lalonde et al., 2016). In children (0-6 years) who sustained mTBI, more social difficulties were reported for boys with mTBI compared to typically developing boys, while no communication difficulties were noted in these groups up to 9 months (Kaldoja et Kolk, 2015). Lastly, in a combined group of infants and toddlers who sustained aTBI, regardless of severity, social skills were comparable to TDC up to 3.90 years post-injury (L. M. Crowe et al., 2012).

msTBI. In children (0-6 years) who sustained msTBI, 20% had normal social function, 41% had mild, 23% had moderate and 16% had severe impairment (Sonnenberg et al., 2010). In the same cohort, children who sustained injury at 2.6 years had poorer social outcomes compared to those who sustained injury at 5.0 years of age.

naTBI

In infants and toddlers who sustained moderate-severe naTBI, social interactions (gaze) were poorer while communicating (gestures and words) and complexity of toy-play was comparable to TDC up to one year post-injury (Landry et al., 2004). In infants with severe naTBI, personal-social skills were poorer compared to OI two months and up to one year post-injury (Keenan et al., 2019).

aTBI & naTBI

In a combined group of infants who sustained severe aTBI or naTBI, sociability and autonomy were found to be impaired up to 6.80 years post-injury (Vassel-Hitier et al., 2019). Also, in a combined group of infants and toddlers who sustained sTBI, more difficulties in personal-social behaviors were observed compared to TDC up to one year post-injury (Keenan et al., 2019).

Adaptive functioning. Fourteen articles (33%) reported adaptive behavior outcomes.

aTBI

mTBI. In toddlers who sustained mTBI, conceptual and practical adaptation as well as global adaptive functioning were comparable to TDC and OI up to 18 months post-injury (Bellerose et al., 2015; Bellerose et al., 2017); however, social adaptation was poorer compared to OI six months and up to 18 months post-injury (Dégeilh et al., 2018). In a combined group of toddlers and preschoolers who sustained mTBI, global adaptive functioning was comparable to OI one month and up to 12 months post-injury (Wrightson et al., 1995).

msTBI. In toddlers who sustained severe aTBI, daily living skills were poorer compared to toddlers with other acquired brain injuries up to 8.50 years post-injury (Pastore et al., 2013). In toddlers who sustained msTBI, global adaptive functioning was in the average range for most children (83.33%) compared to normative data, two months and up to one year post-injury (Prasad et al., 1999).

In children (0-6 years), regardless of injury severity, need for self-care and social functioning assistance were greater in children who sustained TBI compared to OI one month and up to six months post-injury (Coster et al., 1994). Similarly, in children (0-6 years), regardless of injury severity, global adaptive functioning was comparable to TDC, and school/leisure participation and daily living skills were poorer compared to TDC 13-16 years post-injury (Green et al., 2013).

naTBI

Regardless of severity, infants who sustained naTBI presented moderately lower levels of socialization adaptation, communication and daily living skills compared to normative data up to 90 months post-injury (Barlow et al., 2005).

aTBI vs naTBI

Infants who sustained naTBI showed poorer global adaptive functioning compared to those who sustained aTBI up to six months post-injury (Beers et al., 2007), as well as compared to TDC and normative data (Keenan et al., 2007). Infants with naTBI were at greater risk (Risk Ratio: 1.6) for poor adaptive functioning compared to aTBI (Keenan et al., 2007).

aTBI & naTBI

In a combined group of infants and toddlers, adaptive communication was significantly poorer following naTBI compared to aTBI, and was poorer in children with severe injuries compared to those with complicated mild/moderate injuries. Social adaptation was poorer in children with severe injuries compared to those with complicated–mild/moderate injuries, but did not vary by external cause of injury (i.e., aTBI or naTBI; Ewing-Cobbs et al., 2013).

Discussion

This systematic review aimed to document the cognitive, academic, behavioral, socio-affective and adaptive consequences of early TBI (i.e., sustained before 6 years of age), as well as to summarize the state of research in this field and identify limitations and gaps to be addressed in future work. Considering the unique characteristics of this developmental group and associated methodological challenges, we consider limitations of the work to date throughout the discussion, and propose corresponding recommendations and avenues for innovation and action, summarized in Table 4.

Summary of outcomes

Based on the review, evidence for detrimental consequences of early TBI on intelligence and global development, attention, language, executive functions and academic achievement is fairly consensual. Deficits in IQ (Barlow et al., 2005; Beers et al., 2007; Bonnier et al., 2007; Crowe et al., 2014; Louise M Crowe et al., 2012; L. M. Crowe et al., 2012; Ewing-Cobbs et al., 1998;

Ewing-Cobbs et al., 1999; Ewing-Cobbs et al., 2006; Ewing-Cobbs et al., 2013; Keenan et al., 2007; Kieslich et al., 2001; Landry et al., 2004; Prasad et al., 1999; Stipanicic et al., 2008; Vassel-Hitier et al., 2019; Walz et al., 2009; Wetherington et al., 2010), attention (Achenbach et Edelbrock, 1983; Bonnier et al., 2007; Marsh et Whitehead, 2005; Papoutsis et al., 2014; Stipanicic et al., 2008), executive functioning (Bonnier et al., 2007; Crowe et al., 2013; Louise M. Crowe et al., 2012; Ewing-Cobbs et al., 2004; Keenan et al., 2018; Keenan et al., 2019; Stipanicic et al., 2008; Tonks et al., 2011), language (Barlow et al., 2005; Bonnier et al., 2007; Crowe et al., 2014; Ewing-Cobbs et al., 2006; Keenan et al., 2019; Stipanicic et al., 2008; Vassel-Hitier et al., 2019; Wrightson et al., 1995), social cognition (Bellerose et al., 2015; Bellerose et al., 2017; D'Hondt et al., 2017; Ewing-Cobbs et al., 2013; Landry et al., 2004; Walz et al., 2009) and academic achievement (Ewing-Cobbs et al., 2006; Vassel-Hitier et al., 2019) are documented in the literature, but vary as a function of injury characteristics (ex. severity, mechanism, age at injury). These findings are congruent with a previous review by Garcia and colleagues (2015) that concluded that children who sustain early TBI encounter cognitive difficulties including intellectual, attention, language, and executive dysfunction. However, in their respective reviews, Garcia and colleagues (2015) and Wetherington and Hooper (2006) included children older than six years ruling out the possibility of drawing any specific conclusions concerning the unique effects of early TBI. The findings of the current review clarify that difficulties in these domains are not solely driven by the results of older children.

A novelty of the current review is the inclusion of additional functional domains such as socio-affective and adaptive functioning following early TBI. Evidence for difficulties in these domains is less unanimous, and conclusions tend to vary across studies. For example, social skills are fairly consistently reported as being affected by early TBI (Achenbach et Edelbrock, 1983; Ewing-Cobbs et al., 2013; Kaldoja et Kolk, 2015; Keenan et al., 2019; Lalonde et al., 2016; Sonnenberg et al., 2010), whereas the findings are variable for emotion regulation and behavior, (Barlow et al., 2005; Bellerose et al., 2015; Ewing-Cobbs et al., 1999; Gagner et al., 2018; Kaldoja et Kolk, 2015; Keenan et al., 2018; Keenan et al., 2019; Landry et al., 2004; Liu et Li, 2013; McKinlay, Corrigan, et al., 2014; McKinlay et al., 2002; McKinlay et al., 2009; McKinlay et al., 2010; Pastore et al., 2013; Tonks et al., 2011; Wetherington et al., 2010), as well as for adaptive functioning (Barlow et al., 2005; Beers et al., 2007; Coster et al., 1994; Dégeilh et al., 2018; Ewing-Cobbs et al., 2013; Green et al., 2013; Kaldoja et Kolk, 2015; Keenan et al., 2007; Lalonde et al.,

2016; Pastore et al., 2013). In addition to discrepancies among the studies of early TBI, some of the conclusions drawn are inconsistent with studies in school-aged children and adolescents, which in general do not identify negative socio-behavioral outcomes in the very long-term after mTBI. These inconsistencies are likely to be in part methodological, due for example to the multiple different types of measures used to document behavior, and/or to issues of timing of the injury and assessment. For example, those that found problems after early mTBI assessed behavior within 12 months of mTBI (ex. Bellerose et al., 2015; Gagner et al., 2018; Liu et al., 2013), whereas those who did not assessed behavior in the longer term (2 years or more post-injury: ≥ 2 years: Crowe et al., 2012; ≈ 3 years: Wetherington et al., 2010; 5 years: Marsh et al., 2005).

Overall, there is published evidence that children who sustain early TBI exhibit altered functioning in a range of domains including cognitive functioning and academic achievement, along with socio-affective, behavioral and adaptive functioning. The significance of these problems appears to be modulated by a number of factors such that outcomes are generally reported as being worse in the following four situations: 1) TBI occurs at a younger age; 2) injury severity is moderate-severe; 3) mechanism of injury is non-accidental; 4) the comparison group is typically developing children (rather than orthopedic injuries, for example).

Younger age at injury

There is ongoing debate on the question of whether younger age at brain injury incurs better or worse outcome as a function of brain plasticity or vulnerability. On one hand, there is evidence for the notion that sustaining brain injury at a younger age is less detrimental than at older ages likely because of the increased structural and functional plasticity that is present earlier in the developmental course (Anderson et al., 2005; Aram et Ekelman, 1986; Dennis, 1980). Taken in the context of pediatric mTBI research, there is fairly consistent evidence in school-aged children (5-18 years) that *younger* age at injury results in *fewer* post-concussive symptoms and overall better outcomes than older (i.e., adolescence) age at injury (Anderson et Moore, 1995; Zemek et al., 2013). However, this effect appears to be reversed in the early childhood period, such as illustrated in the studies included in this review showing that injury at a *younger* age results in *poorer* outcomes than when sustained at an older age (all TBI severities, ex. Louise M. Crowe et al., 2012; Ewing-Cobbs et al., 2004; Keenan et al., 2018; Keenan et al., 2019; Sonnenberg et al., 2010). The brains of infants and toddlers may be particularly vulnerable to insult because of rapid brain

maturation occurring during those years and sensitive periods for the development of cognitive and social functions (Alexander, 1995; Anderson et al., 2009; Grantham-McGregor et al., 2007; Kieslich et al., 2001; Kolb et al., 2000; Kriel et al., 1989; Thompson et Nelson, 2001). TBI sustained at a younger age and during a sensitive period may impair the development of particular functions (ex. language) and/or alter the emergence of associated cognitive, socio-affective, and behavioral functions (ex. Bonnier et al., 2007; Crowe et al., 2014; Vassel-Hitier et al., 2019). As a whole, the review results suggest that TBI sustained during early development is not benign, cannot solely be interpreted in accordance with brain plasticity mechanisms, and that even milder injuries may temporarily or persistently impede functioning in various domains (Anderson et al., 2005; Bellerose et al., 2015; Bellerose et al., 2017; Crowe et al., 2013; D'Hondt et al., 2017; Dégeilh et al., 2018; Gagner et al., 2018; Kaldoja et Kolk, 2015; Keenan et al., 2018; Lalonde et al., 2016; Liu et Li, 2013; McKinlay, Corrigan, et al., 2014; McKinlay et al., 2002; McKinlay et al., 2009; McKinlay et al., 2010; Papoutsis et al., 2014; Schneider, 1979).

TBI severity

As documented in school-aged children, adolescents and adults, msTBI sustained early in development leads to worse outcomes than milder injuries (Anderson et Catroppa, 2005; Anderson et al., 2005). Babikian and colleagues (2009) present a "double hazard" injury model suggesting that children with younger age at injury and more severe TBI have a reduced rate of normal developmental progress (Anderson et al., 2005; Kriel et al., 1989). In the present review, IQ, attention, executive functioning, language, social cognition, academic achievement, socio-affective, adaptive functioning and social behavior (regardless of age at injury) were generally poorer in children who sustained msTBI compared to mTBI and control groups (OI, TDC; ex. Crowe et al., 2014; Louise M Crowe et al., 2012; L. M. Crowe et al., 2012; Ewing-Cobbs et al., 1999; Ewing-Cobbs et al., 2006; Ewing-Cobbs et al., 2004; Ewing-Cobbs et al., 2013; Green et al., 2013; Keenan et al., 2018; Keenan et al., 2019; Landry et al., 2004; Pastore et al., 2013; Walz et al., 2009; Wetherington et al., 2010).

While it is clear that early msTBI is associated with detrimental consequences, conclusions on the impact of early mTBI are more blurred. Drawing unequivocal conclusions is hampered by problems in *identifying and describing early mTBI*. For example, some studies of accidental mTBI relied on ambiguous definitions or criteria (e.g., Liu et al., 2013; Wrightson et al., 1995). In these

cases, the broad term "head injury" was used in the definition (e.g. diagnosis of a head injury at a hospital emergency department, not severe enough to require admission for observation; Wrightson et al., 1995), and no other objective criteria were considered for inclusion. For these studies, it is not clear whether absence of findings in some areas of functioning (speed of information processing, memory, language, academic achievement, behavior, adaptive skills) is attributable to the inclusion of superficial head injuries (not involving the brain) in the sample, or, conversely, whether significant group differences in the areas of visual closure (Wrightson et al., 1995) and withdrawal (Liu et al., 2013), are explained by the inclusion of more severe injuries (e.g., mild complex TBI). The lack of group differences in these two studies could suggest relatively minor or isolated problems after early mTBI, yet other studies using more definitive inclusion criteria do report certain difficulties (e.g., inhibition, social cognition, social interactions, behavior). Drawing clear and digestible conclusions regarding early accidental mTBI outcomes is challenging. The limited number of studies, ambiguity in definitions and criteria, and lack of harmonisation across domains and measures studied all blur the interpretation of existing work. Special interest groups or expert panels may be useful for developing criteria specific to the early childhood period and what domains constitute priority areas of investigation. Interpretations of the nature and severity of outcomes are confounded by age, mechanism, and severity. While modest sample sizes and multiple levels of analysis often limit the possibility of creating subgroups for comparison, providing descriptive data and fine-grained information (ex. mechanism, age, sex, gender) may facilitate meta-analyses that could clarify the interpretations and conclusions drawn from early mTBI studies.

TBI mechanism (accidental vs non-accidental)

The majority of studies that have compared the outcomes of children with early naTBI to those with accidental injuries find poorer outcomes in the former group (ex. Beers et al., 2007; Ewing-Cobbs et al., 1998; Ewing-Cobbs et al., 1999; Keenan et al., 2007). These children also exemplify the double hazard model put forth by Babikian et al (2015) given that children who sustain naTBI are typically younger than 2 years old and that naTBI often results in moderate-severe injuries, naTBI may occur in family and socio-demographic contexts associated with greater risk for poor outcome (Chevignard et Lind, 2014; Liley et al., 2012; Lind et al., 2016). Household falls typical of accidental early TBI (Haarbauer-Krupa et al., 2018; Kaushik et al., 2015; Loder,

2008) usually involve low velocity translational forces, whereas naTBI often involves a combination of acceleration/deceleration forces and rotational/shearing injury due to shaking (Ewing-Cobbs et al., 2000). While it is still debated whether sudden "shaking" is more likely to result in intracranial injury characteristic of more severe TBI, pathophysiological differences seem to exist and contribute to the variability of outcomes observed following early TBI (Cory et Jones, 2003). Further explanation for the differences observed in outcomes could be the presence of repetitive episodes of injury overtime in naTBI (Adamsbaum et al., 2010). An important skew should be noted in contrasting the outcomes of early aTBI and naTBI: aTBI samples tend to mostly consist of mild injuries whereas naTBI samples are more likely to be moderate-severe in nature. It is therefore possible that the conclusions drawn from this literature reflect a greater overall prevalence of *mild* aTBI compared to *moderate-severe* naTBI, muddying the question of accidental and non-accidental mechanisms are comparable in outcome.

Comparison groups

The majority of studies identified in the present review included a comparison group and those that compared children with early TBI to TDC were more likely to find significantly elevated rates of problems than studies that compared children with mTBI to children with OI. Both TDC and OI present advantages and disadvantages in TBI research. Whereas comparisons with uninjured children recruiting in the community (TDC) allows conclusions to be drawn with regard to the expected developmental trajectory of learning and development, and to identify in what areas children with TBI may fall short of their peers, OI groups account for potential pre-existing differences between children who may be more prone to injury, in addition to controlling for common factors associated with traumatic injuries (ex. pain, fatigue, stress). A study by our group found that young children with OI and TDC are comparable on a broad range of pre-injury and post-injury characteristics (ex. demographic variables, developmental and medical history, behavioral and adaptive profiles, as well as on measures of adaptive functioning, behavior, family functioning, post-concussive symptoms, and cognition (Beauchamp et al., 2017), and cautiously concluded that there is no clear advantage in recruiting OI groups. However, there may be other domains in which the groups differ that were not documented in that study. The decision to use either OI or TDC comparison groups when investigating early TBI should be a function of the aims of the study and the primary outcomes of interest.

Additional challenges identified in the systematic review

The results of the review highlight the use of robust methodology in several instances (ex. prospective and longitudinal study designs), but also point to methodological and clinical challenges associated with conducting research in infants, toddlers and preschoolers with TBI. Some of these have already been discussed in the preceding sections (e.g., definition and diagnosis, terminology, sample composition). In addition, the review highlights limitations regarding *developmental groups*, in that age groups may be created across developmental periods (infancy, toddlerhood, preschool) further complicating terminology and comparisons. *Study design* challenges are also observed with few longitudinal designs and long-term outcomes measured. *Measurement* issues are present in the form of poor harmonisation across studies, precluding direct comparisons across the literature. While the breadth of *outcome domains* studied is a strength of the early TBI literature, conversely almost no information is available regarding post-concussive symptoms, a vital indicator of outcome and recovery, especially after mTBI. *Assessment* limitations include frequent reliance on third party questionnaires with limited direct measurement and lack of performance validity measurement in any of the studies reviewed.

Threats to *performance validity* are a reality across age groups, but may be especially important to understand in young children. School-age children may feign or exaggerate symptoms (Kirkwood, 2015), an effect that can be captured using stand-alone or embedded tools such as the Test of Memory Malingering (Tombaugh, 1996) as of five years (for a systematic review and meta-analysis see Clark et al., 2020). No such tools are available of infants and toddlers, and it is not as clear what incentive or capacity they have to intentionally feign symptoms or problems in the context of TBI, though it is plausible that a young child may implicitly discover a benefit of over-reporting symptoms or problems. For example, a child might realize that they are getting more attention from their parents or that they can stay home from daycare if they report (or exhibit) signs that they are unwell. Finally, collaboration or participation issues can affect the validity and quality of the data collected (e.g., refusal to complete a task, fatigue, oppositional behavior, tantrums, parental separation anxiety). Going forward, these issues should be more clearly or quantitatively reported to aid in understanding the true nature of early TBI consequences.

Considering these limitations and challenges is useful in interpreting the findings of individual studies and drawing cautious conclusions regarding the effects of early TBI, while also providing opportunities for future research, recommendations to move the field forward, and

translation of empirical findings to clinical practice. Table 4 summarizes these points as a way to provide preliminary reflections and building blocks for mobilizing the efforts of those interested in the topic of early TBI and the development of more concrete and concerted initiatives. The suggestions should be considered alongside the usual recommendations for conducting valid and bias-free research.

[Insert Table 4 here]

Strengths and limitations of the review

This review of early TBI was conducted systematically, presents a broad range of post-injury outcomes, includes both studies of naTBI and aTBI, and focuses specifically on injuries under the age of six years. Despite these strengths, a number of limitations should be considered. First, although focussing on injuries before the age of six years facilitates conclusions regarding the specific effect of TBI during early childhood, several articles were excluded from the review because of this criterion. Some excluded studies covered overlapping age or developmental groups, often including toddlers, preschoolers, alongside school-age children (ex. Participants aged 2-9 years). While including these studies would have negated the objective of presenting findings for the youngest portion of the population, it might have provided an opportunity to compare timing of injuries between "early" and "later" childhood. Second, the effect of multiple TBIs was not documented. Only two articles were identified that included multiple injuries. One was nonetheless included in the review because it presented outcomes in the single TBI group separately (Liu et Li, 2013). The other was not included in the results table because it was not possible to dissociate the effects of single versus multiple injuries (Bijur et al., 1996). Third, article selection criteria did not include motor functioning, nor did it cover broad areas of global functioning such as quality of life, or intervention studies that may have reported cognitive or behavioral outcome at pre-test/admission, for example. There is also a gray area as to what studies and measures can be considered to target "adaptive functioning". For inclusion we used a socio-behavioral perspective of this construct (Bellini, 2003). Notably, there is a rich literature on functional disability (a construct that often overlaps with adaptive abilities) in the context of TBI rehabilitation programs that has used measures such as the Functional Independence Measure for children (WeeFIM). These studies were identified in the first stage of the review and met the criteria for the outcome of interest, but all were ultimately excluded for other reasons, mostly due to age at injury (> 6 years

old) or injury groups not exclusive to TBI. Fourth, effects of early TBI on PCS were not reported despite their central importance in mTBI/concussion research. There are few published studies that report PCS, likely due to the fact that no validated measures of PCS exist under the age of five years and that few studies have tracked the effects of early TBI acutely. Current reports of PCS in young children consist of downward adaptation of existing school-aged children questionnaires or chart reviews of symptoms reported (Bellerose et al., 2017; Gagner et al., 2018; McKinlay, Ligteringen, et al., 2014; Suskauer et al., 2018). Efforts are currently underway to validate a developmentally-appropriate measure of PCS in young children (Dupont et al., 2021). Finally, it is worth noting that the review conclusions are subject to inherent publication biases and that the absence of results in any one domain may simply be the reflection of non-significant (and therefore unpublished) findings.

Conclusions

This review provides a comprehensive summary of the consequences of TBI sustained before the age of six years. While it is complex to distill clear conclusions due to the methodological challenges and developmental characteristics of this group, the review highlights that children who sustain TBI during early childhood, a sensitive period for the development of cognitive and social skills and associated behaviors, may show difficulties in a range of outcomes, and these are sometimes apparent even after mTBI. Though it is likely that the majority of children with mTBI will recover entirely, some studies report social and behavioral issues in the longer term. It is critical that research, diagnosis, assessment, clinical management, as well as prevention efforts and consensus definitions be further developed based on this empirical literature and in a manner that is specific to the unique characteristics of early childhood.

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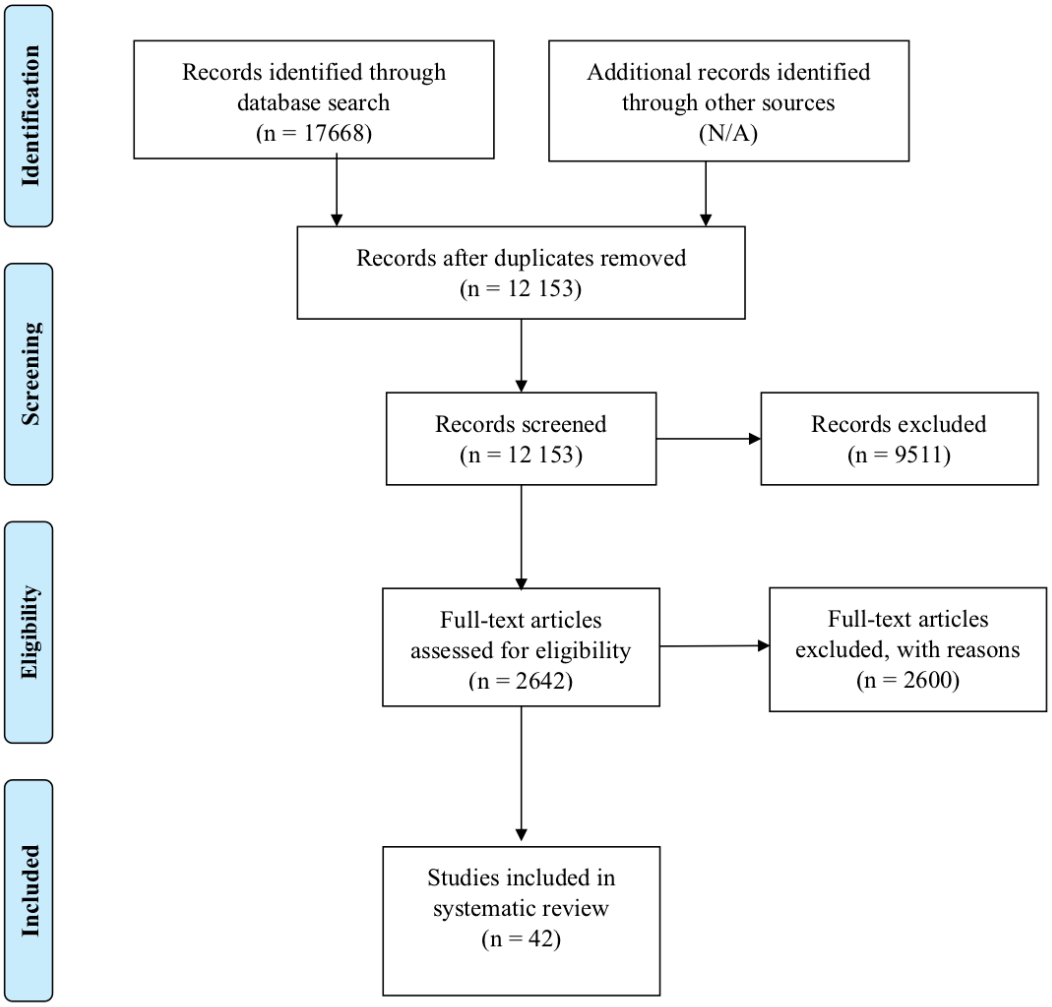

Figure 1. PRISMA Diagram.

Table 1. Studies Identified In The Systematic Review Examining Outcome After Accidental and Non-Accidental TBI In Early Childhood

Reference	Injury severity (n; % male)	Age at injury in months Range (M±SD)	Cause of injury (n; % of TBI group)	Control groups (n; % male)	Study design Follow-up timepoint post-injury in months Range (M±SD)	Cognitive/academic outcomes							Socio-affective, behavioral and adaptive outcomes		
						Intelligence/ Development	Attention	Executive Functioning	Memory	Language	Social cognition	Academic	Emotion regulation & behavior	Social skills	Adaptive Functioning
aTBI															
Bellerose et al. (2015)	mTBI (51; 50.98%)	18-60 (36.00±11.19)	Falls (49; 96.00%)	TDC (50; 34.00%)	L (C-S), P Pre-injury, 6						**Discrepant desires & False Beliefs** ToM mTBI < TDC (6 mos)		**CBCL** Externalizing scale mTBI > TDC (pre-injury & 6 mos)		**ABAS-II** Social & GAC mTBI = TDC (ns; pre-injury & 6 mos)
Bellerose et al. (2017)	mTBI (72; 52.77%)	mTBI 18-60 (35.57±11.59) OI 18-60 (34.37±10.53)	Falls (67; 93.00%)	OI (58; 50.00%) TDC (83; 51.00%)	L (C-S), P Pre-injury, 6 & 18						**Discrepant desires & False Beliefs** ToM mTBI < TDC & OI (6 & 18 mos)				**ABAS-II** Social & GAC mTBI = TDC (ns; pre-injury, 6 & 18 mos)
Coster et al. (1994)[+]	All TBI severity (57; 67.00%)	1 mo-5.60 yrs (2.97±1.43) yrs	Falls (25; 46.00%)	OI (17; NA)	L, P 1 & 6								**CBCL** Total problems (ns)		**PEDI** Functional Skills & Caregiver Assistance ↑ Self-Care & Social Function Assistance post-injury TBI > OI (1 & 6 mos)
Crowe et al. (2014)	mTBI (19; 57.90%)	3wks-	Falls mTBI	TDC	C-S, P ≥ 2 yrs	**WPPSI-III Verbal IQ**				**CELF-P**					

	msTBI (16; 43.80%)	2 yrs; 11 mos mTBI (16.80±10.30) msTBI (12.30±10.60)	(NA; 94.70%) msTBI (NA; 81.30%)	(20; 40.00%)	mTBI NA (47.70±9.00) msTBI NA (46.90±8.20) Ax 3 yrs; 10 mos – 6 yrs: 00 mo old	msTBI (results in average range) < = TDC mTBI (results in average range)				**Core Language Index** Expressive Vocabulary/ Sentence & Word structure msTBI < mTBI = TDC (results in average range) **Bus Story Test** Expressive language msTBI < mTBI = TDC					
Crowe et al. (2012)	mTBI (20; 55.00%) msTBI (33; 53.10%)	6 days - 2 yrs; 11 mos mTBI 1-35 (17.70±10.70) msTBI 0-35 (21.50±12.10)	Falls mTBI (18; 90.00%) msTBI (22; 66.70%)	TDC (27; 40.70%)	C-S, P ≥ 2 yrs mTBI 29-64 (46.80±9.70) msTBI 24-56 (39.20±9.60) Ax 4 yrs; 00 mo - 5 yrs; 11 mos old	**WPPSI-III** VIQ, PIQ, FSIQ msTBI < mTBI = TDC		**WPPSI-III** Information processing (coding subtest) (ns)					**CBCL** (ns)	**SSRS** (ns)	
Crowe et al. (2013)	mTBI (19; 57.90%) msTBI (16; 43.80%)	mTBI (16.80±10.30) msTBI (12.30±10.60)	Falls mTBI (17; 89.50%) msTBI (12; 75.00%)	TDC (20; 40.00%)	C-S, P ≥ 2 yrs mTBI (47.70±8.90) ms TBI (46.90±8.20) Ax 3 yrs; 10 mos - 5 yrs; 11 mos old		**NEPSY-II Auditory Attention** Vigilance and Selective attention (ns)	**WPPSI-III** Information processing (coding subtest) (ns) **Statue subtest** Inhibitory control (average range) msTBI & mTBI < TDC						

								BRIEF-P Parent-rated executive function (ns)							
Crowe et al. 2012 (timing)	Infant (50; NA) mTBI (20; 50.00%) modTBI (23; 56.50%) sTBI (7; 57.10%) Preschool (43; NA) mTBI (11; 54.40%) modTBI (19; 78.90%) sTBI (13; 69.20%)	Infant 0-2 yrs mTBI (1.6±0.90) yrs modTBI (1.7±1.00) yrs sTBI (1.9±0.70) yrs Preschool 3-6 yrs mTBI (5.0±1.30) yrs modTBI (4.9±1.20) yrs sTBI (5.1±1.10) yrs	Falls Infancy (37; 74%) Preschool (21; 49%)	None	C-S, P 24-45 (30.06±NA)	**WPPSI-R/WPPSI-III/WISC-III** VIQ, PIQ, FSIQ sTBI (low average) < mTBI & modTBI (average range)		**WPPSI-R/WPPSI-III/WISC-III** PSI sTBI (low average) < mTBI & modTBI (average range)							
Dégeilh et al. (2018)	mTBI (63; 52%)	mTBI (35.84±11.17)	Falls mTBI (59; 94%) OI (32; 60%)	OI (53; 47.00%)	L, P Pre-injury, 6 & 18 Ax T0 (37.39±11.21) T1 (42.37±11.50) T2 (55.22±11.09)										**ABAS-II** Practical & conceptual mTBI = OI (ns; pre-injury, 6 & 18 mos) Social mTBI = OI (ns; pre-injury) mTBI < OI

															(6 & 18 mos)
D'Hont et al. (2017)	mTBI (18; 72.22%)	mTBI (53.00±8.00)	NA	TDC (15; 46.67%)	L (C-S), P 6						**NimStim Set of Facial Expression** Emotional facial expression processing mTBI < TDC				
Gagner et al. (2018)	mTBI (86; 53.49%) Uncomplicated mTBI (77; NA) Complicated mTBI (9; NA)	mTBI (36.50±11.56)	Falls mTBI (78; 90.70%) OI (35; 56.45%)	OI (62; 50.00%) TDC (81; 50.61%)	L, P 6 Ax (43.52±11.72)								**CBCL** Externalizing scale mTBI > OI (pre-injury) Internalizing externalizing scale mTBI > OI & TDC (6 mos)		
Green et al. (2013)	All TBI severity (17; 58.80%) mTBI (2; 11.80%) modTBI (9; 52.90%) sTBI (6; 35.30%)	0-5 yrs (NA±NA)	Falls (all sample) (11; 64.70%)	TDC (16; 37.50%)	L, P 13-16 yrs Ax TBI 15-18 yrs (16.50±1.00) yrs TDC 14-18 yrs (16.30±1.40) yrs										**SPRS-C Total score** TBI = TDC (ns) School/Leisure sTBI < TDC Living Skills TBI < TDC
Kaldoja et al. (2015)	mTBI (35; 46.00%)	3-65 (NA±NA)	NA	TDC (54; 59.00%)	L, P Pre-injury (3 days), 9 mos								**ASQ:S-E** Self-regulation & autonomy difficulties Pre-injury mTBI Boys > mTBI Girls	**ASQ:S-E** Social difficulties Pre-injury (ns) Post-injury mTBI boys > TD Boys Communication	**ASQ:S-E** Adaptive difficulties Pre-injury mTBI Girls > TDC Girls Post-injury (ns)

													(self-regulation only) mTBI Boys > TD Boys Post-injury <u>Self-regulation</u> mTBI Boys > mTBI Girls mTBI Boys > TD Boys <u>Compliance & Affect</u> (ns)	(ns)	
Lalonde et al. (2016)	mTBI (47; 57.45%)	18-60 (NA±NA)	Falls (45; 95.74%) OI (22; 81.48%)	OI (27; 44.44%) TDC (56; 41.07%)	L (c-s), P Pre-injury, 6 Ax (41.65±11.49)									**MRO (Observational measure)** <u>Parent-child interaction quality</u> mTBI < TDC OI = mTBI & TDC **PCDI** <u>Parent-child dysfunctional interaction</u> mTBI = OI = TDC (ns)	**ABAS-II** <u>Leisure subscale</u> TDC & mTBI > OI (pre-injury) <u>Other subscales</u> mTBI = OI = TDC (ns; pre-injury)
Landry-Roy et al. (2018)	mTBI (84; 54.00%)	mTBI (36.80±11.54)	Falls (76; 91.00%)	TDC (83; 49.00%)	L (c-s), P Pre-injury (in mTBI only), 6 Ax (43.08±11.63)			**Delay of Gratification** <u>Inhibition</u> **&** **Conflict Scale** <u>Cognitive flexibility</u> **&** **Shape Stroop**							

								Inhibition & Cognitive flexibility mTBI = TDC (ns)							
Liu et al. (2013)*	mTBI (167; 57,49%)	< 6 yrs	NA Single injury (97; 14.00%) Multiple injuries (70; 10.00%)	TDC (558; 51,08%)	L (c-s), P Ax 6 yrs old								**CBCL Withdrawn behavior** Single injury & Multiple > TDC		
Marsh and Whitehead (2005)+	mTBI + ModTBI (19; 68.00%)	TBI 2-24; (12.11±7.73) OI 9-27; (18.50±4.80)	Falls (18; 94.70%)	OI (20; 65.00%)	C-S, P 5 yrs TBI 62-79 mos (68.79±5.38) OI 45-77 mos (61.40±9.00) Ax TBI 71-97 mos (80.89±8.18) OI 70-92 mos (79.90±7.79)		**NEPSY-II Visual Attention** TBI < OI 22% TBI impaired range	**NEPSY-II Tower** planning **Design fluency** Cognitive flexibility **Auditory Attention and Response Set** Inhibition TBI = OI (ns)	**NEPSY-II Memory for faces** Visual memory TBI < OI 21% TBI impaired rage **Memory for names, Narrative Memory, Sentence Repetition** Auditive memory TBI = OI (ns)	**NEPSY-II Speeded Naming, Comprehension of Instructions & Verbal fluency** Language TBI = OI (ns)		**WIAT** Basic Reading/Maths Reasoning/Spelling TBI = OI (ns)	**CBCL (parents + teacher)** Total competence, Internalizing + Externalizing + Total problems TBI = OI (ns)		
McKinlay et al. (2014)	mTBI 0-5 yrs (83; NA) Inpatient (61; NA) Outpatient (22; NA)	0-5 yrs (NA±NA)	NA	TDC (972; NA)	L, P (Pre-injury (covariates), 11-20 yrs)								**Self-Report Delinquency Inventory & Interview** Sx drug dependence DSM-IV criteria Inpatient > Outpatient = TDC		

													<u>Property offenses</u> Inpatient > Outpatient = TDC <u>Violent offenses</u> Inpatient = Outpatient > TDC		
McKinlay et al. (2002)	mTBI (101; 51,00%) Outpatient (84; NA) Inpatient (17; NA)	0-5 yrs	Falls Inpatient (NA; NA%) Outpatient (NA; NA%)	TDC and/or OI (789-807; NA%)	L, P (Pre-injury (covariates) Ax 8 yrs (WISC-R) and/or 10-13 yrs (PAT & Rutter & Conners)	**WISC-R** Inpatient = Outpatient = TDC/OI (ns)						**PAT** Inpatient = Outpatient = TDC/OI (ns)	**Rutter & Conners** <u>Conduct & Hyperactivity/ Inattention problems</u> Inpatient > Outpatient + TDC/OI		
McKinlay et al. (2009)	mTBI (76; NA) Inpatient (19; 53.00%) Outpatient (57; 53.00%)	0-5 yrs	NA	TDC and/or OI (839; NA%)	L, P (Pre-injury (covariates) Ax 14-16 yrs old								**SERD & RBPC & DISC & RAPI** <u>Conduct & ODD/Attention deficit/Hyperactivity/Substance abuse/Mood disorder</u> Inpatient > Outpatient + TDC/OI **DISC** <u>Anxiety disorder</u> Inpatient = Outpatient = TDC/OI		

McKinlay et al. (2010)	mTBI (81; NA) Inpatient (21; 52.40%) Outpatient (60; 50.00%)	0-5 yrs	Falls Inpatient (16; 76.00%) Outpatient (NA; NA%)	TDC and/or OI (851; 49.90%)	L, P Ax 7 - 13 yrs old (yearly)									**Rutter & Conners** ADHD & Conduct & Hyperactivity/ Inattention problems Inpatient > Outpatient + TDC/OI		
Papoutsis et al. (2014)	Complicated mTBI (34; 55.88%) Uncomplicated mTBI (18; 55.56%)	Complicated mTBI (23.09±13.58) Uncomplicated mTBI (19.72±14.58)	NA	TDC (33; 54.54%)	R > 7 yrs Complicated mTBI (118.88±14.04) Uncomplicated mTBI (114.00±15.81) TDC (116.48±20.48)		**TEA-ch Sky Attention** Visual selective attention Complicated TBI = Uncomplicated TBI = TDC (ns) **Sky DT** Divided attention Complicated TBI < Uncomplicated TBI= TDC	**WISC-IV Coding** Speed of information processing (ns) **Block Design** Goal setting and organization Complicated TBI = Uncomplicated TBI = TDC (ns) **Digit Span Backwards** Complicated TBI = Uncomplicated TBI = TDC (ns) **BRIEF** Behavioral aspects of EF BRI or MI Complicated TBI = Uncomplicated TBI = TDC (ns)							
Pastore et al. (2013)	sTBI (14; 64.30%)	sTBI (24.79±10.69)	NA	None	C-S, P 8.40 - 16.33 (8.50±10.52)									**CBCL Frequency of problems**		**VABS** Daily living skills

	Brain tumour (18; 77.80%) Vascular or infectious brain lesions (23; 39.10%)				Ax sTBI (34.07±6.89)								Externalizing (50.00%) Destructive (42.90%) Aggressive (35,70%) Internalizing (77.80%) Anxious/Depressed (55.50%) Somatic (55.50%)		sTBI & Brain tumour > Vascular/infectious brain lesions
Prasad et al. (1998)	msTBI (8; 50.00%)	13-32 (20.90± NA)	Car overhead (NA; 62.50%)	None	L, P 2 mos & 1 year	**BSID** Development IQ/motor functioning 2 mos Deficit range (63.00%) 1 yr Normal range (83.33%)									**VABS** Composite score 2 mos & 1 year ≥ Average range (83.33%)
Sonnenberg et al. (2010)	msTBI (93; 61. 29%) Young msTBI (61; 63.93%) Old msTBI (32; 56.25%)	< 6 yrs (3.40±1. 50) yrs Young 0-3 yrs; 11 mos (2.60±1. 10) yrs Old 4-5 yrs; 11 mo (5.0±0.6) yrs	NA	None	L, R Ax msTBI 7 - 9 yrs; 11 mo (8.30±0.70) yrs									**MPAI-P** Social function Normal (20%) Mild (41%) Moderate (23%) Severe impairment (16%) Mild impairment Old (72%) > Young (56%) Severe impairment Young (44%) > Old (28%)	

														Social and cognitive skills Young < Old	
Tonks et al. (2011)+	All TBI severity (28; NA%) mTBI (21; NA%) ModTBI (2; NA%) msTBI (3, NA%) sTBI (2; NA%)	< 5 yrs old	NA	TDC (89; NA%)	C-S, P Ax 8-10 yrs old (14; NA%) (9.20±1.40) 10-16 yrs old (14; NA%) (13.10±2.17)			**DKEFS** Verbal Letter Fluency TBI = TDC (ns) **Tower Test** Planning TBI = TDC (ns) **Number-Letter Switching** Cognitive flexibility TBI = TDC (ns) **WISC-III Digit Span** Working memory 8-10 yrs TBI = TDC (ns) 10-16 yrs TBI < TDC					**SDQ** Socio-emotional difficulties TBI > TDC		
Walz et al. (2009)	msTBI (66; NA) modTBI (42; NA) sTBI (17; NA)	3 - 5 yrs; 11 mos	NA	OI (86: NA%)	C-S, P 1	**Differential Ability Scales (DAS)/General Conceptual Ability (GCA)** sTBI < modTBI & OI					**ToM** False-belief **False contents** sTBI < modTBI & OI **False location/ Control/ ToM total** sTBI = modTBI = OI				

											(ns)					
Wrightson et al. (1995)*	mTBI (78; NA%)	2.50-4.50 yrs	Falls (NA; 78.00%)	OI (86; NA%)	L, P Pre-injury, 1, 6, 12 mos & at 6.5 yrs old			**WISC** Coding Processing Speed mTBI = OI (ns)	**Verbal memory passage** mTBI = OI (ns) **CMS** Paired associate learning mTBI = OI (ns) **CMS** Visual memory test mTBI = OI (ns)	**ITPA** Visual closure (puzzles) At 6, 12 mos post-injury & 6,5 yrs old mTBI < OI **Reynell developmental language scales** mTBI = OI (ns)		**Neale analysis of reading ability/Letter knowledge and writing** mTBI = OI (ns)	**Connors parent** mTBI = OI (ns; pre-injury, 1, 6, 12 mos) **Connors teacher** mTBI = OI (ns; 6.5 yrs old)		**Vineland social maturity scale** mTBI = OI (ns, pre-injury, 1, 6, 12 mos)
naTBI																
Barlow et al. (2005)	Unspecified severity naTBI (25; 60.00%)	2 wks-34 mos (3.50±NA)	Whiplash shaking (13; 52.00%) Impact (12; 48.00%)	None	C-S, L, P 59 mos C-S (13; 52.00%) L, P (12; 48.00%) Ax C-S NA (90±50.00) L,P 1st Ax: NA (16.00±9.90) Last Ax: NA (25.30±9.10)	**BSID-II** Development (8 out of 14) < 1st %ile (2 out of 14) 1st-6th %ile				**Seisha's outcome scale** Speech & Language 64.00% Abnormal[a]			**BSID-II** Behavior problems 52.00%		**VABS** Socialization 48.00% ≤ Moderately low Communication 61.00% ≤ Moderately low Daily Living Skills 52.00% ≤ Moderately low
Ewing-Cobbs et al. (1999)	ms naTBI (28; 25.00%)	2-42 (9.28±8.59)	naTBI (28; 100%)	TDC (28; 50.00%)	L, P 1 & 3	**BSID-II** Mental + physical domains 1 & 3 mos na msTBI < TDC							**BBRS** Orientation & Engagement impairment 1 & 3 mos Attention/		

													arousal (1 mo) Emotion regulation (3 mos) na msTBI > TDC		
Landry et al. (2004)	naTBI (40; NA%) msTBI (25; 28.00%) modTBI (18; NA) sTBI (7; NA)	2-23 (NA±NA)	NA	TDC (22; 36.00%)	C-S, P NA(1.6±NA) mos Ax na msTBI 3-31 (10.92±8.45) TDC 3-30 (11.64±7.16)	**Bayley Mental Development Index** na msTBI < TDC							**Toy-centered activity** Positive affect/Compliance na msTBI < TDC Negative affect na msTBI = TDC (ns)	**Toy-centered activity** Social interactions na msTBI < TDC Communicating /Complexity of independent toy play na msTBI = TDC (ns)	
Stipanicic et al. (2008)	naTBI (11; 45.00%)	0-36 (5.09±3.23)	naTBI with or without impact	TDC (11; 45.00%)	C-S, P NA (78.90±NA) mos Ax n-aTBI (87.64±25.52)	**SB-IV** naTBI < TDC	**NEPSY Auditory Attention** naTBI < TDC **Visual Attention** naTBI = TDC (ns)	**NEPSY Digit Span** Auditory Working Memory naTBI < TDC **Verbal Fluency** naTBI < TDC **Tower** Planning naTBI < TDC **Statue** Inhibition naTBI < TDC **Knock and Tap** Inhibitory control naTBI < TDC **WISC-III Mazes** Planning naTBI = TDC	**CMS Word List** Verbal memory naTBI = TDC (ns) **CMS Dot Location** Visual memory naTBI = TDC (ns)	**NEPSY Comprehension of Instructions** Receptive Language naTBI < TDC				

								(ns) **Halstead-Reitan Battery Progressive Figures** Cognitive flexibility n-aTBI = TDC (ns)							
aTBI vs naTBI															
Beers et al. (2007)[+]	All severity naTBI (15; 47.00%) aTBI (15; 40.00%)	< 3 yrs naTBI (5.75±7.91) aTBI (17.22±11.33)	NA	None	C-S, P 6	**BSID-II/SB4** Intellectual development/ ability naTBI < aTBI									**VABS** Composite score naTBI < aTBI
Ewing-Cobbs et al. (1998)	msTBI (40; 30.00%) naTBI (20; 15.00%) aTBI (20; 50.00%)	1 mo-6 yrs n-aTBI (10.60±14.87) aTBI (35.55±25.35)	naTBI (10; 50.00%) aTBI MVA (passenger) (9; 45.00%)	None	C-S, L, P 1.30 mos	**BSID-II & SB4** Intellectual development/ ability naTBI 45.00% Deficient aTBI 5.00% Deficient									
aTBI vs naTBI/aTBI & naTBI															
Ewing-Cobbs et al. (2013)[+]	All severity naTBI (64; 50.00%) aTBI (61; 59.00%)	0-36 naTBI (8.00±7.90) aTBI (11.30±10.50)	naTBI (41; 64.10%) aTBI Falls (17; 26.56%)	TDC (60; 48.00%)	L, P 2 & 12 mos Ax naTBI (9.80±8.00) aTBI (12.60±10.30) TDC (11.70±8.60)	**BAYLEY Mental Developmental index** Cm naTBI, moderate naTBI & severe naTBI < aTBI (12 mos)					**Toy-centered activity** Initiating social interactions aTBI < naTBI & TDC (2 & 12 mos)				**VABS** Socialization sTBI < cmTBI & mod TBI (12 mos) Communication naTBI < aTBI (severe aTBI < cm aTBI &

											Joint attention sTBI < cmTBI & mod TBI (2 & 12 mos)				moderate aTBI) (12 mos)
Keenan et al. (2007)[+]	All severity naTBI & aTBI (48; 57.70%)	<2 yrs 1.80 – 9.90 (4.20 median)	n-aTBI (25; 52.00%) aTBI NA (23; 48.00%)	TDC (31; NA)	L, P Ax naTBI (3.10±NA) yrs aTBI (3.20±NA) yrs TDC (3.60±0.30) yrs	**MSEL** Development Composite score TBI < TDC < 3 SDs naTBI (40.00%) (RR: 2.60) vs aTBI (4.30%)									**SIB-R** Adaptive behavior TBI (average) < TDC ≥ 3 SDs n-aTBI (RR: 1.6) vs aTBI
aTBI & naTBI															
Bonnier et al. (2007)	sTBI (50; 62.00%) (40; NA) naTBI (29; NA) aTBI (21; NA)	< 3 yrs (12.50±15.00)	naTBI (29; 100%) aTBI MVA (passenger) (12; 57.14%)	None	R NA (6.60±3.90 yrs)	**WPPSI-R/WISC-III/ K-ABC/Brunet-Lézine** Verbal IQ (11/28) Deficient Nonverbal IQ (8/24) Deficient Development (24/46) Deficient	**NEPSY** Visual selective (20/33) Deficient Auditory selective (18/43) Deficient **TEA** Visual RT (20/25) Deficient Auditory RT (24/34) Deficient	**NEPSY** Cognitive flexibility (25/35) Deficient Inhibition (26/35) Deficient Planning (14/26) Deficient **WISC-III/K-ABC** Auditory WM (14/27) Deficient		**EEL/BEP** Expressive language (25/48) Deficient					
Ewing-Cobbs et al. (2006)	msTBI (23; NA)(23; 52.00%) naTBI (10; NA) aTBI	4-71 (21.20±21.90)	naTBI (10; 47.62% 0f msTBI) aTBI Falls	TDC (21; 47.00%)	L, P 3.80-8.30 yrs (5.70±NA) Ax msTBI (89.60±26.20) TDC	**SB4** Composite score 10th %ile: msTBI (48.00%) TDC (19.00%)		**SB4** Bead memory visual short-term memory msTBI = TDC (ns)		**SB4** Vocabulary, pattern analysis, memory for sentences		**WJ-III** Maths msTBI < TDC **GORT-4**			

	(13; NA)		(5; 38.00%)		(101.00±29.00)					msTBI < TDC		Comprehension, Reading & Writing msTBI < TDC **Unfavorable academic outcome** 48% msTBI 5% TDC OR = msTBI 18x > TDC			
Ewing-Cobbs et al. (2004)	msTBI (44; NA) Young (18; 55.56%) Old (26; 50.00%) naTBI (NA; 41.00%) aTBI (NA; 59.00%)	NA Young: (11.20±9.40) Old: (34.20±22.20)	NA	TDC (26; 46.00%)	L, P Young: 11.30 mos Old: 26.80 mos Ax msTBI Young: 11-35 (22.55±5.26) Old: 36-85 mos (61.00±12.66) TDC Young: (22.62±7.53) Old: (57.92±15.59)		**Stationary boxes** Visual scanning msTBI = TDC (ns)	**Delayed response** Visual Working Memory & Inhibitory Control msTBI < TDC **Spatial Reversal** Cognitive flexibility msTBI = TDC (ns)						
Keenan et al. (2018)	n-aTBI & aTBI naTBI & aTBI (386; 64%) mTBI (144; 61%) cmTBI (130; 68%) modTBI (26; 31%) sTBI (86; 72%)	2,5-15 yrs (9.20±4.20) Age groups: 2,5-6 yrs 6-11 yrs 12-<16 yrs	All ages naTBI (2; 1.00%) aTBI Falls (143; 37.00%)	OI (133; 63.00%)	L, P Pre-injury, 3 & 12 mos			**BRIEF/-P** TBI = OI (ns, pre-injury) Inhibitory self-control & metacognition TBI > OI (3 & 12 mos) Working memory mTBI > cmTBI & mod TBI & sTBI & OI (pre-injury) TBI > OI					**SDQ** Total difficulties TBI = OI (ns, pre-injury) sTBI > OI (3 & 12 mos) **CBCL** All subscales TBI = OI (ns, pre-injury)		

								(3 & 12 mos)					Affective, Anxiety & ADHD TBI > OI (3 & 12 mos)		
Keenan et al. (2019)	All severity naTBI & aTBI (123; 55.00%) mTBI (48; 54.00%) cmTBI (45; 47.00%) modTBI (7; 78.00%) sTBI (21; 67.00%)	0-30 (11.60±9.00)	n-aTBI Falls (85; 69.00%) aTBI (21; 17.00%)	OI (45; 60.00%)	L, P Pre-injury, 3 & 12 mos			**ASQ-3** Problem solving Pre-injury 33% sTBI vs 7% OI ≤ 2nd %ile 3 & 12 mos sTBI < OI		**ASQ-3** Communication Pre-injury 24% sTBI vs 2% OI ≤ 2nd %ile 3& 12 mos sTBI < OI			**ASQ-3** Socio-emotional 3& 12 mos sTBI < OI	**ASQ-3** Personal-social 3& 12 mos sTBI < OI	
Kieslich et al. (2001)+	Severe naTBI & aTBI (318; 63.80%)	<2 yrs (64; NA%) 2-6 yrs (38; NA%) > 6 yrs (98; NA%)	aTBI High-velocity injuries (NA; 61.40%) naTBI (NA; 6.60%)	None	R NA (8 yrs, 9 mos±NA)	**FMOS** Normal Development < 2 yrs: 25 (39.10%) 2-6 yrs: 37 (42.10%) Intellectual and/or academical retardation < 2 yrs: 39 (61.10%) 2-6 yrs: 51 (58.00%)						**FMOS** Intellectual and/or academical retardation < 2 yrs: 39 (61.10%) 2-6 yrs: 51 (58.00%)			
Vassel-Hitier et al (2019)	msTBI (21; 40.40) aTBI (8; 62.50%) naTBI (13; 61.50%)	< 18 mos (0.70±0.5) mos aTBI 0.20-1.60 (0.90±0.60) yrs naTBI 0.10-1.10 (0.50±0.30) yrs	aTBI Falls (5; 62.50%) naTBI NA	None	L (C-S), P 7 yrs 3.60-9.40 (6.80±1.80) yrs	**WPPSI-III/WISC-IV** VIQ/VCI 57.10% < 80 PSQ/PSI 76.20% < 80				**Brunet-Lezine revised Scale of infant development** Language/ Communication 67% borderline /deficit range		**Ongoing education** Mainstream school 38% Specialized institutions/classrooms 24% Repeated year/ adaptations 38%		**Brunet-Lezine revised Scale of infant development** Sociability 78% borderline/deficit range	**Brunet-Lezine revised Scale of infant development** Autonomy 78% borderline/deficit range

										% of all TBI with scores ≤- 1.5SD **EVIP-A** Receptive lexicon 57% **ELOLA** Lexical access skills 48% Semantic organization 32% ***Oral comprehension strategies assessment test 0-52** Syntactic comprehension 67% **TCG** Syntactic expression 62%					
Wetherington et al. (2010)*	naTBI & aTBI (51; NA) mTBI (31; 45.16%) msTBI (20; NA)	< 2 yrs mTBI (0.49±0.57) yrs msTBI (0.81±0.62) yrs	aTBI NA (26; NA%) naTBI NA (25; NA%)	TDC (31; 64.50%)	C-S, P ≈ 3 yrs Ax mTBI (3.33±0.38) msTBI (3.25±0.27)	**Mullen Scales of Early Learning** msTBI (low range) < mTBI (low to average) & TDC (average)							**CBCL** Withdrawal behavior msTBI > mTBI & TDC Other behaviors/problems msTBI = mTBI = TDC (ns)		

Note.

General

%ile = Percentile
*= mTBI articles that did not include specific criteria for identifying "an alteration in brain function, or other evidence of brain pathology, caused by an external force."
a = accidental
ax = assessment (age at assessment)
+= all TBI severity (mTBI, modTBI and sTBI) articles that did not include specific criteria for identifying "an alteration in brain function, or other evidence of brain pathology, caused by an external force."
n-a = non-accidental
NA = Non available
ns = non-significant
Sx = symptoms
*+ :the findings should be interpreted with caution and may include participants with unconfirmed TBI or very minor forms of head injury.

Injury severity
cmTBI = complicated mild traumatic brain injury
mTBI = mild Traumatic Brain Injury (otherwise specified refers to uncomplicated mild traumatic brain injury)
modTBI = moderate traumatic brain injury
msTBI = Moderate severe traumatic brain injury
sTBI = Severe traumatic brain injury

Age at injury
Mos = Months
Wk = Week
Yrs = Years

Control group
OI = Orthopedic injury
TDC = Typically Developing children

Study design, Follow-up time point post-injury
Ax = Assessment (age at assessment)
C-S = Cross-Sectional
L = Longitudinal
P = Prospective

R = Retrospective
T1 = Timepoint 1
T2 = Time point 2

Outcomes
%ile = Percentile
OR = Odds ratio
ns = non-significant
RR = Risk ratio
SD = Standard Deviation

Cognitive/Academic and behavioral and socio-affective outcomes
ABAS-II = Adaptive Behavior Assessment System - Second Edition
ADHD = Attention deficit hyperactivity disorder
ASQ-3 = Ages & Stages Questionnaire-3
ASQ:S-E = Ages and Stages Questionnaires: Social-Emotional
BBRS = Bayley Behavior Rating Scale
BEP = Batterie d'Évaluation Linguistique
BSID = Bayley Scales of Infant Development
BSID-II = Bayley Scales of Infant Development–Second Edition
BRI = Behavioral Regulation Index
BRIEF = Behavior Rating Inventory of Executive Function
BRIEF-P = Behavior Rating Inventory of Executive Function –Preschool Version
CBCL = Child Behavior Checklist
CELF-P = Clinical Evaluation of Language Fundamentals – Preschool version
CMS = Children Memory Scale
DAS = Different ability scale
DISC = Diagnostic Interview Schedule for Children
DKEFS = Delis–Kaplan Executive Function System
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4rth edition
DT = Double Task
EEL = Épreuve d'Évaluation du Langage
ELOLA = Mini batterie d'Évaluation du Langage Oral de L'enfant Aphasique
EVIP-A = Échelle de vocabulaire en images Peabody (A)
FMOS = Frankfurt Mental Outcome Scale for children
FSIQ = Full-scale intellectual quotient
GAC = Global adaptive composite
GORT-4 = Gray Oral Reading Tests 4th edition
IQ = Intellectual Quotient
ITPA = Illinois test of psycholinguistic abilities

K-ABC = Kaufman Assessment Battery for Children
MI = Metacognition Index
MPAI-P = Mayo-Portland Adaptability Inventory – Pediatric
MRO = Mutually Responsive Orientation scale
MSEL = Mullen Scales of Early Learning
MVA = motor vehicle accident
NEPSY = A developmental neuropsychological assessment
NEPSY-II = A developmental neuropsychological assessment - Second edition
ODD = Oppositional defiant disorder
Oral comprehension strategies assessment test 0-52 = Épreuve d'évaluation des stratégies de compréhension en situation orale 0-52
PAT = Progressive achievement test
PCDI = Parent-Child Dysfunctional Interaction (In Parental Stress Index – Brief)
PEDI = Pediatric Evaluation of Disability Inventory
PIQ = Performance intellectual quotient
PSI = Processing Speed Index
RAPI = Rutgers Alcohol Problems Index
RBPC = Revised Behavior Problems Checklist
SDQ = Strength and Difficulties Questionnaire
SERD = Self-Report Early Delinquency scale
SIB-R = Scale of Independent Behavior-Revised
SPRS-C = Sydney Psychosocial Reintegration Scale for Children
SSRS = Social Skills Rating System – Preschool version
SB4/SB-IV = Stanford-Binet Intelligence scale 4th edition
TCG = Test de Closure Grammaticale
TEA-Ch = Test of Everyday Attention for Children
ToM = Theory of Mind
VABS = Vineland Adaptive Behavior Scales-First Edition
VCI = Verbal comprehension index
VIQ = Verbal intellectual quotient
WIAT= Wechsler Individual Achievement Test
WISC = Wechsler Intelligence Scale for Children
WISC-III = Wechsler Intelligence Scale for Children Third Edition
WISC-IV = Wechsler Intelligence Scale for Children - Fourth Edition
WISC-R = Wechsler Intelligence Scale for Children - Revised
WJ-III = Woodcock-Johnson III Tests of Achievement
WM = Working memory
WPPSI-III = Wechsler Preschool and Primary Scale of Intelligence – Third edition
WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence Revised

Table 2. Risk Of Bias For Studies Reporting Outcomes Following Accidental TBI

Author, Year	**Participation**	**Attrition**	**Outcomes**	**Confounding**	**Analysis**
Bellerose et al., 2015	Partly	Partly	No	No	No
Bellerose et al., 2017	No	Partly	No	No	No
Coster et al., 1994	Partly	Partly	No	Partly	Partly
Crowe et al., 2014	Partly	Partly	No	No	No
Crowe et al., 2012 (intellectual)	Partly	Partly	No	No	No
Crowe et al., 2013	No	No	No	No	No
Crowe et al. 2012 (Timing)	No	N/A	No	No	No
Dégeilh et al., 2018	No	Partly	No	No	No
D'Hondt et al., 2017	Partly	N/A	No	No	No
Gagner et al. 2018	No	Partly	No	No	No
Green et al., 2013	Partly	Yes	No	Partly	Partly
Kaldoja et al., 2015	Partly	Yes	Yes	No	No
Lalonde et al., 2016	No	Yes	No	No	No
Landry-Roy et al., 2018	No	Partly	No	No	No
Liu et al. 2013	No	N/A	No	Partly	No
Marsh and Whitehead., 2005	Partly	N/A	No	No	No
McKinlay et al., 2014	Partly	Yes	No	No	No
McKinlay et al., 2002	No	Yes	No	No	No
McKinlay et al., 2010	Partly	Yes	No	No	No

McKinlay et al., 2009	Partly	Partly	No	No	No
Papoutsis et al., 2014	No	N/A	No	No	No
Pastore et al., 2013	Partly	N/A	No	Partly	No
Prasad et al., 1999	Partly	Yes	No	Yes	Partly
Sonnenberg et al., 2010	Partly	Yes	No	Partly	No
Tonks et al., 2011	Yes	N/A	No	Yes	Partly
Walz et al., 2009	Partly	N/A	No	No	No
Wrightson et al., 1995	Partly	Yes	No	No	No

Note. N/A : non applicable.

Table 3. Risk Of Bias For Studies Reporting Outcomes Following Non-Accidental and Accidental TBI

Author, Year	**Participation**	**Attrition**	**Outcomes**	**Confounding**	**Analysis**
Barlow et al., 2005	No	Partly	No	Partly	Partly
Beers et al., 2007	Partly	N/A	No	No	Partly
Bonnier et al., 2007	Partly	N/A	No	No	Partly
Ewing-Cobbs et al., 1998	No	Yes	No	No	Partly
Ewing-Cobbs et al., 1999	Partly	Yes	No	No	No
Ewing-Cobbs et al., 2006	Partly	Partly	No	No	No
Ewing-Cobbs et al., 2004	Partly	N/A	No	No	No
Ewing-Cobbs et al., 2013	Partly	Yes	No	No	No
Keenan et al., 2018	Partly	Yes	No	No	No
Keenan et al., 2007	No	Yes	No	No	Partly
Keenan et al. 2019	Partly	Yes	No	No	No
Kieslich et al., 2001	Partly	N/A	No	Yes	Partly
Landry et al., 2004	No	N/A	No	No	No
Stipanicic et al., 2008	Partly	N/A	No	No	Partly
Vassel-Hitier et al. 2019	No	Yes	No	Partly	Partly
Wetherington et al., 2010	Partly	N/A	No	No	No

Note. N/A : non-applicable.

Table 4. Challenges Associated With Conducting Early TBI Research, Methodological Limitations And Recommendations For Future Work and Initiatives

	Current limitations	**Challenges**	**Recommendations**	**Possible avenues-actions**
Definition & Diagnosis	No definition for diagnosing early mTBI and no consensus on the list of commonly accepted inclusion criteria	Children 5 years and under may not exhibit the same signs and symptoms of TBI as older children, adolescents or adults	Develop a consensus to establish a common definition and diagnostic criteria	Organize consensus working groups, special interest groups, and panels of experts
Terminology	Numerous terms are used within the literature across age groups	Early childhood TBI includes several developmental subgroups	Ensure that terms are clearly operationalized and defined	Define early childhood TBI (or early TBI) as sustained in children 5 years and under
				Use developmental labels such as infants, toddlers and preschoolers to help define age subgroups
	Variability in the terms used to describe mechanisms	Terms related to mechanism have evolved over time	Ensure most current terms are used	Report breakdown of mechanisms and causes in study results

Sample composition	Interpretations regarding the nature and severity of outcomes are often confounded by age, mechanism, and severity	Modest sample sizes and multiple levels of analysis limit the possibility of creating subgroups for comparison	Report groups according to mechanism, age, sex and gender	Provide descriptive data and fine-grained information to allow for future meta-analyses when sample sizes are too small to reliably compare subgroups
	Not all studies use comparison groups	Putative differences between comparison and TBI groups are difficult to ascertain given short pre-morbid history and lack of knowledge on emergent conditions	Include at least one comparison group	Continue to document potential differences between typically developing and orthopedically injured children
Design	Few longitudinal designs and long-term outcomes seldom measured	Young children develop extremely rapidly and constructs and tasks appropriate at one age may not be a few months or years later	Continue to encourage longitudinal approaches to better characterize the full scope of consequences across the lifespan	Use developmentally appropriate constructs and tests at each age, and incorporate some core constructs/measures that can be tracked over time and across developmental

				groups, allowing trajectory analyses
Assessment	Some domains (e.g., behavioral, social) almost exclusively based on third party questionnaires with limited or no direct measurement	Fewer standardized measures in early childhood (relative to older children)	Reduce bias by including a mix of questionnaires, observational coding and direct measurement	Consider developmentally appropriate and valid experimental paradigms to document cognitive, social and behavioral outcomes alongside commonly used standardized measures
	No reports of performance validity	Threats to effort and validity due to cooperation and participant challenges at young ages	Document behavior and reasons for reduced participation throughout direct assessment	Include stand-alone and/or embedded measures of validity to all assessment batteries for children ages 5+. Use detailed missing data codes and/or score behavior using observational measures during assessment

		Few or no measure of validity for children 4 and younger	Develop standardized measures of validity for this age group	Consider validating effort performance tests in children under 5 years
Measures	Numerous different measures used across studies precluding direct comparisons across the literature	Few detailed guidelines exist regarding potential common data elements for early TBI	Continue to develop common data elements based on empirical findings in early TBI	Consider experimental tasks that have demonstrated validity as potential measurement tools
Outcome Domains	Broad range of outcomes studied, but almost no information regarding post-concussive symptoms	Infants and toddlers have limited verbal abilities to report abstract symptoms typical of PCS	Limit downward extension of existing measures and instead use developmentally appropriate approaches	Rely on observational approaches in addition to third party reports for collecting data on PCS in children with limited verbal skills