Université de Montréal

Qu'en est-il des tout-petits?

Conséquences d'un traumatisme crânio-cérébral durant la petite enfance

Par

Marilou Séguin

Département de psychologie, Faculté des Arts et Sciences

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Résumé

Le traumatisme crânio-cérébral (TCC) précoce (c.-à-d. subi pendant la petite enfance) constitue l'une des blessures les plus énigmatiques, car il touche à un organe complexe et survient lors d'une période sensible du développement. Or, malgré des données épidémiologiques indiquant une incidence particulièrement élevée du TCC en bas âge, et en dépit des préoccupations grandissantes concernant son impact potentiel sur le fonctionnement et le bien-être, le TCC précoce demeure un problème de santé publique peu connu en comparaison à celui subi chez les enfants d'âge scolaire et dans les contextes sportifs. Aussi, plus souvent qu'autrement, les objectifs, hypothèses, construits et théories étudiés chez le jeune enfant sont extrapolés de ceux utilisés chez les individus plus âgés. Ainsi, ils ne sont pas toujours choisis en prenant en considération les enjeux développementaux particuliers de la petite enfance limitant notre compréhension globale et affinée des conséquences suivant un TCC précoce. Alors, qu'en est-il des tout-petits? L'objectif général de la thèse était de recenser la littérature empirique qui documente les conséquences d'un TCC en bas âge et d'étudier les effets d'une telle blessure sur un domaine de fonctionnement clé de la petite enfance, notamment le tempérament.

Le premier article de la thèse est une revue systématique de la littérature dont l'objectif était de recenser et synthétiser les trouvailles concernant les conséquences cognitives et comportementales suivant un TCC subi durant la petite enfance. Quatre bases de données ont été examinées de 1990 à 2019 en utilisant des termes clés relatifs au TCC et à la petite enfance. Sur 12 153 articles identifiés lors de la recherche initiale, 43 ont été inclus. Cette revue met en lumière qu'un éventail de difficultés peut survenir à la suite d'un TCC précoce lesquelles sont généralement

plus importantes et néfastes lorsque la blessure a été subie à un jeune âge, que sa sévérité est plus grave et que les causes de cette blessure sont non-accidentelles.

Le deuxième article est une étude empirique qui visait à explorer l'effet d'un TCC précoce sur le tempérament, lequel représente la tendance comportementale du jeune enfant, c.-à-d. sa façon de réagir et de s'adapter à son environnement. Ce construit constitue un facteur prédictif important du devenir de l'enfant dans plusieurs domaines de fonctionnement et pourrait ainsi être particulièrement approprié afin d'approfondir et de préciser les connaissances quant aux conséquences d'un TCC durant la petite enfance. Les parents de 173 jeunes enfants (âge: 36 ± 12 mois) ayant subi un TCC léger simple (n = 83), un TCC plus sévère (léger complexe, modéré ou sévère, n = 21) ou une blessure orthopédique (n = 69) ont rempli un questionnaire reflétant les profils de tempérament de leur enfant avant la blessure (rétrospectivement) et à 6 et 18 mois suivant la blessure. Les résultats révèlent que les enfants qui ont subi un TCC plus sévère présentent une évolution plus lente de la trajectoire développementale de la dimension *Dynamisme* du tempérament. En d'autres mots, ces enfants manifestent un niveau d'activité réduit se traduisant par un niveau d'énergie plus faible, une recherche de plaisir à haute intensité diminuée, ainsi qu'une timidité plus importante face à la nouveauté.

De façon générale, cette thèse met en évidence que la survenue d'un TCC au cours de la petite enfance, une période sensible pour l'émergence d'habiletés cognitives et sociales de base, peut occasionner un large éventail de conséquences, et ce, même au plan de la trajectoire du tempérament. Étant donné l'importante prévalence du TCC durant la petite enfance, ainsi que le potentiel de conséquences défavorables, il est essentiel que la recherche, la gestion clinique, l'intervention et les efforts de prévention soient davantage développés de manière à tenir compte des caractéristiques uniques de la petite enfance.

Mots-clés: TCC accidentel; TCC non-accidentel; petite enfance; revue systématique; conséquences; cognition; comportement; tempérament; environnement; parent.

Abstract

Pediatric Traumatic Brain Injury (TBI) constitutes one of the most enigmatic insults, as it affects a complex organ and occurs at a sensitive period in the developmental course. Despite epidemiological data indicating a particularly high incidence of TBI during early childhood and growing concerns regarding its potential impact on child functioning and well-being, early TBI remains a poorly studied public health problem, especially compared to TBI sustained by schooled-aged children and in sports settings. Also, all too often, the objectives, hypotheses, constructs and theories studied in young children with TBI are extrapolated from those used in older individuals and therefore rarely chosen in consideration of the developmental concerns specific to early childhood. These issues limit a comprehensive and refined understanding of the consequences of early TBI. So, what about the little ones? The general objective of the thesis was to review the current state of the empirical literature pertaining to children who have sustained TBI during early childhood, and to study the impact of early TBI on a key domain of this developmental period, namely temperament.

The first article presented in the thesis is a systematic review of the literature aiming to identify and synthetize the findings concerning cognitive and behavioral consequences following early TBI. Four databases were searched from 1990 to 2019 using key terms related to TBI and early childhood. Of 12,153 articles identified during the initial search, 43 were included. This review of the literature highlights that children who sustain early TBI display a range of difficulties which are generally more pronounced and detrimental when injury is more severe, sustained at a young age, and the cause is non-accidental.

The second article constitutes an empirical study aiming to explore temperament after early TBI. Temperament refers to young children's behavioral tendencies, that is, their way of reacting and adapting to their environment. Besides constituting an important predictor of outcome in several areas of functioning, this construct also takes into account the developmental reality of the young child and could thus be particularly suited to investigate and clarify the consequences of early childhood TBI. Parents of 173 young children (age: 36 ± 12 months) with simple mTBI (n = 83), more severe TBI (mild complicated, moderate or severe, n = 21) or orthopedic injury (n = 69) completed a questionnaire reflecting their child's temperament profile before the injury as well as at 6 and 18 months following the injury. The results reveal that children who sustain more severe TBI experience a slower evolution of the developmental trajectory of the *Surgency* dimension of temperament. In other words, these children exhibit a reduced activity level which is reflected by less energy, a reduced desire for high-intensity pleasure-seeking, as well as greater shyness in the face of novelty.

In general, the thesis highlights that the occurrence of TBI during early childhood, a sensitive period for the emergence of basic cognitive and social skills and a time when environmental influences are particularly salient, can cause a large range of consequences, even affecting the trajectory of temperament. Given the high prevalence of TBI in early childhood and the potential for adverse outcomes, it is essential that research, clinical management, intervention and prevention efforts be further developed based on the empirical literature, and in a manner that takes into account the unique characteristics of early childhood.

Keywords: accidental TBI; non-accidental TBI; early childhood; systematic review; consequences; cognition; behavior; temperament; environment; parent.

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Liste des sigles

c.à.d.	c'est-à-dire
e.g.	exempli gratia (for example)
ex.	exemple
i.e.	id est (that is)
vs	versus

Liste des abréviations

AAP	American Academy of Pediatrics
AHT	Abusive Head Trauma
APT	Amnésie post-traumatique
ASPC	Agence de Santé Publique du Canada
BO	Blessure Orthopédique
CBQ	Childhood Behavior Questionnaire
CDC	Centers for Disease Control and Prevention of the United States
ECBQ	Early Childhood Behavior Questionnaire
GCS	Glasgow Coma Scale
IBQ	Infant Behavior Questionnaire
SBS	Syndrome du bébé secoué
SPC	Symptôme post-commotionnel
SSE	Statut socio-économique
TBI	Traumatic Brain Injury
TCC	Traumatisme crânio-cérébral
TCCL	Traumatisme crânio-cérébral léger
TCCa	Traumatisme crânio-cérébral accidentel
TC-ME	Traumatisme crânien causé par la maltraitance des enfants
TCCna	Traumatisme crânio-cérébral non-accidentel

À tous ces enfants dont

cette blessure invisible a teinté leur couleur

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CHAPITRE 1 – INTRODUCTION GÉNÉRALE

Positionnement du problème

Le traumatisme craniocérébral pédiatrique (TCC, subi avant l'âge de 18 ans) peut engendrer des conséquences physiques, cognitives et sociales majeures (Thurman, 2016). Par ailleurs, les jeunes enfants âgés de cinq ans et moins constituent le groupe le plus à risque de subir un TCC et présentent certaines caractéristiques les rendant susceptibles à des effets défavorables. En effet, le cerveau du jeune enfant est particulièrement vulnérable à ce type de blessure en raison des facteurs physiologiques et développementaux propres à cette période. Or, le TCC précoce (c.-à-d., subi durant la petite enfance; 0-5 ans) demeure un problème de santé publique peu étudié en comparaison aux autres groupes développementaux et contextes (p. ex., enfants plus âgés et sportifs) et ce, malgré les préoccupations grandissantes concernant son impact important sur le développement harmonieux de l'enfant.

Bien que la petite enfance soit une période développementale unique, la façon d'étudier les conséquences du TCC en bas âge est souvent calquée sur celle utilisée chez les enfants plus âgés ou même les adultes. En effet, à ce jour, les chercheurs et cliniciens ont tendance à baser leur exploration sur les mêmes domaines que ceux déjà étudiés chez les individus plus âgés tels que le fonctionnement cognitif (p. ex., fonctions exécutives) et peu se sont penchés sur des construits propres à la période développementale dans laquelle se retrouve le jeune enfant. Pourtant, plusieurs d'entre-eux représentent des prédicteurs et déterminants importants du bon développement du jeune enfant et se manifestent uniquement en bas âge. L'attention conjointe, le tempérament, l'attachement et la relation parent-enfant en sont des exemples. Certains de ces domaines de fonctionnement sont également fréquemment utilisés en psychologie développementale comme des marqueurs et facteurs prédictifs de la compétence globale de l'enfant. Entre autres, le tempérament, un construit central et un facteur important pour le bon développement de plusieurs

autres fonctions tant cognitives, comportementales que socio-émotionnelles, pourrait constituer une variable-clé pour avoir une meilleure compréhension du fonctionnement de l'enfant après un TCC précoce. Le tempérament, c.-à-d. la tendance comportementale de l'enfant, ses principaux traits et la façon dont il va réagir et s'adapter à son environnement, n'a toutefois jamais été utilisé comme angle de recherche chez le jeune enfant ayant subi un TCC.

La présente thèse avait donc pour objectif général de recenser et approfondir les connaissances sur les conséquences d'un TCC subi durant la petite enfance. Les objectifs spécifiques étaient de synthétiser les résultats concernant les conséquences cognitives et comportementales suivant un TCC durant la petite enfance et d'explorer son effet sur le tempérament. Le premier chapitre de la thèse est consacré à une introduction générale et présente des informations concernant la définition, l'épidémiologie, la pathophysiologie, et les prédicteurs du TCC. Les considérations développementales propres à la période de la petite enfance sont également abordées dans cette section. Dans le deuxième chapitre sont présentées les conséquences cognitives et comportementales suivant un TCC précoce sous forme d'une revue systématique. Dans le troisième chapitre, le tempérament est détaillé et l'effet d'un TCC en bas âge sur les dimensions du tempérament à travers le temps est exploré et présenté sous forme d'un article empirique. Finalement, le dernier chapitre de la thèse sera dédié à une discussion générale des résultats, suivie des implications théoriques et cliniques de la thèse, de même que ses limites et les avenues futures à prioriser.

Traumatisme crânio-cérébral précoce

Définitions

Le TCC est défini comme étant une altération du fonctionnement cérébral ou autre évidence d'atteinte cérébrale causée par une force physique extérieure de laquelle découle un transfert d'énergie vers la boîte crânienne et les structures cérébrales sous-jacentes (p. 1637; Menon et al., 2010; traduction libre). L'altération du fonctionnement cérébral peut se manifester par une perte ou une altération du niveau de conscience et/ou une altération de l'état mental au moment de la blessure (p. ex., confusion, désorientation) et/ou une amnésie post-traumatique de l'événement (p. ex., l'enfant n'a aucun souvenir de ce qu'il a fait avant, pendant ou après l'événement) et/ou des signes neurologiques (p. ex., perte d'équilibre, altération de la vision).

Au cours de la petite enfance, deux types de TCC peuvent survenir: le TCC de cause accidentelle (TCCa) ou non-accidentelle (TCCna). Le TCC (accidentel ou non) peut également être subdivisé en deux autres catégories selon s'il est associé à une blessure ouverte ou fermée. Une blessure ouverte (ou pénétrante) implique une atteinte cérébrale avec ouverture ou fracture du crâne et peut être causée par une arme blanche (p. ex., couteau), un projectile d'arme à feu ou un accident de voiture à haute vélocité. Quant à une blessure fermée, celle-ci implique une altération cérébrale sans plaie ouverte ni pénétration du crâne et peut être occasionnée par une chute et les forces linéaires et rotatoires impliquées sans que la tête soit heurté et/ou par une collision de la tête avec un objet. Les TCC (TCCa et TCCna) associés à une blessure de type fermé sont la forme la plus prévalente et seront donc exclusivement abordés dans le présent ouvrage.

De façon générale, le TCCa survient lors d'un accident traumatique accidentel impliquant une force physique extérieure appliquée au cerveau, par exemple, lorsque la tête heurte un objet (p.

ex., chute) ou est atteinte par celui-ci (p. ex., activités récréatives) et/ou lors d'une accélération et/ou décélération rapide de la boîte crânienne sans un impact externe direct à la tête (coup de fouet; ex. accident de la route). Un TCCna survient, quant à lui, à la suite de l'application d'une force intentionnelle, c.-à-d. causée par autrui (p. ex., secouement et/ou impact à la tête). Il est important de préciser que bien que l'auteur d'un tel geste n'ait pas nécessairement l'intention de causer des dommages ou des blessures à l'enfant, la force qu'il utilise est dite « intentionnelle » comparativement à celle impliquée dans un accident comme lors d'une chute. Ainsi, puisque les enfants peuvent présenter des histoires, blessures physiques et résultats radiologiques variés, les termes « traumatisme crânien/crânio-cérébral non accidentel » et « Abusive Head Trauma (AHT) » sont maintenant plus communément utilisés pour regrouper l'ensemble des accidents qui peuvent survenir de façon « non-accidentelle ». En 2009, l'Académie américaine de pédiatrie (American Academy of Pediatrics; AAP) a, par ailleurs, émis une recommandation quant à l'utilisation d'une terminologie plus générale et inclusive « Abusive Head Trauma » plutôt qu'un terme plus spécifique impliquant seulement un mécanisme de blessure (p. ex., secouement violent) tel que le « Syndrome du bébé secoué (SBS) », antérieurement utilisé (Christian et Block, 2009). Ainsi, selon les Centres pour le contrôle et la prévention des maladies des États-Unis (Centers for Disease Control and Prevention of the United States; CDC) et l'Académie américaine de pédiatrie (American Academy of Pediatrics; AAP), le TCCna ou l'AHT, est plus spécifiquement défini comme un ensemble de blessures qui surviennent lorsqu'un enfant est soumis à une accélération-décélération et des forces rotationnelles, avec ou sans impact (p. ex., secouement), qui causent des lésions intracrâniennes et/ou cervicales et/ou des blessures physiques (Chiesa et Duhaime, 2009; Christian et Block, 2009).

Au Québec, suite à la plus récente mise à jour de la Déclaration conjointe sur le syndrome du bébé secoué, le terme maintenant privilégié par l'Agence de Santé Publique du Canada (ASPC) pour représenter ce type de blessure (c.-à-d., bébé secoué) est le « traumatisme crânien causé par la maltraitance des enfants » (TC-ME; ASPC, 2020a). Ce terme devant être employé précautionneusement qu'à la fin d'un processus d'évaluation multidisciplinaire (médical, social et légal). Afin d'arrimer la terminologie avec celle employée dans les milieux cliniques québécois, nous utiliserons le terme TCCna pour définir une blessure cérébrale non-accidentelle et considérerons le TC-ME comme faisant partie du TCCna. Dans la présente thèse, les termes TCC accidentel (TCCa) et non-accidentel (TCCna) seront utilisés et lorsque non spécifié, le terme TCC fera référence aux deux types de blessure. De plus, la nomenclature suivante sera utilisée de façon interchangeable pour désigner un TCC subi pendant la période de la petite enfance, c.-à-d. de la naissance à l'âge de cinq ans inclusivement: TCC précoce ou TCC en bas âge.

Classification de la sévérité

Selon les signes probants répertoriés à la suite d'un accident, on classifie généralement la sévérité du TCC en trois catégories soit léger, modéré ou sévère/grave (voir Tableau 1). Cette classification est faite à partir de plusieurs critères dont les principaux sont le score à l'échelle de coma de Glasgow (GCS; Teasdale et Jennett, 1974), la durée de l'altération ou de la perte de conscience, la présence d'une lésion identifiable aux examens radiologiques, les résultats de l'examen neurologique et la durée de l'amnésie post-traumatique (APT).

Tableau 1. Classification de la sévérité du TCC

CARACTÉRISTIQUES	CATÉGORIE DE SÉVÉRITÉ DU TCC		
	LÉGER	**MODÉRÉ**	**SÉVÈRE/GRAVE**
Durée de la perte ou de l'altération de conscience	0-30 minutes	30 minutes à 6h, maximum 24h	> 24h à plusieurs jours, mais obligatoirement > 6h
Résultat obtenu à l'échelle de coma de Glasgow*	13 à 15	9 à 12	3 à 8
Lésions objectivées (fracture ou lésion intracrânienne)	Imagerie cérébrale: positive ou négative	Imagerie cérébrale: généralement positive	Imagerie cérébrale: positive
Examen neurologique	Positif possible (signes focaux possibles)	Positif (signes focaux)	Positif (signes focaux)
Amnésie post-traumatique (APT)	≤ 24h	1-14 jours	Plusieurs semaines

Note. Adaptation des « Orientations ministérielles du Québec pour le traumatisme craniocérébral léger 2005-2010 » par la Direction générale des services de santé et de médecine universitaire, Gouvernement du Québec, 2005, p. 34.
TCC = traumatisme crânio-cérébral.
* à l'urgence ou 30 minutes après le TCC.

L'échelle de coma de Glasgow (GCS) évalue l'état de conscience à partir de trois critères: la réponse motrice, la réponse verbale et l'ouverture des yeux. Pour les enfants âgés de cinq ans et moins (Tableau 2), le score est dérivé à partir d'une échelle adaptée (Reilly et al., 1988; Simpson et Reilly, 1982) où, par exemple, le sourire, les pleurs, les gémissements ainsi que la poursuite d'objets sont des équivalents pour la réponse verbale de l'échelle standard (> 5 ans).

Tableau 2. Échelles de Coma de Glasgow en fonction de l'âge

Échelle de Glasgow standard (> 5 ans)	Échelle de Glasgow (2 à 5 ans)	Échelle de Glasgow (0 à 2 ans)
Ouverture des yeux		
4 – spontanément 3 – aux stimuli verbaux 2 – aux stimuli douloureux 1 – aucune réponse	4 – spontanément 3 – aux stimuli verbaux 2 – aux stimuli douloureux 1 – aucune réponse	4 – spontanément 3 – aux stimuli verbaux 2 – aux stimuli douloureux 1 – aucune réponse
Réponse verbale		
5 – est orienté et parle 4 – est désorienté et parle 3 – paroles inappropriées 2 – sons incompréhensibles 1 – aucune réponse	5 – mots appropriés, sourit, fixe, suit du regard 4 – mots appropriés, pleure, est consolable 3 – hurle est inconsolable 2 – gémit aux stimuli douloureux 1 – aucune réponse	5 – agit normalement 4 – pleure 3 – hurlements inappropriés 2 – gémissements 1 – aucune réponse
Réponse motrice		
6 – répond aux demandes 5 – localise la douleur 4 – se retire à la douleur 3 – flexion à la douleur (décortication) 2 – extension à la douleur (décérébration) 1 – aucune réponse	6 – répond aux demandes 5 – localise la douleur 4 – se retire à la douleur 3 – flexion à la douleur (décortication) 2 – extension à la douleur (décérébration) 1 – aucune réponse	6 – mouvements spontanés intentionnels 5 – se retire au toucher 4 – se retire à la douleur 3 – flexion à la douleur (décortication) 2 – extension à la douleur (décérébration) 1 – aucune réponse

Note. Adaptation de « Traumatisme crânien léger (score de Glasgow de 13 à 15): triage, évaluation, examens complémentaires et prise en charge précoce chez le nouveau-né, l'enfant et l'adulte » par Jehlé, E. et al., 2012, *Annales françaises de médecine d'urgence,* 2(3), Annexe.

Dans la catégorie TCC léger (TCCL), on peut également retrouver le TCCL « non complexe/simple » et le TCCL « complexe ». Le TCCL « non complexe/simple » ou *uncomplicated mild TBI* en anglais, aussi couramment appelé « commotion cérébrale »,

n'implique pas de lésion identifiable à l'imagerie cérébrale classique (p. ex., CT-Scan) alors que le TCCL « complexe » ou *complicated mild TBI* implique, quant à lui, toutes les caractéristiques du TCCL « non complexe » aussi appelé TCC « simple » (une altération/perte de l'état de conscience (0-30 minutes), un score à l'échelle de coma de Glasgow entre 13 et 15, et une amnésie post-traumatique (≤ 24h)), auxquelles s'ajoute une pathologie cérébrale identifiable et objectivée par une imagerie cérébrale classique (Mayer et al., 2017; Williams et al., 1990).

À la suite d'un TCC toutes sévérités confondues, des changements touchant les sphères physique (p. ex., maux de tête, étourdissements, problèmes de sommeil), cognitive (p. ex., confusion, désorientation, difficultés de concentration) et comportementale (p. ex., irritabilité, anxiété) peuvent survenir (Yeates et al., 2009; Zemek et al., 2016). Ces symptômes post-commotionnels (SPC) ne constituent pas des critères formels et objectifs de classification, mais peuvent être, par leur nombre et leur intensité, des indicateurs du niveau de sévérité (Zeldovich et al., 2020) . Les SPC tendent à être davantage intenses et fréquents peu de temps après la blessure (Bernard et al., 2016; Sicard et al., 2020; Whitecross, 2020; Zemek et al., 2016). À la suite d'un TCC léger, ces symptômes s'amendent généralement dans un délai d'un mois, mais peuvent persister au-delà de cette période dans environ 31% des cas (Yeates et al., 2009; Zemek et al., 2016). Chez le jeune enfant, bien que certains de ces symptômes aient été répertoriés (Podolak et al., 2020; Suskauer et al., 2018), l'évaluation des SPC est particulièrement difficile en raison des limites langagières (p. ex., phase pré-verbale) et cognitives (p. ex., capacités d'abstraction), mais également puisqu'il existe à ce jour peu d'outils validés pour cette tranche d'âge. Selon une étude préliminaire de validation d'un outil observationnel des SPC (Dupont et al., 2021), les parents de jeunes enfants (0-5 ans) rapporteraient, dans les jours suivants le TCC léger (TCCL), la présence de symptômes physiques tels que des maux de tête, des problèmes d'équilibre et de sommeil, une

plus grande sensibilité aux bruits, ainsi que davantage de manifestations comportementales en lien avec l'humeur (p. ex., pleure davantage en général et quand il est séparé de ses parents) et une plus grande demande de réconfort (p. ex., veut être pris dans les bras). De plus, ces parents rapportent que les problèmes de sommeil et les demandes de réconfort sont présents un mois après le TCCL. De façon intéressante, bien que les difficultés de sommeil soient aussi présentes chez les enfants plus vieux (Yeates et al., 2009; Zemek et al., 2016), la demande de réconfort, elle, représente une nouvelle catégorie de SPC qui se voit davantage adaptée à la petite enfance et qui pourrait favoriser une meilleure détection et observation de ceux-ci chez cette population.

Épidémiologie

Le TCC pédiatrique est un problème de santé publique majeur à travers le monde. En utilisant les estimations d'incidence les plus conservatrices, c.-à-d. d'environ 50 cas par 100 000 de population, le TCC affecterait mondialement plus de trois millions d'enfants chaque année (Dewan et al., 2016; Dewan et al., 2018; Taylor et al., 2017). De plus, des résultats d'études épidémiologiques indiquent que les enfants âgés de cinq ans et moins constituent le groupe pédiatrique le plus à risque de subir un TCC (Thurman, 2016), avec un taux annuel de 1,85 pour 100 enfants, comparativement à un taux inférieur de 1,17 dans les autres groupes d'âge (entre 0 et 18 ans; McKinlay et al., 2008). Au Canada, les enfants de 4 ans et moins représentent le groupe ayant le taux le plus élevé d'incidence comparativement aux autres groupes d'âge (ASPC, 2020b; Figure 1).

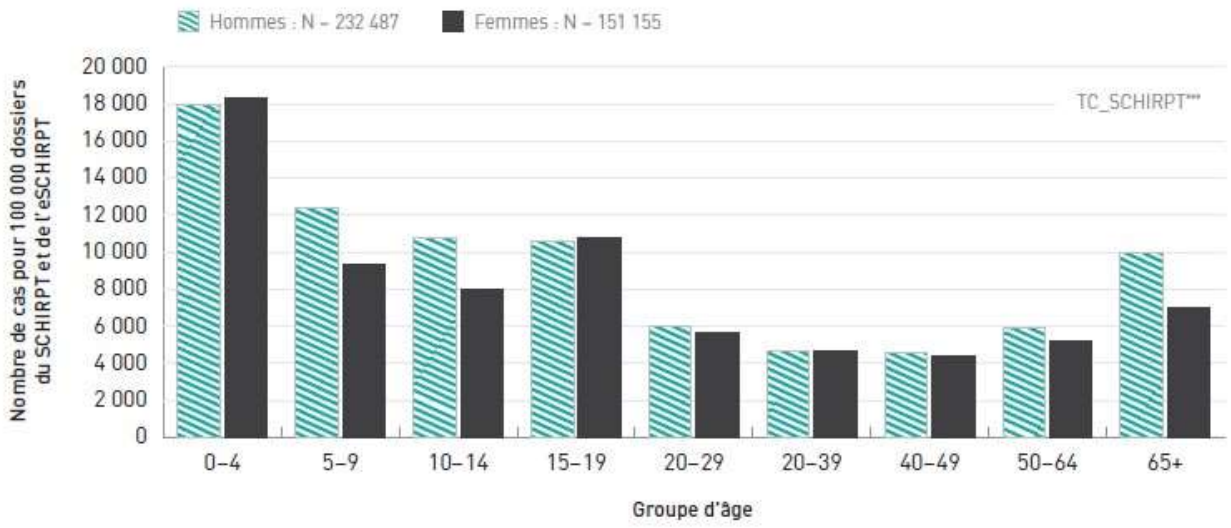

Figure 1. Surveillance sentinelle des visites au service des urgences canadiennes pour traumatismes crâniens, tous mécanismes confondus, 1990 à 2018*

Réimpression autorisée à partir de « Étude des blessures, édition 2020 : Pleins feux sur les traumatismes crâniens tout au long de la vie » par l'Agence de la santé publique du Canada, 2020, p. 56.
Note. eSCHIRPT =Base de données électronique du Système canadien hospitalier d'information et de recherche en prévention des traumatismes; SCHIRPT =Système canadien hospitalier d'information et de recherche en prévention des traumatismes; TC =Traumatisme crânien; * pour 100 000 dossiers du même groupe d'âge.

Au Québec, l'incidence annuelle du TCC pédiatrique serait d'approximativement 4000 cas avec une représentation majoritaire du groupe des 0-5 (53%) comparativement aux autres groupes pédiatriques (INSPQ, 2012; Trudelle et al., 2018).

À travers le monde, le taux d'incidence du TCCna serait estimé à environ 10 à 30 cas par 100 000 nourrissons avec le plus haut taux d'occurrence lors des deux premières années de vie (ASPC, 2020b; Bennett et al., 2011; Fanconi et Lips, 2010; Iqbal O'Meara et al., 2020; Narang et Clarke, 2014; Niederkrotenthaler et al., 2013). Ce taux d'incidence du TCCna serait probablement sous-estimé puisqu'il n'existe pas à ce jour de standard de pratique universellement reconnu au plan diagnostic, et ce, malgré des efforts de précision de la définition et des critères diagnostiques (Iqbal O'Meara et al., 2020; Jenny et al., 1999; Lynøe et al., 2017). Ce manque de lignes directrices

aurait comme répercussion un sous-dépistage, des erreurs diagnostiques ou un repérage tardif du TCCna, faisant en sorte qu'environ 30% des cas ne seraient pas détectés lors d'une première consultation (Iqbal O'Meara et al., 2020; Liley et al., 2012; Nadarasa et al., 2014). Le TCCna surviendrait généralement chez les jeunes enfants avec un ratio d'environ trois garçons pour deux filles (Fanconi et Lips, 2010). D'autres études suggèrent néanmoins que les jeunes filles seraient potentiellement représentées de façon équivalente aux jeune garçons dans la population sinon même plus que ces derniers (Díaz-Olavarrieta et al., 2011; Ferguson et al., 2017).

Causes

Selon les registres hospitaliers des urgences, les chutes représentent la cause la plus fréquente d'hospitalisation et de visite aux urgences chez les enfants âgés de 5 ans et moins (ASPC, 2020b; figures 2 et 3). Chez le jeune enfant, la chute surviendrait soit de sa propre hauteur ou des bras de son parent (Crowe et al., 2010; McKinlay et Hawley, 2013; Trudelle et al., 2018). Selon un article publié par Haarbauer-Krupa et collègues (2019), les causes menant à une chute accidentelle chez des enfants âgés de quatre ans et moins seraient dues à des actions réalisées par l'enfant dans 88% des cas (p. ex., courir, grimper, chute de leur propre hauteur) comparées à 13% des cas où elles seraient attribuables à des actions réalisées par autrui (p. ex., échapper accidentellement l'enfant tenu dans les bras).

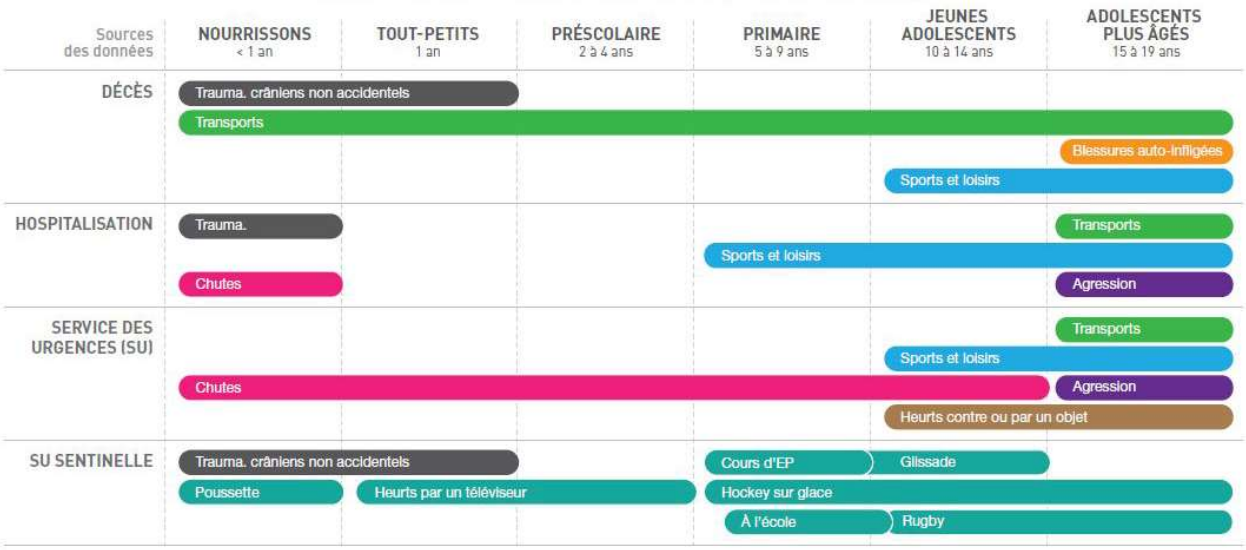

Figure 2. Causes des TCC chez la population pédiatrique (0-19 ans; garçons seulement)

Réimpression autorisée à partir de « Étude des blessures, édition 2020 : Pleins feux sur les traumatismes crâniens tout au long de la vie » par l'Agence de la santé publique du Canada, 2020, p. 7.
Note. SU = Service des urgences; Sentinelle: service de surveillance.

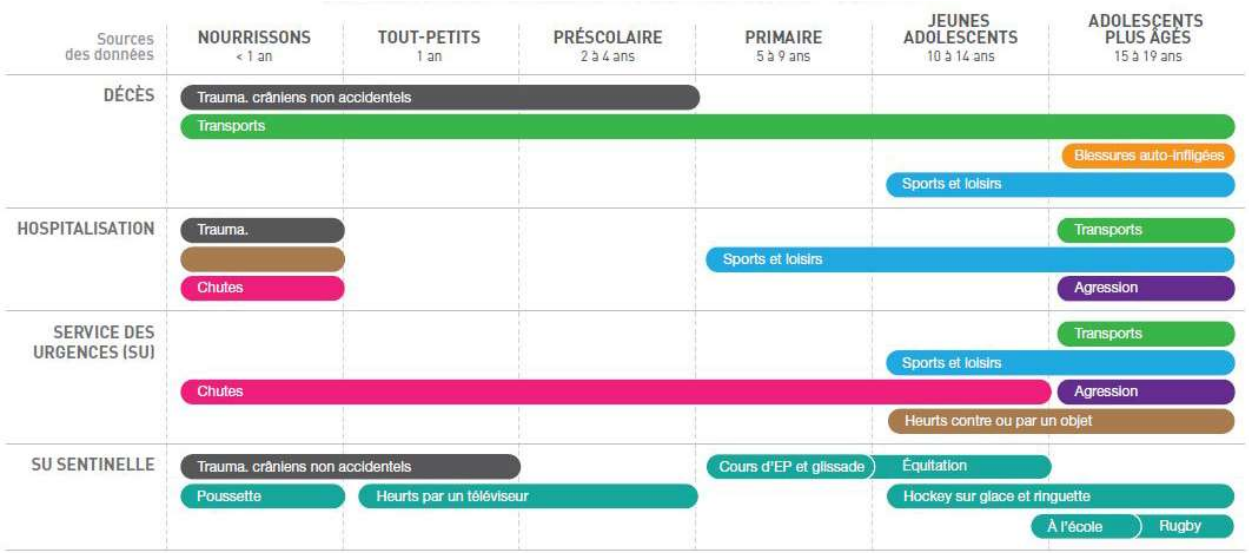

Figure 3. Causes des TCC chez la population pédiatrique (0-19 ans; filles seulement)

Réimpression autorisée à partir de « Étude des blessures, édition 2020 : Pleins feux sur les traumatismes crâniens tout au long de la vie » par l'Agence de la santé publique du Canada, 2020, p. 7.
Note. SU = Service des urgences; Sentinelle: service de surveillance.

Localisation des lésions et processus pathophysiologiques

À la suite d'un TCC, des lésions focales et diffuses, des complications secondaires et des processus pathophysiologiques peuvent survenir et inclure un œdème, une hypoxie ou une ischémie, une augmentation de la pression intracrânienne, des convulsions, ainsi que des complications vasculaires (Gennarelli et Graham, 2005).

Plus précisément, les lésions focales surviennent à la suite d'un impact direct à la tête ou au cerveau (p. ex., choc violent, impact par un objet) et peuvent occasionner des dommages localisés au plan des structures corticales et sous-corticales ciblant généralement les pôles frontaux et temporaux du cerveau et plus précisément, les axes latéraux et inférieurs des lobes frontaux et temporaux. Ces dommages se manifestent souvent par des hématomes et des contusions et sont principalement causés par le contact du cerveau avec les parois osseuses du crâne lors de l'impact. Ce type de lésions peut également occasionner des hémorragies intracrâniennes telles que des hémorragies sous-arachnoïdiennes et des hématomes sous-duraux (Gerber et Coffman, 2007; Zasler et al., 2007).

Quant aux lésions diffuses, elles surviennent généralement à la suite d'incidents causant des blessures engendrant une accélération et/ou décélération de la boîte crânienne (p. ex., accident de la route ou secouement violent), ou impliquent des forces rotatoires. Ce type de lésions engendre le déchirement et un étirement généralisé du tissu cérébral et provoque des hémorragies dans l'ensemble du cerveau. Les lésions diffuses peuvent produire le déchirement de veines ponts qui résultent en des hémorragies intracrâniennes incluant les hémorragies sous-arachnoïdiennes, épidurales et intraparenchymateuses. Les lésions axonales diffuses sont particulièrement

fréquentes suivant un TCC et impliquent le déchirement des axones des neurones, c.-à-d. de la matière blanche du cerveau (Adams et al., 1982; Frati et al., 2017).

Dans le cadre d'un TCCna, les lésions cérébrales engendrées lors d'un « secouement » sont habituellement associées à la présence de la triade suivante: hématomes sous-duraux, hémorragies rétiniennes et blessures cérébrales focales ou diffuses (dommages hypoxiques-ischémiques) et ce, souvent en l'absence de signes apparents de blessure si un examen radiologique n'est pas réalisé (Smith et al., 2019). Bien qu'il n'y ait pas de patron particulier des lésions et processus pathophysiologiques propres au TCCna (Narang et al., 2020), certains signes, tels que des hémorragies sous-durales (multiples, le long des convexités ou interhémisphériques), une ischémie cérébrale, un œdème cérébral et des fractures du crâne (concomitantes avec des lésions intracrâniennes), sont plus fréquents dans les cas de TCCna que de TCCa (Piteau et al., 2012).

Les lésions cérébrales primaires, qui sont dues aux forces initiales du TCC, engendrent une distorsion et une destruction des tissus suite à la blessure. Les conséquences cliniques dépendent majoritairement de la cascade de changements moléculaires et cellulaires qui se produisent suivant la blessure initiale. Les lésions secondaires, qui sont dues à une cascade de changements physiologiques, comprennent entre autres, la dépolarisation, l'excitotoxicité, la perturbation de l'homéostasie du calcium, le stress oxydatif, la perturbation de la barrière hémato-encéphalique, les lésions ischémiques, la formation d'œdème et l'hypertension intracrânienne (Greve et Zink, 2009).

Les enfants de moins de cinq ans sont plus à risque que les individus plus âgés de subir une blessure cérébrale en raison de leurs caractéristiques anatomiques uniques, ainsi qu'en raison de l'immaturité de leur système cérébral (Casey et al., 2000; Huelke, 1998; Stiles et Jernigan, 2010). Environ la moitié de l'accroissement du volume cérébral s'effectue au cours de la première année,

atteignant environ 75% du volume cérébral adulte avant la fin de la deuxième année de vie (Huelke, 1998; Stiles et Jernigan, 2010). Cette croissance rapide crée une disproportion du ratio poids/tête comparativement à celui du reste du corps. Le contrôle des mouvements de la tête est alors plus difficile, d'autant plus que les ligaments et les muscles cervicaux du jeune enfant sont beaucoup plus faibles que ceux de l'adulte (Huelke, 1998). C'est pour ces raisons, qu'en cas d'accident, le cou de l'enfant parvient plus difficilement à réduire la force mécanique appliquée à la tête, augmentant ainsi les risques de blessure cérébrale. Le jeune enfant, en plus d'être plus à risque de subir un TCC en raison de ses caractéristiques anatomiques propres, est également plus à risque que les adultes de subir des blessures diffuses, de l'œdème cérébral et des atteintes hypoxiques et ischémiques post-traumatiques (Levin et al., 2014). Cette vulnérabilité accrue est due, entre autres, au ratio tête/corps plus élevé ainsi qu'à la myélinisation du cerveau plus faible comparativement à chez l'adulte. Finalement, au vu de l'hétérogénéité des conséquences survenant après un TCC en bas âge, il semble que des facteurs propres à l'individu (p. ex., génétique) et environnementaux (p. ex., fonctionnement familial) pourraient influencer leur survenue et ce, au-delà des facteurs propres à la localisation lésionnelle et aux processus pathophysiologiques.

Modèles intégratifs et prédictifs

Plusieurs modèles spécifiques à la population pédiatrique mettent en lumière l'ensemble des facteurs pouvant contribuer et influencer les conséquences et le fonctionnement des enfants suivant un TCC. Bien que la plupart de ces modèles aient été développés en ciblant le TCCa, ils peuvent également s'appliquer au TCCna puisque la majorité des facteurs modulant ces deux types de blessure se chevauchent.

Un modèle théorique bien reconnu dans le domaine du TCC pédiatrique est celui de Yeates et collègues (2009; Figure 4) qui présente un ensemble de facteurs pouvant prédire les trajectoires

des symptômes post-commotionnels (SPC) chez les enfants ayant subi un TCCL et, à plus long-terme, le maintien de conséquences fonctionnelles: les facteurs pré-blessure (p. ex., le fonctionnement cognitif de l'enfant, le fonctionnement familial, etc.) et post-blessure (p. ex., les changements au plan du fonctionnement cognitif de l'enfant, l'ajustement parental, etc.) qui sont liés à l'enfant et à sa famille ainsi que les caractéristiques associées à la blessure (p. ex., indices de sévérité).

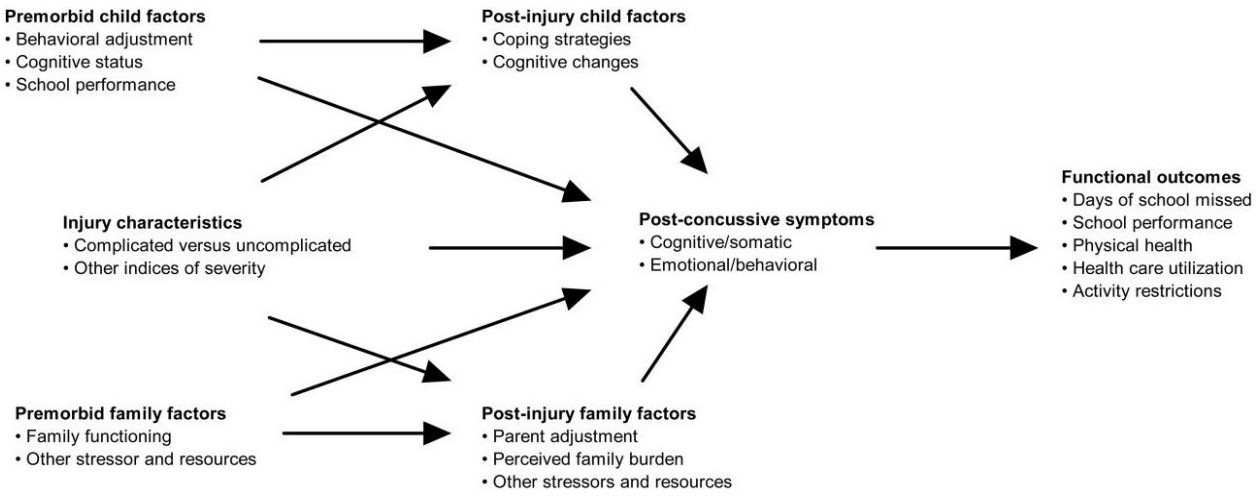

Figure 4. Modèle multidimensionnel de Yeates (2009)

Réimpression autorisée à partir de « Mild Traumatic Brain Injury and Postconcussive Symptoms in Children and Adolescents » par K.O. Yeates, 2010; *Journal of the International Neuropsychological Society*, 6, p. 12. Reproduction de « Longitudinal trajectories of postconcussive symptoms in children with mild traumatic brain injuries and their relationship to acute clinical status » par K.O. Yeates et al., 2009, *Pediatrics,* 123(3), p. 735-743.

Un autre modèle, celui de Dennis (2000), met en relation la capacité de réserve cérébrale et/ou cognitive, l'âge de l'enfant, la localisation de la blessure, ainsi que la notion de plasticité fonctionnelle afin d'expliquer la variabilité des conséquences fonctionnelles suivant un TCC pédiatrique. La plasticité fonctionnelle est définie comme étant une capacité cérébrale individuelle à s'adapter aux pressions environnementales, aux changements physiologiques et aux expériences

par la modification de connexions neuronales préexistantes ou par l'altération de circuits neuronaux (Pascual-Leone et al., 2005). Selon ce modèle développemental, la quantité de *capacité de réserve cérébrale* peut être mesurée directement à l'aide de variables telles que le volume cérébral. La quantité de *capacité de réserve cognitive* peut être mesurée, quant à elle, indirectement à l'aide de variables telles que le fonctionnement prémorbide (p. ex., le fonctionnement cognitif ou comportemental), le statut socio-économique (SSE) et le fonctionnement familial. Ce modèle développemental reconnait que l'âge de l'enfant au moment de la blessure et de l'évaluation (c.-à-d. les stades développementaux) ainsi que la plasticité fonctionnelle qui s'opère après la blessure peuvent influencer le fonctionnement post-accident. De plus, la localisation de la blessure est également présentée comme un facteur ayant un impact sur les conséquences fonctionnelles (p. ex., aspects cognitifs, académiques et psychosociaux) alors que la sévérité ne semble pas être prise en considération dans ce modèle.

Le modèle intégratif biopsychosocial élaboré par Beauchamp & Anderson (2013; Figure 5) met en relation plusieurs facteurs similaires à ceux de Yeates (2009) et de Dennis (2000), afin d'expliquer les différences en ce qui a trait aux conséquences post-TCC pédiatrique. Quatre composantes principales sont présentées: les facteurs internes prémorbides (p. ex., les capacités d'apprentissage, le fonctionnement cognitif, psychologique et adaptatif), les facteurs externes prémorbides (p. ex., le fonctionnement familial, les facteurs démographiques et psychosociaux), les facteurs liés à la blessure (p. ex., l'âge, l'incapacité, la sévérité et la localisation de la blessure), les facteurs post-blessure (p. ex., les fonctions cognitives résiduelles et le fonctionnement familial), ainsi que les conséquences post-blessure (p. ex., la compétence sociale, la psychopathologie, le fonctionnement cognitif, comportemental et adaptatif). En comparaison aux modèles de Yeates et de Dennis, celui de Beauchamp et Anderson (2013) considère davantage de facteurs à prendre en

compte afin d'expliquer et prédire les conséquences post-blessure. Notamment, ce modèle tient compte tant de l'âge de l'enfant au moment de la blessure que de la sévérité de l'atteinte cérébrale, sa localisation et les handicaps associés. De plus, ce modèle met en lumière l'influence de l'environnement, tel que la santé psychologique du parent, sur la récupération et le maintien de conséquences post-TCC.

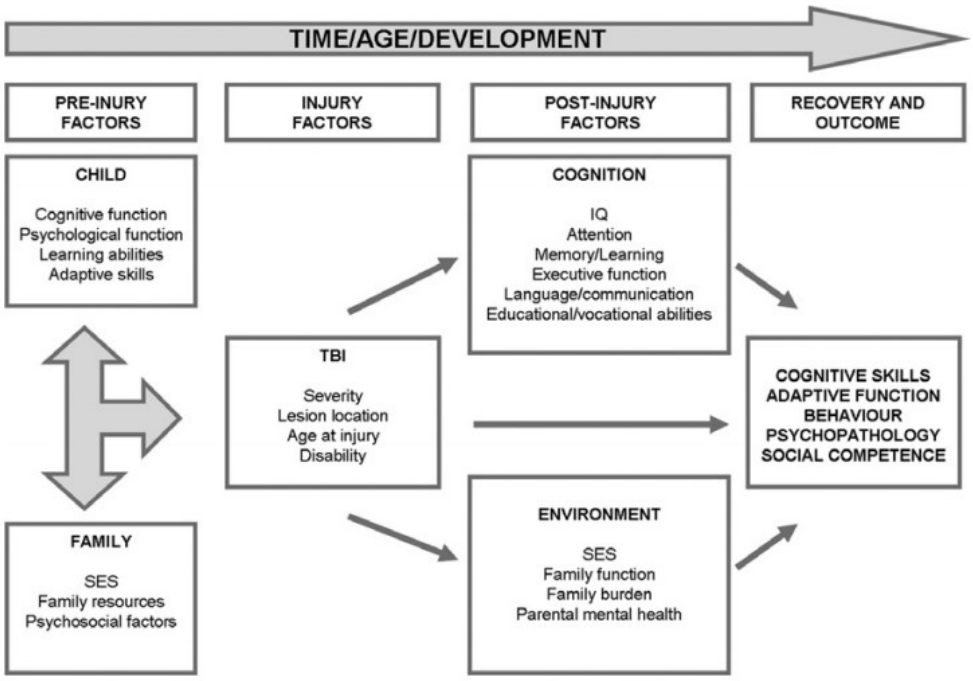

Figure 5. Modèle de Beauchamp & Anderson (2013)

Réimpression autorisée à partir de « Cognitive and psychopathological sequelae of pediatric traumatic brain injury » par M.H. Beauchamp et V. Anderson, 2013, dans *Handbook of clinical neurology*, p. 918.
Note. IQ = Intellectual Quotient; SES = Socioeconomic status; TBI = traumatic brain injury.

Dans l'ensemble, ces modèles théoriques ont plusieurs similarités, notamment, ils considèrent tous qu'un ensemble de facteurs interagissent ensemble afin de prédire les conséquences suivant un TCC: les facteurs propres à l'individu (p. ex., le sexe, l'âge/stade développemental, le fonctionnement adaptatif et comportemental, etc.), les facteurs environnementaux (p. ex., le statut socio-économique), les ressources familiales et les facteurs

psychosociaux, ainsi que les facteurs liés à la blessure. Chez les enfants qui subissent un TCC durant la petite enfance, deux facteurs précédemment nommés, soit l'âge de l'enfant au moment de la blessure (c.-à-d. le stade développemental) ainsi que la sévérité de celle-ci, semblent avoir une influence particulière sur l'issue du TCC. Plusieurs données empiriques et notions théoriques suggèrent qu'en combinaison, ils seraient associés à un devenir particulièrement défavorable, une observation reconnue sous la notion du modèle du « *double-hazard* » (Anderson et al., 2005; Babikian et Asarnow, 2009; Hu et Bentler, 1999). Ce principe explique que plus l'enfant subit un TCC à un jeune âge, et plus cette blessure est considérée comme étant sévère, plus il sera susceptible de présenter des conséquences majeures tant à court qu'à long terme. Ainsi, au-delà de la sévérité de la blessure, l'âge auquel l'enfant subi celle-ci, et par conséquent, le stade développemental dans lequel il se situe au moment de l'accident, revêt une importance majeure et doit être pris en grande considération dans toutes les axes de recherche et de gestion clinique (diagnostic, pronostic, conséquences, intervention, prévention) du TCC précoce.

Considérations développementales

La petite enfance est une période de croissance rapide consacrée au développement de plusieurs fonctions qui sont indispensables au bon fonctionnement de l'enfant (Gilmore et al., 2018; Grantham-McGregor et al., 2007). Au cours des cinq premières années de vie, il existe des périodes sensibles au développement de fonctions cognitives (p. ex., langage) lesquelles sont prédéterminées par les processus de maturation et de plasticité cérébrale (Grantham-McGregor et al., 2007; Figure 6).

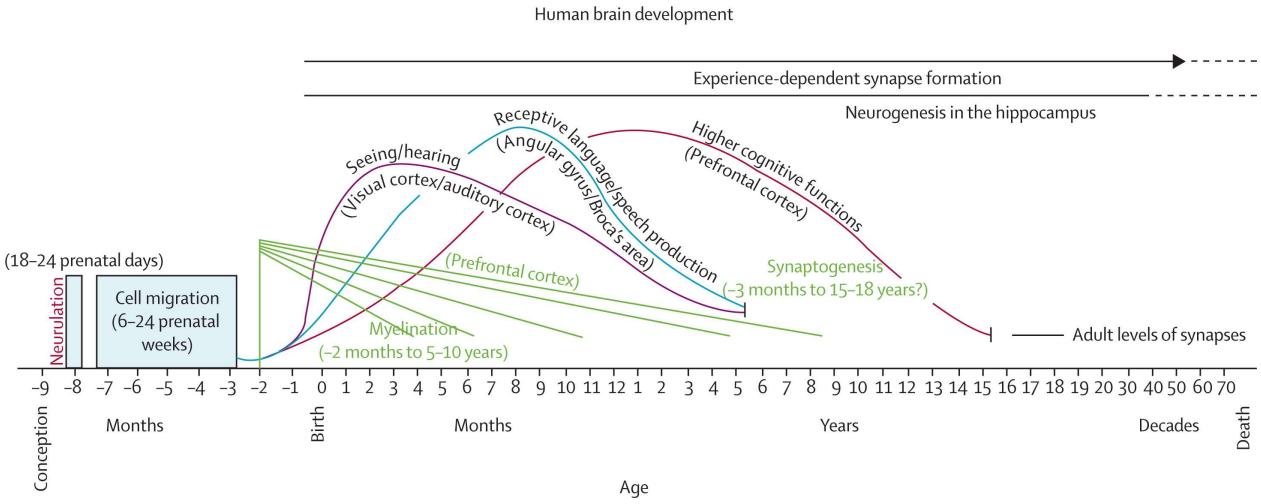

Figure 6. Le développement du cerveau humain.

Réimpression autorisée à partir de « Developmental potential in the first 5 years for children in developing countries » par S. Grantham-McGregor et al., 2007, *The Lancet*, p. 61. Reproduction avec la permission des auteurs et de l'Association de psychologie américaine (R.A. Thompson et C.A. Nelson, Developmental science and the media: early brain development: the global challenge. Am Psychol. 2001; 56: 5–15).
Note. Pendant les premières années de vie (0-5 ans), le cerveau subi de nombreux changements développementaux dictés par les processus de neurogenèse, croissance axonale et dendritique, synaptogenèse, mort cellulaire, élagage synaptique, et myélinisation. Ces changements neuronaux sous-tendent la mise en place de plusieurs fonctions importantes à des moments spécifiques du développement.

Théorie de la plasticité et théorie de la vulnérabilité

La plasticité est une propriété intrinsèque du système nerveux central et réfère à sa capacité dynamique de s'adapter et de répondre à l'environnement (p. ex., expérience, apprentissages ou blessure) via une modification des circuits neuronaux, et ce, tout au long de la vie (Duffau, 2006; Kolb et Gibb, 2011; Mosch et al., 2005). Les mécanismes de plasticité cérébrale contribuent aux processus cellulaires et neuronaux permettant la maturation du cerveau aux plans structurels et fonctionnels, ceci combiné à l'exposition aux apprentissages et à l'expérience. D'une part, la plasticité cérébrale agit au plan synaptique par la potentialisation à long terme (renforcement durable des synapses entre deux neurones qui sont activés simultanément; Bliss et Collingridge,

1993), la synaptogenèse (formation de nouvelles connexions/synapses; Huttenlocher et Dabholkar, 1997b) et l'élagage synaptique (processus normal d'élimination des synapses; Huttenlocher et Dabholkar, 1997b). D'autre part, la plasticité agit au plan neuronal par la neurogenèse (formation de nouveaux neurones), la croissance axonale et dendritique (migration et arborisation des neurones), la myélinisation (formation d'une gaine de myéline autour des fibres nerveuses) et la mort cellulaire (processus normal d'apoptose; Gogtay et al., 2004). Ces processus de plasticité s'opèrent de façon prédéterminée et en réponse à l'exposition expérientielle de l'enfant et permettent le développement des fonctions cérébrales et cognitives, telles que les habiletés sensorielles et motrices, la compréhension et la production du langage et les fonctions cognitives de haut niveau (p. ex., raisonnement, fonctionnement exécutif: Kolb et Gibb, 2011; Kolb et al., 2012). Ainsi, le développement du cerveau se ferait par l'interaction complexe entre facteurs génétiques et environnementaux ou expérientiels, tels que les stimuli sensoriels, le fonctionnement psycho-affectif, les relations parent-enfant et plusieurs autres facteurs.

Dans le cadre d'un TCC subi durant la petite enfance, puisque le cerveau immature est dans une période importante de plasticité cérébrale et que les régions cérébrales sont moins bien différenciées, selon la « théorie de la plasticité », celui-ci serait davantage en mesure de se réorganiser de manière efficace après une atteinte, et ce, sans perte évidente de fonctionnement, comparativement au cerveau mature (Huttenlocher et Dabholkar, 1997a; Kennard, 1936, 1940). Cette théorie est souvent associée aux travaux de Kennard qui avait objectivé une meilleure récupération de la motricité chez de jeunes singes après une lésion du cortex moteur et prémoteur en comparaison aux singes plus âgés (Kennard, 1936, 1940). Ces travaux ont alors été faussement interprétés comme étant une preuve de plasticité cérébrale plus efficace chez le jeune individu par la réorganisation et la relocalisation de la fonction motrice à l'autre hémisphère. Ces travaux ont

été par la suite surnommés le « Principe de Kennard » lequel est censé expliquer la relation linéaire négative entre l'âge au moment de la lésion cérébrale et la récupération (Dennis, 2010). En ce sens, selon la théorie de la plasticité, une blessure cérébrale survenant à un âge plus avancé (adulte) serait plus redoutable qu'une blessure cérébrale précoce (enfant) puisque la capacité du cerveau à se réorganiser diminuerait avec la maturation et la différenciation cérébrale. Des travaux subséquents de Kennard (1942) ont toutefois montré que bien qu'une certaine plasticité du cortex moteur ait été observée chez les jeunes singes, ceux-ci démontraient des déficits similaires à ceux observés chez l'adulte suivant une blessure aux lobes frontaux. Ainsi, à la suite de ces observations, Kennard a modifié son interprétation et a plutôt suggéré que si une région cérébrale est établie du point de vue fonctionnel au moment de la blessure, les conséquences seraient similaires tant chez l'enfant que chez l'adulte, mettant ainsi l'emphase sur l'importance du stade de développement cérébral au moment de la blessure. Or, contrairement à la notion répandue que le jeune cerveau est flexible et apte à se réorganiser et à compenser les dommages, selon la « théorie de la vulnérabilité », des atteintes cérébrales occasionnées tôt dans le développement entraineraient plutôt des conséquences notables (Anderson, Brown, et al., 2011; Anderson et al., 2005). Notamment, les atteintes structurelles et fonctionnelles subies à la suite d'un TCC seraient susceptibles de compromettre le développement normal de plusieurs habiletés cognitives (Anderson, Spencer-Smith, et al., 2011) et d'entrainer des déficits cumulatifs en cascade, en raison du plus faible nombre d'habiletés acquises à cet âge (Anderson et al., 2000). Les jeunes enfants ont peu d'habiletés bien établies et consolidées comparativement aux adultes, et la survenue d'une blessure cérébrale précoce peut perturber les habiletés en émergence et précurseurs aux autres fonctions de plus haut niveau. Notamment, il arrive que des lésions précoces restent silencieuses tant et aussi longtemps que la fonction sous-tendue par les structures anatomiques altérées n'est pas sollicitée au cours du

développement (p. ex., langage). Les difficultés pourraient alors apparaître plus tardivement au moment crucial de la mise en place de cette fonction.

De plus, l'aspect bénéfique de la plasticité cérébrale n'est pas absolu et dépend du type de stimulation ou d'événement qui engendre la mise en place des mécanismes de réorganisation (Sta Maria et al., 2019). À la suite d'une lésion cérébrale diffuse dans un cerveau en pleine maturation, une réponse physiologique est induite et implique un ensemble de perturbations. Celles-ci incluent, sans s'y limiter, les changements ioniques, le stress oxydatif, les changements métaboliques et l'altération de la neurotransmission (Babikian et al., 2011; Giza et Hovda, 2001). Cette réponse physiologique peut donner lieu à un processus de plasticité cérébrale dite « altérée et inadaptée » (Giza et Prins, 2006). La vulnérabilité du jeune cerveau face au TCC serait donc également due, en partie, à son potentiel de plasticité cérébrale augmenté, lequel dans un contexte où des mécanismes d'une plasticité cérébrale altérée et inadaptée pourraient entrer en jeu, serait ainsi plus dommageable que bénéfique pour la récupération. Ceci pourrait expliquer, en partie du moins, pourquoi les jeunes enfants présentent des conséquences fonctionnelles plus importantes suivant un TCC malgré un meilleur potentiel de plasticité cérébrale que les adultes (Anderson et al., 2005; Giza et Prins, 2006 voir Gagner et al., 2021, pour un exemple dans le contexte du TCC léger précoce). En somme, la petite enfance est une période sensible pour l'émergence et le développement d'un grand nombre de fonctions cognitives, sociales et comportementales (Anderson et al., 2009; Anderson et al., 2005; Innocenti, 2007; Sta Maria et al., 2019; Werker et Tees, 2005). De ce fait, une perturbation cérébrale pendant cette période critique rend le jeune enfant vulnérable et susceptible d'altérer l'atteinte des stades développementaux et l'acquisition des habiletés, ce qui pourrait ainsi nuire à son fonctionnement global (Meredith, 2015).

CHAPITRE 2 – RECENSION DES CONSÉQUENCES SUIVANT UN TCC PRÉCOCE

À la suite d'un TCC, chez l'ensemble des patients, que ce soit chez l'adulte, l'adolescent ou l'enfant, on observe des symptômes à plusieurs niveaux tant aux plans physique, affectif, comportemental et cognitif (Anderson, 2012). Sur le plan physique, les atteintes les plus apparentes sont celles qui affectent la motricité et les fonctions sensorielles. On y retrouve les pertes d'équilibre, les mouvements involontaires et/ou les difficultés de coordination des membres, les troubles de la vision, de l'ouïe, de l'odorat, du toucher, en plus des troubles d'élocution (Andruszkow et al., 2014). Dans cette catégorie se retrouvent également des symptômes tels que la fatigabilité, les difficultés de sommeil, la sensibilité aux bruits et à la lumière, les étourdissements et nausées ainsi que les céphalées post-traumatiques (Ponsford et al., 2012). Dans la sphère affective et comportementale, il est fréquent d'observer des changements dans l'auto-régulation et le contrôle des émotions, incluant une labilité émotionnelle, une sensibilité accrue et parfois même des symptômes d'anxiété et de dépression (Bryant et al., 2010; Holsinger et al., 2002; Jorge et al., 2004). On rapporte également une plus grande irritabilité ou frustration, voire même de l'agressivité (Tateno, 2003; Ylvisaker et Feeney, 2007). Des comportements d'impulsivité et d'agitation peuvent également être observés. Enfin, sur le plan cognitif, on y retrouve des difficultés de concentration et de mémoire, ainsi qu'un ralentissement du traitement de l'information (Anderson, 2012; Catroppa et al., 2007; Sullivan et Riccio, 2010).

La littérature scientifique portant sur les conséquences cognitives, comportementales et socio-affectives du TCC pédiatrique chez les enfants d'âge scolaire est exhaustive. Des méta-analyses et revues systématiques visant à documenter les conséquences des TCC subies à l'âge scolaire suggèrent, entre autres, la présence de troubles en lien avec l'attention, le fonctionnement exécutif et la cognition sociale (Babikian et Asarnow, 2009; Babikian et al., 2015; Rosema et al., 2012). Celles-ci rapportent également l'émergence de problèmes comportements internalisés et

externalisés (Kennedy et al., 2017; Li et Liu, 2013), de troubles psychiatriques (Albicini et al., 2017; Emery et al., 2016; Keightley et al., 2014; Narad et al., 2018), ainsi que des séquelles affectives et psychosociales (p.ex., anxiété et dépression; Albicini et McKinlay, 2018; Laliberté Durish et al., 2018). Finalement, ces revues et méta-analyses suggèrent un rendement académique (Mealings et al., 2012) et une qualité de vie plus faibles chez ces enfants comparativement aux enfants qui n'ont pas subi de blessure (Di Battista et al., 2012). Bien que les enfants en bas âge aient un cerveau particulièrement vulnérable au TCC et qu'ils soient à risque de subir des conséquences majeures à la suite de ce type d'atteinte, peu de revues de la littérature ou méta-analyses ont été réalisées afin de synthétiser ces effets (Garcia et al., 2015; Wetherington et Hooper, 2006). Les résultats d'une revue descriptive réalisée par Garcia et collaborateurs (2015) suggèrent que les enfants ayant subi un TCC avant l'âge de cinq ans, rencontreraient des difficultés telles que la présence de comportements externalisés et des problèmes sur les plans de l'attention, du langage, ainsi que du fonctionnement intellectuel et exécutif. Toutefois, cette revue était de type descriptif et n'a pas été réalisée de manière systématique. Une autre revue sur le TCC précoce menée par Wetherington et Hooper (2006) rapporte également des fonctions cognitives et motrices altérées ainsi que des difficultés socio-comportementales. Les auteurs ont toutefois inclus dans leur revue des enfants âgés de six ans et plus, ce qui limite les conclusions pouvant être tirées quant aux conséquences du TCC en bas âge spécifiquement. Finalement, ces revues ont principalement ciblé les conséquences cognitives et comportementales et dans une moindre mesure, le fonctionnement socio-émotionnel et aucunement le fonctionnement adaptatif. Depuis les dernières années, il y a un accroissement important du nombre d'articles publiés concernant les effets d'un TCC précoce et une variété de conséquences sont décrites au sein de cette jeune population. Néanmoins, leurs résultats n'ont pas encore été présentés de façon synthétique et complète. La

prochaine section présentera donc une revue systématique de la littérature sous forme de manuscrit publié, qui avait pour objectif général de recenser l'ensemble des conséquences et plus spécifiquement les conséquences cognitives, comportementales, socio-émotionnelles et adaptatives suivant un TCC durant la petite enfance. Une des hypothèses sous-jacentes était que les caractéristiques liées à la blessure telles qu'un plus jeune âge et une atteinte plus sévère, mèneraient à un devenir plus défavorable chez l'enfant. Conjointement, cette recension visait également à faire état des manques et carences dans la littérature scientifique relativement aux domaines et construits n'étant pas ou peu étudiés suivant un TCC précoce.

ARTICLE 1

What about the little ones?

Systematic review of cognitive and behavioral outcomes

following early TBI

Marilou Séguin[1,2], Charlotte Gagner[2], Carola Tuerk[1,2], Jessica Lacombe-Barrios[1,2], Pascale MacKay[3], *Miriam H. Beauchamp[1,2]

[1] Department of Psychology, University of Montréal, Québec, Canada

[2] Sainte-Justine Research Center, Montréal, Québec, Canada

[3]Department of Psychology, University of Trois-Rivières, Trois-Rivières, Québec, Canada

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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 six 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 to 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 of the unique characteristics of the early childhood period.

Key words: early TBI; preschoolers; cognition; behavior; systematic review.

1. 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, 2009; Verger et al., 2000). During early childhood (i.e., before the age of six years), a range of cognitive and socio-affective functions undergo intense development, including attention and executive skills, 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 of TBI focus on school-aged 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 & Asarnow, 2009; Babikian et al., 2015; Rosema et al., 2012), internalizing and externalizing behavior problems (Albicini & McKinlay, 2018; Durish et al., 2018; Kennedy et al., 2017; Li & 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 cognitive outcomes after pediatric TBI (Albicini et al., 2017; Albicini & McKinlay, 2018; Babikian & 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 (e.g., mild TBI; Emery et al., 2016; Keightley et al., 2014; or nonaccidental TBI; Lopes et al., 2013), on a specific domain (e.g., social functioning; Rosema et al., 2012) or on a wide age range (e.g., 0 – 18 years old; Babikian & Asarnow, 2009; Di Battista et al., 2012; or 0 – 13 years old; Kennedy et al., 2017), but only two reviews include information on the specific effects of early TBI (Garcia et al., 2015; Wetherington & Hooper, 2006). Garcia et al. (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 (e.g., Intellectual Quotient [IQ], executive functioning). Wetherington et al. (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 reviews 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 and 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*). Years searched between 1990 and 2019. 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) Closed head injury;
6) Any mechanism of TBI: accidental TBI (aTBI) or non accidental TBI (naTBI; ex. infantile non-accidental trauma ("shaken baby"), inflicted TBI);
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 adaptive 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, psychometric studies, rehabilitation program and intervention effectiveness studies, 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 (e.g., Activities of Daily Living, Quality of Life), disability or morbidity outcomes.
    b. Non-interpreted/descriptive normative data.
    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 predetermined information from each selected article: (a) authors and year of publication, (b) injury severity, (c) age and type of injury, (d) control group, (e) design and timing of follow-up, (f) cognitive and academic outcomes (intellectual function or development, attention, executive functioning, memory, language, social cognition and academic), and (g) 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: (a) study participation (e.g., is there adequate participation in the study by eligible individuals), (b) study attrition (e.g., response rate is adequate), (c) outcomes (e.g., the method and measurement setting are the same for all study participants), (d) confounding (e.g., important potential confounders are accounted for in the study design), and (e) analysis (e.g., there is no selective reporting of results). Presence of bias was judged as "Yes", "Partly", "No" or "Unsure".

2. Results

Study selection

Details of the search results are presented in Fig. 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 the inclusion and 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 articles were excluded. A final total of 43 articles were 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 the injury. The main findings related to cognitive and academic outcomes are presented in Table 2, and behavioral and socio-affective outcomes in Table 3. For some articles, the percentage or proportion of the population with deficits in the aforementioned domains are reported (Barlow et al., 2005; Bonnier et al., 2007; Ewing-Cobbs et al., 1998, 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 five years (2015 – 2019; Bellerose et al., 2015, 2017; D'Hondt et al., 2017; Dégeilh et al., 2018; Gagner et al., 2018; Kaldoja & 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 Table 1.

[Insert Tables 1, 2 and 3]

Risk of bias

Tables 4 and 5 present the 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 or TBI classification characteristics were vague. Twenty-seven studies (63%) had shortcomings related to "study attrition". One study (2%) had potential risks of bias related to "outcome measurement". Eight

studies (19%) had shortcomings related to “confounding measurement and account”, and 13 studies (30%) presented potential risk of bias regarding “analysis”.

[Insert Tables 4 and 5 here]

Study characteristics

Design

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

Comparison groups

Thirty-four studies (79%) included a comparison group. Nine studies (21%) did not use any comparison groups, impeding the possibility of drawing brain-injury specific conclusions

(Barlow et al., 2005; Beers et al., 2007; Bonnier et al., 2007; Crowe et al., 2012a, b; 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 studies (16%) included children with orthopedic injuries (Coster et al., 1994; Dégeilh et al., 2018; Keenan et al., 2018, 2019; Marsh & Whitehead, 2005; Walz et al., 2009; Wrightson et al., 1995), one study (2%) used an "other acquired brain injuries" comparison group (Pastore et al., 2013), 20 studies (47%) compared their sample to typically developing children (Bellerose et al., 2015; Crowe et al., 2012a, b, 2013, 2014; D'Hondt et al., 2017; Ewing-Cobbs et al., 1999, 2004, 2006, 2013; Green et al., 2013; Kaldoja & Kolk, 2015; Keenan et al., 2007; Landry-Roy et al., 2018; Landry et al., 2004; Liu & Li, 2013; McKinlay, et al., 2014; Papoutsis et al., 2014; Stipanicic et al., 2008; Tonks et al., 2011; Wetherington et al., 2010), and six studies (14%) recruited both children with orthopedic injuries and typically developing children as comparison groups (Bellerose et al., 2017; Gagner et al., 2018; Lalonde et al., 2016; McKinlay et al., 2002, 2009, 2010).

Sample Characteristics

Age

As per the 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., 2013, 2014; Ewing-Cobbs et al., 1999, 2004, 2013; Keenan et al., 2007, 2019; Marsh & 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, 2017; Coster et al., 1994; Crowe et al., 2012a, b; 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 (36–72 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 studies (30%) did not present mean age at injury, and instead presented age at injury as an interval from 0–15 years (Green et al., 2013; Kaldoja & Kolk, 2015; Keenan et al., 2007, 2018; Kieslich et al., 2001; Lalonde et al., 2016; Liu & Li, 2013; McKinlay, et al., 2002, 2009, 2010, 2014; Tonks et al., 2011; Walz et al., 2009). Other studies covered more than one age group. One study (2%) examined both infants and toddlers (Landry et al., 2004). Three studies (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 11 articles (26%) covered all three developmental groups (0–72 months; Crowe et al., 2012a, b; Ewing-Cobbs et al., 1998; Green et al., 2013; Kaldoja & Kolk, 2015; Liu & Li, 2013; McKinlay, et al., 2002, 2009, 2010, 2014; Sonnenberg et al., 2010; Tonks et al., 2011). Overall, the majority of the studies included either infants 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 (Crowe et al., 2012a, b; Ewing-Cobbs et al., 2004; Keenan et al., 2018, 2019; Kieslich et al., 2001; Sonnenberg et al., 2010). Of the studies that investigated both aTBI and naTBI, some articles reported a significant difference for age at injury between the two groups, with the naTBI group being younger than the aTBI group (Ewing-Cobbs et al., 1998, 2006).

Age at assessment (post-injury delay)

Follow-up periods post-injury ranged from one month to 20 years. Most studies (N=19; 44%) documented outcomes within one year post-injury (Beers et al., 2007; Bellerose et al., 2015, 2017; Coster et al., 1994; D'Hondt et al., 2017; Dégeilh et al., 2018; Ewing-Cobbs et al., 1998, 1999, 2013; Gagner et al., 2018; Kaldoja & Kolk, 2015; Keenan et al., 2018, 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 studies (28%) included follow-up periods between two and five years post-injury (Barlow et al., 2005; Crowe et al., 2012a, b, 2013, 2014; Ewing-Cobbs et al., 2004, 2006; Keenan et al., 2007; Liu & Li, 2013; Marsh & Whitehead, 2005; Sonnenberg et al., 2010; Wetherington et al., 2010), and 10 studies (23%) from 6 to 10 years (Bonnier et al., 2007; Kieslich et al., 2001; McKinlay et al., 2002, 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 studies (5%) reported outcomes between 10 and 20 years post-injury (Green et al., 2013; McKinlay et al., 2009), and one study (2%) reported outcomes over 20 years post-injury (McKinlay et al., 2014).

Pre-injury characteristics

Thirteen studies (30%) reported participant characteristics pre-injury (Bellerose et al., 2015, 2017; Dégeilh et al., 2018; Gagner et al., 2018; Kaldoja & Kolk, 2015; Keenan et al., 2018, 2019; Lalonde et al., 2016; Landry-Roy et al., 2018; McKinlay, et al., 2002, 2009, 2014; Wrightson et al., 1995). Studies that assessed pre-injury behavior did so retrospectively, mainly by parental recall on questionnaires, and usually within the first two weeks after injury. Of these studies, some found differences between TBI and comparison groups. First, toddlers who sustained mTBI presented significantly more externalizing behaviors (Child Behaviour Checklist [CBCL]) compared to typically developing children (Bellerose et al., 2015; however, see also Gagner et al., 2018). Second, toddlers and preschoolers had comparable behavior (Strength and Difficulties Questionnaire [SDQ] and CBCL) to those with orthopedic injuries, 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 Rating Scale) of toddlers and preschoolers who sustained mTBI were comparable to those with orthopedic injuries (Wrightson et al., 1995). Fourth, in a group of toddlers and preschoolers who sustained either naTBI or aTBI (all severities), executive functions (Behavior Rating Inventory of Executive Function [BRIEF]) were mostly comparable to those with orthopedic injuries, except for working memory which was poorer in the uncomplicated mTBI group compared to all other groups (complicated mTBI, moderate TBI [modTBI], severe TBI [sTBI], orthopedic injuries: Keenan et al., 2018). Fifth, in a combined group of infants with naTBI or aTBI (all severities), communication (Ages & Stages Questionnaire-3 [ASQ-3]) was poorer in infants who sustained sTBI compared to infants with orthopedic injuries (Keenan et al., 2019). Sixth, in children who sustained mTBI, adaptive functions (Adaptive Behavior Assessment System [ABAS] or Vineland) were comparable to those with orthopedic injuries (Dégeilh et al.,

2018; Wrightson et al., 1995) and typically developing children (Bellerose et al., 2015, 2017; Dégeilh et al., 2018), while toddlers with mTBI and TDC showed higher leisure levels compared to the orthopedic injuries group (Lalonde et al., 2016). Seventh, in children (0 – 6 years) who sustained mTBI, boys with mTBI showed more self-regulation problems (Ages and Stages Questionnaires: Social-Emotional [ASQ-S-E]) compared to girls with mTBI and typically developing boys. Girls who sustained mTBI presented more adaptive difficulties compared to typically developing girls. No difference in social difficulties, communication, compliance, and affect (ASQS-E) were noted between these groups during the pre-injury period (Kaldoja & Kolk, 2015). Other studies (N=3; 7%) used pre-injury characteristics only as confounding variables for main statistical analyses rather than in group comparisons (see McKinlay et al., 2002, 2009, 2014).

TBI characteristics

Type of injury (accidental vs non accidental injury)

Twenty seven studies (63%) focused on aTBI (Albicini et al., 2017; Bellerose et al., 2015, 2017; Coster et al., 1994; Crowe et al., 2012a, b, 2013, 2014; D'Hondt et al., 2017; Dégeilh et al., 2018; Gagner et al., 2018; Green et al., 2013; Kaldoja & Kolk, 2015; Lalonde et al., 2016; Landry-Roy et al., 2018; Liu & Li, 2013; Marsh & Whitehead, 2005; McKinlay, et al., 2002, 2009, 2010, 2014; 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), three studies (7%) examined naTBI (Beers et al., 2007; Landry et al., 2004; Stipanicic et al., 2008), and 13 studies (30%) investigated both aTBI and naTBI (Barlow et al., 2005; Beers et al., 2007; Bonnier et al., 2007; Ewing-Cobbs et al., 1998, 2004, 2006, 2013; Keenan et al., 2007, 2018, 2019;

Kieslich et al., 2001; Vassel-Hitier et al., 2019; Wetherington et al., 2010). For those 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, or neuropsychological abnormality or diagnosed intracranial lesion" from the Centers for Disease Control (Marr & Coronado, 2004; 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). The algorithm 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, 2013, 2012a, b; Green et al., 2013; Keenan et al., 2018, 2019; Papoutsis et al., 2014; Walz et al., 2009; Wetherington et al., 2010) and used similar severity criteria (Alexander, 1995; CDO, 2004; Keith Owen & Taylor, 2005; Marr & Coronado, 2004; Osmond et al., 2010). These typically relied

on a combination of Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974), duration of loss of consciousness, post-traumatic amnesia, and neuroimaging or radiology results.

Some authors did not use TBI severity classification (Wrightson et al., 1995) or used only GCS with 13–15 defined as mTBI, 8–12 as modTBI, and 3–8 as sTBI (Marsh & Whitehead, 2005). Others 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 (Beers et al., 2007). 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 colleagues (1999, 2004, 2013) modified the GCS motor and verbal scales to accommodate the behavior 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. For example, "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 (e.g., modTBI and sTBI) or altered the original GCS cut-offs, for example defining moderate-severe TBI (msTBI) as a GCS of 4–13 (Pastore et al., 2013; Prasad et al., 1999). One group used the Pediatric Performance Category Scale at discharge to classify disability from mild to severe (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 Li (2013) defined mTBI as no loss of consciousness or no hospitalization for treatment due to injury.

No firm consensus emerged regarding the use of neuroimaging findings to classify mTBI in the studies included. Likewise, definitions of concussion, uncomplicated mTBI (no visible structural brain lesions) and complicated mTBI (visible brain lesions on clinical imaging) were not uniform (Papoutsis et al., 2014). Twenty-eight studies (65%) reported alteration of consciousness as<5,<20, <30, or ,<60 min for mTBI (Crowe et al., 2013, Keenan et al., 2018, 2019; Liu & Li, 2013; McKinlay et al., 2010; Papoutsis et al., 2014). The same studies defined sTBI as an alteration of consciousness lasting 24 h or more, or a coma of any duration (Vassel-Hitier et al., 2019; Ewing-Cobbs et al., 1999, 2006, 2013) describe duration of impaired consciousness as the number of days during which 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 to define severity of injury. When reported, post-traumatic amnesia of two hours or less was associated with mTBI and more than two hours with msTBI (McKinlay, et al., 2014). Some authors included amnesia among the documented neurological signs (e.g., Bellerose et al., 2015, 2017). Finally, 16 articles (37%) reported post-concussive symptoms or neurological signs in relation to injury severity classification (e.g., Bellerose et al., 2015, 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). The majority of studies reported only one severity grouping, such as mTBI (Bellerose et al., 2015, 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 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 & Whitehead, 2005; Pastore et al., 2013; Prasad et al., 1999; Stipanicic et al., 2008) to more substantial sample sizes of 100 participants or more (e.g., Ewing-Cobbs et al., 2013; Keenan et al., 2018, 2019; Kieslich et al., 2001; Liu & Li, 2013; McKinlay et al., 2002).

Measures and assessment tools

When reporting cognitive or academic outcomes, nine (21%) studies used direct assessment methods exclusively (Bonnier et al., 2007; Crowe et al., 2014, 2012a, b; Ewing-Cobbs et al., 1998, 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, teachers (Coster et al., 1994; Gagner et al., 2018; Green et al., 2013; Kaldoja & Kolk, 2015; Keenan et al., 2018, 2019; Liu & Li, 2013; McKinlay et al., 2009, 2010, 2014; Pastore et al., 2013), or physicians

(Sonnenberg et al., 2010). The majority of studies combined both direct and indirect assessment methods to describe either cognitive or behavioral outcomes and socioaffective outcomes (N=15; 35%; Barlow et al., 2005; Beers et al., 2007; Bellerose et al., 2015, 2017; Crowe et al., 2012a, b, 2013; Dégeilh et al., 2018; Ewing-Cobbs et al., 1999; Keenan et al., 2007; Marsh & 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%) other studies used a combination of indirect assessment (e.g., 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 Tables 2 and 3, results of group comparisons are reported where possible (e.g., typically developing children vs. TBI vs. orthopedic injuries). Otherwise, percentages (Barlow et al., 2005; Marsh & 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 were 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, 11 (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 are divided according to the three types of injuries (aTBI, naTBI, or both aTBI and naTBI). For each type of injury, outcomes are then separated according to injury severity

(mild, moderate, severe), and 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 or global developmental functioning comparable to that of orthopedic injury groups and typically developing groups up to 10 years post-injury (Crowe et al., 2012a, b, 2013; 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 or global developmental functioning up to three years (verbal IQ; Crowe et al., 2014; Global: Wetherington et al., 2010) and four years (verbal and non-verbal IQ; Crowe et al., 2012a, b) post-injury, compared to typically developing children, and up to one month post-injury when compared to orthopedic injury groups (Walz et al., 2009).

naTBI

Infants and toddlers who sustained naTBI had impaired (Barlow et al., 2005) or poorer developmental and intellectual functioning compared to those who sustained aTBI (Beers et al., 2007; Ewing-Cobbs et al., 1998) and typically developing children (Ewing-Cobbs et al., 1999, 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 & naTBI

In a combined group of infants who sustained severe aTBI or naTBI, global development, as well as verbal and nonverbal 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 (VasselHitier et al., 2019). Finally, more than half of children (0–6 years) with moderate-severe naTBI or aTBI showed intellectual or academic delays up to 8.75 years postinjury (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 typically developing children 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 typically developing children 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 orthopedic injury up to 6.60 years post-injury (Marsh & Whitehead, 2005). In toddlers who sustained complicated mTBI, divided attention was poorer than in those with

uncomplicated TBI or typically developing children up to seven years post-injury (Papoutsis et al., 2014).

msTBI. In infants who sustained msTBI, auditory vigilance and selective attention were comparable to typically developing children 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 typically developing children 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 typically developing children 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 postinjury (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 typically developing children 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 orthopedic injury up to five years post-injury (Marsh & 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 typically developing children 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 typically developing children up to six months post-injury (Landry-Roy et al., 2018). Finally, in toddlers and preschoolers who sustained mTBI, information processing was comparable to orthopedic injury 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 typically developing children up to 3.91 years postinjury (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 (Crowe et al., 2012a, b).

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

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 typically developing children up to 78.90 months post-injury (Stipanicic et al., 2008).

aTBI & naTBI

In a combined group of infants with moderate to severe naTBI or aTBI, visual working memory and inhibition were poorer while cognitive flexibility was comparable to typically developing children 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 orthopedic injury groups 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 typically developing children up to 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 and modTBI only) were poorer compared to orthopedic injury at three and 12 months post-injury (Keenan et al., 2In a combined group of infants with moderate to severe naTBI or aTBI, visual working memory and inhibition were poorer while cognitive flexibility was comparable to typically developing children 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 orthopedic injury groups 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 typically developing children up to 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 and modTBI only) were poorer compared to orthopedic injury at three 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 & 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 orthopedic injury 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 orthopedic injury up to five years post-injury (Marsh & Whitehead, 2005).

msTBI. In infants who sustained moderate to severe aTBI, language skills, such as expressive vocabulary, sentence and word structure, were poorer compared to mTBI and typically developing children 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 years 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 typically developing children, and similar quality of parent–child dysfunctional interaction compared to orthopedic injury groups and typically developing children 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 nine months (Kaldoja & Kolk, 2015). Lastly, in a combined group of infants and toddlers who sustained aTBI, regardless of severity, social skills were comparable to typically developing children up to 3.90 years post-injury (Crowe et al., 2012a, b).

msTBI. In children (0–6 years) who sustained msTBI, 20% had normal social function, 41% had mild impairment, 23% had moderate impairment, 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).

3. Discussion

This systematic review aimed to document the cognitive, academic, behavioral, socio-affective, and adaptive consequences of early TBI sustained before six 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 6.

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 consistent. Deficits in IQ (Barlow et al., 2005; Beers et al., 2007; Bonnier et al., 2007; Crowe et al., 2012a, b, 2014; Ewing-Cobbs et al., 1998, 1999, 2006, 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 & Edelbrock, 1983; Bonnier et al., 2007; Marsh & Whitehead, 2005; Papoutsis et al., 2014; Stipanicic et al., 2008), executive functioning (Bonnier et al., 2007; Crowe et al., 2012a,b, 2013; 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, 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 such as severity, mechanism, and age at injury.

These findings are congruent with a previous review by Garcia et al. (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 et al. (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 consistently reported as being affected by early TBI (Achenbach et Edelbrock, 1983; Ewing-Cobbs et al., 2013; Kaldoja & 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 & Kolk, 2015; Keenan et al., 2018, 2019; Landry et al., 2004; Liu & Li, 2013; McKinlay et al., 2002, 2009, 2010, 2014; 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 & 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 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, 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 (Bellerose et al., 2015; Gagner et al., 2018; Liu et al., 2013), whereas those that did not identify difficulties assessed behavior in the longer term (≥2 years; Crowe et al., 2012a, b; ≈ 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).

1) Younger age at injury

There is ongoing debate regarding whether brain injury at a younger age incurs better or worse outcome as a function of brain plasticity or vulnerability. On one hand, there is evidence that sustaining brain injury at a younger age is less detrimental than at older ages, because of the increased structural and functional plasticity that is present earlier in the developmental course (Anderson et al., 2005; Aram & Ekelman, 1986; Dennis, 1980). Taken in the context of pediatric mTBI research, there is consistent evidence in school-aged children (5–18 years) that younger age at injury results in fewer postconcussive symptoms, and overall better outcomes than older age (i.e., adolescence) at injury (Anderson & 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 that show that injury at a younger age results in poorer outcomes than when sustained at an older age (all TBI severities; e.g., Crowe et al., 2012a, b; Ewing-Cobbs et al., 2004; Keenan et al., 2018, 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 & Nelson, 2001). TBI sustained at a younger age and during a sensitive period may impair the development of functions such as language, or alter the emergence of associated cognitive, socio-affective, and behavioral functions (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 and cannot solely be interpreted in accordance with compensatory 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 & Kolk, 2015; Keenan et al., 2018; Lalonde et al., 2016; Liu et Li, 2013; McKinlay et al., 2002, 2009, 2010, 2014; Papoutsis et al., 2014; Schneider, 1979).

2) TBI severity

As documented in school-aged children, adolescents, and adults, msTBI sustained early in development leads to worse outcomes than milder injuries (Anderson & Catroppa, 2005; Anderson et al., 2005). Babikian and Asarnow (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 comparison groups (i.e., orthopedic injuries and typically developing children; Crowe et al., 2014, 2012a, b; Ewing-Cobbs et al., 1999, 2004, 2006, 2013; Green et al., 2013; Keenan et al., 2018, 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. Conversely, it may be that 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 cloud the interpretation of existing work. Special interest groups or expert panels may be useful for developing criteria specific to the early childhood period and establishing 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 (e.g., mechanism, age, sex, gender) may facilitate meta-analyses that could clarify the interpretations and conclusions drawn from early mTBI studies.

3) 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 (Beers et al., 2007; Ewing-Cobbs et al., 1998, 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 two years old and that naTBI often results in moderate to severe injuries. In addition, naTBI may occur in family and socio-demographic contexts associated with greater risk for poor outcome (Chevignard & 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 or deceleration forces and rotational or 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 & Jones, 2003). Further explanation for the differences observed in outcomes between aTBI and naTBI could be the presence of repetitive episodes of injury overtime in the latter (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 to 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 to severe naTBI, confusing the question of whether accidental and non-accidental mechanisms are comparable in outcome.

4) Comparison groups

Most studies identified in the present review included a comparison group. Those that compared children with early TBI to typically developing children were more likely to find significantly elevated rates of problems than studies that compared children with mTBI to children with orthopedic injuries. Both typically developing children and children with orthopedic injuries present advantages and disadvantages in TBI research. Comparisons using uninjured children recruited from the community allow conclusions to be drawn regarding the expected trajectory of learning and development, and to identify areas in which children with TBI may fall short of their peers. Orthopedic injury 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 such as pain, fatigue, and stress. A study by our group found that young children with orthopedic injuries and typically developing children are comparable on a broad range of pre-injury and post-injury characteristics, including demographic variables, developmental and medical history, behavioral and adaptive profiles (Beauchamp et al., 2017). Children with orthopedic injuries and typically developing children were also found to be comparable on measures of adaptive functioning, behavior, family functioning, post-concussive symptoms, and cognition (Beauchamp et al., 2017). It was cautiously concluded that there is no clear advantage in recruiting orthopedic injury groups. However, there may be other domains in which the groups differ that were not documented in that study. The decision to use either orthopedic injury or

typically developing comparison groups when investigating early TBI should be considered with respect to 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 (e.g., 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, although 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 6 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 6)

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 and preschoolers alongside school-age children (e.g., participants aged two to nine 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 "late" childhood. Second, the effect of multiple TBIs was not documented. Only two articles were identified that included multiple injuries. One was 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 tables 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 function - ing such as quality of life, or intervention studies that may have reported cognitive or behavioral outcome at pre-test or admission, for example. There is also a gray area as to what studies and measures can be considered to target "adap - tive 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 have used measures such as the Functional Independence Measure for children (Msall et al., 1994). 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 post-concessive symptoms were not reported despite their central importance in mTBI or

concussion research. There are few published studies that report post-concessive symptoms, likely because no validated measures of post-concessive symptoms exist under the age of five years, and few studies have tracked the effects of early TBI acutely. Current reports of post-concessive symptoms 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 et al., 2014; Suskauer et al., 2018). Efforts are currently underway to validate a developmentallyappropriate measure of post-concessive symptoms 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. Table While it is complex to distill clear conclusions due to 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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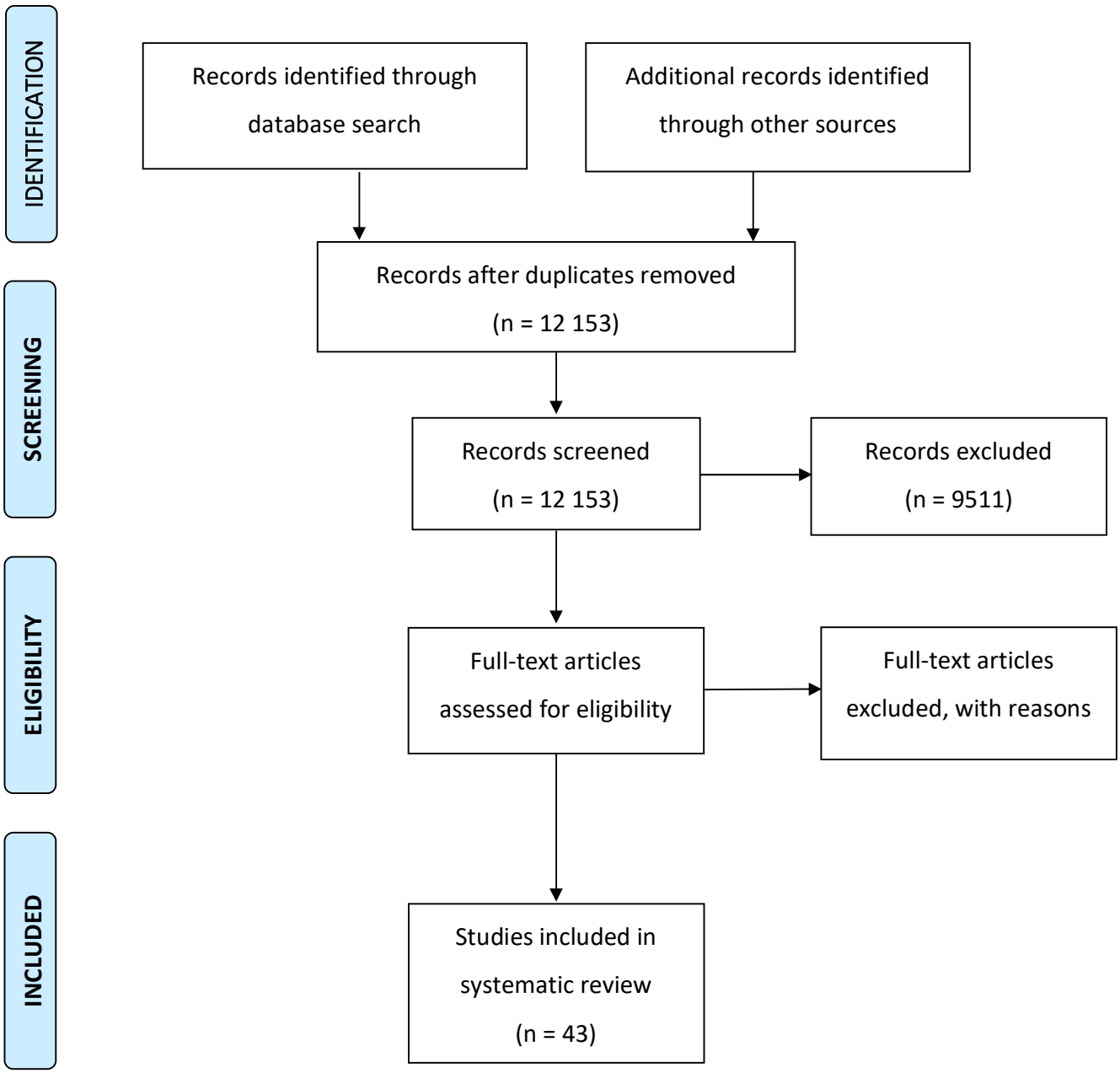
Figures

Figure 1. PRISMA Diagram



Tables

Table 1. Studies identified in the systematic review examining outcome after accidental TBI and non accidental TBI in early childhood: Study characteristics

Study characteristics					
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 Post-injury timepoint in months Range (M±SD)**
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
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
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
Crowe et al. (2014)	mTBI (19; 57.90%) msTBI (16; 43.80%)	3wks-2 yrs; 11 mos mTBI (16.80±10.30) msTBI (12.30±10.60)	Falls mTBI (NA; 94.70%) msTBI (NA; 81.30%)	TDC (20; 40.00%)	C-S, P ≥ 2 yrs mTBI NA (47.70±9.00) msTBI NA (46.90±8.20) Ax 3 yrs; 10 mos – 6 yrs: 00 mo old
Crowe et al. (2012a)	mTBI (20; 55.00%) msTBI (33; 53.10%)	6 days - 2 yrs; 11 mos mTBI 1-35 (17.70±10.70)	Falls mTBI (18; 90.00%) msTBI	TDC (27; 40.70%)	C-S, P ≥ 2 yrs mTBI 29-64 (46.80±9.70) msTBI

		msTBI 0-35 (21.50±12.10)	(22; 66.70%)		24-56 (39.20±9.60) Ax 4 yrs; 00 mo - 5 yrs; 11 mos old
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) msTBI (46.90±8.20) Ax 3 yrs; 10 mos - 5 yrs; 11 mos old
Crowe et al. (2012b)	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 (1.60±0.90) yrs modTBI (1.70±1.00) yrs sTBI (1.90±0.70) yrs Preschool: 3-6 yrs mTBI (5.00±1.30) yrs modTBI (4.90±1.20) yrs sTBI (5.10±1.10) yrs	Falls Infant (37; 74%) Preschool (21; 49%)	None	C-S, P 24-45 (30.06±NA)
Dégeilh et al. (2018)	mTBI (63; 52.00%)	mTBI (35.84±11.17)	Falls mTBI (59; 94.00%) OI (32; 60.00%)	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)
D'Hont et al. (2017)	mTBI (18; 72.22%)	mTBI (53.00±8.00)	NA	TDC (15; 46.67%)	L (C-S), P 6
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	OI (62; 50.00%) TDC (81; 50.61%)	L, P 6 Ax (43.52±11.72)

			(35; 56.45%)		
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
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
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)
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)
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
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)
McKinlay et al. (2014)	mTBI 0-5 yrs (83; NA)	0-5 yrs (NA±NA)	NA	TDC (972; NA)	L, P Pre-injury (covariates), 11-20 yrs

	Inpatient (61; NA) Outpatient (22; NA)				
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)
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
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)
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)
Pastore et al. (2013)	sTBI (14; 64.30%) Brain tumour (18; 77.80%) Vascular or infectious brain lesions (23; 39.10%)	sTBI (24.79±10.69)	NA	None	C-S, P 8.40 - 16.33 (8.50±10.52) Ax sTBI (34.07±6.89)
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
Sonnenberg et al. (2010)	msTBI (93; 61. 29%)	< 6 yrs (3.40±1.50) yrs	NA	None	L, R

	Young msTBI (61; 63.93%) Old msTBI (32; 56.25%)	Young 0-3 yrs; 11 mos (2.60±1.10) yrs Old 4-5 yrs; 11 mo (5.0±0.60) yrs			Ax msTBI 7 - 9 yrs; 11 mo (8.30±0.70) yrs
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)
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
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 6.50 yrs old
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)
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
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)
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) Ax naTBI (87.64±25.52)
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
Ewing-Cobbs et al. (1998)	msTBI (40; 30.00%) naTBI (20; 15.00%) aTBI (20; 50.00%)	1 mo-6 yrs naTBI (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
aTBI vs naTBI/aTBI & naTBI					
Ewing-Cobbs et al. (2013) +	All severity naTBI (64; 50.00%)	0-36 naTBI (8.00±7.90)	naTBI (41; 64.10%) aTBI	TDC (60; 48.00%)	L, P 2 & 12 mos Ax

	aTBI (61; 59.00%)	aTBI (11.30±10.50)	Falls (17; 26.56%)		naTBI (9.80±8.00) aTBI (12.60±10.30) TDC (11.70±8.60)
Keenan et al. (2007)*	All severity naTBI & aTBI (48; 57.70%)	<2 yrs 1.80 – 9.90 (4.20 median)	naTBI (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
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)
Ewing-Cobbs et al. (2006)	msTBI (23; 52.00%) naTBI (10; NA) aTBI (13; NA)	4-71 (21.20±21.90)	naTBI (10; 47.62% 0f msTBI) aTBI Falls (5; 38.00%)	TDC (21; 47.00%)	L, P 3.80-8.30 yrs (5.70±NA) Ax msTBI (89.60±26.20) TDC (101.00±29.00)
Ewing-Cobbs et al. (2004)	msTBI (44; NA) Young (18; 55.56%) Old (26; 50.00%) naTBI (NA; 41.00%) aTBI	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)

	(NA; 59.00%)				TDC Young: (22.62±7.53) Old: (57.92±15.59)
Keenan et al. (2018)	naTBI & aTBI naTBI & aTBI (386; 64.00%) mTBI (144; 61.00%) cmTBI (130; 68.00%) modTBI (26; 31.00%) sTBI (86; 72.00%)	2.50-15 yrs (9.20±4.20) Age groups: 2.50-6 yrs 6-11 yrs 12-15; 11 yrs	All ages naTBI (2; 1.00%) aTBI Falls (143; 37.00%)	OI (133; 63.00%)	L, P Pre-injury, 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)	naTBI Falls (85; 69.00%) aTBI (21; 17.00%)	OI (45; 60.00%)	L, P Pre-injury, 3 & 12 mos
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)
Vassel-Hitier et al. (2019)	msTBI (21; 40.40%) aTBI (8; 62.50%) naTBI (13; 61.50%)	< 18 mos (0.70±0.50) 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
Wetherington et al. (2010)*	naTBI & aTBI (51; NA) mTBI (31; 45.16%)	< 2 yrs mTBI (0.49±0.57) yrs msTBI	aTBI NA (26; NA%) naTBI	TDC (31; 64.50%)	C-S, P ≈ 3 yrs Ax mTBI

	msTBI (20; NA)	(0.81±0.62) yrs	NA (25; NA%)		(3.33±0.38) msTBI (3.25±0.27)

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. Studies identified in the systematic review examining outcome after accidental TBI and non accidental TBI in early childhood: Cognitive and academic outcomes

Cognitive and academic outcomes							
Reference	**Intelligence/Development**	**Attention**	**Executive Functioning**	**Memory**	**Language**	**Social cognition**	**Academic**
aTBI							
Bellerose et al. (2015)						**Discrepant desires & False Beliefs** ToM mTBI < TDC (6 mos)	
Bellerose et al. (2017)						**Discrepant desires & False Beliefs** ToM mTBI < TDC & OI (6 & 18 mos)	
Crowe et al. (2014)	**WPPSI-III** **Verbal IQ** msTBI (results in average range) < TDC				**CELF-P** **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. (2012a)	**WPPSI-III** VIQ, PIQ, FSIQ msTBI < mTBI = TDC		**WPPSI-III** Information processing (coding subtest) (ns)				
Crowe et al. (2013)		**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. (2012b)	**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)				
D'Hont et al. (2017)						**NimStim Set of Facial Expression** Emotional facial expression processing mTBI < TDC	
Landry-Roy et al. (2018)			**Delay of Gratification** Inhibition **&** **Conflict Scale** Cognitive flexibility **&** **Shape Stroop** Inhibition & Cognitive flexibility mTBI = TDC (ns)				
Marsh and Whitehead (2005)[a]		**NEPSY-II** **Visual Attention** TBI < OI 22% TBI in 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% in TBI impaired range **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)
McKinlay et al. (2002)	**WISC-R** Inpatient = Outpatient = TDC/OI (ns)						**PAT** Inpatient = Outpatient = TDC/OI (ns)

Papoutsis et al. (2014)		**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)				
Prasad et al. (1998)	**BSID** Development/IQ/motor functioning 2 mos Deficit range (63.00%) 1 yr Normal range (83.33%)						
Tonks et al. (2011)[a]			**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				
Walz et al. (2009)	**Differential Ability Scales (DAS)/General Conceptual Ability (GCA)** sTBI < modTBI & OI					**ToM** **False beliefs** **False contents** sTBI < modTBI & OI **False location/Control/ToM total** sTBI = modTBI = OI (ns)	
Wrightson et al. (1995)*			**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 & 6.50 yrs old mTBI < OI **Reynell developmental language scales** mTBI = OI (ns)		**Neale analysis of reading ability/Letter knowledge and writing** mTBI = OI (ns)
naTBI							
Barlow et al. (2005)	**BSID-II** Development (8 out of 14) < 1st %ile (2 out of 14) 1st-6th %ile			**BSID-II** Development (8 out of 14) < 1st %ile (2 out of 14) 1st-6th %ile			**BSID-II** Development (8 out of 14) < 1st %ile (2 out of 14) 1st-6th %ile
Ewing-Cobbs et al. (1999)	**BSID-II** Mental + physical domains 1 & 3 mos			**BSID-II** Mental + physical domains 1 & 3 mos			**BSID-II** Mental + physical domains 1 & 3 mos

	na msTBI < TDC			na msTBI < TDC			na msTBI < TDC
Landry et al. (2004)	**Bayley Mental Development Index** na msTBI < TDC			**Bayley Mental Development Index** na msTBI < TDC			**Bayley Mental Development Index** na msTBI < TDC
Stipanicic et al. (2008)	**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 (ns) **Halstead-Reitan Battery** **Progressive Figures** Cognitive flexibility n-aTBI = TDC (ns)	**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 (ns) **Halstead-Reitan Battery** **Progressive Figures** Cognitive flexibility n-aTBI = TDC (ns)	**SB-IV** naTBI < TDC
aTBI vs naTBI							
Beers et al. (2007)*	**BSID-II/SB4** Intellectual development/ability naTBI < aTBI						
Ewing-Cobbs et al. (1998)	**BSID-II & SB4** Intellectual development/ability naTBI 45.00% Deficient						

	aTBI 5.00% Deficient						
aTBI vs naTBI/aTBI & naTBI							
Ewing-Cobbs et al. (2013) [+]	**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) Joint attention sTBI < cmTBI & modTBI (2 & 12 mos)	
Keenan et al. (2007)[+]	**MSEL** Development Composite score TBI < TDC < 3 SDs naTBI (40.00%) (RR: 2.60) vs aTBI (4.30%)						
aTBI & naTBI							
Bonnier et al. (2007)	**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 working memory (14/27) Deficient		**EEL/BEP** Expressive language (25/48) Deficient		
Ewing-Cobbs et al. (2006)	**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 msTBI < TDC		**WJ-III** Maths msTBI < TDC **GORT-4** Comprehension, Reading & Writing msTBI < TDC

							<u>Unfavorable academic outcome</u> 48% msTBI 5% TDC OR = msTBI 18x > TDC
Ewing-Cobbs et al. (2004)		**Stationary boxes** <u>Visual scanning</u> msTBI = TDC (ns)	**Delayed response** <u>Visual working memory & Inhibitory control</u> msTBI < TDC **Spatial Reversal** <u>Cognitive flexibility</u> msTBI = TDC (ns)				
Keenan et al. (2018)			**BRIEF/-P** TBI = OI (ns, pre-injury) <u>Inhibitory self-control & metacognition</u> TBI > OI (3 & 12 mos) <u>Working memory</u> mTBI > cmTBI & mod TBI & sTBI & OI (pre-injury) TBI > OI (3 & 12 mos)				
Keenan et al. (2019)			**ASQ-3** <u>Problem solving</u> Pre-injury 33% sTBI vs 7% OI ≤ 2nd %ile 3 & 12 mos sTBI < OI		**ASQ-3** <u>Communication</u> Pre-injury 24% sTBI vs 2% OI ≤ 2nd %ile 3& 12 mos sTBI < OI		
Kieslich et al. (2001)*	**FMOS** <u>Normal Development</u> < 2 yrs: 25 (39.10%) 2-6 yrs: 37 (42.10%) <u>Intellectual and/or academical retardation</u> < 2 yrs: 39 (61.10%) 2-6 yrs: 51 (58.00%)						**FMOS** <u>Intellectual and/or academical retardation</u> < 2 yrs: 39 (61.10%) 2-6 yrs: 51 (58.00%)

Vassel-Hitier et al. (2019)	**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 **% 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%		**Ongoing education** Mainstream school 38% Specialized institutions/classrooms 24% Repeated year/adaptations 38%
Wetherington et al. (2010)*	**Mullen Scales of Early Learning** msTBI (low range) < mTBI (low to average) & TDC (average)						

Table 3. Studies identified in the systematic review examining outcome after accidental TBI and non accidental TBI in early childhood: Socio-affective, behavioral and adaptive outcomes

Socio-affective, behavioral and adaptive outcomes			
Reference	**Emotion regulation & behavior**	**Social skills**	**Adaptive Functioning**
aTBI			
Bellerose et al. (2015)	**CBCL** Externalizing scale mTBI > TDC (pre-injury & 6 mos)		**ABAS-II** Social & GAC mTBI = TDC (ns; pre-injury & 6 mos)
Bellerose et al. (2017)			**ABAS-II** Social & GAC mTBI = TDC (ns; pre-injury, 6 & 18 mos)
Coster et al. (1994)*	**CBCL** Total problems (ns)		**PEDI** Functional Skills & Caregiver Assistance ↑ Self-Care & Social Function Assistance post-injury TBI > OI (1 & 6 mos)
Crowe et al. (2012a)	**CBCL** (ns)	**SSRS** (ns)	
Dégeilh et al. (2018)			**ABAS-II** Practical & conceptual mTBI = OI (ns; pre-injury, 6 & 18 mos) Social mTBI = OI (ns; pre-injury) mTBI < OI (6 & 18 mos)
Gagner et al. (2018)	**CBCL** Externalizing scale mTBI > OI (pre-injury)		

	Internalizing externalizing scale mTBI > OI & TDC (6 mos)		
Green et al. (2013)			**SPRS-C** **Total score** TBI = TDC (ns) School/Leisure sTBI < TDC Living Skills TBI < TDC
Kaldoja et al. (2015)	**ASQ:S-E** Self-regulation & autonomy difficulties Pre-injury mTBI Boys > mTBI Girls (self-regulation only) mTBI Boys > TD Boys Post-injury Self-regulation mTBI Boys > mTBI Girls mTBI Boys > TD Boys Compliance & Affect (ns)	**ASQ:S-E** Social difficulties Pre-injury (ns) Post-injury mTBI boys > TD Boys Communication (ns)	**ASQ:S-E** Adaptive difficulties Pre-injury mTBI Girls > TDC Girls Post-injury (ns)
Lalonde et al. (2016)		**MRO (Observational measure)** Parent-child interaction quality mTBI < TDC OI = mTBI & TDC **PCDI** Parent-child dysfunctional interaction mTBI = OI = TDC (ns)	**ABAS-II** Leisure subscale TDC & mTBI > OI (pre-injury) Other subscales mTBI = OI = TDC (ns; pre-injury)
Liu et al. (2013)*	**CBCL** **Withdrawn behavior** Single injury & Multiple > TDC		
Marsh and Whitehead (2005)+	**CBCL** **(parents + teacher)** Total competence, Internalizing + Externalizing + Total problems TBI = OI (ns)		
McKinlay et al. (2014)	**Self-Report Delinquency Inventory & Interview**		

	Sx drug dependence DSM-IV criteria Inpatient > Outpatient = TDC Property offenses Inpatient > Outpatient = TDC Violent offenses Inpatient = Outpatient > TDC		
McKinlay et al. (2002)	**Rutter & Conners** Conduct & Hyperactivity/Inattention problems Inpatient > Outpatient + TDC/OI		
McKinlay et al. (2009)	**SERD & RBPC & DISC & RAPI** Conduct & ODD/Attention deficit/Hyperactivity/ Substance abuse/Mood disorder Inpatient > Outpatient + TDC/OI **DISC** Anxiety disorder Inpatient = Outpatient = TDC/OI		
McKinlay et al. (2010)	**Rutter & Conners** ADHD & Conduct & Hyperactivity/Inattention problems Inpatient > Outpatient + TDC/OI		
Pastore et al. (2013)	**CBCL** **Frequency of problems** Externalizing (50.00%) Destructive (42.90%) Aggressive (35,70%) Internalizing (77.80%) Anxious/Depressed (55.50%) Somatic (55.50%)		**VABS** Daily living skills sTBI & Brain tumour > Vascular/infectious brain lesions
Prasad et al. (1998)			**VABS** Composite score 2 mos & 1 year ≥ Average range (83.33%)
Sonnenberg et al. (2010)		**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)+	**SDQ** Socio-emotional difficulties TBI > TDC		
Wrightson et al. (1995)*	**Connors parent** mTBI = OI (ns; pre-injury, 1, 6, 12 mos) **Connors teacher** mTBI = OI (ns; 6.50 yrs old)		**Vineland social maturity scale** mTBI = OI (ns, pre-injury, 1, 6, 12 mos)
naTBI			
Barlow et al. (2005)	**BBRS** Orientation & Engagement impairment (1 & 3 mos) Attention/arousal (1 mo) Emotion regulation (3 mos) na msTBI > TDC		
Ewing-Cobbs et al. (1999)	**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)			**VABS** Composite score naTBI < aTBI
aTBI vs naTBI			
Beers et al. (2007)+			**VABS** Socialization sTBI < cmTBI & mod TBI (12 mos) Communication naTBI < aTBI (severe aTBI < cm aTBI & moderate aTBI) (12 mos)

Ewing-Cobbs et al. (1998)			**SIB-R** Adaptive behavior TBI (average) < TDC ≥ 3 SDs naTBI (RR: 1.60) vs aTBI
aTBI & naTBI			
Bonnier et al. (2007)	**ASQ-3** Socio-emotional 3& 12 mos sTBI < OI	**ASQ-3** Personal-social 3& 12 mos sTBI < OI	
Ewing-Cobbs et al. (2004)		**Brunet-Lezine revised Scale of infant development** Sociability 78% borderline/deficit range	**Brunet-Lezine revised Scale of infant development** Autonomy 78% borderline/deficit range
Keenan et al. (2018)	**CBCL** Withdrawal behavior msTBI > mTBI & TDC Other behaviors/problems msTBI = mTBI = TDC (ns)		
Keenan et al. (2019)	**CBCL** Externalizing scale mTBI > TDC (pre-injury & 6 mos)		**ABAS-II** Social & GAC mTBI = TDC (ns; pre-injury & 6 mos)
Kieslich et al. (2001)[+]			**ABAS-II** Social & GAC mTBI = TDC (ns; pre-injury, 6 & 18 mos)
Vassel-Hitier et al. (2019)	**CBCL** Total problems (ns)		**PEDI** Functional Skills & Caregiver Assistance ↑ Self-Care & Social Function Assistance post-injury TBI > OI (1 & 6 mos)

Table 4. 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 5. 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 6. 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	Include at least one comparison group	Continue to document potential differences between typically developing and

		history and lack of knowledge on emergent conditions		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

CHAPITRE 3 – LE TEMPÉRAMENT: EXPLORATION D'UN CONSTRUIT PERTINENT POUR LE TCC PRÉCOCE

Comme le démontre la revue systématique présentée au Chapitre 2, il existe plusieurs évidences selon lesquelles les jeunes enfants qui ont subi un TCC pendant la petite enfance présenteraient un large éventail de conséquences aux plans du fonctionnement cognitif, comportemental, socio-affectif et adaptatif. Toutefois, bien que plusieurs domaines aient été pris en compte auprès de cette population, cette revue met également en lumière le manque d'études se penchant sur des construits spécifiques à la période de la petite enfance. L'une des raisons pour ceci est qu'il a été longtemps pris pour acquis que les fonctions qui sont plus susceptibles d'être altérées suivant un TCC précoce, seraient exactement les mêmes que celles observées chez les enfants plus âgés et les adultes (p. ex., fonctionnement intellectuel, attentionnel, exécutif), et ce, sans tenir compte des caractéristiques développementales propres au jeune enfant. En effet, celui-ci a longtemps été considéré aux yeux de la recherche comme un « petit adulte » et cette façon de le percevoir a souvent teinté les considérations théoriques et méthodologiques de la recherche auprès du jeune enfant (psychopathologie; Ariès, 1962; Giza et al., 2007). Or, celui-ci évolue dans une période développementale sensible où il acquiert de nombreuses habiletés et compétences et où plusieurs de ses fonctions cognitives, émotionnelles et socio-comportementales sont encore immatures, en émergence ou bien en croissance rapide. Ainsi, le jeune enfant, par ces enjeux développementaux qui lui sont propres, devrait donc être étudié de façon distincte non seulement des adultes, mais aussi des groupes pédiatriques plus âgés (enfants d'âge scolaire et adolescents).

Depuis plusieurs années, la psychologie développementale souligne que plusieurs des construits caractéristiques à cette période précoce sont importants et même prédictifs d'un développement harmonieux chez le jeune enfant et que certains d'entre-eux ne sont souvent plus considérés dans les périodes développementales subséquentes (p. ex., âge scolaire, adolescence et âge adulte). Afin d'illustrer ce propos de manière concrète, considérons ici, à titre d'exemple

uniquement, le domaine du développement social. Il est maintenant reconnu que les adultes ayant subi un TCC démontrent des difficultés par rapport à des aspects plus complexes de la cognition sociale (McDonald et al., 2019; Theadom et al., 2019), tels que l'empathie (c.-à-d. la capacité de ressentir et comprendre les expériences affectives d'autrui; de Sousa et al., 2012; Wood et Williams, 2008). Durant l'enfance, le construit englobant la cognition sociale est généralement opérationnalisé et mesuré par la théorie de l'esprit (ToM; c.-à-d. la capacité de comprendre les états mentaux d'autrui). Les études rapportent d'ailleurs des difficultés à ce niveau chez les enfants d'âge scolaire et les adolescents ayant subi un TCC comparativement à leurs pairs (Dennis et al., 2012; Turkstra et al., 2004). Or, durant la petite enfance, et particulièrement chez le nourrisson (0-2 ans) ou le bambin (2-4 ans), ce même construit n'est pas encore consolidé et doit être mesuré sous sa forme précurseur, en mesurant, par exemple, l'attention conjointe (c.-à-d. la capacité à attirer et à maintenir l'attention d'autrui vers un objet ou une personne dans le but d'obtenir une observation commune). Cette habileté a été démontrée comme étant une fonction essentielle à l'émergence ultérieure de la théorie de l'esprit et d'autres aspects plus complexes de la cognition sociale. Ces construits « de plus bas niveau » constituent fréquemment les fondations pour le développement d'autres fonctions et leur étude en contexte de TCC précoce pourrait être très informative quant aux conséquences pouvant survenir et émerger à plus long terme. Ainsi, il serait critique que la communauté scientifique s'attarde à la manière dont les fonctions et construits étudiés chez les individus plus âgés sont représentés dans leur forme précurseur en se questionnant, par exemple, sur les préalables ou les fonctions de base de ces domaines de plus haut niveau.

À cet égard, un construit développemental clé, qui constitue un précurseur et un facteur prédictif important d'une multitude d'autres domaines, ainsi qu'une avenue fertile afin d'explorer les conséquences d'un TCC durant la petite enfance, est le tempérament. En effet, celui-ci

représente la tendance émotionnelle et comportementale de l'enfant, ses principaux traits, sa « couleur », qui teinte la façon dont il va réagir et s'adapter à son environnement. Le tempérament est un construit qui englobe l'ensemble du fonctionnement de l'enfant, tant au plan émotionnel, comportemental que cognitif et qui se traduit par des manifestations comportementales observables. Ainsi, à la suite d'un TCC durant la petite enfance, une période où plusieurs fonctions sont immatures, peu différenciées ou en émergence, les manifestations du tempérament pourraient informer davantage sur les conséquences comparativement à l'étude d'autres fonctions souvent étudiées chez les individus plus âgés (p. ex., langage, fonctions exécutives, personnalité), puisque celles-ci ne sont pas bien définis en bas âge.

Étymologie et bref historique du tempérament

Le mot « tempérament » vient du mot latin « temperamentum » qui signifie « combinaison proportionnée des éléments d'un tout, combinaison, proportion, mesure; la meilleure combinaison d'éléments pour constituer un principat » ET « mélanger ». Au quatrième et cinquième siècle avant J.-C., selon la médecine grecque et la théorie d'Hippocrate, la santé dépendait du « mélange harmonieux » de quatre éléments appelés « humeurs » soit le sang, le flegme (pituite ou la lymphe), la bile noire et la bile jaune. À partir de cette théorie, Dr Claude Galien (129 à 201) a proposé que la prédominance de l'une de ces « humeurs » résulterait en un *style émotionnel* ou *tempérament* distinctif ce qui formerait l'aspect central des quatre types de tempérament de base. Le type « sanguin » ou « joyeux, enjoué » ou tempérament « actif » reflétait un excès de sang. Le type « mélancolique » ou « triste/morne » reflétait un excédent de bile noire. Le type « colérique » ou « fâché/furieux » ou violent reflétait un excès de bile jaune alors qu'un excès de flegme était associé avec le type « flegmatique » ou tempérament « calme ou passif ». Ainsi, les différences

quant au mélange de ces humeurs auraient équivalu aux différences de tempérament (Digman, 1994). À travers le temps et encore aujourd'hui, le tempérament est largement étudiés et est au cœur de la recherche dans plusieurs domaines tels que par exemple, la psychologie développementale (p. ex., Thomas & Chess), la psychologie de la personnalité (p. ex., Allport, Cattell, Eysenck et Guilford) ou encore l'éducation.

Définition opérationnelle du tempérament

Depuis plusieurs années, la nature et la définition du tempérament font l'objet de controverse dans le domaine de la psychologie développementale. À la suite d'une table de concertation réunissant quatre groupes de chercheurs (Goldsmith et al., 1987), une définition intégrative de leurs quatre approches du tempérament a été présentée (Buss et Plomin, 1975; Goldsmith et Campos, 1982; Rothbart et Derryberry, 1981; Thomas et Chess, 1977):

> Temperament consists of relatively consistent, basic dispositions inherent in the person that underlie and modulate the expression of activity, reactivity, emotionality, and sociability. Major elements of temperament are present early in life, and those elements are likely to be strongly influenced by biological factors. As development proceeds, the expression of temperament increasingly becomes more influenced by experience and context. (p. 524; Goldsmith et al., 1987)

Une autre table de concertation (Shiner et al., 2012) impliquant d'autres chercheurs représentant les mêmes quatre approches du tempérament, a été réalisée afin de discuter des plus récents travaux effectués et proposer une définition alternative, laquelle est maintenant davantage acceptée et consensuelle dans le domaine:

> Le tempérament représente un ensemble de traits qui apparaissent tôt dans l'enfance dans les domaines de l'activité, l'affectivité, l'attention, l'auto-régulation qui sont relativement stables et, ces dispositions sont le produit d'interactions complexes entre des facteurs génétiques, biologiques et environnementaux à travers le temps. (traduction libre: Shiner et al., 2012)

Cette définition partage plusieurs principes et postulats de la définition précédente (1987) et inclut également de nouvelles considérations, améliorations et adaptations des postulats suivants:

1) Stabilité du tempérament: Selon certains travaux dans le domaine du tempérament, ce ne seraient pas tous les traits du tempérament qui seraient stables tôt dans la vie puisque certains systèmes de régulation du tempérament qui contrôlent et inhibent les aspects de réactivité du tempérament apparaissent plus tard dans l'enfance (p. ex., inhibition). Ainsi, lorsque ces systèmes émergent et se développent, ceux-ci peuvent influencer l'expression et, par conséquent, la stabilité de certains traits (Rothbart, 2011). Les traits du tempérament deviennent plus constants et cohérents avec l'âge, montrant une stabilité plus importante dès la période préscolaire (Roberts et DelVecchio, 2000). Les évidences empiriques montrent par ailleurs que la stabilité est de niveau modéré et augmente après l'âge de deux ans en raison de la mise en place de certaines fonctions (p. ex., inhibition comportementale; Fox et al., 2001).
2) Interaction génétique, biologie et environnement: Au plan de la nature du tempérament, certains chercheurs proposent que le tempérament représenterait une prédisposition biologique à réagir de façon singulière à une stimulation donnée (p. ex., réaction émotionnelle). Par exemple, Kagan et collègues suggèrent que le seuil d'activation de l'amygdale serait corrélé à l'activité motrice, la réactivité et l'inhibition. Plus précisément, un seuil bas d'activation de l'amygdale serait associé à des niveaux élevés de ces traits de tempérament et un seuil élevé d'activation à des niveaux bas (Kagan, 1998; Kagan et Snidman, 1991). En revanche, d'autres auteurs font plutôt référence au tempérament comme étant le résultat d'influences environnementales. Bien que ces théories semblent opposées et contradictoires, elles ne sont pas incompatibles. Pendant la période prénatale, l'environnement intra-utérin est déjà influencé par l'expression du

matériel génétique de l'enfant (Huizink, 2012), et l'expérience ainsi que l'environnement continuent de définir et moduler l'expression génétique pendant la période post-natale et lors du développement de l'enfant (Champagne et Mashoodh, 2009). Ainsi, le tempérament ne devrait plus être considéré strictement comme étant dérivé génétiquement et biologiquement à la naissance et plus tard façonné par l'expérience; il devrait plutôt être considéré comme le résultat de l'interaction complexe entre les facteurs génétiques, biologiques et environnementaux agissant ensemble dès le début et tout au long du développement.

3) Affectivité et cognition: La majorité des chercheurs s'entendent sur le fait que les traits du tempérament inclus dans la définition de 1987 constituent des différences individuelles du tempérament en ce qui concerne l'activité, la réactivité, l'affectivité/émotionalité et la sociabilité (Goldsmith et al., 1987). Toutefois, cette définition omet les dimensions d'*attention* et d'*auto-régulation*. Or ces dernières se sont avérées être des traits distinctifs inter-individuels qui émergent tôt dans l'enfance et qui proviennent en partie du développement de systèmes biologiques et cognitifs. En outres, elles influencent le développement des fonctions impliquées dans la réactivité émotionnelle (Rothbart, 2011). Les experts du tempérament reconnaissent maintenant que le traitement affectif et cognitif sont des systèmes intégrés (Derryberry et al., 2006; Forgas, 2008), et que par conséquent, certains aspects du tempérament tels que l'attention et le contrôle inhibiteur représentent des différences individuelles affectives et comportementales dans des domaines traditionnellement considérés comme de nature davantage cognitive.

Approche psychologique de Rothbart

Plusieurs conceptions du tempérament existent dans la littérature et les experts ont, au fil du temps, proposé plusieurs théories différentes du tempérament (voir Goldsmith et al., 1987; Shiner et al., 2012; Zentner et Shiner, 2015). Le tempérament comme *style comportemental* (Thomas et Chess, 1977); *régulation émotionnelle* (Goldsmith et Campos, 1982); *personnalité en émergence* (Buss et Plomin, 1975); *réactivité* et *auto-régulation* (Rothbart et Derryberry, 1981); *inhibition à la nouveauté* (Kagan et Snidman, 1991).

L'approche qui est considérée comme étant l'une des plus globales et intégratives est celle de Rothbart (Rothbart et Ahadi, 1994; Rothbart et Derryberry, 1981). En effet, comparativement aux autres approches, celle privilégiée par Rothbart porte sur la *réactivité* et l'*auto-régulation* au plan émotionnel, mais aussi sur les plans cognitif et moteur (voir Goldsmith et al., 1987; Vaughn et Bost, 1999 pour une discussion plus approfondie sur les différences fondamentales entre les principales perspectives théoriques du tempérament).

Définition du tempérament selon l'approche psychologique de Rothbart

Selon la théorie de Rothbart (1981), le tempérament est reconnu comme étant un ensemble de prédispositions constitutionnelles, c.-à-d. des prédispositions biologiques qui sont relativement stables et qui peuvent être influencées et modifiées à travers le développement par la génétique, la maturation et les expériences de l'enfant (Rothbart et Bates, 2006). Plus précisément, le tempérament est défini comme étant des différences individuelles au plan de la réactivité et de l'auto-régulation dans les domaines de l'affectivité, de l'activité et de l'attention. La *réactivité* représente les dispositions dites « bottom-up » (c.-à-d. réactions automatiques) telles

que l'activation des systèmes physiologiques et comportementaux. Plus concrètement, elle réfère par exemple au temps nécessaire à l'enfant pour réagir à un stimulus, l'intensité de sa réponse et le temps de récupération après une détresse (Rothbart, 2011). L'*auto-régulation*, quant à elle, fait référence aux processus dits « top-down » (c.-à-d. processus volontaires) qui régulent la réactivité et qui incluent les tendances d'approche ou bien de retrait d'un stimulus. Notamment, elle représente le contrôle volontaire de l'attention et de l'inhibition qui permettent de réguler les pensées et émotions (Rothbart, 2011). Cette dimension se développe durant la petite enfance et permet de freiner certaines activités motrices et émotions non régulées. Elle améliore également la capacité de l'enfant à s'adapter aux exigences environnementales (Rothbart et Derryberry, 2002). Ainsi, les tendances individuelles au plan de la *réactivité* et de l'*auto-régulation* chez l'enfant forment ses bases distinctives dans la manière dont il va réagir et s'adapter à son environnement. Le tempérament est donc fortement associé au développement de stratégies d'adaptation en plus d'avoir un effet sur le développement comportemental et socio-affectif ultérieur de l'enfant (Rothbart et Bates, 2006). Finalement, la réactivité et l'auto-régulation sont des domaines relativement orthogonaux, mais qui sont en constante interaction. Les interactions dynamiques, réciproques et continues entre la réactivité et l'auto-régulation contribuent aux différences quant à l'expression et la stabilité du tempérament au fil du temps (Rothbart et Sheese, 2007). La stabilité du tempérament serait encore modérée chez le nourrisson alors qu'à la fin de la première année, le développement des capacités de l'enfant à réguler, modifier son attention ou à se désengager expliquerait, en partie, certains changements comportementaux observés durant cette période. De ces deux domaines sont également dérivés les dimensions fondamentales du tempérament où la réactivité est représentée par les dimensions *Dynamisme* (affectivité positive) et l'*Affectivité*

Négative et la régulation, par le *Contrôle Volontaire*. Ces trois dimensions peuvent être schématisées par trois continuums distincts sur chacun desquels la position de l'enfant varie.

Dimensions et outils de mesure du tempérament selon Rothbart

La majorité des études actuelles concernant le tempérament de l'enfant se base sur la théorie de Rothbart (1981) ainsi que sur la structure du tempérament dérivée d'analyses factorielles réalisées à partir des mesures disponibles (Bridgett et al., 2011; Carranza Carnicero et al., 2000; Gartstein et Rothbart, 2003). Rothbart et collègues ont développé le *Infant Behavior Questionnaire* (IBQ), le *Early Childhood Behavior Questionnaire* (ECBQ; Putnam et al., 2006) et le *Childhood Behavior Questionnaire* (CBQ; Rothbart et al., 2001) reconnus comme étant des mesures rapportées par le parent les plus utilisées en recherche (Gartstein et al., 2012). Les différentes versions du ECBQ et du CBQ (c.-à-d. longue, courte et très courte) se catégorisent selon les trois dimensions fondamentales du tempérament de la théorie de Rothbart: le *Dynamisme*, l'*Affectivité Négative* et le *Contrôle Volontaire* (voir Tableau 1). Ces dimensions ont été développées à partir d'analyses factorielles des scores aux échelles de tempérament chez le nourrisson, l'enfant et l'adulte (Putnam et al., 2001). D'autres versions de ces questionnaires existent telles que les versions brèves fréquemment utilisées en recherche étant donné leurs bonnes propriétés psychométriques ainsi que leur temps de passation réduit (ECBQ; Putnam et al., 2010; CBQ; Putnam et Rothbart, 2006). Ces versions comportent en moyenne 36 questions et se catégorisent également selon les trois dimensions fondamentales du tempérament.

Tableau 1. Les dimensions et sous-échelles du tempérament chez les enfants d'âge préscolaire selon la théorie de Rothbart (1981)

DIMENSIONS et SOUS-ÉCHELLES	DÉFINITIONS
DYNAMISME	
Sourire et Rire	Affect positif en réaction aux changements d'intensité, de rythme, de complexité d'un stimulus
Niveau d'activité	Le niveau d'activité motrice incluant le rythme et l'étendue du déplacement
Approche/Anticipation Positive	Excitation et anticipation positive envers des activités agréables attendues
Plaisir (intensité élevée)	Plaisir découlant d'activités impliquant un haut niveau d'intensité, de rythme et/ou de nouveauté
Impulsivité	Le temps de réaction/initiation
Timidité	Inhibition comportementale face à la nouveauté ou bien les défis, particulièrement sociaux
AFFECTIVITÉ NÉGATIVE	
Colère et Frustration	Affect négatif associé à l'interruption d'une tâche en cours ou bien d'un blocage face à l'atteinte d'un but
Inconfort	Affect négatif associé à la qualité sensorielle des stimulations, incluant l'intensité, le rythme, la quantité de lumière, de son, de mouvement ou de texture
Peur	Affect négatif associé à l'anticipation d'une détresse
Tristesse	Affect négatif et niveaux plus bas d'énergie et d'humeur associés à l'exposition à la souffrance, la déception et la perte d'objet
Capacité à s'apaiser	Taux de récupération d'une détresse ou excitation
CONTRÔLE VOLONTAIRE	
Contrôle attentionnel	La capacité de focuser l'attention et d'orienter l'attention lorsque désiré
Contrôle Inhibitif	La capacité de planifier une action future et d'inhiber des réponses inappropriées
Plaisir (intensité basse)	Plaisir découlant d'activités qui impliquent un faible niveau d'intensité, de rythme et/ou de nouveauté
Sensibilité Perceptuelle	Le niveau de détection et perception de stimulations à faible intensité

Dimension *Dynamisme*

La dimension du *Dynamisme* se manifeste par le sourire, le rire, l'activité et l'appréciation du plaisir à haute intensité ainsi que l'approche et l'anticipation positive de nouveaux stimuli (Rothbart, 1989; Rothbart et Derryberry, 1981). Cette dimension serait associée à l'activité neurochimique du neurotransmetteur de la dopamine. Des données d'études en neuroimagerie fonctionnelle suggèrent que le *Dynamisme* serait associé à l'activité des régions recevant plusieurs projections dopaminergiques telles que l'amygdale baso-latérale, l'hypothalamus latéral, le noyau accumbens, le cortex cingulaire antérieur ainsi que le cortex préfrontal dorsolatéral gauche (pour une revue voir Whittle et al., 2006). Le *Dynamisme* se rapporte aussi aux modèles biologiques mettant l'accent sur les systèmes d'approche et de facilitation comportementale (Behavioral approach system (BAS); Gray, 1982). L'étude du lien entre le tempérament et le comportement a largement été exploré et de nombreuses études montrent que certaines dimensions seraient plus naturellement associées à des problèmes externalisés et d'autres à des problèmes internalisés (p. ex., Abulizi et al., 2017; Hankin et al., 2017; Kostyrka-Allchorne et al., 2020; Olino et al., 2014). La dimension *Dynamisme* serait, quant à elle, généralement associée à des comportements externalisés où un niveau plus élevé de *Dynamisme* prédirait plus de problèmes externalisés (p. ex., impulsivité; Berdan et al., 2008; Davis et Suveg, 2014; Rothbart et Bates, 2006; Rothbart et al., 2001). Toutefois, d'autres chercheurs trouvent qu'un niveau plus faible de *Dynamisme* serait associé à un risque plus élevé de comportements internalisés (Davis et Suveg, 2014; Eisenberg et al., 2009; Gartstein et al., 2012; Kozlova et al., 2020; Northerner et al., 2016). En accord avec cette hypothèse, certains ont trouvé qu'un niveau optimal d'*Affectivité Positive* prédisait un faible niveau de symptômes internalisés (Delgado et al., 2018; Dougherty et al., 2010). Ainsi, un enfant ayant un faible niveau de *Dynamisme* pourrait ne pas avoir un niveau suffisant de comportements d'approche et d'émotion positive et être plus à risque de montrer des comportements internalisés

et inversement, un enfant montrant un niveau trop élevé de cette dimension tendrait à présenter davantage de comportements extériorisés.

Dimension *Affectivité Négative*

La dimension d'*Affectivité Négative* se manifeste, quant à elle, par des émotions de peur, de tristesse, de colère, de frustration, d'inconfort et d'une capacité à s'apaiser plus faible (Rothbart, 1989; Rothbart et Derryberry, 1981). Cette dimension se rapporte au système d'inhibition comportementale (BIS; Gray, 1982) et est liée à l'activité de certaines structures cérébrales dont l'amygdale, l'hippocampe, le cortex cingulaire antérieur et le cortex préfrontal dorsolatéral droit (pour une revue voir Whittle et al., 2006). Au plan comportemental, l'*Affectivité Négative* serait également associée aux comportements de types internalisés et externalisés (Rothbart et Bates, 2006; Rothbart, 2011; Thomas, 1968). Par exemple, la colère et/ou la frustration prédiraient tant la survenue de problèmes internalisés qu'externalisés, alors que la peur et la tristesse favoriseraient davantage l'apparition de difficultés internalisées (Lengua, 2006). Ainsi, un niveau élevé d'*Affectivité Négative* serait un prédicteur robuste de la survenue de problèmes externalisés et internalisés au cours du développement de l'enfant (Crawford et al., 2011; Delgado et al., 2018; Gartstein et al., 2012; Kozlova et al., 2020; Northerner et al., 2016).

Dimension *Contrôle Volontaire*

La dimension du *Contrôle Volontaire* représente, quant à elle, l'habileté à recruter des processus cognitifs de plus haut niveau afin de réguler la réactivité affective et comportementale (c.-à-d. Dynamisme et Affectivité Négative; Rothbart et al., 2000). Comparativement aux biais attentionnels et l'inhibition comportementale associés à l'*Affectivité Négative,* lesquels sont davantage des formes passives et automatiques de régulation, le *Contrôle Volontaire* représente un aspect plutôt volontaire et actif. Cette dimension inclut ainsi les composantes « top-down » du

contrôle attentionnel (c.-à-d. l'allocation flexible des ressources attentionnelles telles que l'attention soutenue, sélective ou alternée) ainsi que le contrôle de l'inhibition (c.-à-d. l'habileté à freiner une réponse comportementale dominante en faveur d'une réponse non-dominante plus appropriée). De plus, la dimension du *Contrôle Volontaire* comprend également les traits de sensibilité perceptuelle (ex. vigilance) ainsi que de plaisir à faible intensité (ex. appréciation d'activités calmes telles que la lecture; Ahadi et al., 1993; Rothbart et Bates, 2006). Contrairement aux deux autres dimensions qui se présentent dès la naissance, cette dimension apparaît vers la fin de la première année de vie et peut-être mesurée de façon fiable vers l'âge de 18 mois (Rothbart et Bates, 2006). La période du nourrisson jusqu'à l'âge préscolaire est un temps de changements majeurs en ce qui concerne les structures cérébrales impliquées dans le *Contrôle Volontaire,* telles que le cortex cingulaire antérieur, le cortex préfrontal dorsolatéral et le cortex orbitofrontal (pour une revue voir Whittle et al., 2006). Finalement, la dimension *Contrôle Volontaire* serait également liée à la fois aux comportements internalisés et externalisés chez l'enfant (Gartstein et al., 2012) où un faible niveau prédirait tant des comportements internalisés (Crawford et al., 2011; Eisenberg et al., 2001) qu'externalisés (Olson et al., 2017; Rothbart et Bates, 2006) chez l'enfant en bas âge. Plus précisément, la recherche sur le tempérament suggère que le *Contrôle Volontaire* jouerait un rôle de modérateur où la combinaison d'un niveau élevé de réactivité émotionnelle/comportementale (c.-à-d. *Dynamisme, Affectivité Négative*) et un faible niveau de *Contrôle volontaire* serait lié au développement de problèmes internalisés et externalisés (Delgado et al., 2018; Dollar et Stifter, 2012; Lonigan et Phillips, 2001).

Trajectoires développementales des dimensions du tempérament

La littérature sur le développement normatif du tempérament nous informe que grâce à la maturation cérébrale et l' influence de l'environnement, les enfants montrent une progression des

dimensions *Dynamisme* et *Contrôle Volontaire* et une diminution du niveau d'*Affectivité Négative* à travers le temps (voir Figure 7; Rothbart, 2011; Zentner et Shiner, 2015).

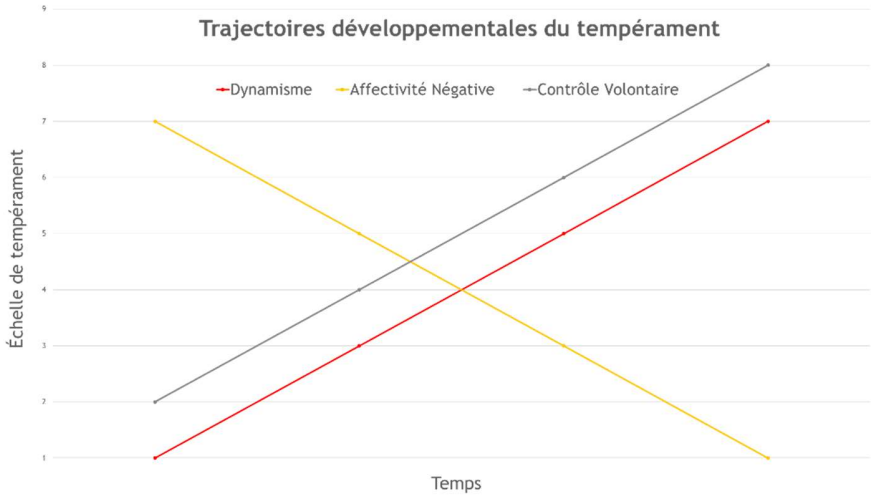


Figure 1. Représentation schématisée des trajectoires développementales normatives du tempérament

Représentation schématisée libre à partir des informations recueillies dans « Becoming who we are: Temperament and personality in development » par M.K. Rothbart, 2011, Guilford Press, chapitre 8.

Tel que mentionné ci-haut, les dimensions du tempérament ont été corrélées à l'activité de régions cérébrales spécifiques. Ces liens entre le tempérament et le cerveau sont par ailleurs mieux expliqués en utilisant une approche de systèmes et de réseaux de connectivité plutôt qu'une perspective localisationniste (p. ex., Henderson et Wachs, 2007; Jiang et al., 2018). Ainsi, les différences individuelles du tempérament peuvent être perçues comme reflétant l'interaction spécifique pour un individu donné de l'activité des structures cérébrales impliquées dans la *réactivité* (c.-à-d. *Dynamisme* et/ou *Affectivité Négative*) et celles impliquées dans l'*auto-régulation* (c.-à-d. *Contrôle Volontaire*). Il peut ainsi être postulé qu'un déséquilibre des systèmes cérébraux associés à ces dimensions, causé par la survenue d'un TCC en bas âge, pourrait influencer les manifestations du tempérament et, par le fait même, son développement ultérieur.

Il a d'ailleurs été démontré chez les enfants plus âgés que des changements touchant la personnalité peuvent survenir et persister jusqu'à deux ans post-blessure chez 40% des enfants et des adolescents ayant subi un TCC sévère (5-14 ans, Max et al., 2000; Max et al., 2006). Selon les travaux de Max et collaborateurs, aucun changement significatif de la personnalité n'a été identifié chez les personnes atteintes de TCC léger ou modéré, bien qu'une forme transitoire de changement de personnalité soit évidente chez 5% des enfants (Max et al., 2000; Max et al., 2006; Max et al., 2001). Néanmoins, l'idée selon laquelle ces changements de personnalité seraient le résultat uniquement de la blessure cérébrale est plutôt remise en question. En effet, selon d'autres approches, ces changements seraient plutôt expliqués par un ensemble de facteurs qui interagissent ensemble aux plans neuropsychologique, biologique et psychosocial et seraient alors décrits dans le cadre d'un modèle biopsychosocial (Yeates et al., 2008).

Chez le jeune enfant, les changements touchant la personnalité n'ont jamais été étudiés, possiblement en raison du fait que la personnalité n'est pas différenciée et que les types distincts de personnalité n'apparaissent que plus tard dans la vie (Zentner et Shiner, 2015). Toutefois, les changements de personnalité chez les adolescents et les adultes peuvent nous laisser croire que des changements au plan de la tendance émotionnelle et comportementale pourraient également survenir chez le jeune enfant. Néanmoins, puisque le jeune enfant n'est pas simplement un « petit adulte », le concept de tempérament, qui représente les principaux traits de l'enfant et caractérise la manière dont il réagit et s'adapte à son environnement, constitue une meilleure représentation des tendances caractérielles (Goldsmith et al., 1987). Malgré l'importante prévalence du TCC chez le jeune enfant ainsi que les conséquences potentielles associées, aucune étude, à notre connaissance, n'a examiné la relation entre le TCC et le tempérament. La prochaine section

présentera donc un article empirique qui avait pour objectif d'explorer l'effet d'un TCC précoce sur la trajectoire développementale du tempérament.

ARTICLE 2

It's a matter of surgency: Traumatic brain injury is associated with changes in preschoolers' temperament

Temperament after early TBI

Marilou Séguin[1,2], Fanny Dégeilh[1,2], Annie Bernier[1],
Ramy El-Jalbout[3], Miriam H. Beauchamp[1,2]

[1] Department of Psychology, University of Montreal, Quebec, Canada
[2] Sainte-Justine Research Center, Montreal, Quebec, Canada
[3] Sainte-Justine Hospital, Montreal, Quebec, Canada

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Abstract

Traumatic brain injury (TBI) can disrupt cognitive, social, and behavioral functioning. Temperament is often used to reflect emotional and behavioral tendencies in young children, but has never been assessed after TBI. **Objective:** Evaluate whether early TBI disrupts the trajectory of temperament**. Method:** Primary caregivers of 173 preschoolers (age: 36 ± 12 months) with uncomplicated mild TBI (83 mTBI), more severe TBI (mild complicated, moderate and severe, 21 msTBI) and with orthopedic injuries (69 OI) reported on their child's temperament retrospectively to assess pre-injury profiles and at 6 and 18 months post-injury. For each domain of temperament (surgency, negative affectivity, effortful control), linear mixed-model analyses were conducted to explore group differences on the rate of change across time. **Results:** There were no pre-injury temperament differences between groups for any domains ($\chi 2$ (2) = 2.84; p = .24; $\chi 2$ (2) = 0.27; p = .87; $\chi 2$ (2) = 1.47; p = .48). There was a significant effect of group on the rate of change across time for surgency ($\chi 2$ (2) = 6.77; p = .03), but not for negative affectivity ($\chi 2$ (2) = 1.47; p = .48) or effortful control ($\chi 2$ (2) = 2.21; p = .33). Children with msTBI showed a lower rate of increase in surgency compared to children with mTBI and OI. **Conclusions:** Developmental trajectories of surgency appear to be affected by more severe TBI. Disruptions in normal developmental trajectories of temperament could underlie some of the socio-behavioral manifestations of TBI in this young age group.

Keyword Selection: Preschool children; traumatic brain injury; temperament; linear mixed-model analysis; surgency;

Public Significance Statement

This study explores whether early brain injury could disrupt temperament and suggests that children with moderate to severe traumatic brain injury show altered developmental trajectories in terms of surgency, a dimension of temperament involved in energy/activation by a tendency to approach new information, for example. Temperament may not be as robust as once thought; it may be vulnerable to brain insult, underpinning socio-behavioral symptoms after pediatric brain injuries.

Introduction

The incidence of TBI is high in children five years and under (McKinlay et al., 2008; Thurman, 2016) and sustaining TBI at such an early age may be associated with poor outcomes and prognosis due to disruptions in the typical development of emerging functions, such as cognition, social skills, and behavior (Vicki Anderson, Celia Godfrey, Jeffrey V. Rosenfeld, & Cathy Catroppa, 2012; Vicki Anderson, Celia Godfrey, Jeffrey V Rosenfeld, & Cathy Catroppa, 2012; Catroppa, Anderson, Godfrey, & Rosenfeld, 2011; Catroppa, Anderson, Morse, Haritou, & Rosenfeld, 2008; Nadebaum, Anderson, & Catroppa, 2007; Ryan et al., 2014). In older children with TBI (5-14 years old), personality changes have been detected and are reported to persist up to 2 years post-TBI in 40% of children and adolescents with severe injuries (Jeffrey E. Max et al., 2000; Jeffrey E. Max et al., 2006; Jeffrey E Max, Robertson, & Lansing, 2001). In the work by Max and colleagues, significant personality changes were not identified in those with mild or moderate TBI, although a transient form of personality changes was evident in 5% of children (Jeffrey E. Max et al., 2000; Jeffrey E. Max et al., 2006; Jeffrey E Max et al., 2001). These personality changes have only been investigated in school-age children with TBI, and thus the findings raise the question of whether they might also occur in younger children. However, this has never been investigated, probably because personality is not differentiated in young children and clear personality categorizations only emerge later in life (Shiner et al., 2012). In children under the age of five, the construct of "temperament" optimally represents children's principal traits and characterizes the ways in which they react and adapt to their environment (H. H. Goldsmith et al., 1987).

Temperament refers to a group of related traits that include emotional, motor and reactive tendencies and regulatory capacities seen early in development, which have genetic underpinnings and that form the building blocks of personality (Mary Klevjord Rothbart & Derryberry, 1981). Specifically, temperament is described as:

> "constitutional differences in reactivity [characteristics of the individual's reaction to changes in the environment] and self-regulation [processes that modulate reactivity], with "constitutional" seen as the relatively enduring biological makeup of the organism influenced over time by heredity, maturation and experience" (Rothbart & Derryberry, 1981; p.38).

Integrating these major concepts of reactivity and self-regulation, Rothbart and colleagues (2001) seminal model of temperament includes three higher order trait domains: *surgency*, which reflects children's predisposition toward high levels of positive emotionality/reactivity, a general tendency for children to approach novelty, to be actively engaged with their environment and to show high levels of motor activity and impulsivity; *negative affectivity,* which characterizes children's predisposition toward different negative affective states/reactions including anger, frustration, fear, and sadness; and *effortful control,* which captures individual differences in self-regulation and the control of reactivity, and includes behavioral regulation and activation control (Samuel P Putnam, Gartstein, & Rothbart, 2006; M. Rothbart & Bates, 2006).

Temperamental traits were initially described as remaining relatively constant over time, leading to a certain misconception that they are present at birth and do not change (Buss & Plomin, 1975; H. H. Goldsmith et al., 1987). However, studies show that temperament is more dynamic than once thought, with age related-changes and sensitivity to environmental factors. For example,

normative data suggest that children's displays of negative emotions might decrease and their displays of socially acceptable positive emotions might increase with age because children's understanding of display rules enhances during the first decade of life (Olino et al., 2011; Mary K Rothbart, Ahadi, & Evans, 2000; Saarni, Campos, Camras, & Witherington, 1998). More precisely, Olino and colleagues investigated children between infancy and 9 years old. In addition, Kochanska and colleagues (1997; 2000) found that due to socialization pressures and increasing internalization of adults' standards of behavior, children become better able and more motivated to regulate their emotion-related behavior (i.e., effortful control) with age. In support of the notion that temperament may be influenced by experience, Laceulle and colleagues (2012) found that adolescents who experience stressful events display slowed temperamental maturation, with lesser decreases in negative affectivity, and lesser increases in effortful control and surgency compared to those who do not experience any stressful events. Together, these studies suggest that temperament may be influenced by a variety of factors such as maturation and experience, and that a traumatic event or acquired injury, such as TBI, may potentially affect the way in which temperament develops subsequent to the injury.

Despite the high prevalence of TBI under the age of five years (McKinlay et al., 2008; Thurman, 2016) and the potential negative consequences on a range of domains of functioning such as cognition, social skills, and behavior, no study has explored putative disruptions in temperament after early TBI. The aim of this longitudinal study was to assess the developmental trajectory of temperament following early pediatric TBI using linear mixed-model analyses. More precisely, the objective was to evaluate whether sustaining a brain injury early in life (18 - 60 months) disrupts the developmental trajectory of temperament compared to injuries that do not

involve the head (orthopedic injury control group, OI). We hypothesized that early pediatric TBI may alter the developmental trajectory of temperament, stopping or slowing its normal progression (i.e. lesser increase of surgency, lesser decrease of negative affectivity and lesser increase of effortful control) in preschoolers who sustain TBI. In accordance with the dose-response effect of TBI (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005), we also expected that more severe TBI would cause greater disruption in the developmental trajectories of temperament than mild TBI.

Materials and methods

Design

The data were collected as part of a larger prospective longitudinal project investigating cognitive and social outcomes of early TBI (Bellerose, Bernier, Beaudoin, Gravel, & Beauchamp, 2015; Gagner, Landry-Roy, Bernier, Gravel, & Beauchamp, 2018; Lalonde, Bernier, Beaudoin, Gravel, & Beauchamp, 2016). Herein, we report data from the pre-injury, 6-, and 18-month post-injury timepoints. This study was approved by the ethics and institutional review committee of the Hospital and conducted in agreement with the Helsinki declaration. The larger study included two types of control groups: children with an orthopedic injury (OI) and typically developing children (TDC). Here, we present data from the OI group only because the TDC group did not have pre-injury data. The OI group provides an optimal comparison for individuals with TBI due to shared injury-related experiences (Babikian et al., 2011) and has been shown to be highly comparable to TDC on pre-morbid characteristics (M. H. Beauchamp, Landry-Roy, Gravel, Beaudoin, & Bernier, 2017).

Participants

Two hundred thirty-one children aged between 18 and 60 months were recruited at the Emergency Department (ED) and divided into three groups: (1) a milder TBI group (children with accidental uncomplicated mild TBI, mTBI; n = 109), (2) a more severe TBI group characterized by positive clinical computerized tomography (CT) or magnetic resonance imaging (MRI) (children with skull fractures, accidental complicated mTBI or moderate-severe TBI, msTBI, n = 23), and (3) children with accidental orthopedic injuries (OI, n = 99).

Participants were recruited in an urban tertiary care pediatric ED between 2011 and 2015. Participants presented to the ED for a TBI or OI and were recruited in one of two ways: Between 9 AM and 9 PM daily, a research nurse approached prospectively families directly for participation in the study. Potentially eligible children who visited the ED outside these hours were contacted by phone by the research coordinator within one week and invited to participate.

The following inclusion criteria were applied to all participants: (1) age at injury between 18 and 60 months; (2) accidental injury; (3) child having at least one parent fluent in English or French. Exclusion criteria for the two groups were as follows: (1) any known congenital, neurological, developmental, psychiatric, or metabolic condition; (2) less than 36 weeks of gestation; (3) prior TBI serious enough to result in a visit to the emergency department.

Diagnostic criterion for TBI was a closed accidental head injury leading to an emergency department consultation defined as: (1) a trauma or acceleration–deceleration movement applied

to the head, (2) at least one of the following symptoms: loss of consciousness or confusion, irritability according to parents, vomiting, amnesia, seizure, drowsiness, dizziness, motor or balance difficulties, blurred vision, hypersensitivity to light, or headaches in a verbal child (Osmond et al., 2010), (3) for the mild TBI group, a recorded pediatric Glasgow coma score (GCS) between 13 and 15 with no evidence of skull fracture or intracranial lesion on diagnostic CT scan or MRI. For the more severe TBI group (msTBI), a GCS between 3 and 12 OR evidence of skull fracture or intracranial lesion on clinical CT or MRI regardless of GCS (Teasdale & Jennett, 1974). Diagnostic criterion for the OI group was a limb trauma leading to a final diagnosis of simple fracture, sprain, contusion, laceration or unspecific trauma to an extremity (e.g. pulled elbow). Children with OI who had also sustained trauma to the head were not eligible. Injury characteristics for the mTBI, msTBI and OI groups are detailed in Table 1 and injury location for the msTBI group is presented in Table 2.

Procedure

At recruitment (Timepoint 0 [T0]), primary caregivers were asked to complete a questionnaire booklet including sociodemographic and pre-injury information. Caregivers were instructed to report data with respect to their child's pre-injury status in order to provide baseline information on pre-morbid child behavioral, environmental factors as well as temperament.

At 6 and 18 months post-injury (Timepoint 1 [T1] and 2 [T2]), primary caregivers completed the same questionnaire booklet as at T0 and were instructed to assess their child's functioning in the last four weeks.

Measures

Injury characteristics

Case Report Form. General medical information was obtained from medical files including cause of injury (for both TBI and OI groups), lowest GCS, and neurological symptoms: drowsiness, hematoma, persistent vomiting, headaches, loss of consciousness, alteration of consciousness, motor or balance difficulties, dizziness, irritability, amnesia, visual symptoms, or seizure. Loss of consciousness (LOC) was measured according to the following categories: none, <1 min, < 5 min, < 1 hrs, 1 to 24 hrs, > 24 hrs, suspected, unknown. Where possible, alteration of consciousness (AOC, i.e., confusion) was also assessed as follows: none, < 1 hrs, 1 to 24 hrs, > 24 hrs.

Sociodemographic and pre-injury characteristics

Sociodemographic Questionnaire. An in-house developmental and demographic questionnaire was completed by the primary caregiver and used to collect information on children's sex, ethnicity, birth characteristics, medical, developmental, and social history as well as parents' education, occupation, and family constellation. Socioeconomic status was measured with parental education and obtained by averaging both parents' educational qualifications on an 8-level scale ranging from 'Doctoral degree' to 'Less than 7 years of school'. When parental highest educational attainment was available for only one parent (e.g., single-parent families), no average was computed. If a child was part of a step family, we used the step-parent's information in the average.

Adaptive functioning. The primary caregiver completed the Adaptive Behavioral Assessment System-II (ABAS-II; Harrison and Oakland, 2003) at T0. The ABAS-II is a parent-report questionnaire that provides a comprehensive assessment of everyday adaptive functioning specifically designed to evaluate patients with neurologic disorders, including TBI (Harrison & Oakland, 2003). The primary caregiver indicates the frequency at which the behavior is demonstrated on a 4-point scale (0 = Is not able, 1 = Never when needed, 2 = Sometimes when needed, 3 = Always when needed). Three standardized domain scores are derived: Conceptual, Social, and Practical and a global score. A higher standard score (M = 100, SD = 10) is indicative of better adaptive skills. This questionnaire has good psychometric properties, including adequate internal consistency (α = .80 to .97) and test–retest reliability (r = .70 to .90; (Harrison & Oakland, 2003)).

Child behavior. At T0, the primary caregiver completed the Child Behavioral Checklist (CBCL; Achenbach and Rescorla, 2001), which is a parental report questionnaire assessing child behavioral and emotional well-being rated on a 3-point scale according to the degree to which the statement describes the child (0 = Not true, 1 = Somewhat or sometimes true, 2 = Very true or often true). This questionnaire has good psychometric properties, with test–retest reliabilities of .68 to .92 and internal consistency coefficients ranging from .66 to .95 (Achenbach & Rescorla, 2001).

Family functioning. At each timepoint, the primary caregiver completed the General functioning scale from the Family Assessment Device (FAD; Epstein *et al.*, 1983) which assesses overall family functioning. Each of the 12 items is rated on a 4-point scale representing the degree

to which the statement describes the family (1 = Strongly agree, 2 = Agree, 3 = Disagree, 4 = Strongly disagree). Higher scores indicate poorer family functioning. This subscale has excellent psychometric properties, with test–retest reliabilities of .71 and internal consistency coefficients of .92 (Epstein et al., 1983; Miller, Epstein, Bishop, & Keitner, 1985).

Primary outcome measure

Temperament. The *Children's Behavior Questionnaire* (CBQ; Rothbart *et al*., 2001) and the *Early Childhood Behavior Questionnaire* (ECBQ; Putnam *et al*., 2006a) were designed to measure temperament in children and were developed to be consistent with the psychobiological model of temperament proposed by Rothbart and Derryberry (1981). The primary caregiver was asked to complete either the Very Short Form of the ECBQ (S. P. Putnam, Jacobs, Gartstein, & Rothbart, 2010) if their child was aged between 18 and 36 months, or the Very Short Form of the CBQ (Samuel P Putnam & Rothbart, 2006) if they were between 3 and 7 years of age. Each of the 36 items is rated on a 7-point Likert scale ranging from "extremely untrue of your child" to "extremely true of your child". Caregivers were also provided with a "not applicable" response option to be used when the child had not been observed in the situation described. For both questionnaires, three dimensions were derived from the 36 items: surgency, negative affectivity and effortful control. Direction of scores on the three temperament dimensions are proportional (e.g., higher scores on surgency dimension indicate higher surgency). The ECBQ and CBQ questionnaires have good psychometric properties; their internal consistency and criterion validity are satisfactory. The internal consistency of the three dimensions scales of these questionnaires in the present sample is acceptable (.61-.74).

Statistical analysis

Demographic and pre-injury characteristics

Data were analyzed using SPSS statistical software (version 24.0; SPSS, Inc., Chicago, IL) and screened for violations of normality. Group comparisons (mTBI vs. msTBI vs. OI) were conducted via univariate analyses of variance (ANOVAs) for the continuous variables: age at injury and at assessments (T1, T2), socioeconomic status (parental education), pre-injury behavioral, adaptive, and family functioning. Chi-square analyses were also conducted to compare sex and ethnicity among groups.

Temperament trajectories

Linear mixed-model analyses (Mirman, 2014), also referred to as multilevel modeling or hierarchical linear modeling (MLM/HLM), allow explicit modeling of the nested structure of repeated longitudinal data by simultaneously assessing within-individual change and between-individual differences in change over time (Curran, Obeidat, & Losardo, 2010; Hoffman, 2015; Singer, Willett, & Willett, 2003). Linear mixed-model analysis easily handles the difficulties generated by small samples. Sample sizes of 30–50 should provide reasonable test statistics when five or fewer variables are included to predict intercepts and slopes (Burchinal, Nelson, & Poe, 2006). For example, growth models have successfully been fitted to samples as small as n = 22 (Huttenlocher, Haight, Bryk, Seltzer, & Lyons, 1991), although sample sizes approaching at least 100 are often preferred. Additionally, there is a close relation between the number of individuals and the number of repeated observations per individual (Muthén & Curran, 1997). As such, the total number of person-by-time observations plays an important role in model estimation as well as statistical power. Linear mixed-model analysis also handles challenges associated with partially

missing data, unequally spaced time points, data collected across a range of ages within any one occasion, and non-normally distributed variables (Burchinal et al., 2006; Hedeker, 2004; Singer et al., 2003). Further, linear mixed-models provide higher statistical power than traditional methods applied to the same data (Curran et al., 2010).

In the present study, linear mixed-models were used to examine group effects on the trajectory of each domain of temperament (Surgency, Negative Affectivity, Effortful Control) over 18 months post-injury. Analyses were carried out in R version 3.3.2 using the lme4 and the multicomp packages.

Three linear models were specified for each domain of temperament and a sequential approach was used to ascertain the best-fitting models of growth in child temperament (Mirman, 2014): *i*) an unconditional growth model (model 1) testing the linear fixed effect of time; *ii*) a conditional model (model 2) examining the fixed effect of group on the intercept (i.e., this model tests for group differences at T0); and *iii*) a conditional model (model 3) examining the fixed effect of group on the rates of change (i.e., this model tests whether group status predicts the slope of the trajectory). Models included maximal random-effect (variance of the individual trajectories around the mean trajectory) structures that allowed the model to converge (Barr, Levy, Scheepers, & Tily, 2013). Missing data in outcome variables were handled by using full information maximum likelihood estimation. The fixed effects of group on initial status and on rate of change in each dimension were added individually (models 2 and 3) and their effects on model fit were evaluated using model comparison. Improvements in model fit were evaluated using a likelihood ratio test

based on -2 times the change in log-likelihood (-2LL) between two competing models, which is distributed as $\chi 2$ with degrees of freedom equal to the number of parameters added.

Results

Final sample: Demographic and pre-injury characteristics

Information on recruitment and follow-up of participants is detailed in Figure 1. Rates of refusal to participate in the study were similar between the 3 groups (54%, 73% and 61% refusal for the mTBI, msTBI and OI groups respectively; $\chi 2(1) = 5.81$, $p = .06$). Across the three groups, there were no differences between those who participated in the study and those who declined participation in terms of age at injury (mTBI: $t(1, 236) = -.34$, $p = .73$; msTBI: $t(1,38) = -1.44$, $p = .16$; OI: $t(1,260) = -1.03$, $p = .31$) and sex (mTBI: $\chi 2(1, n = 238) = 0.001$, $p = .98$; msTBI: $\chi 2(1, n = 38) = 0.21$, $p = .65$; OI: $\chi 2(1, n = 259) = 0.02$, $p = .89$).

Families of 12 mTBI (11%), 1 msTBI (4%) and 17 OI (17%) participants consented to the study but never returned the pre-injury questionnaires and did not show-up for the follow-up assessments (drop-out before T0 in Figures 1 and 2). In addition, 13 mTBI (12%), 1 msTBI (4%) and 13 OI (13%) participants were excluded *a posteriori* from the sample because they did not meet an inclusion criterion and/or presented an exclusion criterion that had not been detected prior to testing: TBI-like symptoms that were better explained by another medical condition (2), insufficient mastery of French or English undetected at screening (4), or developmental or

psychiatric disorder (10). Finally, 1 mTBI and 1 OI participants were not included in the present analyses due to lack of temperament data at all measurement timepoints (complete missing data).

The final sample consisted of 83 mTBI (42 boys, 50.60%), 21 msTBI (13 boys, 61.90%) and 69 OI (31 boys, 44.93%) participants. As detailed in Table 1, the three groups did not differ on demographic variables such as child age at injury, post-injury delays, sex, ethnicity, parental education, pre-injury behavioral, adaptive, or family functioning. Primary caregivers were mostly mothers (88.88%, 100.00% and 88.41% in the mTBI, msTBI and OI groups respectively, $\chi 2$ (4) = 3.17 p = .53).

As linear mixed-model analysis handles partially missing data in the outcome variable with full information maximum likelihood, participants who missed 1 or 2 timepoints were included in the present analyses. 32 mTBI (38.55%), 4 msTBI (19.05%) and 21 OI (30.43%) had at least one missing timepoint on the variable of primary interest. The proportion of missing data was equivalent across the three groups ($\chi 2$(2, n = 173) = 3.21, p = .20). Across the three groups, there was no difference in terms of age at injury (F(1, 171) = 1.63, p = .20), sex ($\chi 2$(1, n = 173) = 0.012, p = .91), ethnicity ($\chi 2$(1, n = 172) = 2.12, p = .15) parental education (F(1, 169) = 0.54, p = .47) between those who had missing data and those with complete data.

Main analyses: Developmental trajectories of temperament

Linear mixed-model analyses on Surgency. For the Surgency dimension of temperament, the best-fitting model was model 3 (Tables 3 and 4). There was no effect of group at T0 (Model 2: $\chi 2$(2) = 2.84; p = .24), but a significant effect of group was found on the rate of change across time

(Model 3: $\chi 2(2) = 6.77$; $p = .03$). At T0, Surgency scores were similar for the three groups and were at an average score of 3.46 (*SE* = 0.13) for the OI group, 3.72 (*SE* = 0.17) for the mTBI group, and 4.16 (*SE* = 0.27) for the msTBI group. The OI and mTBI groups had a linear increase of approximately 0.07 (*SE* = 0.01) and 0.06 (*SE* = 0.01) point per month respectively (Tables 3 and 4; Figure 2). Surgency in the msTBI group increased by approximately 0.02 (*SE* = 0.02) point per month. Post hoc comparisons using Bonferroni correction indicate that the rate of change for Surgency in the msTBI group was significantly slower than in the OI group (*p* (corrected) = .03). A similar trend was observed when the msTBI group was compared to the mTBI group (*p* (corrected) = .08). No significant difference was observed between mTBI and OI groups (*p* (corrected) = 1). Thus, children who sustained a msTBI showed a slow-down in the increase of Surgency developmental trajectory compared to OI and mTBI groups.

Linear mixed-model analyses on Negative Affectivity. For the Negative Affectivity dimension of temperament, the best-fitting model was model 1 (Tables 3 and 4). There was no effect of group at T0 (Model 2: $\chi 2(2) = 0.27$; $p = .87$), nor on the rate of change across time (Model 3: $\chi 2(2) = 1.47$; $p = .48$). Negative Affectivity at T0 was at an average score of 4.63 (*SE* = 0.07). The three groups had similar patterns of change (Tables 3 and 4; Figure 2) with a linear decrease of approximately -0.03 (*SE* = 0.005) point per month. Thus, the developmental trajectory of Negative Affectivity was similar for the three groups.

Linear mixed-model analyses on Effortful Control. For the Effortful Control dimension of temperament, the best-fitting model was also model 1 (Tables 3 and 4). There was no effect of group at T0 (Model 2: $\chi 2(2) = 1.47$; p = .48), nor on the rate of change across time (Model 3: $\chi 2(2)$

= 2.21; p = .33). Effortful Control at T0 was at an average score of 5.14 (*SE* = 0.05). The three groups had similar patterns of change (Tables 3 and 4; Figure 2) with a linear increase of approximately 0.02 (*SE* = 0.003) point per month. Overall, the developmental trajectory of Effortful Control was similar for the three groups.

Discussion

Children who sustain TBI may experience a range of cognitive, behavioral and social consequences. This study focussed on temperament, a construct that is critical in current conceptualizations of child development, yet absent from the literature on pediatric TBI. The objective of this longitudinal study was to explore the developmental trajectories of three fundamental dimensions of temperament (surgency, negative affectivity, effortful control) following early TBI. Using an analytic method sensitive to temporal changes (linear mixed-model analysis), the results are broadly consistent with a dose-response effect of TBI, with more severe TBI resulting in greater effects than mild TBI (Anderson et al., 2005). As such, sustaining a mild complicated, moderate or severe TBI during the preschool years was associated with a significantly lesser increase of surgency over 18 months following injury compared to sustaining mild uncomplicated TBI or OI. Counter to initial hypotheses, the evolution of negative affectivity (e.g. anger, frustration, fear, and sadness) and effortful control traits (e.g. behavioral regulation and activation control; Putnam et al., 2001, Rothbart and al., 2006) appears to follow the expected normative course after TBI in this sample. That is, children with TBI showed rates of decrease in negative affectivity and increase in effortful control up to 18 months post-injury similar to those with orthopedic injuries.

According to normative data on the evolution of temperament, a child's level of surgency increases over time, in keeping with cerebral maturation and increased adherence to social expectations (e.g., school/family; Saarni et al., 1998). Most studies to date bring to light direct linear effects of temperament on social competence (e.g. Rothbart & Bates, 1998; for review: Sanson et al., 2004). For example, preschoolers with positive temperaments are more likely to display socially competent behavior (Farver & Branstetter, 1994; Kochanska et al., 1997; Youngblade & Mulvihill, 1998) than those with a propensity to display a more negative temperament. Moreover, positive affectivity has been associated with resilience and active coping styles (Shiner & Masten, 2012). Alternatively, children with low levels of surgency are more likely to present internalizing behavior problems (Gartstein, Putnam, & Rothbart, 2012), to develop behavioral wariness towards peers, and to show lower levels of social competence (Dollar & Stifter, 2012). The findings of the current study suggest that children with more severe TBI may display "low surgency-like" tendencies/reactions, such as more shy and socially withdrawn behaviors, in the face of novelty than children with milder TBI or orthopedic injuries over an 18-month recovery course. They may also present fewer enthusiastic and approach behaviors, as well as disengagement with their environment over time compared to children who sustain mTBI or OI (Gagner et al., 2018). To our knowledge, this is the first evidence that TBI characterized by positive clinical neuroimaging (skull fracture, complicated mTBI, moderate or severe TBI) sustained before the age of 6 years is associated with a slowing in the developmental trajectory of surgency.

Outcomes after TBI are typically predicted by multiple influences (Babcock et al., 2013; Beauchamp & Anderson, 2012; Ponsford, Draper, & Schönberger, 2008; Wells, Minnes, &

Phillips, 2009; Wood & Rutterford, 2006); it is therefore likely that the etiology of temperamental changes after preschool msTBI is the result of a combination of psychological, neural, and cognitive factors. First, it is possible that psychological features associated with injury and trauma may play a role in inducing changes in the development of surgency following msTBI. Children with more severe TBI may experience Post-Traumatic Stress Disorder (PTSD) and symptoms (Bryant, Marosszeky, Crooks, & Gurka, 2000) including re-experiencing the traumatic event, increased arousal, and avoidance of trauma-related stimuli (DSM-5; APA, 2013). Post-traumatic symptoms are especially common after TBI related to motor vehicle accidents (MVA; Keppel-Benson et al., 2002). Although PTSD was not formally evaluated in the current study, MVA did account for more msTBI (24%) than mTBI (0%) and OI (0%). A traumatic event may lead to a shift, at least temporarily, in selected aspects of an individual's core personality traits such as increased "neuroticism", which is the propensity to experience negative emotions (ex. anxiety-withdrawal, depression-unhappiness, vulnerability-stress reaction), and decreased "agreeableness", which reflects individual differences in cooperation and social harmony (Löckenhoff, Terracciano, Patriciu, Eaton, & Costa Jr, 2009). Löckenhoff and colleagues (2009) observed that changes in these personality traits matched the persistent distress, irritability and avoidance/withdrawal symptoms that are part of the criteria for PTSD. Although speculative, this may suggest that the lower rate of increase in the surgency dimension observed in children who sustained a more severe TBI may be due, at least in part, to psychological symptoms surrounding the event that caused the TBI. Children who sustain more severe TBI may avoid objects, places or even activities and be less inclined to present approach behaviors to novelty. For example, a child who falls from a playground structure may be more reluctant to play in the same location, to go to the park or to engage in activities that may replicate the accident. Other factors, such as pain

resulting from the injury or parental anxiety, may also be associated with increased post-traumatic symptoms (Landolt, Vollrath, Ribi, Gnehm, & Sennhauser, 2003). Concretely, children's level of approach to different situations may be altered by their injury experience because they become less inclined and more anxious to make contact with situations or individuals associated with their injury, and are less interested in seeking out novel and unexpected situations/entities.

Alternatively, the observed changed in surgency after msTBI might have a neural explanation. The neurobiology of temperamental *reactivity* (limbic regions: amygdala and striatum) and *regulation* (prefrontal cortex (PFC): lateral PFC and anterior cingulate cortices) in interaction with neurochemical systems (dopaminergic and serotonergic systems) largely determines the expression of a child's temperament and associated social, emotional, and behavioral outcomes (White, Helfinstein, & Fox, 2010). Brain lesions were present in almost all the children who sustained msTBI in the current sample (18/21) and are likely to have affected both the structure of the brain and potentially the functionality of brain networks underlying the expression of surgency. Functional neuroimaging studies indicate that various dimensions of temperament are associated with functional brain activity in distinct neural networks (Whittle, Allen, Lubman, & Yücel, 2006). Specifically, surgency has been shown to be associated with a left hemisphere lateralised circuit linking subcortical limbic and dorsal prefrontal structures with reduced involvement of the hippocampus, ventral anterior cingulate cortex (ACC) and nucleus accumbens (NAcc). Interestingly, in PTSD, similar regions are also altered including the prefrontal cortex, the hippocampus, and the amygdala. Reduced activation of the prefrontal cortex has been associated with symptoms of social withdrawal, avoidance of trauma reminders and emotional numbing in individuals with PTSD (Ehlers & Clark, 2000; Sherin & Nemeroff, 2011).

Neuroimaging studies investigating the links between the neurobiology of TBI and temperament may be useful to confirm the direct effect of brain lesions on alterations of temperament trajectories.

Contrary to study hypothesis, no significant differences were found regarding the developmental trajectory of negative affectivity in the cohort. According to Rothbart and Bates (1998), the dimension of negative emotionality includes irritability and frustration combined with depressed affects such as fearfulness, tendencies to discomfort, and sadness. In the current preschool cohort, there may be differences in terms of the manifestations of behavior (e.g. avoidance of given situations) rather than psychological components such as *subjective distress* (e.g. depressed affect). Young children may not ruminate or self-reflect on the negative consequences of their injury, but instead may display behavioral changes such as withdraw and/or avoidance following TBI compared to older children or adolescents (see PTSD in children younger than 6 years old, DSM-5; APA, 2013). Changes on negative affectivity may appear only later in life or be observable in forms of neuroticism personality traits (Mary K Rothbart et al., 2000).

From a cognitive perspective, the lack of significant differences in the developmental trajectory of effortful control following preschool TBI is perhaps somewhat surprising, given that this dimension of temperament is thought to be closely linked to executive functions (Barkley, 1997; Miyake et al., 2000), and that these functions are widely documented as being affected following TBI (Anderson et al., 2010; Nadebaum et al., 2007). One possible explanation for the lack of changes on the trajectory of effortful control may be that certain elements of this dimension that represent EF are not yet developed in young children and thus there are limited opportunities

to observe any objective and concrete detrimental consequences (Garon, Bryson, & Smith, 2008). Changes on this dimension may take more time to appear given that executive functions continue to develop into early adulthood (Grantham-McGregor et al., 2007).

From a clinical perspective, presence of disruptions in the development of temperament, such as the lower rate of increase on the developmental trajectory of surgency observed here, may lead to internalizing symptoms and social cognition difficulties (Oldehinkel, Hartman, De Winter, Veenstra, & Ormel, 2004). Moreover, if children are not able to regulate their approach tendencies, this can disrupt their social interactions and increase their risk for behavior problems and need for clinical interventions (Verron & Teglasi, 2018). Longer term follow-up of these children could provide additional information on the consequences of temperament changes and associations with other domains of functioning.

Strengths and Limitations

The study presents a longitudinal design focussing on a large group of children who sustained TBI during a potentially vulnerable developmental period. The study provides a portrait of the preinjury characteristics of the sample, which represents a significant strength of the design and suggests that the changes in temperament are not merely due to pre-injury differences. The inclusion of an orthopedically injured comparison group provides control for a number of general injury characteristics and the linear mixed-model analyses allowed the simultaneous exploration of within-individual change and between-individual differences in change over time. Nonetheless, some limitations need to be considered. First, the use of the very short form of the Early Childhood Behavior Questionnaire (S. P. Putnam et al., 2010) and the Children's Behavior Questionnaire

(Samuel P Putnam & Rothbart, 2006) may have restricted the information on temperament traits reported by the parents. The very short form (36 items) is useful because it is time efficient, but it only provides scores for three broad dimensions of temperament. Subsequent work using the extended versions of these questionnaires could provide additional detail on other temperament dimensions, such as Inhibitory Control and Approach. Moreover, the use of two versions (ECBQ: 12 to 36 months and CBQ: 3 to 7 years old) may be developmentally appropriate to use the corresponding measures based on age, this use of different questionnaires may represent confounding factors especially in presence of a smaller group (msTBI). Also, parent questionnaires are inherently associated with measurement bias. Temperament studies in twins (Neale & Stevenson, 1989), for example, indicate that parental biases may reflect genuine problems with temperament scales, such as stereotyping or comparison with the self or opinion-of-population norms. Moreover, parental distress may also influence the way in which parents perceive their child's temperament before and after the injury during this traumatic period ("good old days bias") (Gunstad & Suhr, 2004; Gunstad & Suhr, 2001; Treutler & Epkins, 2003). The "good old days" bias may minimize the likelihood that the postconcussive symptoms observed, existed prior to the injury and attribute current symptoms directly to the injury. Combining a more observational approach with other measures (e.g. questionnaires) in future work, such as the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith and Rothbart, 1996) may help circumvent these biases. Moreover, due to the nature of this longitudinal study, refusal and attrition of participation constitutes inherent limitations and might be partly due to the high demands of the study. Families had to visit the research installation for several hours, fill out different questionnaires, etc. Moreover, attrition level might also represent a portion of children that recovered comparatively to those who remained who still have post-injury symptoms/problems

and remain in the study. Also, no temperament data were collected during acute and subacute phases post-injury and it is thus unclear how the dimensions of temperament evolved in the first 6 months after the injury. Finally, restriction of injury severity in this sample (i.e., a more severe injury group rather than a complicated mild, moderate, and severe groups) may have limited the observation of differences in trajectories on the other traits. The use of specific injury severity group may help nuance the outcomes.

Conclusion

This study is the first to suggest that sustaining a more severe TBI during the preschool period may affect the way in which temperament develops subsequent to the injury. Given that changes in temperament may be associated with socio-behavioral difficulties in this young age group (Sanson et al., 2004; Verron & Teglasi, 2018) and the possibility of developing personality disorders (Mulder & Joyce, 1997; Widiger, De Clercq, & De Fruyt, 2009), detailed exploration of predictors and a better understanding of the mechanisms underlying changes in temperament following a brain injury may help to identify children at risk and developing possible intervention pathways.

Data availability

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

Competing interests

Authors declare that they have no significant competing financial, professional, or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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Table 1. Demographic and injury characteristics for the mTBI, msTBI and OI groups

	mTBI	**msTBI**	**OI**	***F/chi2***	***p***
	(N = 83)	**(N = 21)**	**(N = 69)**		
Sex [male]. n (%)	41 (50.60)	13 (61.90)	31 (44.93)	1.91	0.39
Parental education. *M* (*SD*)	3.12 (1.13)	3.60 (1.15)	2.92 (0.92)	1.01	0.31
Ethnicity [caucasian]. n (%)	68 (81.9)	15 (71.4)	54 (78.3)	0.62	0.74
Age at injury (months). *M* (*SD*)	35.84 (11.47)	41.02 (12.15)	34.18 (11.20)	2.88	0.06
Post-injury delay T1 (months). *M* (*SD*)	6.71 (1.20)	6.44 (0.77)	6.81 (0.95)	0.93	0.40
Post-injury delay T2 (months). *M* (*SD*)	18.89 (1.23)	18.77 (1.12)	18.77 (1.26)	0.17	0.85
Surgency at T0. *M* (*SD*)	3.79 (1.20)	4.20 (1.15)	3.51 (1.26)	2.63	0.08
Negative Affectivity at T0. *M* (*SD*)	4.48 (0.94)	4.43 (0.85)	4.65 (1.05)	0.72	0.49
Effortful Control at T0. *M* (*SD*)	5.21 (0.76)	5.13 (0.69)	5.05 (0.75)	0.91	0.41
Preinjury CBCL – Internal T score at T0. *M* (*SD*)	49.21 (10.46)	48.26 (10.73)	45.97 (10.20)	1.83	0.16
Preinjury CBCL – External T score at T0. *M* (*SD*)	51.15 (9.17)	48.95 (9.31)	48.13 (9.44)	2.02	0.14
Preinjury CBCL – Total problems T score at T0. *M* (*SD*)	51.99 (9.30)	49.53 (10.03)	49.16 (8.56)	1.93	0.15
Preinjury ABAS – GAC ST score at T0. *M* (*SD*)	94.71 (12.40)	97.56 (14.85)	96.62 (12.99)	0.61	0.54
Preinjury FAD at T0. *M* (*SD*)	1.65 (0.50)	1.59 (0.47)	1.63 (0.45)	0.13	0.88
Cause of trauma					
Accidental fall, *n* (%)	77 (92.77)	9 (42.86)	42 (60.94)		
Other non-accidental accident, *n* (%)	6 (7.23)	7 (33.33)	23 (33.33)		

Road accident, *n* (%)	-	5 (23.81)			
Other[a], *n* (%)	-		4 (5.80)		
Trauma severity[b]					
Minor, *n* (%)	55 (66.27)	1 (4.76)	29 (42.03)		
Moderate, *n* (%)	24 (28.92)	3 (14.29)	37 (53.62)		
Serious, *n* (%)	3 (3.61)	11 (52.38)	1 (1.45)		
Severe, *n* (%)	--	3 (14.29)	--		
Critical, *n* (%)	--	3 (14.29)	--		
Missing, *n* (%)	--	--	2 (2.90)		
Lowest Glasgow Coma Scale, *M* (SD)	14.88 (0.40)	11.29 (3.73)	--		
Number of neurological signs					
Drowsiness, *n* (%)	47 (56.63)	15 (71.43)	--		
Hematoma, *n* (%)	38 (45.79)	13 (61.90)	--		
Persistent vomiting, *n* (%)	34 (40.96)	9 (42.86)	--		
Headaches, *n* (%)	27 (32.53)	8 (38.10)	--		
Loss of consciousness, *n* (%)	16 (19.28)	8 (38.10)	--		
Alteration of consciousness, *n* (%)	14 (16.87)	8 (38.10)	--		
Motor or balance difficulties, *n* (%)	11 (13.25)	6 (28.57)	--		
Dizziness, *n* (%)	12 (14.46)	1 (4.76)	--		
Irritability, *n* (%)	10 (12.05)	11 (52.38)	--		
Amnesia, *n* (%)	4 (4.82)	2 (9.52)	--		
Visual symptoms, *n* (%)	5 (6.02)	3 (14.29)	--		

Seizure, *n* (%)	1 (1.20)	2 (9.52)	--		
Others[c], *n* (%)	21 (25.30)	8 (38.10)	--		

Note. * p<0.05; ** p<0.01; mTBI = mild Traumatic Brain Injury; msTBI = more severe Traumatic; Brain Injury; OI = Orthopedic injury; NA = Non-available; T0 = Time point 0; T1 = Time point 1; T2 = Time point 2; FAD = Family Assessment Device; Other cause of trauma[a] = non-visualize trauma; Injury severity[b] = According to the Abbreviated Injury Scale (AIS): Minor = no treatment required, Moderate = outpatient treatment required, Serious = admission required (but not in Intensive Care Unit (ICU)), Severe = ICU admission and/or basic treatment required, Critical = intubation, mechanical ventilation or vasopressors required. Other symptoms[c] = fatigability, feeling of being slower, calmer, loss of appetite, etc.

Table 2. Injury characteristics for the msTBI group

Participants	Severity	Lowest GCS	Lesion description
1	Complicated mTBI	15	Right temporal bone fracture with mild diastasis (5 mm) and overlying subgaleal hematoma.
2	Complicated mTBI	13	Right temporal bone longitudinal fracture. Left periorbital soft tissue edema and emphysema.
3	Complicated mTBI	15	Right frontal soft tissue hematoma with underlying frontal bone nondisplaced fracture reaching the orbital roof.
4	Complicated mTBI	15	Left posterior fossa epidural hematoma. Left occipital bone fracture.
5	Complicated mTBI	15	Depressed right parietal bone fracture. Wide right parietal lobe epidural hematoma (4 mm).
6	Complicated mTBI	13	Right temporo-parietal soft tissue edema. Left temporal bone fracture.
7	Complicated mTBI	15	Subdural hematoma.
8	Complicated mTBI	15	Linear nondisplaced right occipital bone fracture.
9	Complicated mTBI	15	Petechial hemorrhage in the basal ganglia.
10	Complicated mTBI	15	Left posterior fossa epidural hematoma with mass effect on the underlying cerebellum and 4th ventricle. Left occipital condyle nondisplaced fracture.
11	Moderate TBI	9	Nondisplaced superior orbital fracture with surrounding soft tissue edema.
12	Moderate TBI	9	NA
13	Moderate TBI	10	NA

14	Moderate TBI	11	Right occipital bone nondisplaced fracture with adjacent soft tissue edema.
15	Moderate TBI	9	NA
16	Moderate TBI	12	Subdural hematoma. Occipital fracture.
17	Moderate TBI	8	Depressed fracture of the left parietal bone with subdural hematoma. Overlying soft tissue edema involving the temporal, parietal and occipital bones.
18	Severe TBI	6	Comminuted slightly depressed fracture of the right fronto parietal bone involving the coronal suture. Associated right fronto-parietal subgaleal hematoma. Left nondisplaced frontal bone fracture extending from the coronal suture to the left parietal bone. Left extraaxial frontoparietal hematoma measuring (6 mm). Hemorrhagic intraparenchymal contusion in the left frontal lobe.
19	Severe TBI	7	Complex fracture of the right parietal bone extending from the coronal to the lambdoid suture with mild diastasis. Adjacent cephalhematoma. Hemorrhagic contusion in the right parietal lobe.
20	Severe TBI	3	Extensive right hemispheric subdural hematoma of mixed densities with mass effect and midline shift. Mass effect on the anterior aspect of the superior sagittal sinus.
21	Severe TBI	7	Hemorrhagic contusions in the frontal lobes bilaterally involving the rectus gyri. Bilateral temporal poles epidural hematomas. Multiple fractures involving the left mandible, zygomatic arch, temporal bone. Comminuted fractures of the lamina papyracea bilaterally and nasal bones bifrontal slightly displaced fractures.

Note. mTBI = m = mild; TBI = Traumatic Brain Injury; NA = Not available; mm = millimeter.

Table 3. Results of the growth curve analyses on dimensions of temperament

	Goodness-of-fit	Model improvement		Best-fitting model
	log-likelihood	**χ2**	**p**	
Surgency				
Model 1	-644.73			
Model 2	-643.31	2.84	.24	
Model 3	-639.93	6.77	.03	x
Negative Affectivity				
Model 1	-564.93			x
Model 2	-564.80	0.27	.87	
Model 3	-564.06	1.47	.48	
Effortful Control				
Model 1	-427.82			x
Model 2	-427.09	1.47	.48	
Model 3	-425.99	2.21	.33	

Note. Model 1: model testing the linear fixed effect of time. Model 2: model examining fixed effect of group on the initial status (intercept). Model 3: model examining fixed effect of group on the rates of change (slope).

Table 4. Summary of best-fitting models for each temperament dimensions model

	Surgency (Model 3)	**Negative Affectivity (Model 1)**	**Effortful Control (Model 1)**
Fixes Effects			
Intercept [score at T0] Par. est. (SE)	OI: 3.46 (0.13) mTBI: 3.72 (0.17) msTBI: 4.16 (0.27)	4.63 (0.07)	5.14 (0.05)
Time since injury [months] Par. est. (SE)	OI: 0.07 (0.001) mTBI: 0.06 (0.01) msTBI: 0.02 (0.02)	-0.03 (0.005)	0.02 (0.003)
Random Effects			
Intercept variance	0.48	0.28	0.22
Residual variance	0.73	0.55	0.26

Note. Model 1: model testing the linear fixed effect of time. Model 3: examining fixed effect of group on the rates of change (slope). Par. Est. = parameter estimate; mTBI = mild Traumatic Brain Injury; msTBI = more severe Traumatic; Brain Injury; OI = Orthopedic injury.

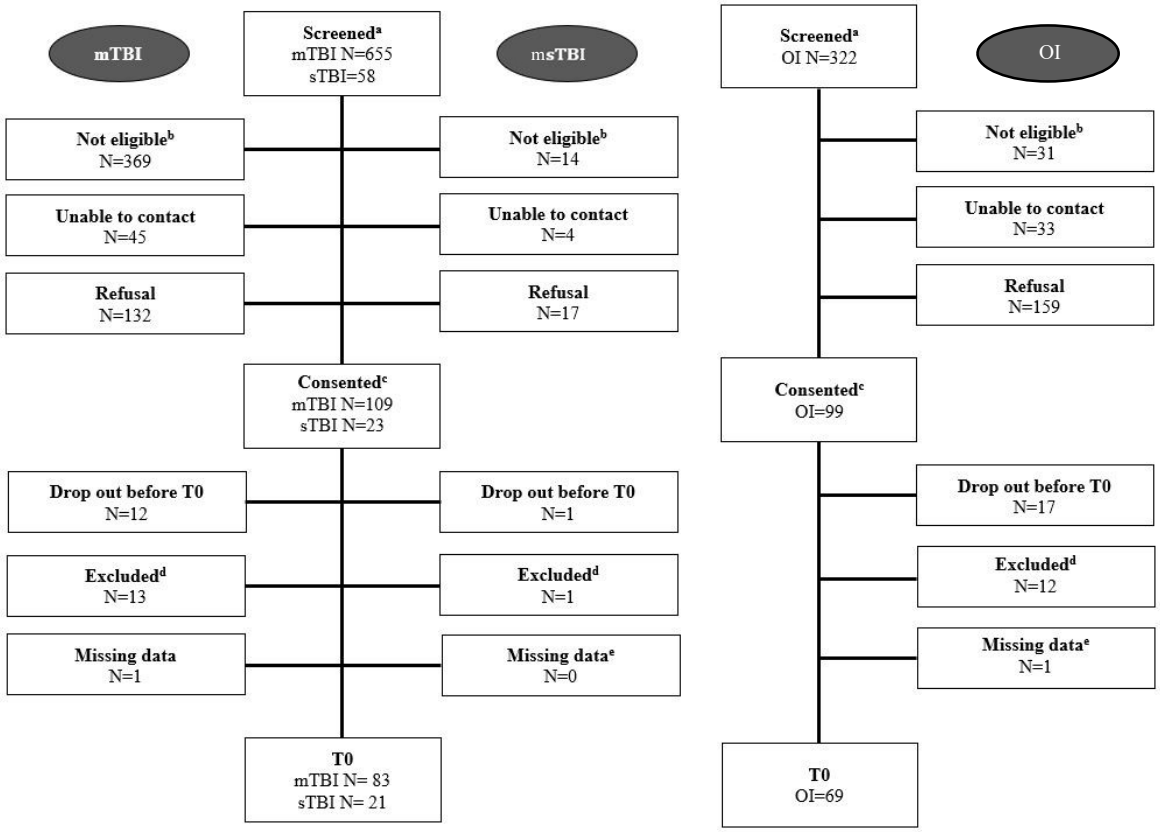

Figure 1. Recruitment and follow-up flowchart for the mTBI, msTBI and OI participants.

Note. mTBI = mild Traumatic Brain Injury; sTBI = more severe Traumatic; Brain Injury; OI = Orthopedic injury. [a] The following emergency department diagnosis were considered for participation in the study: TBI group: traumatic brain injury, head fracture, concussion, intracranial bleeding/hemorrhage, polytrauma. OI group: orthopedic trauma leading to a diagnosis of fracture, sprain, contusion, laceration or any non-specific trauma to an extremity. [b] Potential participants were not eligible because they did not satisfy an inclusion and/or exclusion criterion. [c] Consented refers to those participants whose parents signed a consent form. [d] These participants were excluded a posteriori because they did not satisfy an inclusion and/or presented an exclusion criteria that had

not been detected prior to testing. [e] Missing data refers to participants who consented but had no data on all time points for variables of interest.

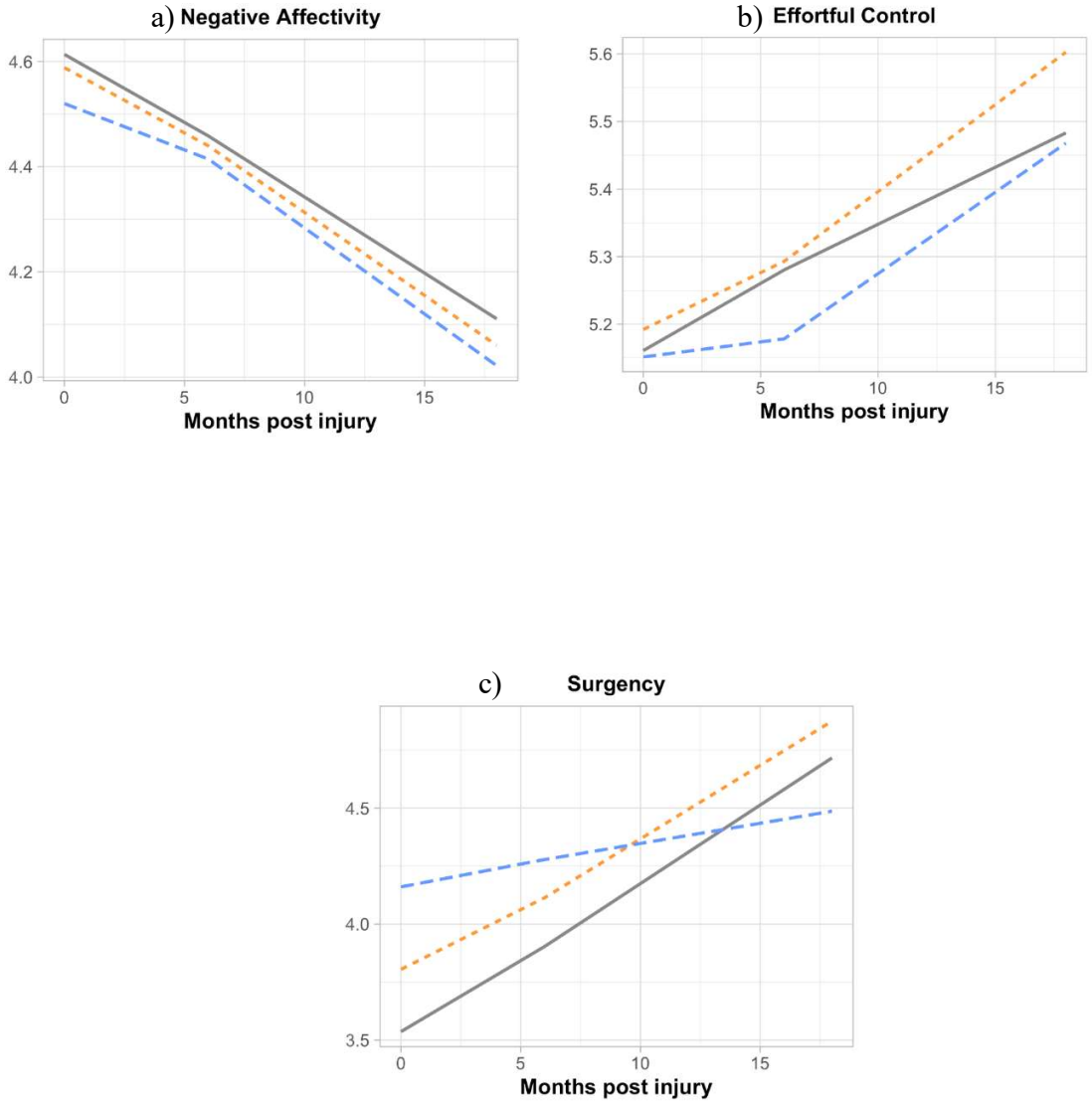

Figure 2. Linear mixed-model analyses on a) Negative Affectivity, b) Effortful Control and c) Surgency

Note. OI= Orthopedic injury (—), mTBI= mild Traumatic Brain Injury (----), msTBI= severe Traumatic Brain Injury (——).

CHAPITRE 4 – DISCUSSION GÉNÉRALE

Retour sur les objectifs généraux de la thèse

À ce jour, en dépit des données épidémiologiques indiquant une incidence particulièrement élevée du TCC en bas âge et de plus en plus d'indices qu'il pourrait entrainer des conséquences développementales importantes, le TCC chez le jeune enfant demeure incompris. En raison de ses caractéristiques physiologiques, des périodes développementales critiques et sensibles qu'il traverse, ainsi que de l'influence de son environnement sur son rétablissement et son développement, le jeune enfant est particulièrement vulnérable aux effets d'un TCC. Bien que le milieu de la recherche s'intéresse de plus en plus au TCC précoce, l'étendue de ses conséquences chez le jeune enfant demeure méconnue. Alors, qu'en est-il des tout-petits? La présente thèse avait pour objectif de faire le point sur la littérature empirique concernant le TCC précoce, ainsi que d'explorer son effet sur le tempérament, un construit n'ayant jamais été étudié auparavant dans cette population. Dans les prochaines sections, un résumé et une discussion approfondie des résultats seront présentés. Ces résultats seront ensuite considérés à la lumière des notions théoriques établies en neuropsychologie pédiatrique. Des considérations méthodologiques propres à l'étude du TCC précoce seront présentées ainsi que les forces et les limites de la thèse. Pour terminer, les avenues futures de recherche et les retombées cliniques de ces travaux seront discutées.

Synthèse et discussion des résultats

Revue systématique des conséquences d'un TCC précoce

Le premier article de la thèse est une revue systématique de la littérature qui visait à recenser et à documenter les conséquences cognitives, académiques, comportementales, socio-affectives et adaptatives suivant un TCC en bas âge (< 6 ans). Les résultats de 43 articles ont été analysés. Dans

l'ensemble, il s'avère que les enfants qui subissent un TCC précoce présentent des difficultés dans plusieurs domaines. L'ampleur des difficultés serait modulée par des facteurs développementaux et liés à la blessure, dont l'âge, la sévérité et le mécanisme. Ainsi, les jeunes enfants qui subissent un TCC sont exposés à des difficultés plus importantes lorsque la blessure est modérée à sévère, de nature non-accidentelle et subie à un plus jeune âge.

Les études rapportant les conséquences d'un TCC précoce plus substantiel (c.-à-d. subi à un plus jeune âge, sévérité modéré-sévère et mécanisme non-accidentel) sont plutôt consensuelles et montrent des atteintes dans la quasi-totalité des domaines incluant le fonctionnement cognitif, comportemental, socio-affectif, adaptatif et le rendement académique. En revanche, les études ayant ciblé les TCCL sont beaucoup moins unanimes sur l'étendue des difficultés. Il faut cependant préciser qu'en ce qui a trait au TCC plus sévère, certaines fonctions apparaissent tout de même préservées, notamment, certaines composantes attentionnelles (attention visuelle, balayage visuel, attention auditive et vigilance auditive). De plus, une étude incluant des jeunes enfants ayant subi un TCC modéré-sévère a montré que les fonctions exécutives étaient en partie préservées. Toutefois, notons que ces résultats s'appuient sur un questionnaire subjectif complété par les parents et qu'ils ne concordent pas avec les performances aux mesures directes (Crowe et al., 2013).

Pour les formes les plus légères de TCC, le fonctionnement cognitif et le rendement académique ultérieur apparaissent généralement indemnes. En effet, la majorité des études qui ont évalué le fonctionnement intellectuel et/ou ses sous-composantes, la vitesse de traitement de l'information, l'attention et les fonctions exécutives (à l'exception de l'attention divisée et l'inhibition qui sont altérées), la mémoire, le langage ou le rendement académique, rapportent peu ou pas de difficultés significatives à court ou à long terme comparativement aux autres groupes de comparaison (enfants ayant subi une blessure orthopédique ou enfants au développement typique).

En revanche, d'autres articles rapportent des résultats mitigés en ce qui concerne le contrôle attentionnel et des fonctions exécutives (Crowe et al., 2013; Papoutsis et al., 2014). Par exemple, Papoutsis et collaborateurs (2014) mettent en évidence une attention divisée plus faible chez les jeunes enfants qui ont subi un TCCL complexe comparativement à ceux qui ont subi un TCC simple. Finalement, quelques études ont évalué la cognition sociale et rapportent des difficultés au plan du traitement des émotions faciales (D'Hondt et al., 2017) et de la théorie de l'esprit (Bellerose et al., 2015, 2017).

Quant à elles, les études portant sur les conséquences comportementales, affectives, et adaptatives post-TCCL présentent des résultats qui sont plutôt variables. Les résultats sont contradictoires concernant la présence de comportements internalisés et externalisés ainsi que de difficultés de régulation émotionnelle (p. ex., Bellerose et al., 2015; Gagner et al., 2018; Kaldoja et Kolk, 2015; Liu et Li, 2013; Wrightson et al., 1995). Les conséquences au plan social sont également mitigées, alors que certaines études rapportent des difficultés sociales (Kaldoja et Kolk, 2015; Sonnenberg et al., 2010) et une moindre qualité de la relation parent-enfant (Lalonde et al., 2016), d'autres ne notent aucune difficulté sociale (Crowe et al., 2012; Kaldoja et Kolk, 2015). Les conclusions sont également équivoques concernant le fonctionnement adaptatif, avec une étude qui rapporte des difficultés dans cette sphère (Dégeilh et al., 2018) et d'autres qui n'en décèlent pas (Bellerose et al., 2015, 2017; Dégeilh et al., 2018; Kaldoja et Kolk, 2015; Lalonde et al., 2016; Wrightson et al., 1995).

Cette importante variabilité des résultats semble découler de considérations méthodologiques concernant les définitions et critères d'inclusion du TCCL précoce utilisés, les construits et domaines étudiés, les mesures utilisées, l'intervalle entre l'accident et l'évaluation ainsi que les stades développementaux ciblés. L'absence de consensus quant aux conséquences

comportementales, affectives et adaptatives soulève des questionnements quant à la méthode optimale pour évaluer le devenir du jeune enfant après un TCC. D'autres défis méthodologiques pourraient aussi expliquer ces divergences et sont abordés dans une section subséquente de la discussion (*cf*. Considérations méthodologiques et recommandations pour la recherche sur le TCC précoce).

Le tempérament après un TCC précoce

Le deuxième article avait pour but d'évaluer l'effet d'un TCC subi pendant la petite enfance sur la trajectoire développementale du tempérament. Les parents de jeunes enfants ayant subi un TCC « plus sévère » (c-à-d. un TCC caractérisé par une lésion structurelle intra-crânienne objectivée par neuroimagerie et incluant donc les TCCL complexe, modéré ou sévère), un TCCL simple ou une blessure orthopédique (BO) ont complété un questionnaire pour documenter le tempérament de leur enfant avant la blessure, ainsi qu'à 6 et 18 mois post-blessure. Pour chaque dimension du tempérament (*Dynamisme, Affectivité Négative, Contrôle Volontaire*), des analyses de modèles linéaires mixtes ont été réalisées afin d'explorer et comparer les taux de changement entre les trois groupes, c.-à-d. la trajectoire développementale des dimensions du tempérament à travers le temps. D'abord, bien que le groupe d'enfants qui ont subi une blessure plus sévère montre une certaine tendance à avoir un niveau de *Dynamisme* légèrement plus élevé que les deux autres groupes, les résultats n'ont montré aucune différence de groupe pour chacune des dimensions du tempérament avant la blessure. Par ailleurs, aucune différence de groupe quant aux trajectoires développementales de l'*Affectivité Négative* et du *Contrôle Volontaire* n'a été observée. Ceci suggérant que l'évolution de ces deux dimensions est similaire pour les trois groupes d'enfants et ce, jusqu'à 18 mois suivant la blessure. En revanche, un effet significatif de groupe a été relevé sur

le taux de changement du *Dynamisme* à travers le temps, de sorte que les jeunes enfants ayant subi un TCC plus sévère montrent une progression moins rapide de cette dimension comparativement à celui des deux autres groupes (TCCL simple et BO). Les jeunes enfants ayant subi un TCC plus sévère ne rejoignent pas la trajectoire développementale de leurs pairs et ce, même après un délai de 18 mois suivant la blessure. En d'autres mots, ces enfants manifestent un niveau d'activité réduit se traduisant par un niveau d'énergie plus faible, moins de recherche de plaisir à haute intensité, ainsi qu'une plus grande timidité face à la nouveauté.

Puisqu'aucune différence concernant les trois dimensions du tempérament n'a été observée entre les groupes avant la blessure, la présence d'un changement de la trajectoire du *Dynamisme* chez les enfants avec un TCC plus sévère suggère un effet spécifique de la blessure cérébrale et plus précisément, un effet de la sévérité de celle-ci sur l'évolution de cette dimension. Autrement dit, le fait de subir un TCC plus sévère semble avoir une influence sur la façon dont l'enfant réagit et s'adapte à son environnement à la suite de ce type de blessure. Afin d'explorer les raisons pour lesquelles un changement est observé sur cette dimension, les facteurs connus pour influencer le tempérament seront discutés (maturation cérébrale, expérience de l'enfant et influence de l'environnement).

Maturation cérébrale

Au cours de la petite enfance, le cerveau se développe rapidement et l'enfant traverse plusieurs étapes développementales durant lesquelles des changements neuronaux surviennent. Une altération cérébrale durant cette période sensible est particulièrement redoutable puisqu'elle peut perturber la mise en place des structures et fonctions de base, nuire à la séquence développementale et engendrer un effet développemental en cascade. Par ailleurs, bien que les enfants qui ont subi un TCC plus sévère soient légèrement plus âgés au moment de la blessure que

les autres enfants de l'étude, cette tendance n'est pas significative, mais peut avoir contribuer à l'effet observé. Il est donc possible que la survenue de lésions cérébrales structurelles susceptibles d'avoir altéré à la fois la structure du cerveau et le fonctionnement des réseaux cérébraux sous-tendant l'expression de la dimension *Dynamisme* puisse expliquer les changements observés au plan de la trajectoire du tempérament. Cette hypothèse est appuyée par l'idée que des différences individuelles dans les patrons d'activité des régions frontales peuvent refléter certaines tendances affectives et comportementales (pour une revue voir Coan et Allen, 2004). Une asymétrie de l'activation au repos des régions frontales gauches serait associée à des tendances d'approche, à l'expression d'affects positifs et à la régulation des émotions et du comportement (Fox et Davidson, 1988). En revanche, une asymétrie d'activité cérébrale frontale droite serait associée à des tendances de retrait et à l'expression d'affects négatifs (Nass et Koch, 1987). Les enfants avec une asymétrie droite auraient tendance à se retrouver facilement en position de détresse, à être plus difficiles à apaiser et à avoir des difficultés à maintenir et diriger leur attention (Nass et Koch, 1987; Schmidt et al., 2009). Ainsi, bien que l'activité cérébrale n'ait pas été mesurée dans notre étude, selon la théorie de la spécificité d'activation hémisphérique (Davidson, 1984, 1992; Heller, 1990), il est possible que la blessure cérébrale altère l'activité cérébrale frontale des hémisphères. Il est à noter que l'hétérogénéité du groupe de TCC plus sévère, en plus du faible nombre d'enfants, peuvent avoir influencer les résultats de l'étude. En étant plus inclusif et en ayant inclus des enfants qui ont subi des lésions extracérébrales, l'analyse et l'interprétation des résultats sont plus conservatrices, mais pourrait masquer certains effets surtout chez les enfants avec un TCC modéré-sévère. Les résultats auraient possiblement été plus franc avec un groupe d'enfant qui ont subi des blessures sévères. Néanmoins, parmi les enfants ayant subi un TCC plus sévère, la majorité d'entre eux (18 sur 21) présente des lésions objectivées à l'imagerie cérébrale. Ces lésions sont susceptibles d'avoir altéré l'activité des structures associées au *Dynamisme,* telles que l'amygdale baso-latérale,

l'hypothalamus latéral, le noyau accumbens, le cortex cingulaire antérieur ainsi que le cortex préfrontal dorsolatéral gauche (pour une revue voir Whittle et al., 2006). Une étude chez des enfants d'âge scolaire en rémission à la suite d'une résection d'une tumeur cérébrale et de traitements de chimiothérapie et de radiothérapie montre également un niveau de *Dynamisme* plus faible que leurs pairs neurotypiques. Plus concrètement, les camarades de classe de ces enfants décrivent chez eux, un niveau plus faible de leadership et de popularité, ainsi qu'un niveau plus élevé de sensibilité émotionnelle et d'isolement comparativement aux autres élèves (Salley et al., 2015). De plus, une étude explorant le développement cérébral des enfants prématurés et le tempérament montre que des altérations de la connectivité fonctionnelle de l'amygdale pendant la période néonatale sont associées à une augmentation de l'inhibition comportementale et de la détresse face à la nouveauté, de même que davantage de comportements internalisés tels que rapportés par les parents à l'âge de deux ans (Rogers et al., 2017). De plus, une étude récente montre que des anomalies de la matière grise et blanche détectées par imagerie cérébrale chez des enfants prématurés prédisent un tempérament « sous-réactif », c.-à-d. moins de vocalisation et d'engagement lors des moments de proximité (p. ex., câlins), une diminution de la capacité à prendre du plaisir dans les activités stimulantes et une certaine passivité au plan émotionnel (Tamm et al., 2020). L'ensemble de ces résultats s'accordent avec l'hypothèse selon laquelle l'atteinte de certaines structures cérébrales à la suite du TCC pourrait expliquer une modification de la trajectoire développementale du *Dynamisme*, telle qu'observée dans notre étude. En plus des conséquences de la lésion cérébrale sur les régions associées au tempérament, d'autres considérations liées à l'expérience pourraient contribuer à expliquer les différences en matière d'évolution du tempérament. Ceci demeurant toutefois à être vérifié par des études futures.

Expérience du jeune enfant

En raison de son jeune âge et de ses habiletés cognitives encore peu développées, l'enfant est limité dans ses moyens pour bien comprendre et partager son expérience d'un événement traumatique tel qu'un TCC. Or, bien qu'il puisse effectivement être difficile de saisir l'expérience de l'enfant entourant le trauma, celle-ci mérite d'être considérée et pourrait être une piste intéressante à considérer dans l'interprétation des changements touchant le tempérament. Sur ce point, la récente étude de Willard et collègues (2021) est particulièrement éclairante. Ces auteurs ont étudié le tempérament chez de jeunes enfants (3-6 ans) en bonne santé et d'autres ayant reçu un diagnostic de cancer n'impliquant pas de lésions cérébrales (p. ex., leucémie lymphoblastique et rétinoblastome). Les parents des enfants en bonne santé ont rapporté un plus haut niveau de *Dynamisme* comparativement aux enfants ayant un cancer. Comme dans notre étude sur le TCC précoce, aucune différence en ce qui a trait aux dimensions d'*Affectivité Négative* et de *Contrôle Volontaire* n'a été rapportée entre les deux groupes, suggérant que parmi les trois dimensions du tempérament, le *Dynamisme* est particulièrement sensible aux perturbations causées par une condition médicale.

Il a d'ailleurs été rapporté que les jeunes qui subissent une blessure « stressante et traumatique », qu'elle soit d'origine cérébrale ou non, peuvent vivre des symptômes post-traumatiques (p. ex., évitement de certains stimuli et augmentation de la réactivité émotionnelle) dans 25 à 57% des cas (pour une revue voir Brosbe et al., 2011). Un TCC plus sévère peut être vécu comme un événement potentiellement « stressant et traumatique » en soi, de même que le séjour hospitalier et les réactions et appréhensions du parent face à la nouvelle condition médicale et la vulnérabilité de son enfant. Ce phénomène est connu sous l'appellation « stress traumatique du contexte médical pédiatrique » (pour un modèle du « *Pediatric Medical Traumatic Stress* » voir

Price et al., 2016) et réfère aux réactions de l'enfant et celles de son parent face à la blessure, la sévérité, la douleur, les procédures et les traitements médicaux, ainsi que la perception subjective de l'importance de la condition médicale (National Child Traumatic Stress Network, 2004). Dans notre étude, les enfants ayant subi un TCC plus sévère ont vécu significativement plus de blessures jugées « sérieuses, sévères ou critiques » (81%) que les autres groupes (TCCL: 4% et BO: 2%), selon l'Abbreviated Injury Severity scale (AIS; Greenspan et al., 1985), qui permet de classer la sévérité globale de la blessure au plan anatomique selon six niveaux (mineur, modéré, sérieux, sévère, critique, maximum). Ainsi, il est possible que les familles dont l'enfant a subi un TCC plus sévère aient été davantage exposées au stress médical et à un risque plus élevé de développer des symptômes de stress post-traumatique comparativement aux enfants des deux autres groupes (p. ex., augmentation de la réactivité émotionnelle et évitement de certains stimuli). L'examen des réponses de ces parents au questionnaire de tempérament semble appuyer cette hypothèse. En effet, les réponses révèlent que les enfants ont moins tendance à « aimer aller dans les grosses glissoires ou faire d'autres activités dangereuses », « aller haut et vite lorsqu'on les pousse sur la balançoire », semblent « moins plein d'énergie même durant la soirée », ont davantage tendance « à se détourner parfois de nouveaux amis par timidité » et « à être très difficile à apaiser lorsqu'il est perturbé ». De façon intéressante, Suskauer et collègues (2018) ont aussi montré que de jeunes enfants ayant subi un TCC présentent une diminution de l'engagement (p. ex., refus de s'engager dans ses activités habituelles; diminution de l'intérêt dans les jeux; comportement plus calme qu'à l'habitude), des difficultés de régulation comportementale (p. ex., augmentation des crises, pleurs plus fréquents), une augmentation de la dépendance (p. ex., augmentation des plaintes; davantage de pleurnichements) et une plus grande recherche de réconfort auprès de son parent. En somme, certains de ces symptômes et manifestations semblent faire écho au construit du tempérament, plus particulièrement, à la dimension du *Dynamisme* (p. ex., activité réduite) et dans une moindre

mesure à la dimension d'*Affectivité Négative* (p. ex., difficultés à s'apaiser) lesquelles, rappelons-le, représentent les pôles de réactivité émotionnelle et comportementale du tempérament. Face à ces manifestations, les réponses du parent pourraient également avoir une influence non-négligeable sur l'évolution des tendances émotionnelles et comportementales du jeune enfant.

Influence de l'environnement

Durant la petite enfance, le parent a une place centrale dans le quotidien de son enfant. Qui plus est, les conduites parentales sont susceptibles de renforcer ou réguler certaines tendances réactionnelles, émotionnelles et comportementales du jeune enfant (p. ex., Arcus, 2001; Arcus et Kagan, 1995; Bates et al., 2012; Calkins et Fox, 1992; Rubin et al., 2002; Rubin et al., 1995). Premièrement, la surprotection parentale, qui peut refléter une préoccupation excessive pour la sécurité et la protection de l'enfant, se traduit par une aide et un réconfort physique dans des situations où de tels comportements ne sont pas requis (p. ex., Maccoby et al., 1983). Deuxièmement, l'intrusion réfère à des comportements contrôlants qui ne tiennent pas compte des signaux de l'enfant (p. ex., Calkins et al., 2004). Troisièmement, le manque de sensibilité parentale réfère à l'incapacité d'un parent à détecter les signaux de son enfant, à les interpréter et à y répondre adéquatement (p. ex., Ainsworth et al., 1978). Ainsi, le parent pourrait de façon involontaire ou non, par ses pratiques parentales (p. ex., surprotection, intrusion et sensibilité), réguler et contrôler les réactions et/ou comportements à la place de l'enfant. Certains auteurs suggèrent également que les demandes de réconfort auprès du parent reflèteraient un besoin de régulation ou de co-régulation des réactions émotionnelles et comportementales vécues par l'enfant (pour une revue voir Zimmer-Gembeck et Skinner, 2010). Autrement dit, l'enfant réaliserait ces demandes d'aide afin que son parent l'aide à s'*adapter* et *réguler* ses réactions face au contexte de l'événement. Ceci pourrait également suggérer que l'enfant réagit de façon automatique (p. ex., diminution de l'approche,

activité réduite, timidité, pleurs, difficulté à s'apaiser, etc.) et, puisqu'il est dépourvu de stratégies d'auto-régulation et d'adaptation en raison de son jeune âge, il nécessiterait davantage d'aide externe de la part de son parent. Ainsi, dans notre étude, certaines pratiques du parent pourraient en partie expliquer pourquoi aucune différence n'est observée en ce qui concerne la dimension *Contrôle Volontaire.* Des études futures qui documenteraient les styles parentaux pourraient être utiles pour confirmer ou infirmer cette interprétation. De plus en plus d'études rapportent que le parent joue également un rôle essentiel dans la récupération de leur enfant après un TCC (p. ex., Catroppa et al., 2016; McNally et al., 2013; Tuerk et al., 2020). Plusieurs d'entre-elles mettent en évidence l'importance de l'état psychologique du parent, ses conduites parentales et son support dans le contexte du TCC précoce (p. ex., Beauchamp, Séguin, et al., 2020; LeBlond, 2019; Schorr et al., 2020; Wade et al., 2011). Ainsi, le rôle du parent dans le rétablissement du jeune enfant ayant subi un TCC semble particulièrement important et ce, même au-delà des facteurs neurophysiologiques liés à la blessure et ceux associés à l'expérience de l'enfant. L'importance du rôle parental sera discutée dans la section suivante concernant les contributions théoriques de la thèse.

Retombées théoriques et pistes d'explications additionnelles

La revue systématique de la littérature réalisée dans le cadre de cette thèse a permis de mettre en lumière un large éventail de conséquences post-blessure lesquelles semblent majoritairement influencées par les facteurs liés à la *blessure* dont l'âge, la sévérité et le mécanisme. Ces résultats sont compatibles avec les modèles prédictifs des conséquences post-TCC (p. ex., Beauchamp et Anderson, 2013; Figure 1) qui tiennent compte de plusieurs facteurs prédicteurs du rétablissement. Si les facteurs liés à la blessure semblent jouer un rôle prépondérant

pour prédire le fonctionnement post-TCC, il ne faut toutefois pas négliger ceux liés à l'enfant et à l'environnement.

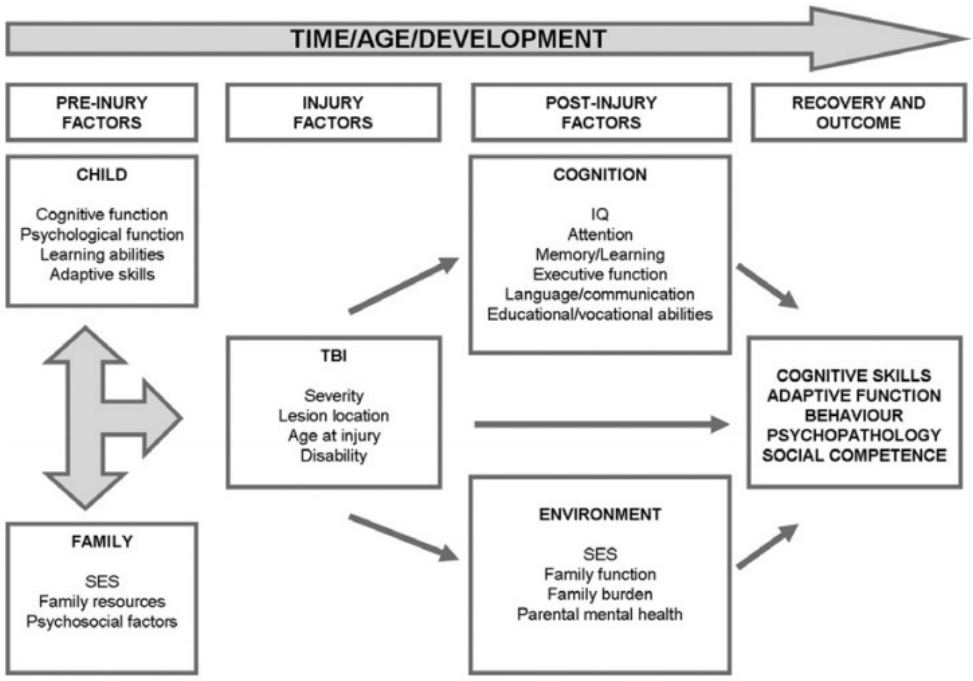

Figure 1. Modèle de Beauchamp & Anderson (2013)

Réimpression autorisée à partir de « Cognitive and psychopathological sequelae of pediatric traumatic brain injury » par M.H. Beauchamp et V. Anderson, 2013, dans *Handbook of clinical neurology*, p. 918.
Note. IQ = Intellectual Quotient; SES = Socio-Economic Status; TBI = Traumatic Brain Injury.

Facteurs liés à la blessure

Les résultats et conclusions de la revue appuient la théorie de la vulnérabilité suggérant que plus une blessure survient tôt dans la vie, plus l'enfant risque de présenter des conséquences défavorables (Anderson et al., 2005). Au cours de la petite enfance, le jeune enfant traverse plusieurs étapes développementales sensibles durant lesquelles plusieurs changements neuronaux, cognitifs, comportementaux et socio-affectifs surviennent. Une altération dans la mise en place des structures et fonctions de base pourrait engendrer un effet développemental en cascade. De plus,

les résultats de la revue supportent la relation « dose-réponse » suggérant que plus une blessure est sévère plus celle-ci occasionnera des conséquences importantes. Bien que la survenue d'un TCC modéré ou sévère soit généralement associée à des atteintes plus importantes, le TCCL peut aussi entraîner des conséquences. En lien avec les deux points précédents, la revue permet aussi d'appuyer la notion de « *double-hazard* » ou « doublement à risque » (Escalona, 1982), laquelle suggère que plus une blessure survient tôt dans la vie et plus celle-ci est sévère, plus les conséquences seront défavorables comparativement à une blessure plus tardive et légère. Finalement, les enfants qui subissent un TCCna présentent des conséquences plus néfastes que ceux ayant un TCCa précoce et sévère, ce qui suggère la notion du « *triple-hazard* » ou « risque triple » (blessure précoce, sévère et non-accidentelle). Toutefois, ce facteur de risque supplémentaire n'est possiblement pas circonscrit au mécanisme; il pourrait dans certains cas refléter un environnement familial plus défavorable.

Facteurs liés à l'enfant et à l'environnement

Dans les modèles théoriques et prédictifs des conséquences suivant un TCC pédiatrique, les facteurs propres à l'enfant comprennent son fonctionnement cognitif, psychologique et adaptatif. Les résultats de la présente thèse pourraient contribuer à revisiter cette liste, en y ajoutant le tempérament puisqu'il englobe plusieurs sphères du fonctionnement de l'enfant. En effet, la manière dont l'enfant s'adapte et réagit à sa blessure peut influencer la survenue et le maintien de conséquences défavorables, que ce soit aux plans psychologique, cognitif, socio-comportemental, émotionnel ou adaptatif. Les facteurs environnementaux incluent, quant à eux, les caractéristiques familiales et parentales. À ce titre, une étude de notre groupe, effectuée dans la même cohorte d'enfants que ceux dans l'article 2, propose un modèle prédictif de la qualité de la vie incluant des prédicteurs liés à la blessure, l'enfant et l'environnement (Tuerk et al., 2020; Annexe A). Les

résultats d'analyses de régressions hiérarchiques montrent qu'une prédisposition génétique à la plasticité cérébrale (soit la présence du polymorphisme BDNF (Brain-Derived Neurotrophic Factor) Val66Met) est un prédicteur indépendant et significatif d'une meilleure qualité de vie six mois post-TCCL. De plus, les résultats montrent que l'état psychologique du parent prédit la qualité de vie de l'enfant 18 mois post-TCCL, et ce, au-delà de la dimension *Affectivité Négative* du tempérament. Cette étude met l'emphase sur le fait que les facteurs génétiques impliqués dans la neuroplasticité peuvent jouer un rôle important dans la récupération six mois après le TCCL, mais qu'au fil du temps, les facteurs familiaux semblent devenir les principaux déterminants de la qualité de vie post-TCC. Ces résultats soulignent et réitèrent l'importance de ne pas négliger les facteurs familiaux dans le contexte du TCC précoce.

Interaction des facteurs liés à la blessure, à l'enfant et au parent

La distinction entre les comportements habituellement présents chez le jeune enfant et ceux associés à la blessure peut représenter un défi pour le parent, ce que notre équipe de recherche a tenté de conceptualiser à l'aide du modèle « Perception, Attribution, and Response after Early Non-inflicted Traumatic Brain Injury » (PARENT; Beauchamp, Séguin, et al., 2020; Annexe B). Ce modèle démontre les avenues possibles de rétablissement à la suite d'un TCCL en fonction des SPC que l'enfant vit et la perception, l'attribution et la réponse du parent face à ceux-ci. Ce modèle est principalement centré sur les SPC et le TCCL, mais pourrait également s'appliquer à d'autres types de manifestations émotionnelles et comportementales (p. ex., tempérament), ainsi que d'autres niveaux de sévérité de blessure cérébrale (p. ex., TCC modéré-sévère).

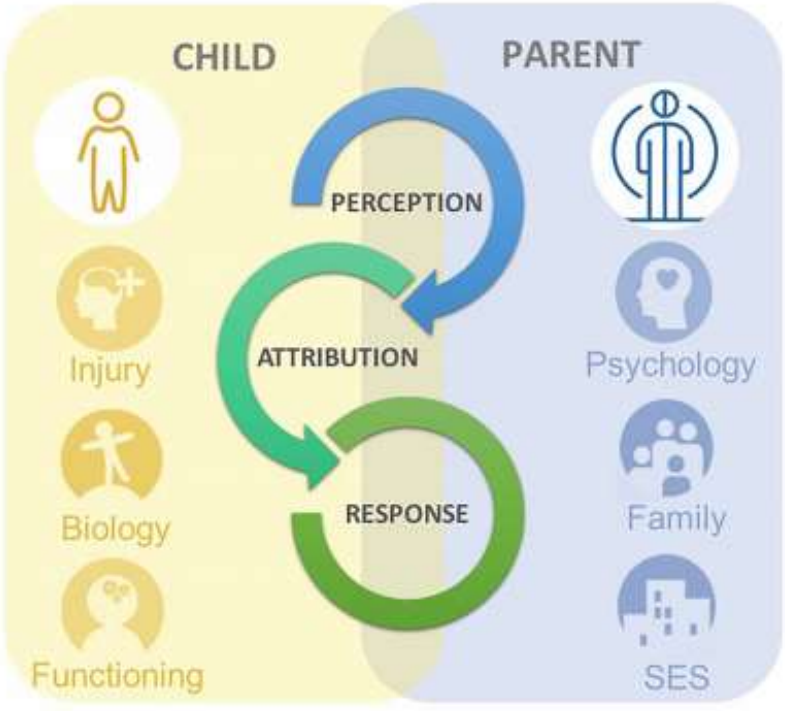

Figure 2. Le modèle "Perception, Attribution, and Response after Early Non-inflicted Traumatic Brain Injury" (PARENT)
Réimpression autorisée à partir de « The PARENT model: a pathway approach for understanding parents' role after early childhood mild traumatic brain injury » par M.H. Beauchamp, M. Séguin, C. Gagner, G. Lalonde, A. Bernier, 2020, *The Clinical Neuropsychologist*, p. 9.

Note. SES = Socioeconomic status.
Les flèches circulaires représentent les trois étapes importantes (Perception-Attribution-Réponse, PAR) du rôle des parents au moment de la blessure de leur enfant ce qui contribuera à déterminer le comportement et le fonctionnement de l'enfant ainsi que son rétablissement suivant la blessure. L'ombrage jaune représente les caractéristiques de la blessure chez l'enfant (p. ex., le type de blessure, la sévérité, SPC), les facteurs biologiques (p. ex., l'âge, le sexe, la génétique, le tempérament, le sommeil) et fonctionnel (p. ex., les caractéristiques prémorbides, fonctionnement cognitif, comportemental et affectif) et la couleur bleue représente l'état psychologique du parent (p. ex., tout problème de santé psychologique ou mentale prémorbide, santé psychologique et humeur actuels), famille (p. ex., satisfaction maritale, fardeau familial, style parental) et les facteurs environnementaux (p. ex., SSE, ressources) qui influencent respectivement le processus PAR.

Le modèle PARENT (Beauchamp, Séguin, et al., 2020) montre que la capacité des parents à percevoir, attribuer et réagir adéquatement aux symptômes et manifestations comportementales de leur enfant teinte la direction et le rythme du processus de rétablissement de l'enfant. Ainsi, en

plus des vulnérabilités physiologiques et développementales, le jeune enfant est sensible à son environnement et, plus précisément, aux pratiques de son parent. D'ailleurs, une récente revue systématique montre que plusieurs facteurs psychologiques du parent (p. ex., anxiété) peuvent influencer façon dont celui-ci rapporte la nature et le nombre de symptômes de son enfant (Smith et al., 2020). Il va de soi que des recherches futures seront nécessaires pour élucider les interactions entre ces facteurs et leur influence sur le rétablissement du jeune enfant (*cf.* section « Avenues futures »).

Finalement, l'influence bidirectionnelle entre le tempérament de l'enfant et les pratiques du parent (Kiff et al., 2011; Klein et al., 2016) est reconnue comme ayant une influence sur le développement de l'enfant (Belsky, 1997; Belsky et al., 2007; Perry et al., 2018). De façon intéressante, il n'existerait pas de types de tempérament ou de conduites parentales qui seraient fondamentalement problématiques. Ce serait plutôt l'interaction entre ces derniers qui serait pertinente à considérer, car elle pourrait influencer, amplifier ou atténuer les manifestations émotionnelles et comportementales de l'enfant. Cette interaction est représentée par le concept « goodness-of-fit » qui réfère à la compatibilité entre le tempérament d'un individu et leur environnement (Chess et Thomas, 1991). Lorsque les caractéristiques, les attentes et les demandes de l'environnement rencontrent celles de l'enfant, il y a « goodness-of-fit », ce qui favoriserait un développement optimal. Par exemple, lorsqu'un enfant est réticent face à la nouveauté et que son parent ne l'expose pas de façon marquée à de nouvelles situations et préconise plutôt une progression graduelle selon le rythme de l'enfant. En revanche, s'il n'y a pas d'adéquation, de compatibilité entre l'enfant et son environnement, un « poorness-of-fit » pourrait survenir et nuire au bon développement (ou rétablissement) de l'enfant, et même avoir des effets collatéraux sur le couple et la famille (Chess et Thomas, 1991; Han et Park, 1996). Par exemple, lorsqu'un enfant est

fonceur et explore rapidement et positivement son environnement et que son parent arbore un style parental de surprotection et se montre réticent face à l'exploration de son enfant. Dans ce cas, le parent teinte l'approche positive de l'enfant par ses propres anticipations. En résumé, la relation bidirectionnelle entre les caractéristiques du jeune enfant et celles de leurs parents est déterminante dans le développement cognitif, comportemental, socio-affectif des enfants et peut jouer un rôle important dans le rétablissement post-blessure (p. ex., Bates et al., 2012; Sameroff, 2009). Afin d'illustrer l'influence du parent, voici un exemple d'un enfant qui a subi un TCC plus sévère lors d'une chute dans un module de jeu. Le parent, par ses réactions (p. ex., anxiété) et son style parental (p. ex., surprotection) peut influencer le comportement de son enfant en limitant les sorties au parc ou bien toute autre situation jugée dangereuse selon lui. À long terme, ces limitations (p. ex., socialisation réduite) pourraient influencer négativement le développement de différentes sphères chez l'enfant (p.ex., sphère sociale). Ainsi, il serait non seulement important d'ajouter le tempérament aux modèles théoriques et prédictifs des conséquences suivant un TCC précoce, mais plus encore, la notion d'adéquation des réponses du parent face aux manifestations post-blessure de son jeune enfant.

Considérations méthodologiques et recommandations pour la recherche sur le TCC précoce

Cette thèse a permis de mettre en lumière plusieurs enjeux et limites méthodologiques lesquels sont occasionnés par des défis relatifs à la recherche en TCC précoce.

Définition et description du TCC précoce

Tel que soulevé dans la revue systématique, une grande variabilité est observée quant à la terminologie utilisée et la façon dont le TCC précoce est défini en ce qui a trait à la période

développementale (p. ex., nourrisson, bambin, préscolaire), à la sévérité (léger/commotion cérébrale, modéré, sévère) et aux mécanismes de la blessure (p. ex., TCCa, TCCna, bébé secoué, etc.). Le manque de terminologie claire entrave non seulement la recherche, mais également la pratique clinique. Une étude épidémiologique réalisée au Québec a aussi mis en évidence une grande disparité quant aux critères cliniques du TCCL utilisés dans les études. Ces différences engendreraient une grande variabilité dans les critères d'inclusion des participants ainsi que les données de recensement (Keays et al., 2018). À ce jour, il n'existe aucune définition et aucun critère précis et clair pour décrire le TCC précoce. Un travail de définition et d'opérationnalisation serait nécessaire afin d'homogénéiser la terminologie associée au TCC précoce. Ainsi, poursuivre les efforts pour développer un consensus, par exemple en organisant des regroupements et comités d'experts, pourrait représenter une avenue d'action possible pour harmoniser la nomenclature et les activités de recherche en TCC précoce.

Domaines et construits étudiés

Dans la littérature sur le TCC précoce, divers domaines sont étudiés, mais peu d'études se concentrent sur des construits et domaines spécifiques au jeune enfant. Plusieurs études examinent les habiletés sociales, mais peu se sont penchées sur leurs précurseurs qui sont pourtant en pleine croissance durant la petite enfance (p. ex., Bellerose et al., 2015, 2017; D'Hondt et al., 2017). De la même façon, aucune autre étude ne s'est penchée sur l'effet d'un TCC précoce sur le tempérament et aucune étude ne documente l'attachement. Les résultats de la présente thèse soulignent l'intérêt de réaliser des études qui tiennent davantage compte de construits qui sont spécifiques à la petite enfance. Ceci pourrait favoriser une meilleure compréhension des conséquences du TCC précoce.

Échantillon

L'interprétation de la nature et de la sévérité des conséquences suivant un TCC précoce est souvent confondue par l'âge, le mécanisme et la sévérité de la blessure. Les tailles d'échantillons modestes et les analyses de comparaisons multiples limitent la possibilité de créer des sous-groupes. Bien qu'il ne soit pas possible de faire des analyses statistiques avec de petits groupes, rapporter les données descriptives quant à l'âge, le sexe, le genre, le mécanisme et la cause de la blessure pourrait permettre la réalisation de méta-analyses.

Procédure

Dans le domaine de la recherche en TCC précoce, peu d'études longitudinales sont réalisées et, par conséquent, peu de construits et domaines sont mesurés à long terme. Les jeunes enfants se développent rapidement et les construits spécifiques ainsi que les tâches appropriées à un âge peuvent ne plus l'être à un âge ultérieur. L'inclusion de construits et mesures qui peuvent être opérationnalisés et observés à travers les stades développementaux du jeune enfant pourrait ainsi favoriser la réalisation d'analyses de trajectoires développementales et ainsi mieux définir l'étendue des conséquences à travers la vie de l'enfant.

Mesures

L'évaluation de certains domaines (p. ex., fonctionnement comportemental et social) chez les jeunes enfants est souvent basée sur des mesures indirectes, c.-à-d. sur les observations et/ou les réponses d'un tiers à des questionnaires avec peu ou pas de mesures directes (p. ex., mesures observationnelles en laboratoire). Ces mesures subjectives peuvent introduire des sources de biais liés aux perceptions, attentes et préoccupations du parent répondant. Ainsi, l'inclusion et l'utilisation d'un ensemble de mesures diversifiées tels que des questionnaires, mesures

observationnelles et mesures directes (p. ex., tâches neuropsychologiques) pourraient aider à réduire les biais du répondant. Actuellement, très peu de mesures objectives existent afin de mesurer le tempérament du jeune enfant (Zentner et Bates, 2008). L'un des outils les plus utilisés est le « Laboratory Temperament Assessment Battery (Lab-Tab) », un instrument standardisé pour l'évaluation en laboratoire du tempérament. Cette batterie comprend un ensemble de sous-tests d'une durée d'administration d'environ trois à cinq minutes qui simulent des situations quotidiennes dans lesquelles on peut observer de manière fiable des différences individuelles dans l'expression des émotions, dans l'approche/l'évitement, le niveau d'activité et la régulation du comportement.

De nombreuses mesures standardisées ou expérimentales sont utilisées dans les études sur le TCC et peu de lignes directrices existent concernant les « Common Data Elements » pour le TCC précoce (CDE; Gagnon et al., 2018; Whyte et al., 2010). Il serait important de continuer à développer ces éléments communs. Dans les recherches futures, les tâches expérimentales bien validées devraient être considérées comme outils de mesure potentiels, en complément aux questionnaires et aux autres mesures objectives.

Forces et limites

Forces. La revue de la littérature portant sur les conséquences d'un TCC en bas âge a été menée de façon systématique et comprend à la fois des études sur les TCCa et les TCCna, ce qui permet de rassembler les conséquences possibles suivant un TCC précoce. De plus, cette thèse met en lumière les différents défis en TCC précoce et propose des recommandations pour la recherche et la prise en charge. Certaines de ces recommandations sont reflétées dans l'étude empirique. Cette étude longitudinale dresse un portrait des caractéristiques pré-blessure de l'échantillon et suggère

que les changements observés ne sont pas simplement dû à des différences pré-blessure. De plus, l'inclusion d'un groupe de comparaison composé d'enfants avec une blessure orthopédique fournit un contrôle supplémentaire. En outre, l'utilisation d'analyses de modèles mixtes linéaires ont permis d'explorer simultanément les changements intra-individuel ainsi que l'évolution au fil du temps des différences inter-individuelles. Au plan théorique, la thèse permet de faire le pont entre les domaines de la recherche en psychologie développementale et ceux du TCC précoce, et de présenter l'interaction entre les facteurs liés à la blessure, à l'enfant et à l'environnement (surtout le parent) afin d'expliquer la survenue des difficultés suivant un TCC en bas âge et de comprendre leur persistance dans le temps.

Limites. Bien que la recension des études portant sur les blessures subies avant l'âge de six ans facilite la synthèse des conclusions concernant l'effet du TCC pendant la petite enfance, plusieurs articles ont été exclus en raison de ce critère. Par ailleurs, les effets d'un TCC précoce sur les SPC n'ont pas été rapportés malgré leur importance. Il y a peu d'études publiées à ce sujet, probablement en raison du fait qu'aucune mesure validée n'existe pour documenter les SPC avant l'âge de six ans. Notons aussi que l'utilisation de la forme très courte de l'ECBQ (Putnam et al., 2010) et le CBQ (Putnam et Rothbart, 2006) peut avoir restreint les informations sur les traits de tempérament signalés par les parents. Le formulaire très court (36 éléments) est utile, car il est efficace en termes de temps, mais il ne fournit que des scores limités pour les trois dimensions du tempérament. Il a d'ailleurs été soulevé que le CBQ rapportait possiblement davantage des comportements en lien avec le niveau d'activité du *Dynamisme* plutôt qu'un score global de l'ensemble des autres traits (c.-à-d. affectivité positive: sourire et rire, approche/anticipation positive et le niveau d'activité: plaisir à haute intensité et impulsivité; Allan et al., 2013). De plus, les questionnaires destinés aux parents sont intrinsèquement associés à un biais de mesure en raison de stéréotypes, d'opinions

personnelles ou de leur état psychologique tel que mentionné dans la section « Considérations méthodologiques » (Neale et Stevenson, 1989). Dans cette étude, les différences individuelles des enfants ont été contrôlées en évaluant rétrospectivement le tempérament de l'enfant, mais cela peut être influencé par le « *Good old times bias* », c.-à-d. une perception trop positive de la condition de l'enfant avant la blessure (Gunstad et Suhr, 2001; Gunstad et Suhr, 2004; Iverson et al., 2010; Treutler et Epkins, 2003). Finalement, la taille de l'échantillon des enfants ayant subi un TCC plus sévère et l'inclusion d'enfants qui ont subi un TCCL complexe avec ceux-ci peut avoir eu un effet sur la détection de changements dans les trajectoires développementales.

Avenues futures

Les futures recherches gagneraient à étudier les effets du TCC précoce en considérant tant les facteurs liés à la blessure, à l'enfant que ceux provenant de l'environnement familial et plus particulièrement du parent. Les prochaines études devraient également chercher à mieux comprendre les symptômes vécus par les jeunes enfants suivant un TCC et de clarifier quels symptômes sont reliés au fait d'avoir vécu un événement traumatique et quels sont ceux qui découlent de l'atteinte cérébrale. Ceci pourrait potentiellement aider à cibler les symptômes ou conséquences qui sont plus à risque d'être maintenus dans le temps. Des études incluant des groupes de comparaison qui ont vécu un événement similaire (p. ex., événement traumatique et hospitalisation et effets sur le système familial) pourraient aider à identifier la spécificité de ces symptômes afin d'optimiser l'évaluation et la prise en charge du TCC précoce. De plus, des études d'imagerie cérébrale pourraient aider à étudier les corrélats neurologiques qui sous-tendent les changements de tempérament suivant un TCC en bas âge. Aussi, l'étude des changements de tempérament à l'aide de mesures directes telles que des mesures observationnelles (Laboratory Temperament Assessment Battery (Lab-TAB); Goldsmith et Rothbart, 1996) et de mesures

indirectes telles que les questionnaires complets du ECBQ et CBQ (Putnam et al., 2010; Putnam et Rothbart, 2006) pourrait favoriser une meilleure compréhension des effets d'un TCC sur le tempérament. L'utilisation de ces outils pourrait également permettre de comparer les observations subjectives du parent aux mesures objectives en laboratoire. Par ailleurs, un enfant qui subit un TCC peut vivre une quantité importante de stress due au contexte de l'événement, mais aussi en raison des procédures médicales et des changements familiaux, et ainsi avoir de la difficulté à s'auto-réguler et s'adapter face à tout ceci. Une étude actuelle de notre groupe se penche d'ailleurs sur l'étude du stress après un TCC en bas âge (p. ex., Kids' Outcomes And Long-term Abilities (KOALA); Beauchamp, Dégeilh, et al., 2020) ce qui permettra sans doute de préciser les facteurs prédicteurs des conséquences suivant un TCC chez le jeune enfant. Finalement, les recherches futures devraient également poursuivre les efforts quant à la description des trajectoires développementales et donc privilégier des études à devis longitudinaux pour ainsi suivre l'évolution et le développement à la suite d'un TCC en bas âge.

Retombées cliniques

La thèse a permis de mettre en lumière l'éventail des conséquences à la suite d'un TCC en bas âge. Du point de vue clinique, il apparait important que de l'éducation, de la réassurance et un soutien aux parents soient fournis dès leur arrivée à l'urgence afin de réduire la détresse psychologique, limiter les biais et préconceptions, optimiser la perception, l'attribution et la réaction du parent et ainsi réduire la survenue et le maintien de manifestations comportementales défavorables. Sachant que les facteurs parentaux peuvent avoir un effet important sur les conséquences post-blessure, et ce, même à long terme, les interventions axées sur les habiletés parentales pourraient être un moyen important de favoriser la récupération. Par exemple, il existe un programme d'intervention ciblant l'interaction parent-enfant (Interacting Together Everyday:

Recovery After Childhood TBI; I-InTERACT) chez des familles d'enfants qui ont subi un TCC modéré-sévère entre trois et neuf ans. Le programme comprend des modules psychoéducatifs sur les effets d'un TCC sur l'enfant (comportement, stress, communication) et la parentalité. Les résultats montrent des améliorations en matière d'habiletés parentales, lesquelles auraient un effet médiateur sur la présence de problèmes de comportement chez leur enfant (Aguilar et al., 2019). Considérant que l'état psychologique ainsi que les pratiques parentales sont des prédicteurs significatifs de l'émergence de problèmes de comportement et d'une moins bonne qualité de vie (Gagner et al., 2018; Tuerk et al., 2020), les efforts d'intervention pourraient se concentrer davantage sur l'éducation de bonnes pratiques parentales à adopter vis-à-vis leur enfant, plutôt que sur l'enseignement de comportements à prévenir et à éviter chez l'enfant (p. ex., restrictions face à la reprise des activités sociales, sportives et récréatives).

De façon générale, il apparaît important de sensibiliser les services de garde et les centres de la petite enfance aux symptômes et conséquences possibles du TCC précoce et de poursuivre des stratégies de prévention des accidents (p. ex., chute) chez les jeunes enfants. Finalement, les *orientations ministérielles* gagneraient à formuler des recommandations spécifiques aux jeunes enfants, qui, tel que discuté tout au long de la thèse, présentent des caractéristiques uniques à sa période développementale. Ceci permettrait de mieux baliser les modalités de prises en charge clinique en instaurant une place plus importante au rôle du parent dans celles-ci.

Conclusions générales

La présente thèse a permis d'accroître les connaissances et d'avoir une meilleure vue d'ensemble sur les conséquences d'un TCC subi en bas âge. Dans un premier temps, le travail a permis de mettre en lumière le fait que la petite enfance est une période sensible pour l'émergence

et le développement du fonctionnement cognitif, comportemental et socio-affectif, et que les enfants ayant qui subissent un TCC durant cette période, peuvent présenter des difficultés dans plusieurs de ces domaines à court et même à long terme. Les défis méthodologiques ont été mis en évidence et des recommandations ainsi que des avenues d'actions possibles ont été proposées afin d'optimiser la recherche sur le TCC chez les jeunes enfants, qui constituent un groupe unique, pour d'innombrables raisons discutées dans cette thèse. Dans un second temps, le travail a montré qu'un TCC plus sévère subi à un âge précoce peut venir teinter la couleur de l'enfant, à savoir son tempérament, un construit global hautement pertinent à étudier chez les tout-petits en plein développement puisqu'il est reconnu comme étant prédicteur de plusieurs autres domaines de fonctionnement. Finalement, la thèse et les articles supplémentaires présentés en annexe soulèvent des pistes pour mieux comprendre la variabilité des conséquences observées à la suite d'un TCC précoce et en particulier, l'importance de l'adéquation des réponses du parent aux manifestations post-blessure de son enfant afin d'optimiser le rétablissement.

En conclusion, la survenue d'un TCC en bas âge est associée à des conséquences dans un éventail de domaines. Il va sans dire que les jeunes enfants ayant subi un TCC méritent une attention particulière et qu'il est essentiel que la recherche, le diagnostic, l'évaluation, la prise en charge, ainsi que les efforts de prévention soient davantage développés sur la base de la littérature empirique et d'une manière qui soit spécifique aux caractéristiques uniques de la petite enfance.

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ANNEXES

ANNEXE A

ARTICLE 3

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

Carola Tuerk[1], Charlotte Gagner[1,2], Fanny Dégeilh[1,2], Jenny Bellerose[1,2], Gabrielle Lalonde[1,2], Catherine Landry-Roy[1,2], Marilou Séguin[1,2], Louis de Beaumont[3,4], Jocelyn Gravel[2], Annie Bernier[1], Miriam H. Beauchamp[1,2]

(1) Department of Psychology, University of Montreal, P.O. Box 6128 Downtown Station, Montreal, Quebec H3C 3J7, Canada

(2) Sainte-Justine Hospital Research Center, 3175 Côte Sainte-Catherine Road, Montreal, Quebec H3T 1C5, Canada

(3) Hôpital du Sacré-Coeur de Montréal Research Centre, 5400 Gouin Blvd West, Montreal, Quebec H4J 1C5, Canada

(4) Department of Surgery, University of Montreal, P.O. Box 6128 Downtown Station, Montreal, Quebec H3C 3J7, Canada

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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 ts between 2.4 and 7.2, ps < .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: $\chi2\ (1) = .07$, $p = .79$, OI: $\chi2(1) = .01$, $p = .95$, TDC: $\chi2\ (1) = 1.85$, $p = .17$) 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 ($\chi2(2) = 2.72$, $p = .26$). 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 ($\chi2(1) = 4.06$, $p = .04$); 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 ($\beta = 0.28$, $p = .02$), MRO-Snack ($\beta = 0.32$, $p = .03$), Age at injury ($\beta = 0.26$, $p = .04$) and PCS-I ($\beta = -0.33$, $p = .03$) 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 ($\Delta F(3,40) = 0.91$, $p = .41$). 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 ($\beta = 0.26$, $p = .05$), 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 ($\Delta F(3,46) = 3.07$, $p = .04$). Parental Distress was an independent significant predictor of PedsQL at this stage ($\beta = -0.40$, $p = .004$), 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 ($\Delta F(3,43) = 2.59$, $p = .06$). At this stage, PSI-Parental Distress ($\beta = -0.40$, $p = .01$) and Age at Injury ($\beta = 0.31$, $p = .02$) 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 ($\Delta F(3,40) = 1.54$, $p = .22$). 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 ($\beta = -0.31, p = .04$), with lower parental distress predicting better QoL.

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

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 ($\Delta R^2 = 0.32, p < .0001, F(5,58) = 5.79, p = .001$) with PSI-Parental Distress emerging as a significant independent predictor of PedsQL ($\beta = -0.57, p < .0001$). Neither the addition of Age nor PCS-I in step 3 ($\Delta R^2 = 0.07, p = .06, F(7,56) = 5.36, p < .0001$), nor cognitive-behavioral factors in step 4 ($\Delta R^2 = 0.02, p = .64, F(10,53) = 3.90, p = .001$) 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 ($\Delta R^2 = 0.11, F(5,58) = 1.81, p = .14$), injury (i.e., Age and PCS-I; $\Delta R^2 = 0.04, F(7,56) = 1.69, p = .16$) nor cognitive-behavioral factors ($\Delta R^2 = 0.03, F(10,53) = 1.36, p = .26$) 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 = Glasglow 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.
*$p < .05$, **$p < .01$.

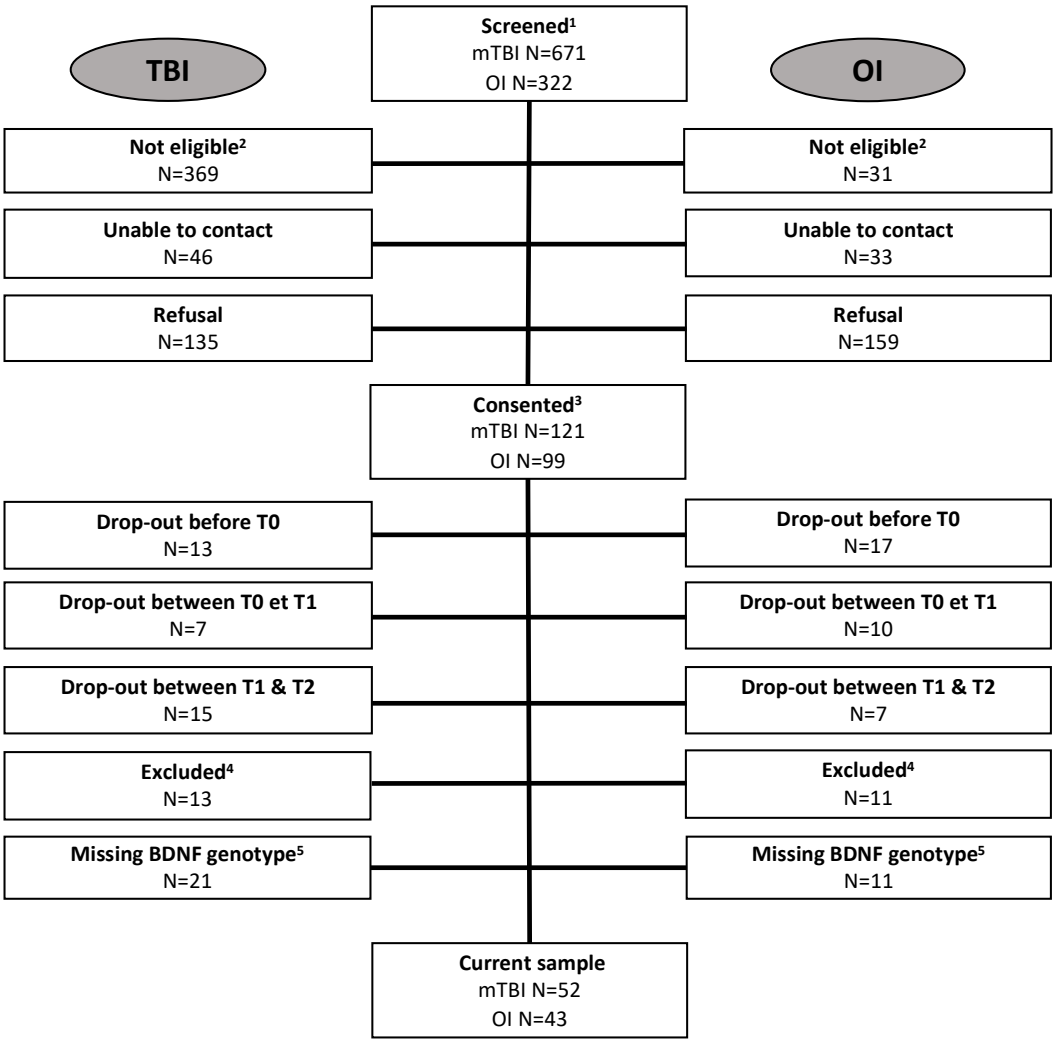

Fig 1. Recruitment and follow-up chart of participants of mTBI and OI participants.

(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).

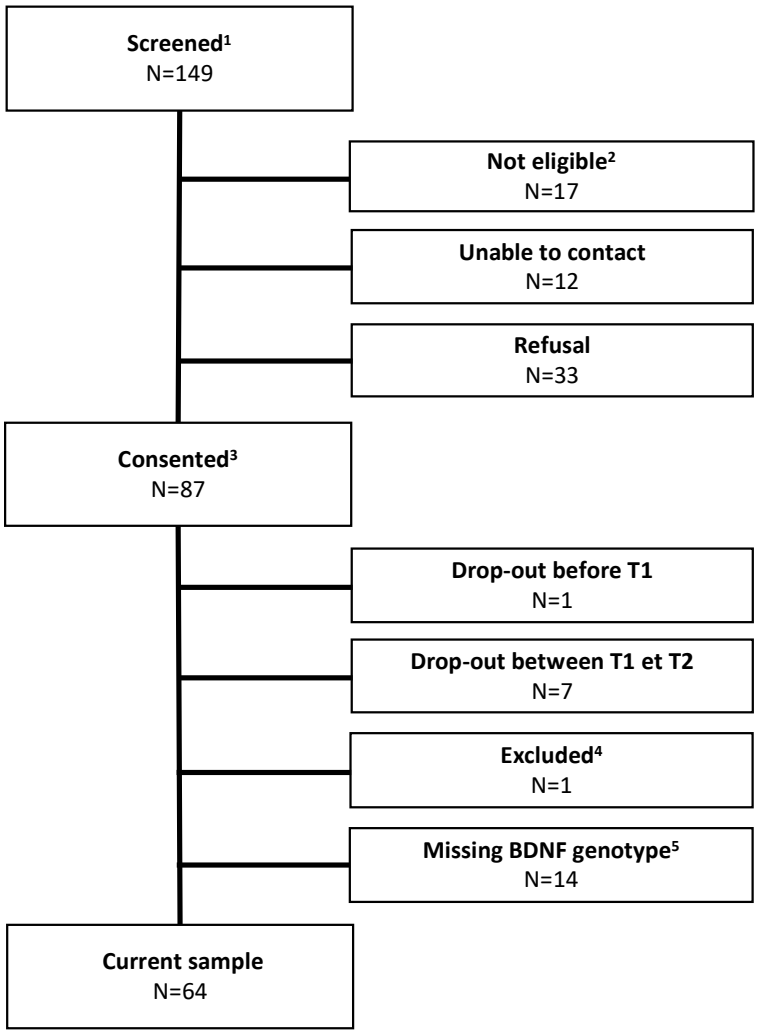

Fig. 2. Recruitment and follow-up chart for TDC participants.

(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).

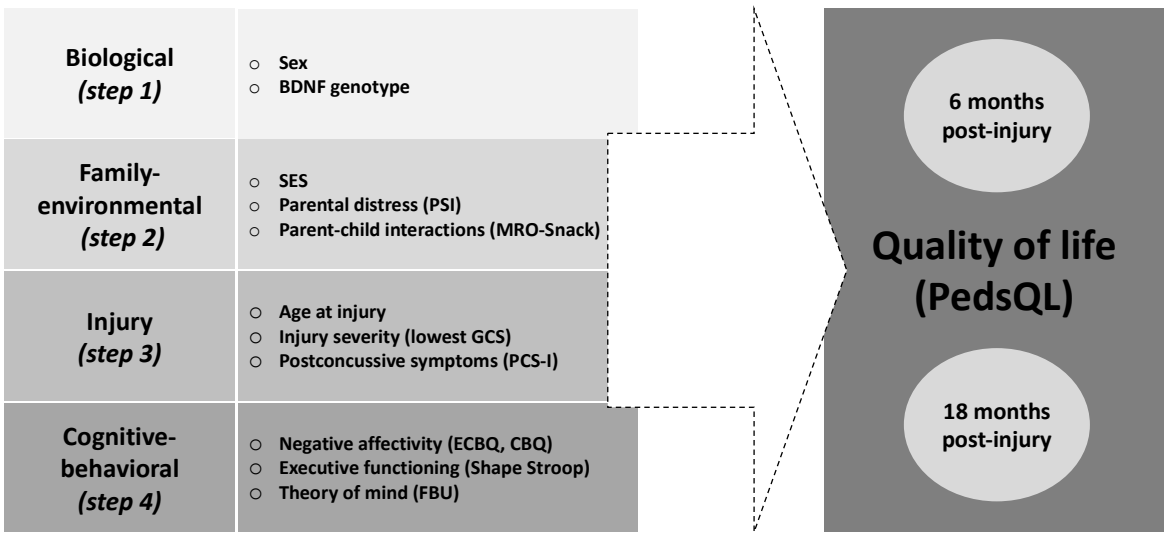

Fig. 3. Illustration of the 4-step hierarchical regression model predicting quality of life at 6 and 18 months post-injury.

ANNEXE B

ARTICLE 4

The PARENT model: A pathway approach for understanding parents' role after early childhood mild traumatic brain injury

Miriam H. Beauchamp[1,2], Marilou Séguin[1,2], Charlotte Gagner[1,2], Gabrielle Lalonde[1,2], Annie Bernier[1]

[1]Department of Psychology, University of Montreal, Canada

[2]Sainte-Justine Hospital Research Center, Montreal, Canada

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Abstract

Objective: Mild traumatic brain injury (mTBI or "concussion") is a highly prevalent health condition in children, and those under the age of 6 years have the highest rate of Emergency Department presentation for suspected head injuries. The outcome of mTBI is determined by a range of child (injury, biological, functional) and environmental (socio-economic status, parent, family) factors. The aim of this work is to present evidence supporting the central role of parental and familial factors in pediatric mTBI recovery, and to illustrate ways in which parental factors can especially influence the outcome of early mTBI, defined as injuries sustained by infants, toddlers and preschoolers.

Method: The manuscript first presents a topical review of empirical studies providing evidence that family functioning and parental factors such as their mental or affective state, parenting style, and the quality of their interactions with their child, are affected by and determine the course of recovery after pediatric mTBI. Then, a pathway approach and conceptual model are proposed to illustrate probable scenarios associated with how parents detect and react to their child's post-concussive symptoms and changes in behavior after early mTBI.

Conclusion: The "Perception, Attribution, and Response after Early Non-inflicted Traumatic Brain Injury" (PARENT) model suggests that parental roles and factors are especially influential in the context of early brain injuries, and that parents' ability to perceive, attribute and respond to the symptoms experienced by their child in a well-adjusted and adaptive manner critically sets the direction and rhythm of the early mTBI recovery process.

Keywords: traumatic brain injury, concussion, early childhood, parent, parent-child interactions, mental health, model, predictors, behavior, post-concussive symptoms

Introduction

Mild traumatic brain injuries (mTBI), also called concussions, are a focus of intense scientific and clinical study due to their high prevalence, variable outcome, and complex prognostic challenges. Current evidence suggests that while the majority of children who sustain mTBI recover within one month of injury, some will continue to experience post-concussive symptoms (PCS) and functional difficulties several months post-injury (Zemek et al., 2016). Media and public attention in this field tends to focus on sports-related injuries because of the high visibility afforded to professional contact sport leagues, such as football, rugby, soccer and hockey, the high likelihood that concussions will occur in these contexts, and the risk of repeated injuries in professional athletes. Within pediatric TBI (0-18 years), mTBI sustained during adolescence has drawn significant attention because of documented prevalence peaks between 15 and 19 years (Hyder, Wunderlich, Puvanachandra, Gururaj, & Kobusingye, 2007; McKinlay et al., 2008). However, within the pediatric range, it is in fact at the youngest ages that mTBI occurs most (Crowe, Babl, Anderson, & Catroppa, 2009; C. A. Taylor, Bell, Breiding, & Xu, 2017). Yet, research and care pertaining to early childhood mTBI (i.e., before the age of 6 years) critically lags behind that pertaining to older age groups. Outcome after mTBI sustained early in life is subject to different sources of influence due to the unique characteristics of infants, toddlers and preschoolers and their environment, such as the heightened presence of parents in their everyday interactions and the predominant role played by parents in determining their child's early developmental life course. In this conceptual paper, we discuss reasons why the gap in early childhood mTBI literature exists, review evidence suggesting the critical importance of parents after a young child sustains TBI, and

present a pathway-based model for understanding the interaction between child PCS and parental response.

Considerations specific to mTBI sustained during early childhood

A number of challenges and considerations are associated with early childhood mTBI. First, plasticity theory suggests the young brain is flexible and can easily reorganize after sustaining insult (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005), and this notion has long led scientists and clinicians to assume that early childhood brain injury has no ill effects due to adaptive compensation or reorganization. Support for this concept comes almost exclusively from the study of severe injuries and it is unclear how the phenomenon applies (or not) to mTBI, though it is assumed that early injuries that are mild in nature would be all the more benign. While the concept, coined the "young age plasticity privilege" by Dennis and colleagues (2013), has empirical support and is true of some types of brain lesions (often those that are focal rather than diffuse in nature; Cacucci & Vargha-Khadem, 2019; Staudt, 2010), there are also instances when brain insult sustained early in development can have detrimental consequences (Anderson et al., 2009; Crowe, Catroppa, & Anderson, 2015) or when increased plasticity may actually be maladaptive (see Gagner, Tuerk, De Beaumont, Bernier, & Beauchamp, 2020, for an example in the context of early mTBI). Furthermore, early childhood is a sensitive period for brain maturation and the emergence and development of a large number of cognitive, social and behavioral functions (Gilmore, Knickmeyer, & Gao, 2018; Thompson & Nelson, 2001), and disruption during these decisive times, even if transient as in mTBI, could in some cases affect function and cause a gap in milestone or skill attainment.

Second, early mTBI lacks a consensual definition, creating clinical confusion on how to diagnose it. This contrasts with the way in which mTBI is detected, studied and treated in older children and adolescents, for whom consensual diagnostic criteria have been published (e.g., Holm, Cassidy, Carroll, & Borg, 2005; McCrory et al., 2017), definitions for persistent PCS have been developed (Zemek, Duval, Dematteo, & al., 2014), and valid measures to track PCS exist (e.g., Iverson, Lovell, & Collins, 2003; Sady, Vaughan, & Gioia, 2014; Yeates et al., 2001). Empirical evidence in school-age children indicates that in most cases, PCS resolve after the acute phase of injury. For example, Zemek and colleagues (2016) found that PCS were no longer present in about 70% of their cohort 28 days after injury. While it is hypothesized that this is also the case in young children, there are no large-scale studies depicting the presence and evolution of PCS after early mTBI. The lack of definition for early mTBI and information on PCS course and recovery is related to the absence of any validated, developmentally-appropriate measure for documenting the effects of mTBI in children from birth to 5 years. Capturing and quantifying signs and symptoms of mTBI in young children poses a considerable challenge given that many infants, toddlers and preschoolers are either pre-verbal or have limited vocabulary to express themselves. This is compounded by the fact that expressing and reporting many PCS relies on a sound understanding of abstract concepts, such as “dizziness” or “confusion”, as well as requiring introspection and self-observation, abilities that are not yet accessible to young children. Notably then, clinicians’ ability to diagnose and manage early mTBI rests largely on parents’ sensitivity, awareness and reporting of potentially subtle physical, cognitive or behavioral manifestations that emerge post-injury. In addition to known mTBI symptoms such as vomiting, headache, or sleep disturbance, young children exhibit non-specific behavioral manifestations such as persistent crying, comfort seeking or irritability

(Beaudoin, Désiré, & Beauchamp, 2017; Podolak et al., 2020; Suskauer, Shruti, Reesman, & Slomine, 2017). Yet, parents themselves may lack the knowledge to correctly identify PCS and may find it difficult to differentiate between behavior changes induced by the brain injury and behavioral manifestations, such as fatigue, tantrums, or inattentiveness, that are not uncommon during early childhood and are part of daily or weekly fluctuations experienced by young children.

This brings us to a third consideration, that of the role of parents after their child sustains early mTBI. Multiple lines of pediatric theoretical and empirical evidence converge to show that outcome, such as PCS, are predicted by the complex interplay of both pre- and post-injury child and environmental factors (Babikian, McArthur, & Asarnow, 2013; Beauchamp & Anderson, 2013; Yeates et al., 2012; Zemek et al., 2016). However, the first few years of life constitute a distinct developmental period in which less is known of pre-morbid functioning (e.g., diagnoses such as Attention Deficit Hyperactivity Disorder (ADHD), Learning Disabilities or Mental Health problems are not establishes) and in which biological (e.g., brain maturation, genetics, sleep, temperament) and environmental (e.g., socio-economic status, parenting, parent mental health) factors and their interactions are likely to be weighted differently than at older ages. In particular, the heightened presence and role of parents in the daily lives and interactions of their infant, toddler or preschooler may significantly influence the child's own reactions and recovery after mTBI. In contrast, as children enter the formal academic system around the age of 5 years, and as they spend increasing amounts of time with educators and carers, and later with peer groups in adolescence, the salience of the parental factor may fade.

The role of parents in pediatric TBI risk and recovery

Decades of developmental psychology literature leave little doubt as to the central role parents play in their child's emerging cognitive, affective, and social development. From the importance of secure attachment (Groh et al., 2014), to variations in maternal (Raby, Roisman, Fraley, & Simpson, 2015) and paternal sensitivity (Volling et al., 2019), and the effects of the quality of parent-child relations on a range of outcome domains (Aksan, Kochanska, & Ortmann, 2006), a multitude of early caregiving characteristics are known to modulate the ways in which children develop, react, cope, and transition through both expected milestones and unexpected developmental perturbations (such as TBI). Associations between parent mental health and child development are also extensively documented, particularly findings linking the presence of parental anxiety, stress and/or depression to attachment insecurity, poorer parent-child relationships, maladaptive behavior and global dysfunction (Atif, Lovell, & Rahman, 2015; Barnes & Theule, 2019; Field, 2018; Skreden et al., 2012; Webb, Ayers, & Rosan, 2018). Transferring these developmental notions to the field of pediatric TBI, authors have documented the contribution of parental and family factors on pediatric TBI prognosis and outcome, though mainly in the context of moderate-severe injuries.

Family functioning after pediatric TBI

Across TBI severity levels and ages, there is extensive literature highlighting the reciprocal effects of pediatric TBI and global family functioning, with studies showing that childhood TBI affects parents, siblings and the family environment (Rashid et al., 2014), and that premorbid family functioning, the quality of the post-injury home environment and degree of family burden influence

child recovery (Stancin, Wade, Walz, Yeates, & Taylor, 2008; H. G. Taylor et al., 2001; Yeates et al., 2012; Yeates, Taylor, Walz, Stancin, & Wade, 2010). Findings specific to early TBI indicate that the quality of the home environment and family functioning are predictive of cognitive and academic success after complicated mild (i.e., mTBI associated with abnormal structural neuroimaging results, Bigler et al., 2015) to severe TBI in children aged 3 to 7 years (Anderson et al., 2012; Durber et al., 2017; Durish et al., 2018), and that severe TBI in this young age group has adverse consequences on family adaptation (Stancin, Wade, Walz, Yeates, & Taylor, 2010).

Parent mental health and affective state before and after pediatric TBI

Children of parents with mental health problems, such as psychotic or mood disorders, are at significantly higher risk of sustaining TBI (Lowery Wilson, Tenovuo, Gissler, & Saarijarvi, 2019). Parent affective state and mental health are also key determinants of child behavior *after* TBI, with poorer caregiver psychological functioning associated with greater child externalizing behavior problems (Raj et al., 2014), and parent psychiatric symptoms predicting greater internalizing problems in adolescents with complicated mild to severe TBI (Peterson et al., 2013). Even milder pediatric TBI are associated with increased parental stress (Hawley, Ward, Magnay, & Long, 2003), which is known to be linked to negative parent–child interactions (Le, Fredman, & Feinberg, 2017). In one mTBI study (McNally et al., 2013), parent psychological adjustment, such as parent distress, was found to predict parent but not child reporting of PCS, suggesting that parent mental health may be especially important to consider when outcome is determined solely on the basis of parent perspective, as is typically the case after early mTBI. It is also common for parents of children with TBI to experience anxiety, and high parental trait-anxiety is associated with dysfunctional parenting practices and child disinhibition after acquired brain injury (Chavez-Arana

et al., 2019). Notably, in children aged 3-6 years who sustain moderate-severe TBI, parental distress and depression may be present many years after the injury and affect parental coping strategies (Narad, Yeates, Taylor, Stancin, & Wade, 2017; Stancin et al., 2010). Maternal distress contributes to increased child behavior difficulties even in the context of early mTBI (age at injury 1.5-5 years) (Gagner, Landry-Roy, Bernier, Gravel, & Beauchamp, 2018). Together, these findings suggest that poor parent mental health and coping are risk factors for the occurrence of, and poor recovery from, pediatric TBI. In particular, a parent's psychological state is likely to influence how they respond to their child's injury.

Parenting style, behavior and interactions after pediatric TBI

There are robust observations of the association between parenting behaviors and styles and pediatric brain injury outcome. Parents may become either more protective or punitive towards their child after injury (Woods, Catroppa, Barnett, & Anderson, 2011). For example, in the acute phase post-injury, parents may endorse a more permissive approach, possibly because they feel relieved that their child is well, or, they may exert more dysfunctional levels of discipline if their child exhibits more behavior problems (Woods et al., 2011). Studies focussing on parenting style and parent-child interactions are particularly applicable to study of early TBI given the stronger influence parents are likely to have on their children earlier in life (Schorr, Wade, Taylor, Stancin, & Yeates, 2019; Treble-Barna et al., 2016). Potter and colleagues (2011) report that after moderate-severe TBI in children 3-6 years, higher levels of authoritative parenting are associated with greater cognitive difficulties 12-18 months postinjury. In the same cohort, lesser parental warm responsiveness and higher negativity were associated with externalizing behaviors and attention problems among children, suggesting that parenting quality could facilitate or impede behavioral

recovery (Wade et al., 2011). Interestingly, the relation between TBI and parenting is likely to be reciprocal, in that early TBI itself affects parenting quality and parent-child interactions. Building on previous work from their group (Wade et al., 2003; Wade et al., 2008), Fairbanks and colleagues (2013) found that parents and children with complicated mild-moderate TBI demonstrated lower levels of warm responsiveness six months post-injury compared to controls. The effects of parenting style may also transfer to older pediatric groups, with evidence that in children 8-17 years who sustain moderate-severe TBI, higher parental distress is associated with authoritarian parenting practices, and both high distress and authoritarian parenting correlate with lower child adaptive functioning (Micklewright, King, O'Toole, Henrich, & Floyd, 2012).

While most of the research pertaining to the link between parenting and pediatric TBI has been conducted in the context of more severe TBI, emerging evidence suggests that similar effects may be observable after mild, uncomplicated TBI (or concussion). Our group found that mTBI sustained between 1.5 and 5 years of age was associated with reduced quality parent-child interactions six months post-injury, characterized by less positive, mutually binding, and cooperative relationships (Lalonde, Gravel, Bernier, & Beauchamp, 2016). Notably, parental perception of *more* PCS in their child was associated with *higher* quality parent-child interactions, suggesting that parents' ability to detect and/or attribute PCS in young children may benefit positive outcome (Lalonde, Bernier, Beaudoin, Gravel, & Beauchamp, 2019).

In sum, there is extensive literature supporting the idea that parents' pre-morbid and post-injury functioning, behavior, psychological state, parenting style, and coping strategies are key

determinants in child TBI outcome. We propose that this "parent factor" is likely to be one of the most important distinguishing features of early childhood TBI, when parent-child relations are especially salient and parents exert major influence on the course of their child's development. We further posit that in an age group where symptom reporting depends solely on third party reports, such parental factors are also crucial in the accurate detection, identification and response to PCS, and that parents' ability to identify and correctly interpret PCS may in large part determine child outcome and post-injury evolution, as well as access to clinical resources. To better understand the complex interplay of parent-child factors after early mTBI, we mapped possible scenarios that bring together child PCS and parent factors using a pathway approach.

Probable pathways of parent reactions to early childhood mTBI

Figure 1 presents five scenarios depicting the probable chain of reactions from the time of injury and possibility that the child experiences PCS, and leading to either favourable or unfavourable outcome after early mTBI. In some cases, mTBI may cause such minor changes that other than the initial, acute symptoms leading to a diagnosis of mTBI, the injury causes no lingering effects on the child in the days following injury (true absence of PCS). In others, PCS may be genuinely present, but may or may not be detected by the parent (true presence of PCS).

True absence of PCS

Pathway 1 – Well-adjusted parental response: As in school-age children, it is suspected that a considerable number of young children will not experience mTBI symptoms other than those seen acutely, at the time of injury. Thus, one of the most probable pathways in the true absence of any

PCS is that parents do not perceive any symptoms or changes in their child's behavior, and accordingly do not change their parenting practices or behavior. The parental response is therefore logically considered to be appropriate and aligns with the child's post-injury functioning, which is comparable or unchanged with respect to their pre-morbid functioning. This early mTBI pathway is favorable given the absence of clinically significant PCS and the presence of well-adjusted parental response.

Pathway 2 - Maladjusted parental response: A second probable scenario occurs when a child who sustains mTBI experiences no PCS in the days or weeks following their injury; however, the child manifests typical early childhood behavioral manifestations (e.g., irritability, inattentiveness, crying, fatigue) that resemble some PCS. The parent perceives these behaviors and attributes them to the injury, yet the fluctuations are simply normal or pre-existing day-to-day variations in infant, toddler or preschooler affect and behavior. The parent thus falsely attributes the changes to the injury and adjusts his or her own reactions and behavior or parenting style, becoming for example more lenient and permissive and "excusing" difficult behaviors as part of the injury profile. If the child is more irritable or oppositional and this is tolerated by the parent, the child may inherently be encouraged to continue to behave in this way. The child thus continues to display behavior perceived as difficult to manage by the parent and to engage in negative interactions, which may persist long-term. This circle of misattribution and behavior change on the part of both the parent and the child may eventually result in maladaptive parent-child interactions and poorer overall family functioning (Davidov, Knafo-Noam, Serbin, & Moss, 2015; Serbin, Kingdon, Ruttle, & Stack, 2015). In this case, the parent's response is considered to be maladaptive due to the incorrect attribution.

True presence of PCS

Pathway 3 - Maladjusted parental response: A third possibility is that the child genuinely experiences PCS that persist over at least a few days or even weeks post-injury and therefore exhibits changes in behavior in relation to their injury. However, in the context of early childhood mTBI, it may be difficult for the parent to identify PCS because of young children's limited (or non-existent) verbal and introspective abilities (Beaudoin et al., 2017; Bernard, McKinlay, Krieser, Testa, & Ponsford, 2017; Suskauer et al., 2017), in addition to the similarities between day-to-day early childhood behaviors and PCS (noted in Pathway 2, e.g., irritability, inattentiveness, crying, fatigue), which may mask or limit parental detection of true symptoms. A parent who fails to detect PCS or who attributes PCS manifestations to the challenging behaviors associated with early childhood may be less understanding or tolerant of the child's difficulties and not likely to adjust his or her parenting style, behaviors or reactions to the post-injury context, thus persisting with regular demands on the child. This can potentially create a vicious circle of inappropriately high demands on the injured child, which the child cannot meet, causing frustration, opposition and/or worsening behavior, and globally impacting parent-child interactions and family functioning. This pattern may represent the mechanism underlying observation that *fewer* parent-reported PCS in the six months following mTBI sustained between 18 and 60 months are associated with *worse* parent-child interaction quality (Lalonde et al., 2019). Notably, in this pathway scenario, carryover effects of a maladaptive parent-child relationship may affect other family members, siblings for instance, or could cause conflict between parents themselves, eventually leading to more widespread family distress or dysfunction, such as has been reported after more severe TBI (Perlesz, Kinsella, & Crowe, 2000; Rashid et al., 2014; Sambuco, Brookes, & Lah, 2008; Stancin et al., 2008; Wade, Taylor, Drotar, Stancin, & Yeates, 1998).

Pathway 4: Well-adjusted parental response: A fourth possibility is that the child genuinely experiences PCS after their injury, the parent perceives their child as displaying behavioral changes and correctly attributes the changes to PCS and the mTBI. These parents are likely to become more vigilant and sensitive to their child's needs, affects and demands. A parent who attributes the observed behavioral difficulties to the TBI itself could be more accepting of the child's difficulties. As a result, they may be more responsive, appropriately adjusting their own behavior to that of their injured child and modulating their demands on the child as a function of what the child is able to manage as they progress through the recovery process. This well-adjusted reaction could preserve and even enhance the synchrony and harmony of their mutual relationship, thus improving interactions and the family environment and functioning more broadly.

Pathway 5: Accurate perception and attribution, but inappropriate response

A somewhat less likely, but possible, alternative pathway in the context of genuine PCS might be observed if a parent accurately perceives their child's PCS, correctly attributes the manifestations to the injury, adapts their behavior/response, but not in a way that is optimally adjusted to the child. For instance, the parent might become too lenient (e.g., becoming too lax in the daily routine and/or sleep schedule to accommodate the injured child) or conversely, too overprotective (e.g., not allowing the child to climb in the playground where they were injured and thus causing fear or frustration on the part of the child). Such a pathway would ultimately result in unfavourable outcome (as in Pathway 3) because despite progressing through the first two steps (correct perception and attribution), the parent's response is not well-adjusted to the child's needs and could

further disrupt systems and functions known to be affected after pediatric TBI such as sleep patterns, behavior or temperament (Bramley et al., 2017; Gagner, Landry-Roy, Laine, & Beauchamp, 2015; Lalonde et al., 2019; Landry-Roy, Bernier, Gravel, & Beauchamp, 2018; Seguin, Degeilh, Bernier, El-Jalbout, & Beauchamp, 2020).

Summary of the pathways: The PARENT model

The four pathways analyzed suggest that different early mTBI outcomes are likely to occur as a function of the interaction between child injury characteristics (presence/absence of significant PCS) and parent reactions (well-adjusted or maladaptive). Three key processes need to align to optimize child and family functioning after early mTBI: the parent's accurate perception of PCS and related behavioral changes (if any), their ability to appropriately attribute such changes to their child's mTBI, and the ways in which they adjust their own response, behaviors, parenting style and interactions.

Figure 2 summarizes these pathways and effects in a conceptual depiction named the PARENT model, for "**P**erception, **A**ttribution, and **R**esponse after **E**arly **N**on-inflicted **T**raumatic Brain Injury", and sets the Perception-Attribution-Response (PAR) process within the broader context of child- and parent-related factors known to contribute to outcome after pediatric TBI. The blue shading represents the parents' contribution to the PAR process. The split parent icon underscores the unique contributions each parent makes to the process. In addition to more general environmental factors (e.g., SES, resources), family (e.g., marital satisfaction, family burden, parenting style) and parent psychological factors, in particular, may either overshadow, taint or

impede their ability to adequately perceive-attribute-respond (PAR), such as if they are experiencing negative emotions (high anxiety, depression, stress/distress, guilt), or, improve these abilities if they are free from negative psychological states and traits and optimally positioned to cope, adjust and accompany their child through the mTBI recovery period. The weight of these parental factors may be increased or diminished according to the characteristics of their child's injury. Feelings of guilt, denial, distress and avoidance are documented in parents of children with moderate-severe TBI (Brown, Whittingham, Sofronoff, & Boyd, 2013; Stancin et al., 2008), but may also be present after milder injuries (Ganesalingam et al., 2008), and are associated with child behavior after early mTBI (Gagner et al., 2018). For example, a parent who witnesses (e.g., parent sees their child fall down the stairs) or who was involved in (e.g., car accident while parent was driving; child falls off the changing table) their child's accident may experience higher levels of guilt, worry or distress. As suggested in the literature reviewed in this paper, the influence of diminished parent psychological states can occur both as a function of pre-morbid parental mental health problems, or psychological changes subsequent to their child's injury.

The yellow shading around the child portion of the model on the right suggests that the child too influences the PAR process and parent-child interaction as a function of the injury (e.g., type of injury, severity, PCS), biological (e.g., age, sex, genetics, temperament, sleep), and functional (e.g., pre-morbid characteristics, post-injury cognitive, behavioral and affective functioning) characteristics they bring to the relationship. Ultimately, the model suggests a circular effect through which the parental portion (PAR) either helps or hinders child recovery, which influences child behavior either positively or negatively, and the parent is either well- or ill-equipment to further adjust to the child's behavioral manifestations, and so on.

Discussion

Multiple lines of evidence from developmental psychology and neuropsychology converge to highlight the central role played by parents during the course of their young child's recovery from brain injury. Factors associated with parent psychological state, parenting style, interaction quality, and overall family functioning are key contributors to pediatric TBI outcome.

The strength of parental contribution is likely to be exceptionally high during early childhood when parents are especially present in the lives of their young children and when children are particularly permeable to their influence. In the context of early TBI, the parent plays an important role in guiding the child through an unexpected injury and the recovery process, especially given their limited verbal, introspective and self-regulation abilities, which hinder them from conveying their symptoms and affective states. Among the central adult figures in their daily life, the young child relies in part on the parent for comfort and reassurance, as well as to make sense of the injury experience. In children who do not benefit from parental support, PCS that are not optimally addressed could in some cases transform into more complex behavioral problems. For example, a child who experiences irritability or fatigue might be more prone to tantrums or other externalizing manifestations, such as those observed in previous work (Gagner, Degeilh, Bernier, & Beauchamp, 2020; Gagner et al., 2018). In the absence of reassurance to understand these affective states or if punished, the child may not learn to self-regulate leading to further disruptive behaviors (Sharp & Fonagy, 2008).

Mapping probable behavioral pathways starting from the time of sustaining early mTBI suggests complex interactions between how parents perceive their child to be post-injury (i.e., Are they able to identify subtle changes in their child's functioning or behavior?), their understanding of expected child development and common consequences of pediatric mTBI (i.e., Do they recognize the common symptoms of mTBI and correctly attribute their child's behavior changes to the injury?), and their ability to react and adapt appropriately to their child's changes or difficulties (i.e., Do they adjust their expectations and interactions to take into account injury-related problems?). Stated more simply, the PARENT model suggests that a parent's ability to *perceive, attribute and respond* to PCS could determine the direction of outcome and recovery after early mTBI. These processes are overshadowed by parents' own emotional state. For example, the parent may have a history of psychological or mental health problems that pre-date their child's injury and/or may experience feelings and states, such as guilt, stress, anxiety or depression, after the injury, all of which may impact their interactions with their child.

This model could be useful in understanding differential outcome trajectories after early mTBI. For example, the double or triple hazard effect introduced by a parent who experiences difficulties in perceiving, attributing and responding to PCS could explain why children with seemingly comparable injury factors may have drastically different outcomes, or why at the individual level, some children display more severe or persistent problems even after minor injuries, a phenomenon referred to in the pediatric TBI literature as the "miserable minority" (Rohling, Larrabee, & Millis, 2012; Wood, 2004; Yeates, 2010). The effects depicted in the PARENT model align with empirical evidence and theoretical notions from both pediatric and adult mTBI suggesting that acute problems after mTBI are both neurological and psychological in nature (Silverberg & Iverson,

2011), while long-term problems are more likely to be the result of unidentified or untreated symptoms that have become worse because of psychological factors or maladjusted behaviors (e.g., stress, catastrophizing, anxiety, depression, maladaptive coping) (Degeilh, Bernier, Gravel, & Beauchamp, 2018; Gagner, Degeilh, et al., 2020; Hou et al., 2012). In other words, a vicious cycle between child and parent responses might be created and maintained when true mTBI symptoms (i.e., those with a neurological basis) are not identified and addressed.

It is relevant to consider the perception/attribution portions of the model in light of literature suggesting children with mTBI should ideally be compared to comparison groups of children who sustain orthopedic injuries (OI) not involving the head (Beauchamp, Landry-Roy, Gravel, Beaudoin, & Bernier, 2017). Children with OI are thought to share common injury-related experiences and pre-morbid characteristics, though injuries to the head are assumed to have an additional impact on functioning. We suggest that the challenge for parents of children with early mTBI is that the child's injury is physically invisible and therefore harder to associate with observed behavior changes or other manifestations. In contrast, parents of children with OI, whose arm or leg is likely to be in a bandage, sling or cast, are likely to be constantly reminded that their child may understandably be in pain, tired, or irritable, and will therefore more easily attribute these manifestations to the injury. Similarly, parents of children with moderate to severe TBI are likely to have a clearer sense of the relation between their child's brain injury and their behavior given the clinical (e.g., intensive care, neurosurgery, prolonged hospitalization, and/or rehabilitation services) and functional (e.g., polytrauma or other associated visible injuries, persistent or long-term physical disabilities) realities associated with structural brain lesions. Parents of children with mTBI do not have a visual reminder that their child's difficult behaviors may be to do with their

injury. A related issue in terms of perception/attribution is that there is currently no validated approach to documenting PCS in children 5 years and under. Existing PCS scales (Iverson et al., 2003; Sady et al., 2014; Yeates et al., 2001) are only applicable to school-age children and are not developmentally appropriate given that they rely heavily on the ability of the injured child to verbally report any symptoms experienced. The PARENT pathway and model underscore the critical need to develop tools to assist parents and clinicians in identifying PCS in young children and support ongoing efforts in this regard (Beaudoin et al., 2017; Suskauer et al., 2017)

Applications and extensions of the PARENT model

The PARENT model may be useful for health professionals seeking to better understand the factors involved in modulating outcome after early childhood mTBI, and in sensitizing and educating parents on their role and influence in recovery. In this respect, the model could provide a basis for developing interventions and/or knowledge mobilisation strategies within clinical settings and the community.

A number of intervention efforts are already underway to improve parent-child relations after moderate-severe pediatric TBI. A systematic review identified six intervention trials involving parent training for parents of children with TBI (Brown, Whittingham, Boyd, & Sofronoff, 2013) and suggests that some of these interventions may improve parenting skills and adjustment, thus alleviating behavioral and emotional disturbances. In addition, the I-InTERACT program is a brief, online parent skills training program reported to decrease behavior problems after early moderate-severe TBI in children (Wade et al., 2017) and is based on Wade and colleagues' previous work

aiming to improve post-TBI parenting skills and decrease parental distress (Antonini et al., 2014; Raj et al., 2015; Wade et al., 2015). A case study approach also describes the use of parent-child interaction therapy for the management of problem behaviors after severe TBI (Cohen, Heaton, Ginn, & Eyberg, 2012). However, none of the parent-child interventional approaches to date have focused on the distinct features of mTBI. The PARENT model could be used to provide additional, specific loci of intervention and to adapt intervention approaches to the context of milder injuries, which introduce challenges to the parent-child relationship that are different from those observed after more severe injuries.

Although the model was specifically developed with early, mild, non-inflicted TBI in mind, it may be valuable in reflecting on the outcome of other types of TBI or brain insult. The term non-inflicted is used in the model to suggest that it is primarily applicable to injuries sustained accidentally, given that those that occur in an abusive context are likely to be influenced by additional injury and family factors. For example, abusive head injuries tend to result in more severe and therefore more overt sequelae (Iqbal O'Meara, Sequeira, & Miller Ferguson, 2020) and the role of parents in perceiving symptoms may be altered or masked by distinct affective load depending on suspected perpetration (Powell & Sorenson, 2020).

As mentioned throughout this work, variations in the type and severity of brain insult, as well as the multiple factors known to predict outcome modulate the various steps of the model. For example, pre-existing neurodevelopment conditions (e.g., ADHD), a history of repetitive injuries, and the amplitude of parent psychological factors, as well as their knowledge and views on TBI

are thought to act on each step. Though we suggest that the effects portrayed in the model are strongest at younger ages when children are especially dependent on their parents and when their social environment is largely constrained to the home, the model may be at least partially applicable to older pediatric age groups who sustain TBI. Parental roles and influences are relevant throughout late childhood and adolescence (Lantagne et al., 2018; Micklewright et al., 2012; Peterson et al., 2013). The model could also be useful in interpreting some of the challenges ensuing from moderate-severe TBI, though the perception and attribution of consequences and behavior changes in that context may be much more obvious and therefore play a lesser role in determining parental response. Finally, though developed specifically with pediatric TBI in mind, the model may be relevant for other medical conditions associated with brain insult known to have significant impacts on parent and family functioning.

Limitations

Given that the aim of this work was to focus on the role and influence of parents in their child's post-mTBI recovery, the PARENT model does not explicitly consider the child's role, nor does it comprehensively portray the numerous other factors, some of which are represented in Figure 2, known to mediate mTBI outcome. As such, it is implicit that children themselves react both to their injury and to their parents' behavior and affect. The PARENT model should be considered alongside more comprehensive models illustrating the pre-morbid, environmental, biomarker, child, and injury factors involved in predicted pediatric TBI outcome (Beauchamp & Anderson, 2013; Bernard, Ponsford, McKinlay, McKenzie, & Krieser, 2016; McNally et al., 2013; Rausa, Anderson, Babl, & Takagi, 2018; Yeates et al., 2012; Zemek, Farion, Sampson, & McGahern, 2013). Also, the model does not differentiate between maternal and paternal roles and reactions,

though it is inherent that each will contribute distinct pre-morbid states and traits, parenting styles, and coping strategies (Narad, Yeates, et al., 2017; Wade et al., 2010). There is evidence that mothers and fathers differ in their assessment of their child's behavior and in their parenting (De Los Reyes et al., 2015; Schoppe-Sullivan & Fagan, 2020; van der Veen-Mulders, Nauta, Timmerman, van den Hoofdakker, & Hoekstra, 2017; Volling et al., 2019) and that, in the context of pediatric TBI, their perception of child PCS (Coghlin, Myles, & Howitt, 2009), marital adjustment and family functioning diverges (Bendikas, Wade, Cassedy, Taylor, & Yeates, 2011), as do their emotional state and coping strategies (Narad, Taylor, et al., 2017; Wade et al., 2010). Finally, parental ability to perceive and attribute PCS is also related to their access to reliable tools to help them do so, and there currently exist no validated measure of PCS for children under 5 years of age. Efforts to develop such tools will undoubtedly be of assistance in improving parents' knowledge on possible physical, cognitive and behavioral manifestations in young children and their ability to detect such changes (see for example preliminary data on the REACTIONS inventory, Beaudoin et al., 2017).

Conclusions

Early childhood brain injuries should be considered through an appropriate developmental lens. Just as efforts to map and understand the consequences of pediatric TBI as a whole should not be directly extrapolated from adult research ("Children are not little adults") (Figaji, 2017; Giza, Mink, & Madikians, 2007), the diagnosis, management, and treatment of mTBI in the youngest developmental groups should not be exclusively derived from what is known of the same types of injuries in older children and adolescents. The review and PARENT model proposed here suggest that the role and influence of parents should be a central consideration in the study and management

of early TBI. Parents who are sensitive to subtle changes in behavior and functioning in their infant, toddler or preschooler who sustains mTBI, and are able to relate these changes to expected manifestations of mTBI (or concussion), are more likely to be inclined to adjust their own response and parenting post-injury, thus optimizing child outcome and development in the weeks, months and years post-injury.

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Disclosure statement

None of the authors have any conflict of interest.

Data availability statement

The article is a conceptual review and does not include empirical data.

Figure captions

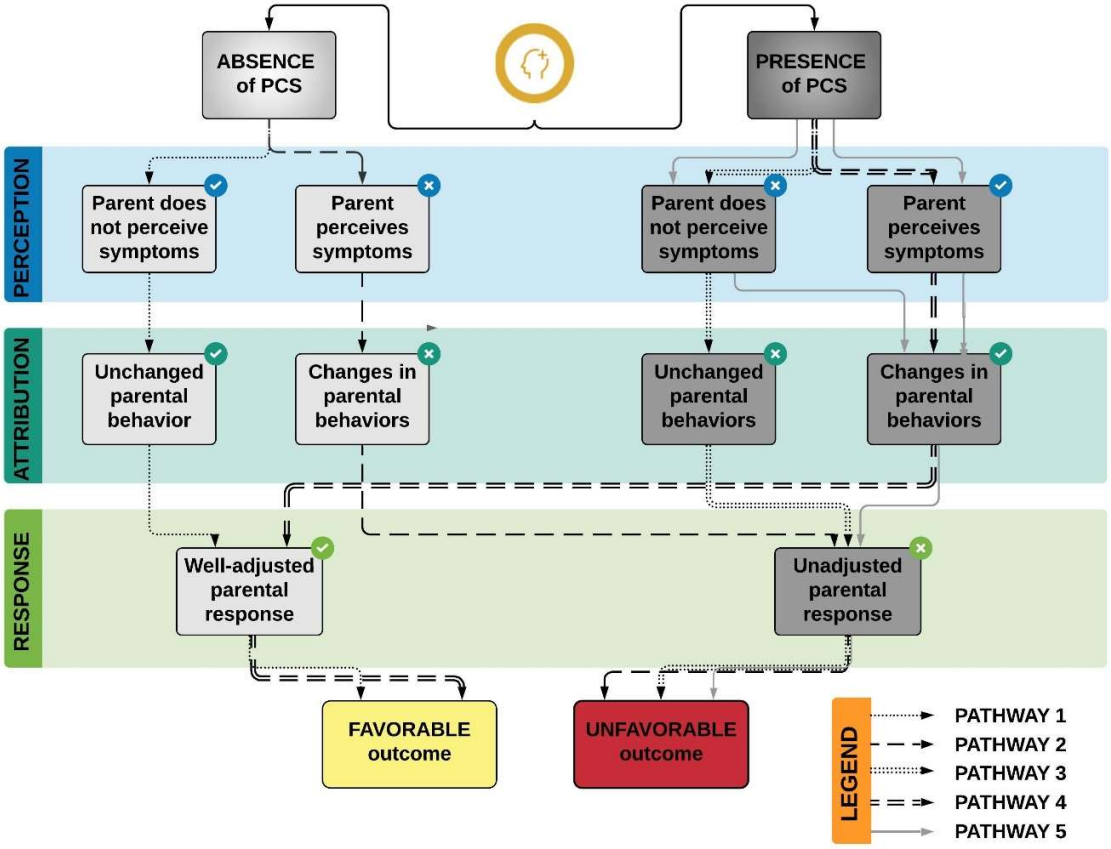

Figure 1. PARENT Pathways: Five pathways depicting the probable chain of reactions from the time of injury and possibility that a child experiences PCS, and leading to either favourable or unfavourable outcome after early mTBI. While it is assumed that a majority of children will not experience PCS beyond the acute phase of injury, there are some who may have persistent symptoms. Symptom manifestation may also be a function of severity (e.g., uncomplicated versus complicated mTBI) and head injury history (e.g., multiple TBI).

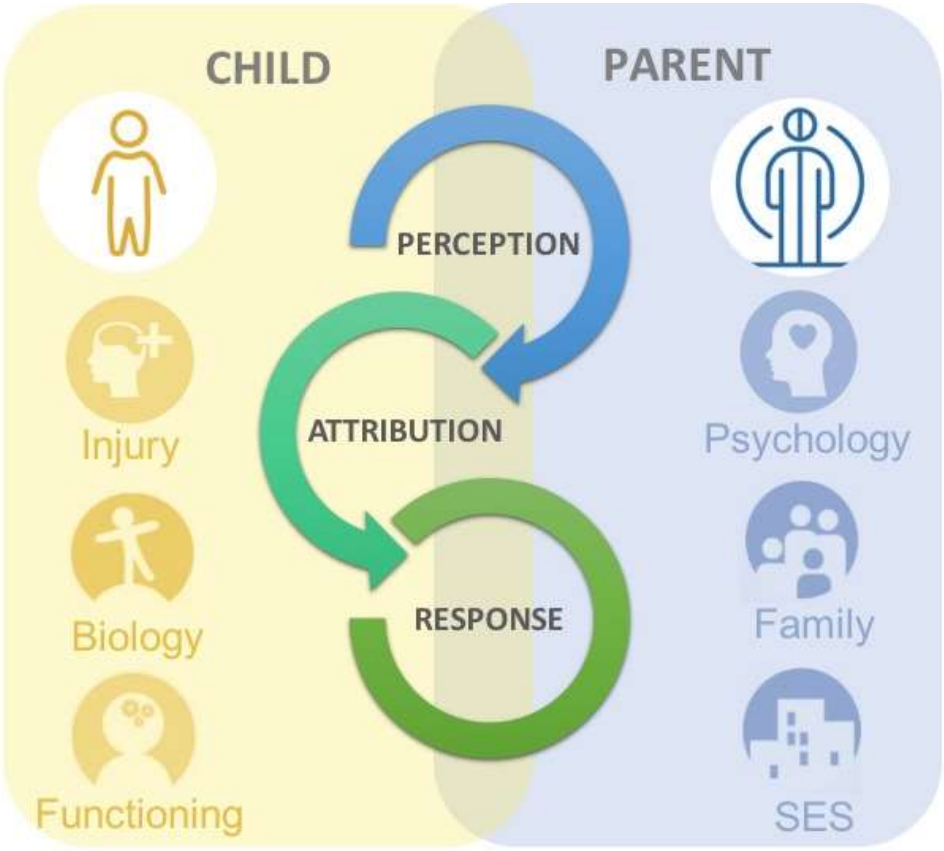

Figure 2. The "**Perception, Attribution, and Response after Early Non-inflicted Traumatic Brain Injury" (PARENT)** model. Beginning at the time of the child's injury, the circular arrows represent three important steps (Perception-Attribution-Response, PAR) in the role of parents after their young child sustains mTBI, which will contribute to determining child behavioral and functional outcome. The yellow shading represents child injury (e.g., type of injury, severity, PCS), biological (e.g., age, sex, genetics, temperament, sleep), and functional (e.g., pre-morbid characteristics, post-injury cognitive, behavioral and affective functioning) factors and the blue shading represents parent psychological (e.g., any pre-morbid psychological or mental health problems and current mental health and mood), family (e.g., marital satisfaction, family burden, parenting style) and environmental (e.g., SES, resources) factors that respectively influence the PAR process.

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