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Surface-based abnormalities of the executive frontostriatial circuit in pediatric TBI

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ABSTRACT

Childhood traumatic brain injury (TBI) is one of the most common causes of acquired disability and has significant implications for executive functions (EF), such as impaired attention, planning, and initiation that are predictive of everyday functioning. Evidence has suggested attentional features of executive functioning require behavioral flexibility that is dependent on frontostriatial circuitry. The purpose of this study was to evaluate surface-based deformation of a specific frontostriatial circuit in pediatric TBI and its role in EF. Regions of interest included: the dorsolateral prefrontal cortex (DLPFC), caudate nucleus, globus pallidus, and the mediodorsal nucleus of the thalamus (MD). T1-weighted magnetic resonance images were obtained in a sample of children ages 8–13 with complicated mild, moderate, or severe TBI (n = 32) and a group of comparison children with orthopedic injury (OI; n = 30). Brain regions were characterized using high-dimensional surface-based brain mapping procedures. Aspects of EF were assessed using select subtests from the Test of Everyday Attention for Children (TEA-Ch). General linear models tested group and hemisphere differences in DLPFC cortical thickness and subcortical shape of deep-brain regions; Pearson correlations tested relationships with EF. Main effects for group were found in both cortical thickness of the DLPFC ($F_{1,60} = 4.30$, $p = 0.042$) and MD mean deformation ($F_{1,60} = 6.50$, $p = 0.01$) all with lower values in the TBI group. Statistical surface maps revealed significant inward deformation on ventral-medial aspects of the caudate in TBI relative to OI, but null results in the globus pallidus. No significant relationships between EF and any region of interest were observed. Overall, findings revealed abnormalities in multiple aspects of a frontostriatial circuit in pediatric TBI, which may reflect broader pathophysiological mechanisms. Increased consideration for the role of deep-brain structures in pediatric TBI can aid in the clinical characterization of anticipated long-term developmental effects of these individuals.

1. Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in young children ages 5–14 (Araki et al., 2017; Dennis et al., 2017). Among children who have survived a severe TBI, the majority experience long-term disability (Lindsey et al., 2019).

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Neuropathologically, TBI is associated with neuronal loss and diffuse axonal injury in multiple brain regions, most commonly in frontal and temporal areas (Marco et al., 2011).

Cognitive impairment is a common feature in pediatric TBI, with the type and severity dependent upon the magnitude of injury. Children who sustain a TBI often experience deficits in a range of neuropsychological domains, including memory, attention, spatial reasoning, speeded perceptual motor skills, and executive functioning (Ewing-Cobbs et al., 2004; Taylor et al., 2008). In particular, executive dysfunction has significant implications for everyday activities (Slomine et al., 2009), and is typically associated with lesions in the prefrontal cortex (Bigler, 2001; Stuss, 2011). In pediatric TBI populations, difficulties in various aspects of executive functioning, including behavioral control and regulation, may be evident up to 6 months postinjury (Dennis et al., 2001; Levin and Hanten, 2005). Levin and colleagues (2001) also observed that orbitofrontal cortical lesions strongly related to errors and rule-breaks on tasks of executive functioning, while dorsolateral frontal lesions were closely associated with deficits in problem solving ability (Taylor, 2004).

Multiple lines of evidence indicate that the broad features of executive functioning are dependent upon dense frontostriatial circuitry that involves interactions between frontal lobes, basal ganglia, and specific thalamic nuclei (Leunissen et al., 2014). One specific frontostriatial loop involving reciprocal connections between the dorsolateral prefrontal cortex, caudate nucleus, globus pallidus, and mediodorsal nucleus of the thalamus is the dorsolateral prefrontal circuit (Bonelli and Cummings, 2007). The dorsolateral prefrontal (DLPF) circuit is thought to mediate various aspects of executive functioning, including goal selection, planning, monitoring, and the ability to incorporate feedback during task performance (Alvarez and Emory, 2006). Research in adults with severe TBI has observed impairment in executive functioning tasks when lesions involve the DLPF circuit (Zappalà et al., 2012). In studies of pediatric TBI, focal lesions and disruption to the development of these frontally guided and distributed networks may also be key in understanding cognitive deficits related to injury mechanisms (Levin and Hanten, 2005).

Although frontal and temporal regions are considered most susceptible to injury following TBI, deep brain structures are also known to be vulnerable (Wilde et al., 2007). Traumatic deep gray matter lesions in components of frontostriatal circuitry, such as the caudate, thalamus, globus pallidus, and putamen, are frequently observed in adults with severe TBI (Clarençon et al., 2017). In a volumetric study of pediatric TBI, Wilde and colleagues (2007) found volumetric decreases of the hippocampus, amygdala, and globus pallidus in children with TBI that were relatively symmetric, providing support for a more diffuse and global, rather than a focal, injury process (Bigler et al., 2013a; Wilde et al., 2007). In additional pediatric TBI volumetric studies, reductions in the caudate and putamen have also been found as a result of early TBI (Serra-Grabulosa et al., 2005), suggesting these structures may exhibit similar degrees of developmental vulnerability to different injury processes given they all originate from a common pool of immature neurons (Wilde et al., 2007). Previous work has also found that reciprocal white matter connections between the thalamus and cortex are highly susceptible to injury in pediatric TBI, likely due to injury-related atrophy resulting in transneuronal degeneration (Tasker, 2006), a form of neuronal degeneration that may spread to involve other connected nerve cells. Despite its relatively protected position, the thalamus in particular may be susceptible to TBI-related pathological change due to transneuronal cell death processes, given its extensive network of interconnectedness with the cerebral cortex (Fearing et al., 2008; Rosen et al., 2006). Previous studies have implemented shape analysis to examine subcortical changes in adult TBI, for example, Leunissen and colleagues (2014) utilized this approach to characterize the thalamus, putamen, and caudate and found localized atrophy of executive and rostral-motor zones of the basal ganglia, as well as the thalamus. As observed in the adult TBI literature, focused investigation of the collective frontostriatal circuitry involving both cortical and deep brain structures may assist in providing additional insight into the brain sequalae and cognitive features of pediatric TBI.

The overarching goal of this project was to examine structures of the DLFP circuit in a sample of children with TBI relative to age-matched children with orthopedic injury (OI) and to determine if changes to the circuit were related to various aspects of executive functioning. Currently, no research has taken a focused approach to investigating structural abnormalities of frontostriatal circuitry in pediatric TBI and examining whether these changes relate to behavioral performance. The first aim of the study was to characterize the structure of DLFP circuitry components, namely the dorsolateral prefrontal cortex (DLPFC), caudate nucleus, globus pallidus, and mediodorsal nucleus of the thalamus, using high-dimensional brain mapping procedures, which are capable of detecting submillimeter alterations in the morphology of gray matter structures (Csernansky et al., 2004). We hypothesized that the TBI group would demonstrate abnormalities in all structures of this circuit (thinner cortex and localized volume loss of deep brain nuclei) relative to the OI group. The second aim was to evaluate whether structural abnormalities in these regions would relate to impairments in executive functioning in the TBI group. We hypothesized that abnormalities in the caudate nucleus and globus pallidus would demonstrate the strongest association with executive dysfunction in this group.

2. Material and methods

This study utilized a subset of participants from a multi-site NIH-funded study of brain injury in children: Social Outcomes of Brain Injury in Kids (SOBIK; R01 HD048946, PI: Yeates) (Bigler et al., 2013a; Yeates et al., 2007). The subset was derived from two of the data collection sites that utilized GE-branded magnetic resonance imaging (MRI) scanners (the third used Siemens) to maintain consistency in image acquisition parameters and avoid spurious differences due to scanner type. Data were collected according to established ethical guidelines as outlined by the Declaration of Helsinki and the methods and procedures were approved by Institutional Review Board at each data collection site. Participants contributed imaging data, as well as measures of cognition, social information processing and adjustment, measures of environmental variables including family functioning, and direct observations of interactions with familiar and unfamiliar peers. Informed parental consent and child assent were obtained before participation, and the dataset was anonymized prior to utilization for this study.

2.1. Participants

Participants were identified from hospital medical records and trauma registries at metropolitan children's hospitals as part of the larger SOBIK project and recruited by phone (Yeates et al., 2013). All participants were 8 to 13 years of age and had experienced a TBI or OI. Participants were excluded if they had a: (a) history of more than one serious injury requiring medical treatment; (b) premorbid neurological disorders; (c) injury determined to be a result of child abuse or assault; (d) history of severe psychiatric disorder requiring hospitalization; (e) sensory or motor impairments that would prevent valid administration of study measures; (f) primary language other than English; (g) any medical contraindication to MRI; and (f) need for full-time special education. Participants in the OI group were excluded if a structural lesion was displayed in an MRI scan or if they had any injury to the head. Children with a history of premorbid learning or attentional problems were not excluded from the study; groups did not significantly differ on the distribution of these concerns.

Both groups experienced a mechanical injury and hospitalization, but only those in the TBI group sustained a brain injury based on Glasgow Coma Scale scores (GCS) (Teasdale and Jennett, 1974). The total TBI subset sample (n = 32) was stratified by injury severity based upon GCS scores, and included individuals with complicated mild (n =

13, GSC score of 13–15 with intracranial lesion), moderate (n = 5, GCS score of 9–12), and severe (n = 14, GCS score of ≤ 8) TBI. Detailed information regarding brain lesion severity and location can be found in work by Bigler and colleagues (2013b). In brief, 68 % of the TBI participants demonstrated as least one quantitative MRI abnormality – the frontal region contained 73.5 % of all white-matter hyperintensities (WMH), 74.1 % of all hemorrhagic lesions and 72.3 % of all focal encephalomalacia; the temporal region contained 15 % of all WMH, 19.4 % of all hemorrhagic lesions and 26.6 % of all focal encephalomalacia; the parietal-occipital regions contained 11.5 % of all WMH, 6.4 % of all hemorrhagic lesions and 1.4 % of all focal encephalomalacia; and 15.3 % of the TBI sample had abnormalities of the corpus callosum (Bigler et al., 2013b). The OI subset comparison group consisted of 30 participants who sustained bone fractures that were not skull or facial and experienced no loss of consciousness or any other indications of brain injury. Inclusion criteria for the OI control group included no known head injury or loss of consciousness, and a GCS of 15. Demographic data are available in Table 1. Additionally, TBI and OI groups from the site utilizing the Siemens-branded MRI scanner were compared to TBI and OI groups from the subset used in the analyses.

2.2. Measures

The Wechsler Abbreviated Scale of Intelligence (WASI) was administered, with the FSIQ score used to characterize general intellectual functioning (Wechsler, 2011). Parental socioeconomical status (SES) was measured using a standardized composite score based on Likert-scaled questions of parental education, parent occupation status, and mean family outcome collected on a self-report questionnaire. The Test of Everyday Attention for Children (TEA-Ch; Manly et al., 2001) was administered and a composite score that represented executive aspects of cognition (EF) was constructed using three subtests: Creature Counting Timing, Walk/Don't Walk, and Code Transmission using a previously described approach (Robinson et al., 2014). The TEA-Ch is a cognitive battery that measures selective attention, sustained attention, and the switching of attentional processes based on Petersen and Posner's (2012) theory of attention. It is ideal for children based on its likeness to a game and allows children to feel more comfortable during testing (Chan et al., 2008). The Creature Counting subtest requires participants to utilize switching attentional processes by counting "creatures" from the top of the page down, but to use the arrows on the page as a cue to switch the direction of their counting (Manly et al., 2001). The Walk/Don't Walk subtest is a measure of effortful inhibition, which requires participants to mark footprints on a paper path using a pen after the presentation of a "go" tone, but inhibit marking after they hear a different "stop" tone (Robinson et al., 2014; Treble-Barna et al., 2017). The Code Transmission task is a measure of sustained auditory attention that requires participants to monitor a stream of monotonous digits for the occurrence of a particular target sequence and then to report the digit that occurred immediately before (Manly et al., 2001).

2.3. Image acquisition parameters

Magnetic resonance images of the brain were collected within one-year post-injury for all participants at two SOBIK collection sites using a GE Signa Excite 1.5 T machine. Imaging protocols included: a thin slice ($\sim$1mm^3) volume acquisition T1-weighted ultrafast 3D Gradient Echo SPGR; dual-echo proton density (PD)/T2 weighted sequence; fluid attenuated inversion recovery (FLAIR); and a gradient recalled echo (GRE) (Bigler et al., 2013b).

2.4. Image processing

Raw T1-weighted images were processed using the FreeSurfer (FS) (https://surfer.nmr.mgh.harvard.edu/) version 6.0 toolkit (Dale et al., 1999; Fischl et al., 1999) and manually edited according to established guidelines (Segonne et al., 2007); any processing or topological errors were corrected to ensure accuracy of the cortical mantle. Definition of the DLPFC region of interest (ROI) involved a combination of labels derived from a standard FreeSurfer parcellation scheme (Destrieux et al., 2010) and was based on published neuroanatomical regions (Hoshi, 2006; Mylius et al., 2013), which included: middle frontal gyrus, inferior frontal sulcus, and middle frontal sulcus (see Supplementary Fig. 1).

Subcortical surface features of the caudate, globus pallidus, and the thalamus were derived through the application of large deformation high dimensional brain mapping procedures (Csernansky et al., 2004). Specifically, large deformation diffeomorphic metric mapping (LDDMM) was used, which is an atlas-based transformation technique that aligns a template image of each structure with the target regions in each subject through diffeomorphic mapping of voxel intensities, then generates surfaces by superimposing a tessellated graph over each subject image (Khan et al., 2008). The diffeomorphic transformation allows the individual surface points to be independently matched, preserving any unique surface features. Resulting images of each deep-brain structure were manually inspected by trained raters and corrected/reprocessed if needed to ensure accuracy of each surface map. Delineation of the mediodorsal nucleus of the thalamus (MD) was accomplished using a manual landmarking procedure guided by an expert neuroanatomist on a template surface as outlined in Cobia et al. (2017). Surface displacement (in mm) from a common template was averaged across all vertices in each subject and was representative of localized volume loss.

Table 1
Demographic Characteristics of Study Sample.

	TBI (n = 32)		**OI (n = 30)**		**Statistic**		
	Mean	(SD)	Mean	(SD)	*t*-test	df	*p*
Age (at injury)	7.67	(2.0)	7.75	(1.86)	0.17	60	0.86
Parental SES	0.06	(0.78)	0.42	(0.96)	−1.75	5.89	0.13
Maternal Education (years)	14	(2.16)	15.26	(2.23)	−2.27	59.42	0.03*
Scan Time from Injury (years)	2.64	(1.33)	2.81	(1.15)	−0.50	60	0.30
	Mean	(SD)	Mean	(SD)	*F*-test	df	*p*
WASI FSIQ	101.03	(13.14)	112.53	(13.06)	11.76	1	0.001**
EF Composite	8.41	(2.3)	9.50	(2.2)	3.63	1	0.06
	N	(%)	N	(%)	X^2	df	*p*
Sex (% male)	28	(66 %)	27	(90 %)	3.76	2	0.15
Race (% White)	21	(88 %)	18	(60 %)	0.04	1	0.85
Injury Mechanism: MVA/Sports/Fall	15/6/11	(47 %/19 %/34 %)	2/23/5	(7 %/76 %/17 %)	−1.21	60	0.001**
Learning Disability (% Yes)	1	(6.5 %)	3	(10 %)	1.21	1	0.27
Premorbid ADHD (% Yes)	1	(3.1 %)	1	(3.4 %)	0.005	1	0.94

*p < 0.05.
**p < 0.005.

As previously mentioned, data utilized for this study was derived from two different collection sites and given the potential introduction of error for these site differences neuroComBat harmonization procedures as outlined by Fortin and colleagues (Fortin et al., 2018) were used to control for this variability. We adapted the R implementation of their freely available code (https://github.com/Jfortin1/ComBatHarmonization) to harmonize cortical thickness values of the DLPFC and shape deformation values of the caudate, globus pallidus, and thalamus with site as the harmonized variable ("batch" vector) while group status was held constant during harmonization ("mod" vector) to prevent inadvertent harmonization of unique group features. Final harmonized values were then used in subsequent analyses described below.

2.5. Statistical analyses

Analyses were conducted using R version 3.6.2 and SPSS version 26. The presence of missing data and outliers was assessed and accounted for using mean imputation and Winsorization procedures, which included fencing outliers within 3 SD of the mean based on the outlier function in R. Demographic comparisons for age at injury, parental SES, maternal years of education, and years from injury to scan time utilized t-tests for independent samples, with chi-square analyses for sex and race variables, injury mechanism, and proportion of premorbid learning and attention problems. Analysis of variance (ANOVA) models were used to compare group performance on the WASI FSIQ and EF composite score.

Repeated-measure ANOVA (RM-ANOVA) models with group as the between-subjects effect, hemisphere as the within-subjects effect, and a group-by-hemisphere interaction were used to evaluate differences in cortical thickness of the DLPFC and mean displacement of the MD. Shape deformation *t*-statistic contrast maps that tested group differences for both the caudate and globus pallidus were constructed using the composite surface at every graphical vertex and used Random Field Theory (RFT) to correct for multiple comparisons (Worsley, 2004). Lastly, two-tailed Pearson correlation coefficients were calculated to determine potential associations between brain structures in the DLPF circuit and the TEA-Ch EF composite score. Correction for multiple comparisons for the RM-ANOVA and correlation analyses was accomplished using the false-discovery rate (FDR) approach (Benjamini and Hochberg, 1995).

3. Results

3.1. Data screening

Regarding cognitive data, 6 TEA-Ch subtest scores of 186 possible were missing from among 5 subjects in the TBI group (none from OI) and were addressed using a linear interpolation method for imputing the data.

3.2. Demographic and cognitive variables

The groups (see Table 1) did not differ on age at injury ($t_{60} = 0.17$, $p = 0.86$), sex ($\chi^2_2 = 3.76$, $p = 0.15$), race ($\chi^2_1 = 0.04$, $p = 0.85$), or parental SES ($t_{5.89} = -1.75$, $p = 0.13$); however, the OI group did demonstrate greater maternal years of education ($t_{59.42} = -2.27$, $p = 0.03$), and had a great proportion of sports-related injuries relative to the TBI group, while TBI had a greater ratio of MVA and fall injuries ($\chi^2_2 = -1.21$, $p = 0.001$). Furthermore, groups significantly differed on the WASI FSIQ ($F_{1,60} = 11.76$, $p = 0.001$), but not on the TEA-Ch EF composite score ($F_{1,60} = 3.63$, $p = 0.06$); however, an effect size calculation of the EF composite revealed a small-medium effect ($d = 0.48$). Demographic comparisons were also conducted between SOBIK participants that had imaging data collected on the GE MRI scanner (this study) versus those with the Siemens brand (not included in this study) to evaluate potential sampling bias. The TBI groups only differed on sex ($\chi^2_2 = 14.52$, $p = 0.002$) with a greater proportion of males in the GE MRI scanner group than in the Siemens brand, and the OI groups did not differ on any demographic variable.

3.3. Analysis of the DLPFC and MD nucleus of the thalamus

Cortical thickness RM-ANOVA results of the DLPFC revealed a significant main effect for group ($F_{1,60} = 4.30$, $p = 0.042$) that survived FDR correction, with TBI demonstrating thinner cortex than OI. Neither the main effect for hemisphere ($F_{1,60} = 2.15$, $p = 0.15$) nor the group-by-hemisphere interaction ($F_{1,60} = 0.33$, $p = 0.57$) was significant. RM-ANOVA results for the MD also revealed a significant main effect for group ($F_{1,60} = 6.50$, $p = 0.01$) that survived FDR correction, with the TBI group displaying greater inward deformation of the MD nucleus relative to OI. The effect of hemisphere ($F_{1,60} = 1.20$, $p = 0.28$) and the interaction between group and hemisphere ($F_{1,60} = 0.01$, $p = 0.92$) were not significant for MD.

3.4. Shape analysis of the caudate nucleus and globus pallidus

Caudate. Visual inspection of surface contrast *t*-maps (Fig. 1A) revealed three significant regions of inward deformation in the TBI group relative to the OI group, along the left medial and ventral, as well as right ventral aspects of the caudate, that survived RFT correction.

Globus Pallidus. Visual inspection of surface contrast *t*-maps (Fig. 1B) revealed subtle inward deformations along the medial aspects of the left globus pallidus in the TBI relative to OI group, but these did not survive RFT multiple-comparison correction.

3.5. Dorsolateral prefrontal loop relationships with executive functioning

Pearson correlation coefficients were calculated to explore associations between brain regions that were significantly different between groups and the EF composite score for all participants. For both the DLPFC (mean cortical thickness) and MD (mean shape deformation), values from the right and left hemisphere were averaged into a single measure (given no hemisphere effects in the RM-ANOVA models) for the analysis. For the caudate, mean group-level shape deformation was extracted from both the left medial/ventral and right ventral regions that emerged in the significant TBI-OI surface contrasts (i.e., the "blue" regions in Fig. 1A). No significant correlations were observed between DLPFC, MD, or the right and left caudate ROIs with the EF composite.

4. Discussion

The overall aim of this study was to determine whether abnormalities of frontal-subcortical circuitry are a prominent feature of pediatric TBI, and if they relate to aspects of executive functioning. Results of the study revealed partial support for our first hypothesis, with the TBI group noted to have significant abnormalities in the DLPFC, mediodorsal nucleus of the thalamus, and caudate nucleus relative to the OI group. We were unable to confirm our second hypothesis regarding relationships between structural abnormalities in these regions and executive functioning in the TBI group. We believe detection of these small, but meaningful, brain effects was due to our utilization of shape analytic procedures (Csernansky et al., 2004). This approach not only enhanced the reliability and accuracy of mapping critical brain structures across subjects (Khan et al., 2008), but also allowed estimation of subtle brain alterations between our groups. Furthermore, this novel method has yet to be investigated in pediatric TBI populations. Overall, TBI appears to adversely impact components of this specific frontostriatal circuit in pediatric populations when characterized using surface-based measures of brain morphology.

Regarding analysis of the DLPFC, we found that the TBI group demonstrated greater cortical thinning of this region relative to the OI group. Cortical thinning is commonly reported in pediatric TBI

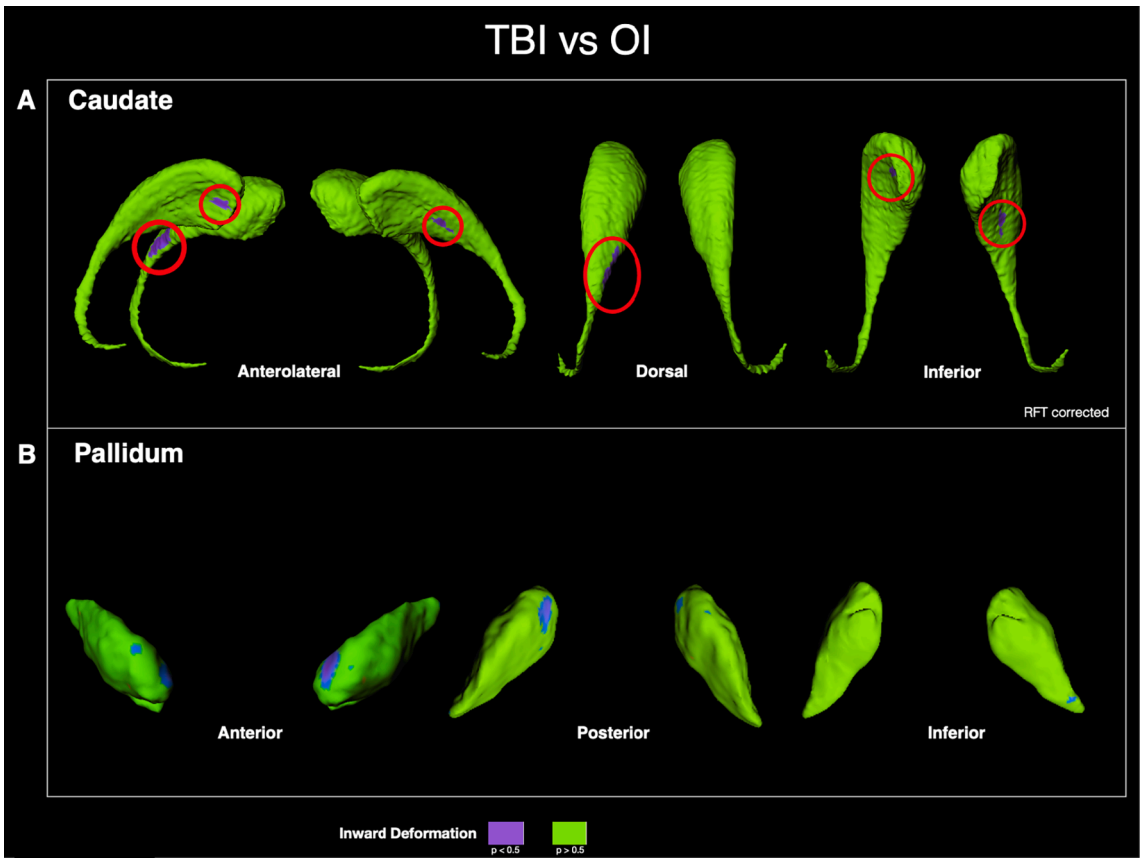

Fig. 1. A) Caudate nucleus and B) globus pallidus surface shape displacement maps between pediatric traumatic brain injured (TBI) and orthopedic injured control (OI) participants. Cooler colors indicate significant regions of inward shape differences in TBI. Random field theory (RFT) corrected results are in panel A only.

populations; McCauley and colleagues (2010) observed multiple areas of cortical thinning in a pediatric sample, particularly in frontal regions. Mayer and colleagues (2015) also found that cortical thinning in frontal regions tended to emerge 4 months post injury in a sample of pediatric mild TBI. Previous work by Merkley and colleagues (2008) indicated that changes in cortical gray matter thickness they observed in pediatric TBI patients was likely a result of multiple etiologies, including focal cortical injury from impact compression and contusion. These theories are based on neuroanatomical and neuropathological investigations of those mechanisms in individuals with TBI (Bigler, 2007). Another study examining longitudinal changes in cortical thickness found that at 3 months post injury, pediatric TBI patients displayed decreased cortical thickness bilaterally in many regions, including the DLPFC, compared to controls (Wilde et al., 2012). Furthermore, fMRI work has shown decreased activity bilaterally in the DLPFC in pediatric mild TBI, suggesting a corresponding adverse functional consequence of cortical reductions in this region (Huang et al., 2020). Overall, MRI-based measures of cortical thinning appear to be a common result in pediatric TBI populations, particularly in the DLPFC and is reinforced by our findings.

Localized volume loss in the mediodorsal nucleus of the thalamus was also observed in the TBI group in our analyses, indicating that the pathophysiology of TBI can include alterations to deep brain nuclei. Indeed, studies of pediatric (Bigler et al., 2013b) and adult (Maxwell et al., 2006) TBI have shown some degree of atrophy in various subcortical structures including the thalamus, but did not examine how the degree of atrophy can impact the overall shape of these structures. Previous work suggests neuronal loss in the thalamus may occur due to excessive immune response of cells after TBI, Maxwell and colleagues (2006) found that this neuronal loss is localized to MD parvocellular thalamic layers in moderately disabled patients and more widespread neuronal loss in MD magnocellular thalamic layers in severely disabled patients after TBI. Salmond and colleagues (2005) examined adults with moderate to severe TBI using voxel-based morphometry (VBM) and found broad reductions in gray matter density in the thalamus in this older population. In a pediatric population, the thalamus is especially vulnerable to acute and delayed neuronal injury (Brooks et al., 2000; Fearing et al., 2008; Natale et al., 2002) and our MRI-based method using surface-shape features is supportive of this literature.

Regarding abnormal thalamic shape features in our study, one potential explanation consistent with the findings of Wood and Bigler (1995) is that inward deformation of the MD may be the result of mechanical impact from ventricular cerebral spinal fluid (CSF) due to rapid head deceleration during injury. Previous simulation studies have suggested the position of the thalamus near the base of the brain, where space is restricted, results in higher shear strain from forces exerted during the injury (Guberman et al., 2020a; Sabet et al., 2008). Mechanical processes such as these may explain related thalamic vulnerability to blunt force trauma, despite being located deep within the cerebrum. Damage to this structure may contribute to deficits in cognitive and behavioral processing given its various integrative and relay functions, and the cumulative evidence, along with our work, suggests it can be routinely affected by TBI.

Results from our analysis of the caudate and globus pallidus revealed TBI-related abnormalities in the caudate only, with no significant shape differences between groups in the globus pallidus. Shape analysis indicated this was localized in right ventral and left ventral/medial regions via inward surface deformation. The distinct locations of the observed shape abnormalities suggests that the caudate, like the thalamus, may be susceptible to mechanical forces of CSF movement due to rapid head deceleration given it forms the lateral wall of the lateral ventricles. Other work suggests our observed shape abnormalities may be the result

of injury to cell bodies contained in the caudate after TBI (Povlishock and Katz, 2005), which could result in cytotoxic or apoptotic cell death (Warner et al., 2010a,b). Our findings are consistent with previous work where Hermans and colleagues (2017) described atrophy of both the caudate and globus pallidus in adults with TBI also using a similar surface-based procedure. In addition, other surface-based studies have found abnormalities in the caudate, with changes mainly localized in areas that are closely connected with the prefrontal cortex (Leunissen et al., 2014). Using a network diffusion model to characterize progressive deafferentation and gray matter thinning in a sample of pediatric TBI participants, Poudel and colleagues (2020) also noted vulnerability of cortico-striatial networks (with prominent component loadings for the caudate) to the injury mechanisms of TBI. Overall, our findings align with previous work that indicates abnormalities of the caudate, as measured by computational anatomy procedures, may be a feature common in both adult and pediatric TBI and warrant further consideration of this structure in future MRI studies of the condition.

We failed to detect meaningful relationships between components of the DLPF circuit and executive control in our TBI sample using shape analysis. Previous fMRI work has noted that various aspects of executive functioning, such as set shifting and cognitive control, correspond to activation in the DLPFC (Friedman and Robbins, 2022) or caudate (Monchi et al., 2006) in healthy and TBI populations (Xu et al., 2018), thus there is some precedent for this line of inquiry. Our lack of a finding may be explained by several factors, such as a relatively small sample or incomplete characterization of executive functioning with the TEA-Ch, however, other theoretical considerations may have affected this outcome. Executive functioning, and its components, develop throughout adolescence into young adulthood (Best and Miller, 2010; Ferguson et al., 2021) and the anatomical variability of these functions (Cieslik et al., 2013) may be greater for our participants given they are early in this developmental trajectory, thus resulting in a more diffuse relationship with brain structure. Furthermore, it is also important to note the current sample was unique in that inclusion criteria required participants to be able to attend regular public school, suggesting they may have experienced some recovery of function (as recently noted by Keenan et al., 2021), thus resulting in lesser variability in executive performance. Using broader pediatric samples, including those with greater impairments, may have likely resulted in more substantial abnormalities thus increasing our ability to detect meaningful effects. Overall, the long-term consequences of pediatric TBI and the potential for downstream developmental alterations in higher order reasoning merits further investigation.

The most significant limitation of the current study is our relatively small sample size, which potentially limited our power to detect smaller effects. For example, our inability to find significant group differences in the EF composite score may have been a function of small sample sizes given the effect size of this contrast was small to medium (Cohen's $d = 0.48$). Furthermore, the confounding effects of a TBI sample comprised of varying severity types can only speak to general features of TBI and not the unique impacts of those severity levels alone. Some work by Guberman and colleagues (Guberman et al., 2020b) has also noted that certain behavioral features in childhood, such as inattention–hyperactivity and externalizing problems, were predictive of later TBI, and while our samples did not differ on diagnostic aspects of learning and attention issues, it is possible premorbid subclinical behavioral features (e.g., conduct problems) may have had some influence on the brain findings. However, the brain imaging literature in this area primarily implicates regions associated with emotion regulation, such as the cingulate, amygdala, insula, and orbitofrontal cortex (Brito et al., 2009; Fairchild et al., 2011), which were not the focus of our study. Another limitation was our executive functioning composite was compromised of a subset of tests from the TEA-Ch, restricting our ability to capture broader aspects of this construct. Our methods for estimating surface-based characteristics is relatively robust and utilized in multiple populations (e.g., Csernansky et al., 2004; Fischl, 2012), and have been histologically validated against characterizing tissue loss in the brain (Cardinale et al., 2014; Hanko et al., 2019). However, population-specific atlases would improve mapping accuracy and are still in development (Dickie et al., 2017), which would aid in determining the specific mechanisms involved in the pathophysiology of TBI. Lastly, we examined a limited set of prefrontal regions in our study and future work would benefit from the inclusion of additional prefrontal regions of interest implicated in executive functioning, including orbitofrontal and ventromedial prefrontal cortex, and their connected deep-brain circuitry. Indeed, lesions to the orbitofrontal cortex have been found to predict errors and rule-breaks on tests of executive functioning in pediatric TBI (Levin et al., 2001; Taylor, 2004).

5. Conclusions

Overall, findings from our study provide insight into the impact of TBI on cortical-subcortical morphology and its potential relationship with executive functioning. Previous research indicates that the basal ganglia and prefrontal regions are associated with executive functioning and that injury to these areas result in cognitive impairment (Hikosaka and Isoda, 2010; Leunissen et al., 2014; Ward et al., 2013), making this a crucial area of inquiry in children with TBI given their developmental trajectories. In sum, characterizing features of the dorsolateral prefrontal circuit in pediatric TBI and their association with executive functioning will advance our understanding of injury mechanisms, as well as identifying specific neural targets for improving deficits in behavioral functioning.

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CRediT authorship contribution statement

Kaitlyn M. Greer: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. **Aubretia Snyder:** Software, Data curation. **Chase Junge:** Software, Data curation. **Madeline Reading:** Software, Data curation. **Sierra Jarvis:** Software, Data curation. **Chad Squires:** Software, Data curation. **Erin Bigler:** Writing – review & editing. **Karteek Popuri:** Software, Data curation, Writing – review & editing. **Mirza Faisal Beg:** Software, Data curation, Writing – review & editing. **H. Gerry Taylor:** Writing – review & editing. **Kathryn Vannatta:** Writing – review & editing. **Cynthia A. Gerhardt:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition. **Kenneth Rubin:** Writing – review & editing. **Keith Owen Yeates:** Resources. **Derin Cobia:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Keith Yeates is supported by the Ronald and Irene Ward Chair in Pediatric Brain Injury from the Alberta Children's Hospital Foundation. Derin Cobia currently serves as a consultant for Sage Therapeutics on a project unrelated to the present study. Kaitlyn Greer, Aubretia Snyder, Madeline Reading, Sierra Jarvis, Chase Junge, Chad Squires, Erin Bigler, Karteek Popuri, Faisal Beg, H. Gerry Taylor, Kathryn Vannatta, Cynthia A. Gerhardt, and Kenneth Rubin report no financial and personal relationships with commercial interests conflicting with the contained work.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

FreeSurfer atlas labels used in the bilateral definition of the dorsolateral prefrontal cortex (DLPFC) region of interest for calculation of FreeSurfer-derived cortical thickness, including: middle frontal sulcus (white), middle frontal gyrus (blue), and inferior frontal sulcus (yellow). Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103136.

References

Alvarez, J.A., Emory, E., 2006. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol. Rev. 16, 17–42. https://doi.org/10.1007/s11065-006-9002-x.

Araki, T., Yokota, H., Morita, A., 2017. Pediatric traumatic brain injury: characteristic features, diagnosis, and management. Neurol. Med.-chir 57, 82–93. https://doi.org/10.2176/nmc.ra.2016-0191.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc.: Ser. B (Methodol.) 57 (1), 289–300.

Best, J.R., Miller, P.H., 2010. A developmental perspective on executive function. Child Dev. 81, 1641–1660. https://doi.org/10.1111/j.1467-8624.2010.01499.x.

Bigler, E.D., 2001. The lesion(s) in traumatic brain injury: implications for clinical neuropsychology. Arch. Clin. Neuropsych. 16, 95–131. https://doi.org/10.1093/arclin/16.2.95.

Bigler, E.D., 2007. Anterior and middle cranial fossa in traumatic brain injury: relevant neuroanatomy and neuropathology in the study of neuropsychological outcome. Neuropsychology 21 (515), 531. https://doi.org/10.1037/0894-4105.21.5.515.

Bigler, E.D., Yeates, K.O., Dennis, M., Gerhardt, C.A., Rubin, K.H., Stancin, T., Taylor, H. G., Vannatta, K., Wood, R.L., 2013a. Neuroimaging and social behavior in children after traumatic brain injury: Findings from the Social Outcomes of Brain Injury in Kids (SOBIK) study. Neurorehabilitation 32 (4), 707–720.

Bigler, E.D., Abildskov, T.J., Petrie, J., Farrer, T.J., Dennis, M., Simic, N., Taylor, H.G., Rubin, K.H., Vannatta, K., Gerhardt, C.A., Stancin, T., Yeates, K.O., 2013b. Heterogeneity of brain lesions in pediatric traumatic brain injury. Neuropsychology 27, 438–451. https://doi.org/10.1037/a0032837.

Bonelli, R.M., Cummings, J.L., 2007. Frontal-subcortical circuitry and behavior. Dialogues Clin. Neurosci. 9 (2), 141–151.

Brito, S.A.D., Mechelli, A., Wilke, M., Laurens, K.R., Jones, A.P., Barker, G.J., Hodgins, S., Viding, E., 2009. Size matters: increased grey matter in boys with conduct problems and callous–unemotional traits. Brain 132, 843–852. https://doi.org/10.1093/brain/awp011.

Brooks, W.M., Stidley, C.A., Petropoulos, H., Jung, R.E., Weers, D.C., Friedman, S.D., Barlow, M.A., Sibbitt, W.L., Yeo, R.A., 2000. Metabolic and cognitive response to human traumatic brain injury: a quantitative proton magnetic resonance study. J. Neurotraum. 17 (8), 629–640.

Cardinale, F., Chinnici, G., Bramerio, M., Mai, R., Sartori, I., Cossu, M., Russo, G.L., Castana, L., Colombo, N., Caborni, C., Momi, E.D., Ferrigno, G., 2014. Validation of FreeSurfer-estimated brain cortical thickness: comparison with histologic measurements. Neuroinformatics 12, 535–542. https://doi.org/10.1007/s12021-014-9229-2.

Chan, R.C.K., Wang, L., Ye, J., Leung, W.W.Y., Mok, M.Y.K., 2008. A psychometric study of the Test of Everyday Attention for Children in the Chinese setting. Arch. Clin. Neuropsych. 23, 455–466. https://doi.org/10.1016/j.acn.2008.03.007.

Cieslik, E.C., Zilles, K., Caspers, S., Roski, C., Kellermann, T.S., Jakobs, O., Langner, R., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2013. Is there "one" DLPFC in cognitive action control? evidence for heterogeneity from co-activation-based parcellation. Cereb. Cortex 23 (2677), 2689. https://doi.org/10.1093/cercor/bhs256.

Clarençon, F., Bardinet, É., Martinerie, J., Pelbarg, V., de Champfleur, N.M., Gupta, R., Tollard, E., Soto-Ares, G., Ibarrola, D., Schmitt, E., Tourdias, T., Degos, V., Yelnik, J., Dormont, D., Puybasset, L., Galanaud, D., Consortium, N.I. for C.E. and R. (NICER), 2017. Lesions in deep gray nuclei after severe traumatic brain injury predict neurologic outcome. PLoS ONE 12, e0186641.

Cobia, D.J., Smith, M.J., Salinas, I., Ng, C., Gado, M., Csernansky, J.G., Wang, L., 2017. Progressive deterioration of thalamic nuclei relates to cortical network decline in schizophrenia. Schizophr. Res. 180, 21–27. https://doi.org/10.1016/j.schres.2016.08.003.

Csernansky, J.G., Wang, L., Joshi, S.C., Ratnanather, J.T., Miller, M.I., 2004. Computational anatomy and neuropsychiatric disease: probabilistic assessment of variation and statistical inference of group difference, hemispheric asymmetry, and time-dependent change. Neuroimage 23, S56–S68. https://doi.org/10.1016/j.neuroimage.2004.07.025.

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis I. Segmentation and surface reconstruction. Neuroimage 9, 179–194. https://doi.org/10.1006/nimg.1998.0395.

Dennis, E.L., Babikian, T., Giza, C.C., Thompson, P.M., Asarnow, R.F., 2017. Diffusion MRI in pediatric brain injury. Child's Nerv. Syst. 33, 1683–1692. https://doi.org/10.1007/s00381-017-3522-y.

Dennis, M., Guger, S., Rocadin, C., Barnes, M., Schachar, R., 2001. Attentional–inhibitory control and social–behavioral regulation after childhood closed head injury: Do biological, developmental, and recovery variables predict outcome? J. Int. Neuropsych. Soc. 7, 683–692. https://doi.org/10.1017/s1355617701766040.

Destrieux, C., Fischl, B., Dale, A., Halgren, E., 2010. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. Neuroimage 53 (1), 15. https://doi.org/10.1016/j.neuroimage.2010.06.010.

Dickie, D.A., Shenkin, S.D., Anblagan, D., Lee, J., Cabez, M.B., Rodriguez, D., Boardman, J.P., Waldman, A., Job, D.E., Wardlaw, J.M., 2017. Whole brain magnetic resonance image atlases: a systematic review of existing atlases and caveats for use in population imaging. Front. Neuroinform. 11, 1. https://doi.org/10.3389/fninf.2017.00001.

Ewing-Cobbs, L., Prasad, M.R., Landry, S.H., Kramer, L., DeLeon, R., 2004. Executive functions following traumatic brain injury in young children: a preliminary analysis. Dev. Neuropsychol. 26, 487–512. https://doi.org/10.1207/s15326942dn2601_7.

Fairchild, G., Passamonti, L., Hurford, G., Hagan, C.C., von dem Hagen, E.A.H., van Goozen, S.H.M., Goodyer, I.M., Calder, A.J., 2011. Brain structure abnormalities in early-onset and adolescent-onset conduct disorder. Am. J. Psychiat. 168, 624–633. https://doi.org/10.1176/appi.ajp.2010.10081184.

Fearing, M.A., Bigler, E.D., Wilde, E.A., Johnson, J.L., Hunter, J.V., Li, X., Hanten, G., Levin, H.S., 2008. Morphometric MRI findings in the thalamus and brainstem in children after moderate to severe traumatic brain injury. J. Child Neurol. 23, 729–737. https://doi.org/10.1177/0883073808314159.

Ferguson, H.J., Brunsdon, V.E.A., Bradford, E.E.F., 2021. The developmental trajectories of executive function from adolescence to old age. Sci. Rep-uk 11, 1382. https://doi.org/10.1038/s41598-020-80866-1.

Fischl, B., 2012. FreeSurfer. Neuroimage 62 (2), 774–781.

Fischl, B., Sereno, M.I., Dale, A.M., 1999. Cortical surface-based analysis II: inflation, flattening, and a surface-based coordinate system. Neuroimage 9, 195–207. https://doi.org/10.1006/nimg.1998.0396.

Fortin, J.-P., Cullen, N., Sheline, Y.I., Taylor, W.D., Aselcioglu, I., Cook, P.A., Adams, P., Cooper, C., Fava, M., McGrath, P.J., McInnis, M., Phillips, M.L., Trivedi, M.H., Weissman, M.M., Shinohara, R.T., 2018. Harmonization of cortical thickness measurements across scanners and sites. Neuroimage 167, 104–120. https://doi.org/10.1016/j.neuroimage.2017.11.024.

Friedman, N.P., Robbins, T.W., 2022. The role of prefrontal cortex in cognitive control and executive function. Neuropsychopharmacol 47, 72–89. https://doi.org/10.1038/s41386-021-01132-0.

Guberman, G.I., Houde, J.-C., Ptito, A., Gagnon, I., Descoteaux, M., 2020a. Structural abnormalities in thalamo-prefrontal tracks revealed by high angular resolution diffusion imaging predict working memory scores in concussed children. Brain Struct. Funct. 225, 441–459. https://doi.org/10.1007/s00429-019-02002-8.

Guberman, G.I., Robitaille, M.-P., Larm, P., Ptito, A., Vitaro, F., Tremblay, R.E., Hodgins, S., 2020b. A prospective study of childhood predictors of traumatic brain injuries sustained in adolescence and adulthood. Can. J. Psychiatry 65, 36–45. https://doi.org/10.1177/0706743719882171.

Hanko, V., Apple, A.C., Alpert, K.I., Warren, K.N., Schneider, J.A., Arfanakis, K., Bennett, D.A., Wang, L., 2019. In vivo hippocampal subfield shape related to TDP-43, amyloid beta, and tau pathologies. Neurobiol. Aging 74 (171), 181. https://doi.org/10.1016/j.neurobiolaging.2018.10.013.

Hermans, L., Beeckmans, K., Michiels, K., Lafosse, C., Sunaert, S., Coxon, J.P., Swinnen, S.P., Leunissen, I., 2017. Proactive response inhibition and subcortical gray matter integrity in traumatic brain injury. Neurorehab. Neural Re. 31 (228), 239. https://doi.org/10.1177/1545968316675429.

Hikosaka, O., Isoda, M., 2010. Switching from automatic to controlled behavior: cortico-basal ganglia mechanisms. Trends Cogn. Sci. 14, 154–161. https://doi.org/10.1016/j.tics.2010.01.006.

Hoshi, E., 2006. Functional specialization within the dorsolateral prefrontal cortex: a review of anatomical and physiological studies of non-human primates. Neurosci. Res. 54, 73–84. https://doi.org/10.1016/j.neures.2005.10.013.

Huang, M.-X., Swan, A.R., Quinto, A.A., Huang, J.W., De-la-Garza, B.G., Huang, C.W., Hesselink, J.R., Bigler, E.D., Wilde, E.A., Max, J.E., 2020. Resting-state magnetoencephalography source imaging pilot study in children with mild traumatic brain injury. J. Neurotraum. 37, 994–1001. https://doi.org/10.1089/neu.2019.6417.

Keenan, H.T., Clark, A.E., Holubkov, R., Cox, C.S., Ewing-Cobbs, L., 2021. Trajectories of children's executive function after traumatic brain injury. Jama Netw. Open 4 (3), e212624. https://doi.org/10.1001/jamanetworkopen.2021.2624.

Khan, A.R., Wang, L., Beg, M.F., 2008. FreeSurfer-initiated fully-automated subcortical brain segmentation in MRI using Large Deformation Diffeomorphic Metric Mapping. Neuroimage 41 (735), 746. https://doi.org/10.1016/j.neuroimage.2008.03.024.

Leunissen, I., Coxon, J.P., Caeyenberghs, K., Michiels, K., Sunaert, S., Swinnen, S.P., 2014. Subcortical volume analysis in traumatic brain injury: The importance of the fronto-striato-thalamic circuit in task switching. Cortex 51, 67–81. https://doi.org/10.1016/j.cortex.2013.10.009.

Levin, H.S., Hanten, G., 2005. Executive functions after traumatic brain injury in children. Pediatr. Neurol. 33 (79), 93. https://doi.org/10.1016/j.pediatrneurol.2005.02.002.

Levin, H.S., Song, J., Ewing-Cobbs, L., Roberson, G., 2001. Porteus maze performance following traumatic brain injury in children. Neuropsychology 15, 557–567. https://doi.org/10.1037/0894-4105.15.4.557.

Lindsey, H.M., Wilde, E.A., Caeyenberghs, K., Dennis, E.L., 2019. Longitudinal neuroimaging in pediatric traumatic brain injury: current state and consideration of factors that influence recovery. Front. Neurol. 10, 1296. https://doi.org/10.3389/fneur.2019.01296.

Manly, T., Anderson, V., Nimmo-Smith, I., Turner, A., Watson, P., Robertson, I.H., 2001. The differential assessment of children's attention: the Test of Everyday Attention for Children (TEA-Ch), normative sample and ADHD performance. J. Child Psychol. Psychiatry 42 (8), 1065–1081.

Marco, A.-D.-D., McDonald, S., Kelly, M., Tate, R., Johnstone, S., 2011. A meta-analysis of response inhibition and Stroop interference control deficits in adults with traumatic brain injury (TBI). J. Clin. Exp. Neuropsyc. 33, 471–485. https://doi.org/10.1080/13803395.2010.533158.

Maxwell, W.L., MacKinnon, M.A., Smith, D.H., McIntosh, T.K., Graham, D.I., 2006. Thalamic nuclei after human blunt head injury. J. Neuropathol. Exp. Neurol. 65, 478–488. https://doi.org/10.1097/01.jnen.0000229241.28619.75.

Mayer, A.R., Hanlon, F.M., Ling, J.M., 2015. Gray matter abnormalities in pediatric mild traumatic brain injury. J. Neurotraum. 32, 723–730. https://doi.org/10.1089/neu.2014.3534.

McCauley, S.R., Wilde, E.A., Merkley, T.L., Schnelle, K.P., Bigler, E.D., Hunter, J.V., Chu, Z., Vásquez, A.C., Levin, H.S., 2010. Patterns of cortical thinning in relation to event-based prospective memory performance three months after moderate to severe traumatic brain injury in children. Dev Neuropsychol 35, 318–332. https://doi.org/10.1080/87565641003696866.

Merkley, T.L., Bigler, E.D., Wilde, E.A., McCauley, S.R., Hunter, J.V., Levin, H.S., 2008. Diffuse changes in cortical thickness in pediatric moderate-to-severe traumatic brain injury. J. Neurotraum. 25, 1343–1345. https://doi.org/10.1089/neu.2008.0615.

Monchi, O., Petrides, M., Strafella, A.P., Worsley, K.J., Doyon, J., 2006. Functional role of the basal ganglia in the planning and execution of actions. Ann. Neurol. 59 (257), 264. https://doi.org/10.1002/ana.20742.

Mylius, V., Ayache, S.S., Ahdab, R., Farhat, W.H., Zouari, H.G., Belke, M., Brugières, P., Wehrmann, E., Krakow, K., Timmesfeld, N., Schmidt, S., Oertel, W.H., Knake, S., Lefaucheur, J.P., 2013. Definition of DLPFC and M1 according to anatomical landmarks for navigated brain stimulation: Inter-rater reliability, accuracy, and influence of gender and age. Neuroimage 78, 224–232. https://doi.org/10.1016/j.neuroimage.2013.03.061.

Natale, J.E., Cheng, Y., Martin, L.J., 2002. Thalamic neuron apoptosis emerges rapidly after cortical damage in immature mice. Neuroscience 112, 665–676. https://doi.org/10.1016/s0306-4522(02)00098-2.

Petersen, S.E., Posner, M.I., 2012. The attention system of the human brain: 20 years after. Annu. Rev. Neurosci. 35 (73), 89. https://doi.org/10.1146/annurev-neuro-062111-150525.

Poudel, G.R., Dominguez D, J.F., Verhelst, H., Vander Linden, C., Deblaere, K., Jones, D. K., Cerin, E., Vingerhoets, G., Caeyenberghs, K., 2020. Network diffusion modeling predicts neurodegeneration in traumatic brain injury. Ann. Clin. Transl. Neur. 7 (3), 270–279.

Povlishock, J.T., Katz, D.I., 2005. Update of neuropathology and neurological recovery after traumatic brain injury. J. Head Trauma Rehab. 20, 76–94. https://doi.org/10.1097/00001199-200501000-00008.

Robinson, K.E., Fountain-Zaragoza, S., Dennis, M., Taylor, H.G., Bigler, E.D., Rubin, K., Vannatta, K., Gerhardt, C.A., Stancin, T., Yeates, K.O., 2014. Executive functions and theory of mind as predictors of social adjustment in childhood traumatic brain injury. J. Neurotraum. 31, 1835–1842. https://doi.org/10.1089/neu.2014.3422.

Rosen, G.D., Mesples, B., Hendriks, M., Galaburda, A.M., 2006. Histometric changes and cell death in the thalamus after neonatal neocortical injury in the rat. Neuroscience 141, 875–888. https://doi.org/10.1016/j.neuroscience.2006.04.035.

Sabet, A.A., Christoforou, E., Zatlin, B., Genin, G.M., Bayly, P.V., 2008. Deformation of the human brain induced by mild angular head acceleration. J. Biomech. 41, 307–315. https://doi.org/10.1016/j.jbiomech.2007.09.016.

Salmond, C.H., Chatfield, D.A., Menon, D.K., Pickard, J.D., Sahakian, B.J., 2005. Cognitive sequelae of head injury: involvement of basal forebrain and associated structures. Brain 128, 189–200. https://doi.org/10.1093/brain/awh352.

Segonne, F., Pacheco, J., Fischl, B., 2007. Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. IEEE T. Med. Imaging 26 (518), 529. https://doi.org/10.1109/tmi.2006.887364.

Serra-Grabulosa, J.M., Junqué, C., Verger, K., Salgado-Pineda, P., Mañeru, C., Mercader, J.M., 2005. Cerebral correlates of declarative memory dysfunctions in early traumatic brain injury. J. Neurol. Neurosurg. Psychiatry 76 (129), 131. https://doi.org/10.1136/jnnp.2004.027631.

Slomine, B.S., Gerring, J.P., Grados, M.A., Vasa, R., Brady, K.D., Christensen, J.R., Denckla, M.B., 2009. Performance on measures of "executive function" following pediatric traumatic brain injury. Brain Inj. 16, 759–772. https://doi.org/10.1080/02699050210127286.

Stuss, D.T., 2011. Functions of the frontal lobes: relation to executive functions. J. Int. Neuropsych. Soc. 17 (759), 765. https://doi.org/10.1017/s1355617711000695.

Tasker, R.C., 2006. Changes in white matter late after severe traumatic brain injury in childhood. Dev. Neurosci.-basel 28, 302–308. https://doi.org/10.1159/000094156.

Taylor, H.G., 2004. Research on outcomes of pediatric traumatic brain injury: current advances and future directions. Dev. Neuropsychol. 25, 199–225. https://doi.org/10.1080/87565641.2004.9651928.

Taylor, H.G., Swartwout, M.D., Yeates, K.O., Walz, N.C., Stancin, T., Wade, S.L., 2008. Traumatic brain injury in young children: Postacute effects on cognitive and school readiness skills. J. Int. Neuropsych. Soc. 14, 734–745. https://doi.org/10.1017/s1355617708081150.

Teasdale, G., Jennett, B., 1974. Assessment of coma and impaired consciousness: A practical scale. Lancet 304, 81–84. https://doi.org/10.1016/s0140-6736(74)91639-0.

Treble-Barna, A., Zang, H., Zhang, N., Taylor, H.G., Yeates, K.O., Wade, S., 2017. Long-term neuropsychological profiles and their role as mediators of adaptive functioning after traumatic brain injury in early childhood. J Neurotraum 34, 353–362. https://doi.org/10.1089/neu.2016.4476.

Ward, P., Seri, S., Cavanna, A.E., 2013. Functional neuroanatomy and behavioural correlates of the basal ganglia: evidence from lesion studies. Behav. Neurol. 26, 219–223. https://doi.org/10.3233/ben-2012-120264.

Warner, M.A., de la Plata, C.M., Spence, J., Wang, J.Y., Harper, C., Moore, C., Devous, M., Diaz-Arrastia, R., 2010a. Assessing spatial relationships between axonal integrity, regional brain volumes, and neuropsychological outcomes after traumatic axonal injury. J. Neurotraum. 27, 2121–2130. https://doi.org/10.1089/neu.2010.1429.

Warner, M.A., Youn, T.S., Davis, T., Chandra, A., de la Plata, C.M., Moore, C., Harper, C., Madden, C.J., Spence, J., McColl, R., Devous, M., King, R.D., Diaz-Arrastia, R., 2010b. Regionally selective atrophy after traumatic axonal injury. Arch. Neurol-chicago 67, 1336–1344. https://doi.org/10.1001/archneurol.2010.149.

Wechsler, D., 2011. Wechsler Abbreviated Scale of Intelligence-II. Pearson Inc, San Antonio, TX.

Wilde, E.A., Bigler, E.D., Hunter, J.V., Fearing, M.A., Scheibel, R.S., Newsome, M.R., Johnson, J.L., Bachevalier, J., Li, X., Levin, H.S., 2007. Hippocampus, amygdala, and basal ganglia morphometrics in children after moderate-to-severe traumatic brain injury. Dev. Med. Child Neurol. 49 (294), 299. https://doi.org/10.1111/j.1469-8749.2007.00294.x.

Wilde, E.A., Merkley, T.L., Bigler, E.D., Max, J.E., Schmidt, A.T., Ayoub, K.W., McCauley, S.R., Hunter, J.V., Hanten, G., Li, X., Chu, Z.D., Levin, H.S., 2012. Longitudinal changes in cortical thickness in children after traumatic brain injury and their relation to behavioral regulation and emotional control. Int. J. Dev. Neurosci. 30, 267–276. https://doi.org/10.1016/j.ijdevneu.2012.01.003.

Wood, D.-M.-G., Bigler, E.D., 1995. Diencephalic changes in traumatic brain injury: relationship to sensory perceptual function. Brain Res. Bull. 38, 545–549. https://doi.org/10.1016/0361-9230(95)02026-0.

Worsley, K., 2004. Developments in Random Field Theory, in: Frackowiak, R.S.J., Friston, K.J., Frith, C.D., Dolan, R.J., Price, C.J., Zeki, S., Ashburner", John T., Penny"], "William D. (Eds.), Academic Press, Burlington, pp. 881–886. https://doi.org/10.1016/b978-012264841-0/50047-0.

Xu, H., Wang, X., Chen, Z., Bai, G., Yin, B., Wang, S., Sun, C., Gan, S., Wang, Z., Cao, J., Niu, X., Shao, M., Gu, C., Hu, L., Ye, L., Li, D., Yan, Z., Zhang, M., Bai, L., 2018. Longitudinal changes of caudate-based resting state functional connectivity in mild traumatic brain injury. Front. Neurol. 9, 467. https://doi.org/10.3389/fneur.2018.00467.

Yeates, K.O., Bigler, E.D., Dennis, M., Gerhardt, C.A., Rubin, K.H., Stancin, T., Taylor, H. G., Vannatta, K., 2007. Social outcomes in childhood brain disorder: a heuristic integration of social neuroscience and developmental psychology. Psychol. Bull. 133, 535–556. https://doi.org/10.1037/0033-2909.133.3.535.

Yeates, K.O., Gerhardt, C.A., Bigler, E.D., Abildskov, T., Dennis, M., Rubin, K.H., Stancin, T., Taylor, H.G., Vannatta, K., 2013. Peer relationships of children with traumatic brain injury. J. Int. Neuropsych. Soc. 19, 518–527. https://doi.org/10.1017/s1355617712001531.

Zappalà, G., de Schotten, M.T., Eslinger, P.J., 2012. Traumatic brain injury and the frontal lobes: What can we gain with diffusion tensor imaging? Cortex 48, 156–165. https://doi.org/10.1016/j.cortex.2011.06.020.