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Deep-Brain Shape Features Differentially Relate to Social Outcomes in Pediatric Traumatic Brain Injury

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Honors Thesis

DEEP-BRAIN SHAPE FEATURES DIFFERENTIALLY RELATE TO SOCIAL OUTCOMES IN PEDIATRIC TRAUMATIC BRAIN INJURY

by
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ABSTRACT

DEEP-BRAIN SHAPE FEATURES DIFFERENTIALLY RELATE TO SOCIAL OUTCOMES IN PEDIATRIC TRAUMATIC BRAIN INJURY

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Pediatric traumatic brain injury (TBI) is a global issue with major health consequences. The integrity of brain structures and their social functional correlates are at risk in children with TBI. In this study, magnetic resonance images of the thalamus, caudate, putamen, and globus pallidus were examined in a pediatric TBI group from the Social Outcomes of Brain Injury in Kids (SOBIK). Shape deformations of these structures were compared to an orthopedically injured (OI) control. Additionally, the correlation between shape deformation and theory of mind (ToM) measures were mapped and compared. This study found inward deformations in the ventral thalamic nuclei in the TBI group compared to OI. Significant correlations between shape deformations and ToM scores were found in all structures of the OI group. In the TBI group, correlations were present primarily in the globus pallidus. These findings suggest that the recruitment of these structures for ToM-related tasks differs in this group of TBI and OI participants.

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Finally, I want to thank my wife for her loving support, even in the midst of her own hard work and achievements as a BYU undergraduate student. Thanks to my parents and siblings as well for always having faith in me and listening to me drone on about neuroscience in a patient and friendly way.

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Traumatic brain injuries (TBI) are a common and debilitating injury in children (Araki, Yokota, and Morita, 2017). TBI is defined as a mechanical injury to the brain caused by either a penetrating or non-penetrating impact injury (Capizzi, Woo, and Verduzco-Gutierrez, 2019). The severity of TBI can initially be gauged by the individual's Glasgow Coma Scale (GCS) score immediately post injury. Using this scale, injuries can be classified as mild (GCS between 13 and 15), moderate (GCS between 9 and 12), or severe (GCS between 3-8). After a mild TBI, if abnormal findings are revealed in later medical treatment, such as brain bleeding, that injury can be classified as complicated mild TBI (Capizzi, Woo, and Verduzco-Gutierrez, 2019). A current CDC report reveals that TBI is more common in males than females, though the reason why this is the case is not well understood (Centers for Disease Control and Prevention [CDC], 2022). Children, adolescents, and older adults are at a higher risk for TBI than adults and young adults, perhaps because of diminished motor control at those ages, as well as widespread sports participation for younger groups (CDC, 2022). In children, the most common causes of TBI include motor vehicle accidents, falls, and sports-related injuries (Araki, Yokota, and Morita, 2017).

TBI at an early age puts children at risk for significant adverse long-term outcomes, including cognitive and social impairment (Tonks et al., 2008; Dennis et al., 2012; Wolfe et al., 2015). Social impairment is a broad term that describes deviation from the typical social skill advancements that are observed in maturing children (Rosema, Crowe, and Anderson, 2012). TBI is relevant to the discussion of social

impairment because the disruption of the neural correlates to social abilities has been shown to lead to impairment in those abilities (Ewing-Cobbs et al., 2008; Bava and Tapert, 2010). For example, TBI studies in children have demonstrated decreased cognitive theory of mind (ToM) ability (Dennis et al., 2012); difficulty in emotive expression and comprehension (Bigler et al., 2013 b); challenges recognizing facial expressions and their purpose in social communication (Dennis et al., 2013 a); deficits in cognitive, affective, and conative theory of mind (ToM) (Dennis et al., 2013 b); and fewer reciprocal friendships, though individuals experience greater peer support and tend to be less victimized (Yeates et al., 2013; Heverly-Fitt et al., 2014; Wolfe et al., 2015). For children with severe TBI, social adaptability can be impaired, which is connected to deficits in executive function and processing speed (Shultz et al., 2016). These impairments can worsen over time, making early detection and treatment especially critical (Tonks et al., 2008).

Brain abnormalities resulting from TBI can be highly variable (Bigler et al., 2013 a). Common abnormalities include white matter hyperintensities (WMH), hemosiderin deposits, encephalomalacia, atrophy, and traumatic shear lesions. These are most often present in the frontal, temporal, and occipital lobes, where proximity to the skull and the momentum of the head during injury are more likely to produce a brain injury (Bigler et al., 2013 a). TBI appears to precede widespread cortical thinning in both adult and pediatric patients, most notably in the prefrontal cortex, cingulate gyrus, and temporal gyri (McCauley et al., 2010; Merkley et al., 2008). Deep-brain grey matter is not protected from TBI by virtue of being deeper in the skull; in fact, global volume loss has been observed in the thalamus after TBI (Fearing et al., 2008; Leunissen et al., 2013).

The position of the thalamus near cerebrospinal fluid (CSF) is thought to be related to its susceptibility in TBI; the momentum of CSF could cause mechanical injury to brain tissue during a sudden impact (Wood and Bigler, 1995). In addition, post-injury histological studies suggest that neuronal death in the thalamus following injury to the cortex in rat models (Rosen et al., 2006). The basal ganglia are also at risk for focal morphometric abnormalities after TBI (Leunissen et al., 2013). Lesions and volume loss were found in the thalamus and globus pallidus in adult and pediatric patients after TBI (Leunissen et al., 2013; Wilde et al., 2007).

The functional effects of TBI are thought to be caused by tissue damage in important processing circuits in the brain (Sharp et al., 2014). Many deficits are linked to volume deficits in the cortex and subcortical nuclei, as well as connectivity abnormalities resulting from decreased white matter integrity (Bigler et al., 2013 a; Königs et al., 2017). In addition to cortical-layer brain damage, deep-brain structures such as the basal ganglia and thalamus are also susceptible to the effects of pediatric TBI (Bigler et al., 2013 a). The basal ganglia participate in a wide range of cognitive and behavioral functions that may affect later social outcomes, including direct and indirect movement pathways, regulating pain, and forming and performing habitual behaviors (Haber 2016; Barcelo, Filippini & Pazo, 2011; Graybiel & Grafton 2015). Volume loss in the thalamus and basal ganglia as a result of mild or severe TBI has been observed in previous studies (Bigler et al., 2013 a; Fearing et al., 2008; Leunissen et al., 2013; Bigler, 2021). This volume loss has been linked to decreased social and affective outcomes; as it pertains to this paper, decreased performance in theory of mind measures and emotional recognition

ability are of particular interest (Bigler et al., 2013 b; Dennis et al., 2013 a; Dennis et al., 2013 b).

Over time, researchers' ability to analyze brain characteristics have adapted to accommodate different needs. For example, shape analysis is one approach that has shown promise in detecting subtle structural brain abnormalities and has been used to study various neurodevelopmental and neurodegenerative disorders (Csernansky et al., 2004 b). For example, volume reduction in the thalamus has been related to thalamic shape abnormalities in subjects with schizophrenia, which appears to increase asymmetry between the cerebral hemispheres (Csernansky et al., 2004 a). Shape abnormalities have also been observed in the globus pallidus and other deep-brain structures, and these shape abnormalities predict cognitive performance for early-onset and adult-onset cases (Gutman et al., 2022; Cobia et al., 2022). In a sample of children with autism spectrum disorder, shape analysis revealed that specific surface deformities of the putamen and caudate related to impairments in motor, social, and communication skills (Qiu et al., 2010). Furthermore, anterior caudate abnormalities in the sample strongly correlated with socialization and communication impairment (Qiu et al., 2010). In addition, the thalamus was shown to have persistent shape abnormalities across ASD individuals when age is accounted for (Schuetze et al., 2016). Shape analysis has also been used previously to characterize the integrity of subcortical structures and link shape changes to neuropsychological function in veterans with TBI (Tate et al., 2016; Tate et al., 2019). Tate and colleagues found that areas of the thalamus had significant decreases in surface area, while areas of the caudate and nucleus accumbens were expanded (2016). Shape changes in the caudate and thalamus were found to be related to processing speed and

free recall memory (Tate et al., 2019). Given these findings, studying shape features of deep-brain structures may be useful in clarifying similar symptoms in pediatric TBI. Currently, there is no existing literature that has specifically examined relationships between shape changes of relevant deep-brain nuclei in pediatric TBI and ToM as a social outcome.

While global volume loss in the thalamus and basal ganglia has been previously identified as a characteristic of TBI, the objective of this study is to characterize patterns of shape integrity of the thalamus and basal ganglia in a sample of pediatric TBI participants compared to an orthopedically injured (OI) control group (Bigler et al., 2013 a). Furthermore, the project aims to determine whether shape features relate to social affective outcomes (as measured by a global ToM score) separately in each group, and if patterns differ. The thalamus and basal ganglia are of particular interest because of their susceptibility to damage in TBI and their involvement in a wide range of cognitive functions. Given that these structures experience general volume loss in TBI, it is hypothesized that inward deformations of the thalamus, caudate, putamen, and globus pallidus will occur in the TBI group. It is also hypothesized that shape features in the thalamus and caudate will positively correlate with ToM in the TBI group, which will differ from the pattern in the OI group, which will be in the thalamus, caudate, putamen, and globus pallidus.

Methods

This study utilized data originally collected in the NIH-funded Social Outcomes of Brain Injury in Kids study (SOBIK; R01 HD048946, PI: Yeates) (Yeates et al., 2007).

Brain scans were collected from three locations, two of which used GE Signa Excite magnetic resonance imaging (MRI) scanning machines while the other employed a Siemens Symphony MRI scanner. Brain scans from pediatric TBI (n = 82) and orthopedic injury (OI, n = 61) groups were collected with informed guardian consent and participant assent. In addition to brain scans, data were collected from demographic statements on sex, race, socioeconomic status, parental education levels, and age, as well as a broad battery of cognitive and clinical tests. Testing included the Wechsler Abbreviated Scale of Intelligence (WASI), Test of Everyday Attention for Children (TEA-Ch), and evaluations of pre-morbidity for learning disability and attention deficit hyperactivity disorder (ADHD). This study focuses on the MRI acquisitions and measures of ToM. ToM was measured by performance on the Jack and Jill Test (JJT), Emotional and Emotive Faces Task (EEFT), and Literal Truth, Ironic Criticism, and Empathic Praise Task (LTT). All locations followed ethical requirements established by the Declaration of Helsinki, and the data was anonymized after acquisition before the conduction of this study.

Participants

As part of the SOBIK study, participants aged 8 to 13 years were identified from metropolitan children's hospital records and trauma registries and recruited by phone (Yeates et al., 2013). Exclusion criteria were as follows: 1) premorbid history of more than one serious injury requiring medical treatment, 2) premorbid neurological disorders, 3) injury determined to be a result of child abuse or assault, 4) history of severe psychiatric disorder requiring hospitalization, 5) sensory or motor impairments that would prevent valid administration of study measures, 6) primary language other than

English, 7) any medical contraindication to MRI, and 8) need for full-time special education. OI participants were excluded if there was a previous head injury or if any structural lesions were observed on MRI. Participants with a history of learning disability or deficits in attention were not excluded, as the OI and TBI groups did not differ in the distribution of these subjects.

The Glasgow Coma Scale was used to classify brain injury in the TBI group. OI participants also experienced a traumatic mechanical injury but sustained no brain injury according to the GCS criteria (Teasdale and Jennett, 1974). TBI participants were subsequently stratified by TBI severity to include complicated mild (n = 25, GCS between 13-15 with intracranial lesion), moderate (n = 13, GCS between 9-12), and severe (n = 44, GCS $\leq$ 9) TBI. Out of all TBI subjects, MRI data for 68% of TBI participants contained at least one quantifiable abnormality, including white matter hyperintensities (WMH), hemorrhagic lesions, and focal encephalomalacia (Bigler et al., 2013b). 73.5% of WMH were contained in the frontal lobes, as well as 74.1% of hemorrhagic lesions and 72.3% of focal encephalomalacia. The temporal lobes contained 15% of WMH, 74.1% of hemorrhagic lesions, and 26.6% of focal encephalomalacia. The parietal-occipital regions contained 11.5% of WMH, 6.4% of hemorrhagic lesions, and 1.4% of focal encephalomalacia. OI participants were included if the MRI had showed bone fractures, indicating traumatic injury, but were excluded if fractures were present in the skull or face. In addition, participants could be included if they had a GCS of 15 and no known history of head trauma or loss of consciousness. Further details on the injury characterizations and findings can be found in Bigler and colleagues (2013 b).

Measures

The primary social affective outcomes of interest include a Theory of Mind Composite score derived from a combination of cognitive, affective, and conative measures, namely – the Jack and Jill Task, the Emotional and Emotive Faces Task, and the Literal Truth, Ironic Criticism, and Empathic Praise Task. The score was computed as an arithmetic average of the accuracy percentages recorded for each of the three tasks and represents the percentage of correct responses in all three of the ToM tasks used.

The Jack and Jill Task is a cognitive ToM test first designed by Dennis and colleagues in 2012. It is intended to be used as an estimate of the participant's ability to understand the cognitive state or thinking processes of another individual, quantified as the percentage of correct evaluations. Child participants view cartoon frames of a character (Jack) hiding a ball from another (Jill). Jack places the ball in either a red or blue hat. Then, Jack will switch or not switch the ball to the hat of the other color, an event that is or is not witnessed by Jill. In the final panel, Jill is shown thinking about the location of the ball. Participants decide if the final panel is an accurate representation of what Jill believes about the ball's location. The combination of Jack switching the ball to the other hat while not witnessed by Jill is the key ToM measure, because participants must understand that Jill will believe the ball is in the original hat (Dennis et al., 2012). Performance on this task was recorded as the percentage of correct location identifications.

The Emotional and Emotive Faces Task is an affective ToM test used to evaluate a participant's ability to understand another individual's emotional state and emotive expression (Dennis et al., 1998). Participants listened to 25 short stories about fictitious

individuals and the context of their feelings (Bigler et al., 2013 b). Participants were instructed that the character could feel one emotion but display another. Participants were then presented with cartoon faces, each depicting one of five easily recognizable emotions: happy, sad, fearful, disgusted, and angry. Participants then matched the emotive cartoons with the character's feelings and emotive expression. The testing aspects were scored as a percentage of correct matches to both the internal feelings of the character described and the outward expression of a socially acceptable emotion.

The Literal Truth, Ironic Criticism, and Empathic Praise Task is a measure of conative ToM, which quantifies the participant's ability to decipher literal words versus intended meaning given the context and method of speech delivery (Bigler et al., 2013 b). Participants were presented with a cartoon figure depicting common tasks, such as raking leaves or building a block tower. The tasks were depicted as being done well or poorly. These cartoons were presented with comments made by an observing character, such as "you made a great tower." Participants understood that this character was generally kind or rude, depending on the condition of the test. The text of the comment was also presented with an audio recording of the words, allowing for the detection of neutral, empathic, or ironic intonations. Participants were scored on their accuracy in identifying the relationship between spoken words and actual meaning. Accuracy was reported as a percentage of questions answered correctly out of 100.

Image Acquisition and Processing

The Cleveland study utilized a Siemens Symphony MRI scanner, and both Columbus and Toronto used a GE Signa Excite scanner. Scanners at all three locations used 1.5 T magnetic fields. Each image was collected with four sequences: thin-slice

volume acquisition T1-weighted ultrafast 3D Gradient echo SPGR, dual-echo proton density (PD)/T2 weighted sequence, fluid attenuated inversion recovery (FLAIR), and gradient-recalled echo (GRE) (Bigler et al., 2013 b).

T1-weighted brain scans were processed using version 6.0 of FreeSurfer and manually edited for errors according to established guidelines (Segonne et al., 2007). The thalamus, putamen, globus pallidus, and caudate nucleus were defined as regions of interest (ROIs) and mapped using large deformation diffeomorphic metric mapping techniques (LDDMM) (Csernansky et al., 2004 b). LDDMM generates smooth, reliable surfaces by comparing each ROI to a defined template. The template is used to graph the true anatomical shape based on voxel intensities in the MRI (Khan et al., 2008). The application of a template for mapping allows shape variations in individual subjects to be maintained, as each point is matched to its corresponding template. Trained reviewers examined the resulting maps to confirm the accuracy of the subcortical structure boundaries and reprocessed the mapping when necessary.

Since the data utilized from the SOBIK project was collected from multiple sites, variations in the data due to MRI scanner type, subject position within the scanner, field strength, and other non-biological factors had to be accounted for (Han et al., 2006). To accomplish this, neuroComBat procedures developed by Fortin and colleagues were adapted to minimize variability (Pomponio et al., 2020; Fortin et al., 2018; Johnson et al., 2007). Fortin and colleagues published code for use in harmonization procedures (https://github.com/Jfortin1/ComBatHarmonization), and this study used the R implementation to harmonize vertex-wise deformation data in all subcortical ROIs. ‘Site’ was defined as the variable to be harmonized (“batch” vector), while group differences

due to TBI versus OI were kept constant ("mod" vectors). The post-harmonization data for the thalamus, caudate, putamen, and globus pallidus was then used for the subsequent statistical models described below.

Statistical Analysis

R and SPSS software were used to conduct various comparison tests between the TBI and OI groups and ToM composite scores. T-tests were used to compare differences in group composition including age, parental socioeconomic status, maternal education, and scan time from injury. Characteristics of sex, race, injury mechanism (motor vehicle accident, sports injury, or fall), presence of a learning disability, and presence of ADHD were compared using chi-square tests. An analysis of variance (ANOVA) model was utilized to compare groups on the ToM composite score.

Group differences in shape deformation of the thalamus, caudate, putamen, and globus pallidus were compared using t-statistic contrast maps. The contrast maps were generated for each structure where group differences in shape deformation were compared at each vertex and Random Field Theory (RFT) was implemented as a method to control for multiple comparisons (Worsley, 2004). To evaluate the pattern of associations between shape deformation in each ROI and ToM performance, additional statistical surface maps were generated where a two-tailed Pearson correlation coefficient was calculated between deformation scores and the ToM composite score at each vertex; these were done separately per group (OI and TBI) and also used RFT to correct for multiple comparisons.

Results

Data Screening

3 TBI subjects who were included in the study were missing data for the JJT, and 4 were missing scores for the EEFT. In the OI group, 1 was missing the JJT and 6 were missing the EEFT. In each case, linear interpolation was used to impute the data to allow the inclusion of each subject without affecting the study sample statistics.

Demographic and Theory of Mind Composite Analyses

The OI and TBI groups did not differ by age ($t_{134} = 0.104$, $p = 0.9171$), scan time from injury ($t_{140} = -1.514$, $p = 0.132$), or IQ ($f_{81, 60} = 1.1495$, $p = 0.5741$). However, they differed in ZSES ($t_{124} = -3.125$, $p = 0.002$) and years of maternal education ($t_{131} = -3.374$, $p = 0.001$), with the OI group having higher levels in both variables. TBI and OI groups did not differ by sex ($\chi^2_1 = 0.408$, $p = 0.523$), race ($\chi^2_2 = 1.91$, $p = 0.385$), learning disability ($\chi^2_1 = 1.321$, $p = 0.25$), or premorbid ADHD ($\chi^2_1 = 0.213$, $p = 0.641$). However, a significant difference existed for mechanism of injury, with motor vehicle accidents being much more frequent in the TBI group and sports injuries being more frequent in the OI group ($\chi^2_2 = 24.551$, $p = 0.001$). ANOVA testing revealed that the OI and TBI groups differed in ToM Composite, with the OI group having a higher average ToM Composite, which reflects higher accuracy in the tests ($f_1 = 9.91$, $p = 0.002$).

Shape Analysis of the Thalamus, Caudate, Putamen, and Globus Pallidus

Visual inspection of the contrast t-maps for the thalamus revealed significant inward deformation in the ventral nuclei of the TBI group compared to the OI group (Figure 1). These deformation differences survived RFT multiple-comparison correction.

Visual inspection of the contrast t-maps for the caudate, putamen, and globus pallidus revealed no significant deformation differences between the TBI and OI groups that survived RFT corrections.

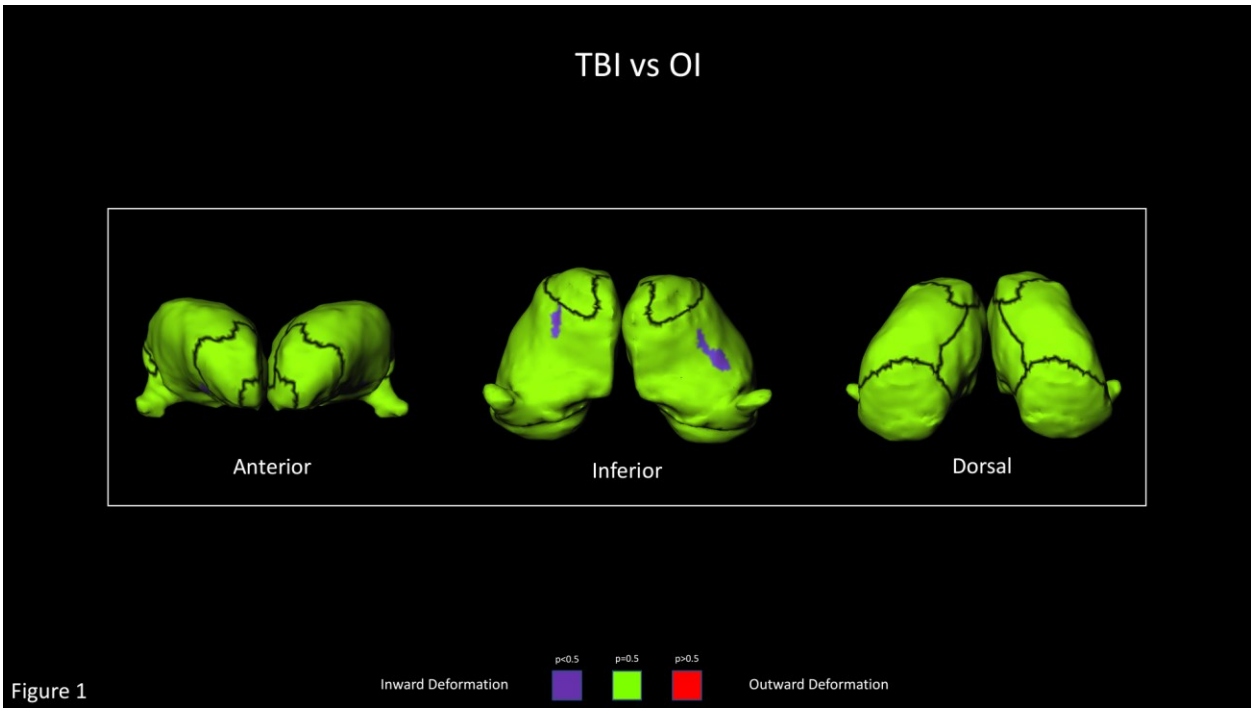

Figure 1: a comparison of shape deformation in the thalamus between TBI and OI samples. Violet-colored areas represent an inward deformation of the TBI group relative to the OI group corrected for multiple comparisons using random field theory (RFT).

Deep Brain Relationships with ToM Composite Score

The Pearson correlation maps generated for the OI group revealed multiple significant correlations between shape deformation and ToM composite that survived RFT multiple-comparison correction. Visual inspection of the Pearson coefficient correlation map for the thalamus in the OI group found significant positive correlation between the shape of the anterior and medial surfaces with ToM composite scores (Figure 2A). For the caudate, significant positive correlations were noted in the left head

and right tail (Figure 2B). For the globus pallidus, significant correlations in the ventral right surface and posterior left surface were observed (Figure 2C). Finally, for the putamen, significant positive correlations were observed in the left medial surface (Figure 2D).

In the TBI group, areas of significant surface correlation with ToM composite were present in only three of the four ROIs and relatively sparse compared to OI. Visual inspection of these Pearson coefficient correlation maps revealed some vertices on the right ventral thalamic surface that had negative correlation with ToM composite scores (Figure 3A). For the globus pallidus, small areas of positive correlation on the right lateral and anterior surfaces and a few vertices on the left posterior surface were noted (Figure 3B), as well as on the medial surface of the right putamen was noted (Figure 3C). No significant correlation with ToM composite scores were noted for the caudate.

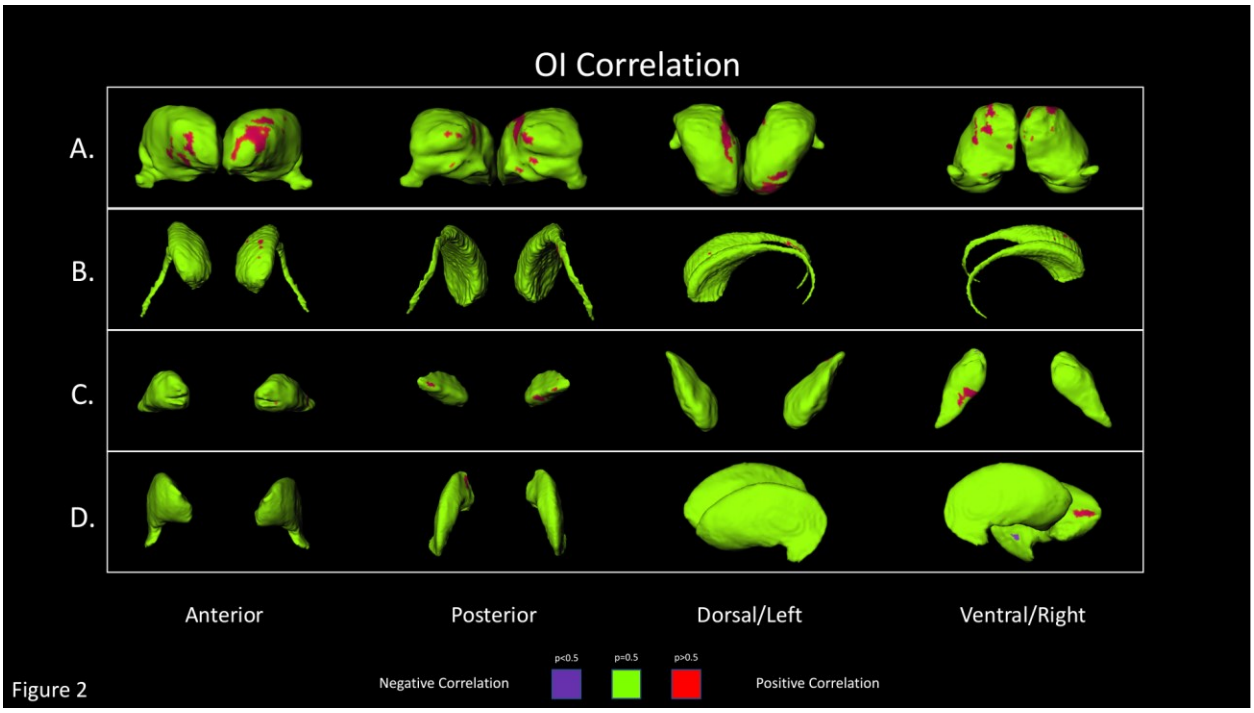

Figure 2

Figure 2: Correlation maps of shape deformation and ToM performance in the OI group. Significant positive correlations are noted in warmer colors, and negative correlations in cooler colors. Correlations are corrected for multiple comparisons using random field theory (RFT). A: thalamus. B: caudate. C: globus pallidus. D: putamen.

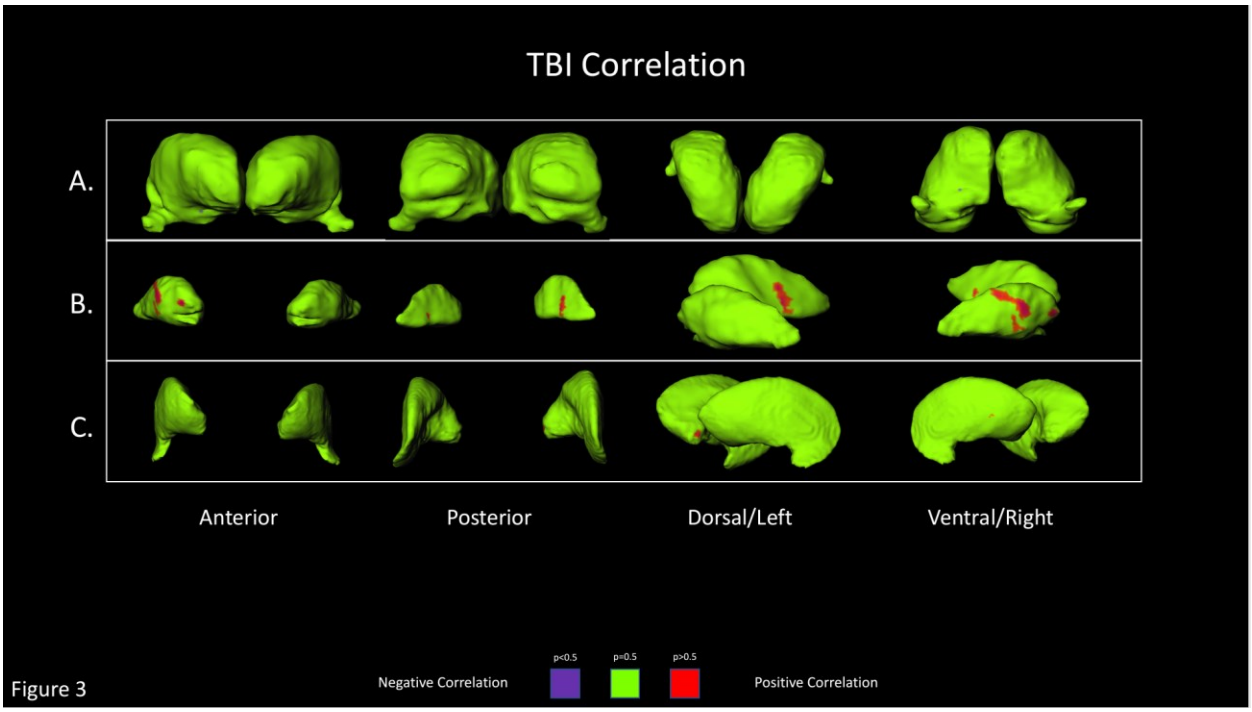

Figure 3: Correlation maps of shape deformation and ToM performance in the TBI group. Significant positive correlations are noted in warmer colors, and negative correlations in cooler colors. Correlations are corrected for multiple comparisons using random field theory (RFT). A: thalamus. B: globus pallidus. C: putamen.

Discussion

This study aimed to determine if shape abnormalities of the thalamus and basal ganglia are a prominent characteristic of pediatric TBI, and whether the morphology of these structures related to social affective performance in ways that differed from an

orthopedically injured comparison. It was predicted that inward deformations would be observed in the thalamus, caudate, putamen, and globus pallidus of the TBI group compared to OI, and that shape deformations of the thalamus and caudate would positively correlate with ToM composite score in the TBI group. Regarding the first prediction, inward deformations of the caudate, putamen, or globus pallidus could not be confirmed. An inward deformation was found in the ventral nuclei of the thalamus, but no significant differences that survived multiple comparison corrections were indicated in the caudate, putamen, or globus pallidus. Regarding the second prediction, multiple correlations between surface shape and ToM scores were found in several structures for both OI and TBI groups. In the TBI group, the most notable correlations were positive and present in the globus pallidus. These results reveal that for the OI group the thalamus, caudate, putamen, and globus pallidus are related ToM performance, whereas only the globus pallidus was related for the TBI group. Overall, this study confirms that the shape integrity of the thalamus may be at risk in pediatric TBI, and that the relationship between deep-brain structure integrity and social outcomes is altered in this group.

In the context of current literature on pediatric TBI, deep-brain structure is one part of more broadly observed elements of brain circuitry that involves both the cortex and white matter (Dennis et al., 2021). Disruption to white matter integrity, cortical thickness, and cortical and subcortical structural volume abnormalities can also contribute to poor outcomes that are associated with pediatric TBI (Dennis et al. 2021, Greer et al., 2022, Bigler et al., 2013 a). Together, these findings suggest that TBI presents a multifaceted threat to brain structure and functionality.

Shape analysis allows the detection of localized atrophy, which is helpful for characterizing the integrity of deep-brain nuclei (Leunissen et al., 2014). This study lends support to the heterogeneity of lesions to deep-brain structures in pediatric TBI. Lesions of varying severity have been found previously in the thalamus, caudate, putamen, globus pallidus, and surrounding white matter for pediatric TBI patients; however, to our knowledge, this study of one of only a few that utilizes shape analysis of these deep-brain structures to further characterize TBI in children (Bigler et al., 2013 a; Bartnik-Olson et al., 2021). An initial look at the results of shape differences between the OI and TBI groups appears to disagree with the findings of Greer and colleagues, which was conducted on a similar subject group (2022). However, the present study included an additional 45 subjects from a third SOBIK data collection site, which comprised 43% of the total subjects included. Discrepancies in deformation trends may be attributable to the inclusion of these subjects, or perhaps in TBI severity between the two study samples. Still, a discrepancy between the findings in both study samples suggests that broader research in larger populations of pediatric TBI subjects is needed to enable robust conclusions about shape integrity. Overall, the findings of this paper provide support that the thalamus may be adversely affected in children who experience TBI.

Shape deformations in subcortical structures resulting from TBI are thought to be due to the mechanical impact of CSF in the ventricles due to sudden deceleration during impact (Wood and Bigler, 1995). While inward deformations might be thought to lead to increased grey matter density due to compression in the thalamus and other subcortical nuclei, Marco and colleagues observed neuronal and white matter loss in TBI (2011). Rat models have indicated that chronic neuroinflammation might contribute to cell death after

TBI (Acosta et al., 2013). Neuronal, glial, and white matter atrophy are generally implicated in loss of function in brain circuitry (Pekna and Pekny, 2012; Kraus et al., 2007; Verger et al., 2001). However, if it is true that the mechanical impact of CSF cases shape deformation in deep brain structures, then we might expect to observe shape changes in surfaces closer to the ventricles. In this study, only the ventral thalamic nuclei exhibited significant deformation, indicating that other causes of shape change may have been at play in this sample. For example, the ventral thalamic nuclei have anatomical connections to the primary somatosensory and primary motor cortices through thalamocortical projections (Nakagawa, 2019). If that circuitry were disrupted in this sample, perhaps by axonal shearing, then surfaces changes in the thalamus might be observed to change due to retrograde transneuronal degeneration (Chang et al., 2016).

In this study sample, the inward deformation of the ventral thalamic nuclei of the TBI group did not necessarily overlap with the sites of ToM correlation changes between the two groups. In addition, clear differences in correlation patterns exist between the OI and TBI groups. Some correlation with the ToM composite score was indicated for outward deformations in the putamen, globus pallidus, and thalamus in the TBI group, compared to more widespread areas of correlation for all structures in the OI group. This finding suggests that these structures are related to the accuracy in ToM-sensitive tasks, but correlations do not necessarily change as a direct result of shape changes due to TBI. This finding also suggests that the recruitment of subcortical structures for processing ToM may be abnormal in pediatric individuals with TBI. Previous literature has associated subcortical processing with ToM performance and other social processing measures. For example, the basal ganglia are implicated in ToM because of their role in

mirroring and internalizing the actions of others (Agnew, Bhakoo, and Puri, 2007). In boys with autism, basal ganglia shapes are predictive of social and communication difficulties (Qiu et al., 2010). The thalamus and basal ganglia have been found to be involved in ToM in other neurological pathologies including multiple sclerosis, schizophrenia, and autism spectrum disorder (Yokote, Okano, and Toru, 2021; Andreasen, Calarge, and O'Leary, 2008; Cheng et al., 2015). The striatum and nucleus accumbens have also been linked to social learning and reward, which might account for why ToM performance appears to decrease in the sample of TBI subjects in this study (Day et al., 2007; Pasupathy and Miller, 2005).

One primary limitation in this study was the relatively small sample size. Marek and colleagues demonstrated that reproducible results for brain-wide associations can take thousands of brain scans, where this study was only able to utilize just 143 (2022). The discrepancy in shape difference findings between this study and Greer and colleagues also illustrates that sample size may create significant differences in results. Additionally, an increased sample size has the potential to increase the power of our findings, allowing more minute significant differences and correlations with ToM to be found. It should also be noted that the TBI group consisted of varying TBI severities; therefore, the findings of this study are limited to general features of TBI and has no specificity for different TBI types. In addition, the measures used in this study are only estimates of ToM and cannot give indication to broader aspects of the skill. While the structures under review in this study are linked to ToM and other social skills, it is important to remember that social skills have not been found to be localized in the brain (Rosema, Crowe, and Anderson, 2011). Non-biological factors such as access to

healthcare or social reception after injury were not measured in this study but could have contributed to ToM performance.

The methods used for estimating surface maps are robust and have been utilized in multiple populations (Csernansky et al., 2004 b; Fischl, 2012). FreeSurfer is widely used for brain mapping and statistics, and its use as a method for identifying brain anatomy has been verified with histological studies (Cardinale et al., 2014; Hanko et al., 2019). This study also uses a population-specific atlas to improve mapping accuracy (Dickie et al., 2017).

Conclusion

This study found significant differences in the shape of ventral thalamic nuclei of OI and TBI groups that survived multiple comparisons. No significant differences were found in the globus pallidus, putamen, or caudate nucleus. These nuclei are involved in thalamocortical projections to the primary somatosensory and primary motor cortices, suggesting that these functional connections may be altered in TBI. While thalamic volume reductions have previously been observed in a study of the same population, this new finding indicates that thalamic shape integrity may decline in correlation with TBI in kids. The basal ganglia may also be reduced in volume, but the findings of this study suggest that the anatomical shape of the structures remain largely intact. Given these findings, the first hypothesis of this study is not supported because no shape deformation differences were found in the caudate of the TBI group relative to the OI group.

Significant correlations were noted between the shape of the thalamus, globus pallidus, and putamen and ToM Composite in the TBI and OI groups. Correlation patterns existed in every ROI in the OI group but were not found in the caudate of the TBI group.

Additionally, visual inspection suggests that these correlation patterns are very different between the two groups, with a greater number and wider distribution of areas of significant correlation present in the OI group relative to the TBI group. For TBI subjects, the correlation patterns were not localized to the same areas of significant shape deformation differences compared to the OI group (ventral thalamic nuclei, see Figures 1 and 3). Thus, it cannot be concluded that ToM-sensitive task performance correlates with changes in shape integrity as a result of TBI. However, it can be concluded that the relationship of these subcortical structures to ToM tasks appears to be different between the TBI and OI groups in this study. Although shape integrity may not be predictive of ToM performance after TBI, this study supports the conclusion that thalamus, caudate, putamen, and globus pallidus are related to ToM tasks. This evidence gives partial support to the second hypothesis of this study because the correlation patterns between the OI and TBI groups appeared to be different, though correlations with ToM Composite were not found in the caudate of the TBI group.

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APPENDIX

	TBI (n = 82)		OI (n = 61)		Statistic		
	Mean	**SD**	**Mean**	**SD**	**t-test**	**df**	**p**
Age at injury	7.83	1.94	7.79	1.80	0.10424	134.11	0.9171
Parental ZSES	-.0.22	0.94	0.3	1.01	-3.1248	124	0.002*
Maternal Ed	13.66	2.3	14.95	2.24	-3.3739	131.25	0.001*
Scan time from injury (years)	2.54	1.22	2.82	1.00	-1.5141	139.71	0.1323
	Mean	**SD**	**Mean**	**SD**	**F-test**	**df**	**p**
WASI FSIQ	99.2	14.37	109.85	13.40	1.1495	81/60	0.5741
ToM Composite	60.14	18.49	65.58	16.87	9.91	1	0.002
	N	**%**	**N**	**%**	**Chi-sq (*TBI)**	**df**	**p**
Sex (% male)	54	65.8537	37	60.6557	0.408	1	0.523
Race (% white)	64	78.0388	54	88.5246	1.91	2	0.385
Injury Mechanism: MVA/Sports/ Fall	31/29/ 22	37.8/35.4/ 26.8	3/43/15	4.9/70.5/ 24.6	24.551	2	0.001*
Learning Disability (% yes)	3	3.6586	5	8.1967	1.321	1	0.25
Premorbid ADHD (% yes)	4	4.878	2	3.2787	0.218	1	0.641

Table 1: demographics and statistics for traumatic brain injury (TBI) and orthopedic injury (OI) groups. SD: standard deviation. df: degrees of freedom. ZSES: Z socioeconomic status. MVA: motor vehicle accident. ADHD: attention deficit hyperactivity disorder.