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Effects of Traumatic Brain Injury on Pediatric Brain Volume

Sanam Jivani Lalani

A dissertation submitted to the faculty of  
Brigham Young University  
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

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## ABSTRACT

### Effects of Traumatic Brain Injury on Pediatric Brain Volume

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Doctor of Philosophy

This study investigated the effects of lesion presence within larger brain networks (e.g., default mode network (DMN), salience network (SN), and mentalizing network (MN)) in the chronic phase of a pediatric traumatic brain injury (TBI) and the effect on social function. We compared children with a TBI to children with an orthopedic injury (OI) with three different aims. The first aim was to determine whether network volume differed by group (e.g., TBI vs. OI). Second, investigate if lesion presence in a sub component region of the network resulted in total network volume loss for that network. Finally, learn whether network volume would predict outcome on the Behavior Assessment System for Children, Second Edition (BASC-2).

Approximately 184 participants (65% male; 70% Caucasian) between the ages of 6-17 years completed testing and a structural MRI scan in the chronic stage (at least one-year post-injury) of the injury. Injury severity included complicated mild, moderate, and severe TBI. Radiological findings were analyzed using recommendations from the Common Data Elements' core (presence or absence of a lesion) and supplementary (lesion type and location) recommendations. Volumetrics for all participants were obtained with FreeSurfer to quantify total network volumes for the DMN, SN, and MN. The parent of each participant completed a behavioral measure for externalizing and internalizing behaviors. Three sets of statistical analyses were completed, including multivariate analysis of covariance, analysis of covariance, and multiple regression, for each of the three aims of the study, respectively.

There were significant differences in total DMN volume between the two groups and participants with lesions solely in the MN had lower total MN volume. Moreover, lower total MN volume was associated with worse functioning on measures of externalizing and internalizing behaviors. The larger implications, including developmental and social implications, of these findings are discussed.

Keywords: pediatric, traumatic brain injury, volume, social function, externalizing behaviors, internalizing behaviors, default mode network, salience network, mentalizing network

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### Effects of Traumatic Brain Injury on Pediatric Brain Volume

Traumatic brain injury (TBI) remains the leading cause of death and disability in children (Carli & Orliaguet, 2004). Childhood TBI can result in heterogeneous and diffuse lesions, often resulting in social-emotional problems that are difficult to quantify (Bigler, Abildskov, et al., 2013; Bigler, Yeates, et al., 2013). Social behavioral problems found in children following a TBI are not directly linked to any single brain region (Greenham, Spencer-Smith, Anderson, Coleman, & Anderson, 2010); rather, they are thought to be part of a complex pattern of connections among various brain networks. Reciprocally, brain networks commonly injured during a TBI are often implicated in social function (Adolphs, 2001; Dennis et al., 2013; Johnson et al., 2005). For example, Yeates, Ris, Taylor, and Pennington (2009) suggest focal lesions after a TBI are usually larger and occur more often in the frontal and anterior temporal regions (Wilde et al., 2005), while diffuse axonal injury commonly appears in the gray and white matter boundaries of the basal ganglia, periventricular regions, superior cerebellar peduncles, fornices, corpus callosum, and brainstem fibers. These regions are individual parts of larger brain networks.

These networks such as the Default Mode Network (DMN), Central Executive Network (CEN), and the Salience Network (SN) are commonly affected in pediatric TBI (Dennis et al., 2013). Additional networks identified by these authors include the Mentalizing Network (MN) and the Mirror Neuron/Empathy Network (MNEN), which specifically relates to social cognition. While no brain function is localized to one brain area, neuroimaging and lesion studies have identified broad functions associated with specific neural networks. For example, studies suggest the DMN is concerned with self-related cognitive activity, autobiographical, and social functions (Dennis et al., 2013). A subcomponent of the DMN includes the ventromedial

prefrontal cortex (vmPFC), an area often implicated in aggression and poor impulse control (Bechara, Tranel, & Damasio, 2000; Qiu et al., 2014), and sensation seeking in adults (Castellanos-Ryan et al., 2014). Damage to the vmPFC can lead to difficulty integrating motivational, risk/reward assessment, emotional and the social aspects of behavior (Stuss, 2011). The SN detects internal and external events relevant to a goal, which ultimately guides behavior. This network has extensive connections with structures that register and utilize affective information (e.g., human emotion, rewards; Dennis et al., 2013). The insula, a subcomponent of the SN, has been implicated as a mediator of interactions with other networks but individually has been linked with external attention and internally oriented cognitions (Menon & Uddin, 2010). In fact, Bonnelle et al. (2012) found that poor structural integrity of the SN resulted in inefficient regulation of the DMN, thus resulting in poor cognitive control in a population of patients with TBI. Additionally, adaptive attentional processes are thought to function in conjunction with the dmPFC within the anterior insula (Olsen et al., 2013). The MN network allows one to think of the mental state of others as well as within oneself (Dennis et al., 2013) and plays a general role in identifying salient events; specifically, the superior temporal sulcus has been involved in spatial neglect or spatial attention (Chechlacz et al., 2013).

This project studies the DMN, SN, and MN because these networks impact social function, whereas the CEN is predominantly concerned with executive functions such as planning and decision-making (Dennis et al., 2013). Keysers and Fadiga (2008) describe the MNEN as primarily involved with imitation and understanding other's actions. However, the MNEN is composed of brain regions associated with mirror neurons that are located in areas not commonly affected in TBI (e.g., dorsal and ventral premotor area, supplementary motor area, posterior parietal area, some temporal regions, and somatosensory cortex); therefore, it is not

included in the present study. The total network volume for each network investigated in this study is comprised of the sum of the volume of the smaller neuroanatomical regions within the network. The neuroanatomical structures and the method for calculating the volume of each network is described in Table 1. Therefore, the current data suggests a link between the chosen networks, behavioral changes, and neuroanatomical lesions, post-TBI.

Table 1

*Neural Networks Comprised of Associated FreeSurfer Regions*

Neural network	FreeSurfer regions
<b>Default Mode Network (DMN)</b>	
Ventromedial prefrontal cortex (vmPFC)	Frontal pole + medial orbito-frontal cortex
Posterior cingulate cortex (PCC)	Posterior cingulate + cingulate isthmus
Inferior parietal lobule (IPL)	Inferior parietal lobe + precuneus
Hippocampal formation (HF)	Hippocampus + entorhinal cortex + parahippocampal cortex
<b>Salience Network (SN)</b>	
Ventrolateral prefrontal cortex (vlPFC)	Pars orbitalis
Insula (I)	Insula short volume + insula large central volume
Anterior cingulate cortex (ACC)	Rostral anterior cingulate + caudal anterior cingulate
Amygdala (A)	Amygdala volume
<b>Mentalizing Network (MN)</b>	
Dorsomedial prefrontal cortex (dmPFC)	Caudal middle frontal cortex + rostral middle frontal cortex
Superior temporal sulcus (STS)	Superior temporal gyrus + bank superior temporal sulcus + middle temporal gyrus
Temporo-parietal junction (TPJ)	Supramarginal gyrus
Temporal pole (TP)	Temporal pole

*Note.* This table is adapted from Dennis et al. (2013).

With regard to neuropsychiatric symptoms, studies show that sustaining a moderate to severe brain injury as an adolescent or adult, resulted in increased self-report of difficulty with cognitive dysfunction and adaptive behaviors, as well as demonstrating increased levels of internalizing and externalizing problems. Specific problems include difficulty with goal directed thought and action, as well as emotion regulation and issues with anxiety, depression, attention, and aggression, when compared to healthy controls (Finnanger et al., 2015). Moreover, previous research suggests younger age at injury predicts more self-reported externalizing problems such as aggression (Finnanger et al., 2015) and that emotional symptoms can negatively impact psychosocial outcome as far as 10-years post injury (Draper, Ponsford, & Schonberger, 2007). A review of neuropsychiatric complications following TBI found that lateral lesions were associated with increased risk of developing depression compared with medial lesions. Specifically, right lateral lesions were linked to increased risk of anxious depression and left anterior lesions were linked to increased risk for major depression (Kim et al., 2007).

One way to measure emotional problems in children is by using the Behavior Assessment System for Children, 2<sup>nd</sup> edition (BASC-2). The BASC-2 is a broad-based measure of behavior and emotional function that captures internalizing (i.e., anxiety, depression, and somatization scales) and externalizing (i.e., hyperactivity, aggression, and conduct problem scales) problems in composite scales (Reynolds & Kamphaus, 2004). According to Li and Liu (2013), children often experience higher rates of internalizing (e.g., withdrawal, anxiety, and depression) and externalizing (e.g., aggression, impulsivity, hyperactivity) problems after an injury, as well experience new onset psychiatric disorders that could ostensibly be measured by the BASC-2. Indeed, the BASC-2 has been used in several studies to determine the social outcome of children following TBI. Starkey and colleagues (2018) followed a group of children with mild TBI over a

span of 24 months. Using the BASC-2 internalizing and externalizing composites, they found significant decreases in internalizing scores between 12 and 24 months. However, there was no significant change in the externalizing composite scores over that time. Interestingly, the number of children meeting the “clinically significant” internalizing problems criteria increased with time while the “at risk” number decreased. In contrast, there was little change in the number of kids meeting the clinically significant or at-risk criteria in externalizing, over time. Thaler, Mayfield, Reynolds, Hadland, and Allen (2012) conducted a study of kids with moderate to severe TBI, a typically developing comparison group, and the BASC-2 standard sample of subjects. Using all subscales and composites of the BASC-2, one finding suggested teachers of kids with TBI reported more problems at school as measured by the Behavior Symptoms Index (BSI), an overall measure of problem behaviors, than the typically developing comparison group. Barney and colleagues (2011) also studied severe TBI in a group of adolescents and found the results of parent responses on the BASC attention and hyperactivity scales measured different constructs of attention than neuropsychological testing. With regard to adaptive functioning, Shultz et al. (2016) found injury group differences approximately two years following TBI with the severe TBI group exhibiting more pronounced deficits than children with mild or moderate TBI. In addition, the authors found these children exhibited consistent impairment in social domains, specifically social skills, social participation, and leisure activities.

The networks investigated in this study are associated with specific aspects of emotional function such as autobiographical and social functions (DMN), efficient regulation of activity in other networks and managing affect (SN), and the ability to think about the mental states of oneself (MN) and others (Dennis et al., 2013). These types of qualities are measured by the internalizing and externalizing composites of the BASC-2.

Another important construct when studying TBI is understanding of the time course following the injury because studies have found that specific injury characteristics (i.e., injury type and location) stabilize with time particularly in the chronic stage of a TBI (Bigler, Abildskov, et al., 2013; Ross, 2011). Anderson, Catroppa, Morse, Haritou, and Rosenfeld (2005) found that children with mild to moderate TBI showed cognitive gains in the first 12 months after injury that remained stable until 30 months post injury. The group later found that although these children stabilized, they remained below developmental expectations for their age group by 5 years post-injury (Anderson, Godfrey, Rosenfeld, & Catroppa, 2012). In addition, Levin et al. (2008) found that presence of a cerebral lesion in children with complicated mild TBI was predictive of poor cognitive outcome 12 months after injury. Therefore, we believe quantifying damage to neural networks should occur in the chronic stage of TBI in children, after lesion stabilization and the concomitant changes in regional brain volume.

A common location for lesions in TBI is within the temporal lobes due to proximity to the anterior and middle fossa of the skull (Bigler, 2007; Bigler et al., 2010; Yeates et al., 2009). The temporal lobes play an integral role in the makeup of the DMN (e.g., hippocampal formation), the SN (e.g., amygdala) and the MN (e.g., superior temporal sulcus, temporo-parietal junction, and temporal pole). Temporal lesions and subsequent volume loss has been linked to mood disturbances. For example, low hippocampal volume has been associated with mood disturbances in adults with an observed interaction suggested between mood disorders and TBI severity (Jorge, Acion, Starkstein, & Magnotta, 2007).

In an effort to identify temporal lobe damage in children post-injury, Schelten's Visual Rating Scale (Scheltens et al., 1992) data was used. Kapeller et al. (2003) suggested visual rating scales that provide detailed instructions as well as different aspects of white matter changes (e.g.,

periventricular changes and deep white matter changes) are a reliable way to measure white matter changes versus those scales that provide few instructions and only global scores. The Schelten's Visual Rating Scale is a five-point scale that visually measures hippocampal atrophy. The scale assesses three aspects of atrophy: width of the choroidal fissures, width of the temporal horns, and height of the hippocampal formation. The specific instructions are outlined in Scheltens et al. (1992). The Schelten's Visual Rating Scale has shown good interrater and intrarater reliability as well as validity compared to volumetric measures in different MRI sequences (Galton et al., 2001). The ratings scale works well to identify white matter changes particularly when compared to quantitative methods that are time consuming and technically challenging (Kapeller et al., 2003).

Relatedly, in an effort to improve standardization within the field of TBI research, the present study utilized recommendations put forth by the TBI task force for lesion identification using neuroimaging. The task force, created in a collaboration with the National Institutes of Neurological Disorder and Stroke (NINDS) and other federal agencies, recommended the use of common data elements (CDEs) so that the findings in this study could be consumed in a standardized manner with other studies utilizing similar neuroimaging techniques in similar populations (Duhaime et al., 2010). Duhaime et al. (2010) have five major components to their recommendations. First, they operationally define each type of lesion found with the various neuroimaging modalities. Second, the authors recommend listing the radiological protocols in an appendix in the publication. Third, they recommend including specifics, given the rapid changes in technology. As such, they recommend a "core, supplementary, and emerging" level of detail to include. A core level of detail is recommended for all projects. This would include a simple presence or absence of a lesion type, while supplemental data may include details around

anatomic findings. Emerging level details would reflect techniques used that are not widely available or are novel. The current study includes core and supplemental level details; specifically, the binary presence or absence of a lesion and “supplementary” level data includes: lesion name and lesion location for the lesions that were located in the networks under review in this study. The fourth and fifth recommendations are centered around the creation and use of a flexible and public database of the neuroimaging data, beyond the scope of the current study. The authors went on to clarify CDE guidelines specifically for a pediatric TBI population including clarity around common lesions that are present in the chronic phase an injury and how to identify these on neuroimaging. These recommendations were included in the present study (Duhaime, Holshouser, Hunter, & Tong, 2012).

### **Purpose**

Previous studies have investigated lesion type and location in pediatric TBI and found generalized white matter (WM) and gray matter (GM) loss, increased ventricular volume, and greater whole brain volume loss linked to injury severity (Bigler, Abildskov, et al., 2013). However, no studies have investigated the effects of lesion presence within a larger brain network and its effect on total volume for that network or the impact of network level changes on social function for children in the chronic stage of a traumatic brain injury.

### **Specific Aims and Hypotheses**

#### **Specific Aim 1**

Determine if network volume is different based on group membership (TBI vs. orthopedic injury (OI)).

**Hypothesis 1.** Group membership (TBI or OI) will predict network volume (DMN, SN, and MN).

**Specific Aim 2**

Determine if the presence of a lesion in any subcomponent region of the network resulted in total network volume loss for that network.

**Hypothesis 2.** Children in the TBI group with a lesion in network (TBI+) will have lower network volumes compared to children with a TBI and a lesion elsewhere in the brain but without identified damage in that network (TBI-) and compared to the typically developing orthopedic injury group (OI).

**Specific Aim 3**

Determine if network volume will predict outcome on the Behavior Assessment System for Children, Second Edition (BASC-2).

**Hypothesis 3.1.** Low DMN volume will predict higher T-scores on the externalizing behavior scale (EBC) but not on the Internalizing symptoms scale (ISC).

**Hypothesis 3.2.** Low SN volume will predict higher T-scores on the externalizing behaviors scale (EBC) and the internalizing symptoms scale (ISC).

**Hypothesis 3.3.** Low MN volume will predict higher T-scores on the externalizing behavior scale (EBC) and the internalizing symptoms scale (ISC).

**Methods****Measure of Injury Severity**

Injury severity is based on a Glasgow Coma Scale (GCS) score (Teasdale & Jennett, 1974). GCS scores measure the level of consciousness in a patient and has been used as a measure of injury severity as a result of neurotrauma. GCS scores range from 3-15 with a score of 3 representing complete coma and 15 representing a normal level of consciousness. Thus, a score of 3 represents a severe injury while a score of 15 indicates a mild traumatic brain injury.

The GCS score is based on eye response, verbal response, and motor response assigned at the time of evaluation, whether on the site of the accident or upon admission to the hospital, by trained professionals (Teasdale & Jennett, 1974). If a patient with a mild TBI has a positive finding on the initial neuroimaging (e.g., a skull fracture evident on a CT scan), the mild TBI rating becomes a “mild complicated” TBI. While limitations exist with the use of GCS score to assess injury severity (e.g., in cases of medically induced comas), a GCS score is the most widely used measure for quantifying injury severity in TBI and can reliably predict outcome when the GCS score is acquired reliably (Teasdale, Knill-Jones, & van der Sande, 1978). Therefore, the GCS score was used as a measure of injury severity in this study.

### **Participants**

Participants for this study represent two archival datasets, each described in detail below, and discussed briefly here. Both of the original TBI datasets were part of larger studies conducted with various aims at sites all over the United States and Canada. This study includes a subset from the original of approximately 184 total participants between the ages of 6-17 years. All children have a history of injury that required a hospital stay; either an orthopedic injury (excluding trauma to the head) or a traumatic head injury (TBI) ranging in severity from mild complicated to severe. The TBI ratings are based on an injury severity score assigned at the time of hospital admission. Each participant included in the study received a structural MRI scan in the chronic stage of the TBI, at least one-year post-injury. Because the current study includes a subset from two larger datasets, the number of participants included in each of the analyses described below varied based on the available data per variable under investigation.

Although the participants were recruited for two different studies (e.g., SOBIK, BCM) with differing aims, both studies broadly explored the long-term effects of pediatric brain injury

and included all levels of injury severity. The SOBIK study was unique in that a majority of the children had a mild complicated injury (54%). In addition, since the focus of the SOBIK study was on social behavior inside a mainstream rather than self-contained classroom, inclusion criteria required even the most severely injured participant had to be functional in a classroom setting several months following the injury. The BCM study was a longitudinal study with expected levels attrition by 18 months post-injury; however, in contrast to the SOBIK study, the BCM 18-month post-injury subset included a majority of participants with severe brain injury (70%). Of note, the BCM subset is much smaller compared to the SOBIK, see additional details below.

The final sample of participants included in the study were 65% male and 34% female (approximately 1% were not classified). Race and ethnicity included 70% Caucasian, 13% African American, approximately 8% Hispanic, less than 1% Asian, and approximately 4% identified as multi-racial (N=181). Approximately 5% of the data did not include a race or ethnicity. Additional participant characteristics are provided in Table 2.

Table 2

*Participant Characteristics*

	TBI		OI		$\chi^2$	<i>p</i>
	N	N%	N	N%		
Sex	99		82		.03	.87
Male		65%		66%		
Female		35%		34%		
Race/Ethnicity	94		81		3.15 <sup>1</sup>	.53
Caucasian		72%		75%		
African American		13%		15%		
Hispanic or Latino		11%		5%		
Asian		0%		1%		
Multiracial/Other		4%		4%		
	N	M (SD)	N	M (SD)	<i>F</i>	<i>p</i>
Injury Age (years)	99	8.78 (3.02)	82	8.80 (2.69)	.002	.96
Scan Age (years)	99	11.17 (2.57)	82	11.33 (2.34)	.20	.65
TICV (cm <sup>3</sup> )	76	1464.25 (142.40)	68	1496.98 (160.26)	1.68	.20

*Notes.* TICV = total intracranial volume; TBI = traumatic brain injury; OI = orthopedic injury; The number of participants in each group varied slightly in each variable due to missing data; <sup>1</sup>Four cells in this analysis had less than the required five occurrences.

**Social Outcomes of Brain Injury in Kids (SOBIK) study dataset.** This multisite study aimed to better understand the social outcomes of childhood TBI. Details regarding the participant demographics and methods for this study, outlined below, can also be referenced elsewhere (Bigler, Abildskov, et al., 2013).

***SOBIK participants.*** Participants for this study were recruited between 2006 and 2010. A total of 143 participants (age range = 8.6 to 10.3) were recruited from The Hospital for Sick Children and the University of Toronto in Toronto, Canada, The Research Institute at Nationwide Children's Hospital and Ohio State University in Columbus, Ohio, and The Rainbow Babies & Children's Hospital and Case Western Reserve University in Cleveland, Ohio. Participants included children with TBI (n=82) and those with orthopedic injury (OI) that did not involve trauma to the head (n=61). Children with TBI were included if they received a day of injury GCS score of 12 or less (severe TBI n=25; moderate TBI n=13) or had a complicated mild brain injury (e.g., GCS score 13-15 and positive neuroimaging finding of a skull fracture or other brain insult; mild complicated TBI n=44). Out of 143 children recruited for the study, 124 had usable neuroimaging data (TBI n=72; OI n=52). The remaining participants (n=19) were not included due to poor scan quality as a result of movement artifact (n=5), artifact due to existing metal in the patient (e.g., dental braces; n=7), or other mechanical reasons (n=7).

***Magnetic Resonance Imaging.*** Neuroimaging data was acquired in the chronic phase of injury (at least one-year post-injury; mean = 2.7 years post-injury). All sites used a scanner with a magnetic field strength of 1.5 Tesla. The Toronto, Ontario and Columbus, Ohio sites used a GE Signa Excite scanner and the Cleveland, Ohio site used a Siemens Symphony scanner. Each site in the SOBIK study used the same sequence to acquire structural MRI data: thin slice, volume acquisition T1-weighted ultrafast 3-dimensional gradient echo (e.g., MPRAGE or FSPGR based on scanner type), a dual-echo proton density (PD)/T2-weighted sequence, a Fluid-Attenuated Inversion Recovery (FLAIR), and a Gradient Echo (GRE) sequence. To check for uniformity of image acquisition and image quality across the different sites, an identical phantom imaging scan was performed before each acquisition.

**Baylor College of Medicine (BCM) longitudinal dataset.** This longitudinal project set out to examine the relationship between cognitive deficits and the pathophysiology of closed head injury. The goal of the study was to improve assessment and interventions for children with brain injury.

***BCM participants.*** The participant demographics and methods used in the study are outlined below and have been presented elsewhere (Levin et al., 2008; Wu et al., 2010). The study design recruited participants from admissions to emergency rooms at Level 1 trauma centers in Houston, Texas, Dallas, Texas, and Miami, Florida. Participants were excluded from the study if MRI scan was contraindicated (e.g., metal braces) or if there was history of previous head injury, child abuse, preexisting neurological disorder, psychiatric disorder, learning disability, low birth weight (birth weight of less than 2,500 g), penetrating gunshot wound to the brain, hypoxia (PO<sub>2</sub> less than 96 mm Hg for age of 6-16 years) or hypotension (systolic blood pressure two standard deviation below the mean for the age group). Participants were asked to come in for a follow up MRI and cognitive assessment at 3, 12, 18, and 24 months post-injury. Participant drop out is common in longitudinal studies, therefore the sample size for this project decreased between the initial recruitment (N = 144, TBI = 75) and 18 months post-injury (N = 88, TBI = 50). The current study investigated brain injury correlates in the chronic stage of the injury; therefore, a subset of participants with data acquired at 18-months post-injury was obtained from this larger project and included in the present study. The sample included participants with a day of injury GCS score between 3 and 15. All participants with a GCS score between 13-15 also had positive CT scan findings indicative of a mild complicated TBI.

Accounting for normal attrition, participants who had all the required behavioral data at 18 months post-injury included children aged 7 to 17 years. The TBI group consisted of 10 males

and 7 females (n=17, mean age at injury=13.37 years) with injury severity ranging from complicated mild to severe TBI (severe n=12, moderate n=2, complicated mild n=3). The OI group was included in this study to control for risk factors that predispose children to injury. The OI group consisted of 21 participants (17M, 4F, mean age at injury=11.72 years) with injuries requiring overnight stay for upper or lower extremity fractures.

***Magnetic Resonance Imaging.*** MRI scanning took place on Phillips 1.5 Tesla Intera scanners at Texas Children's Hospital in Houston, Texas, the Rogers MRI Center, the University of Texas Southwestern Medical Center, Dallas, Texas, or the Miami Children's Hospital, Miami, Florida. All scanners performed quality assurance testing and were well maintained throughout the study. This study acquired a diffusion tensor imaging (DTI) sequence used to analyze the structural white matter integrity of the participant's brain. The sequence is as follows: transverse multislice spin echo, single-shot, echo-planar imaging sequences were applied (10,150.5 ms repetition time; 90 ms echo time; 2.7-mm-thick slices with 0-mm gap). A 256-mm field of view (FOV) was used with a voxel size of 2.69 x 2.69 x 2.7 mm (receiver FOV = 100%). Fifteen direction diffusivities were used (number of b value = 2; low b value = 0 s/mm<sup>2</sup>; high b value = 860 s/mm<sup>2</sup>) and 2 acquisitions of high-b images, averaged, to ensure better signal-to-noise ratio. A total 55 slices were acquired in approximately 6 minutes. In addition, this study also acquired a T1-weighted 3-D sagittal acquisition series (15 ms repetition time, 4.6 ms echo time, 1.0-mm-thick slices with 0-mm gap. A 256-mm FOV (receiver FOV = 100%) was used with a voxel size of 1.0 x 1.0 x 1.0 mm).

### **Lesion Analysis**

One way to identify and qualify brain lesions due to a TBI is with visual clinical ratings; an "eye ball" test declaring whether a lesion does or does not exist, established by Bigler (2007).

This method requires the rater be trained in identifying a variety of brain lesions on various MRI sequences. The rater must achieve high inter-rater reliability with a neuroradiologist or experienced rater prior to rating alone. Inter-rater reliability is analyzed using the Kappa statistic. However, in an effort to contribute to the standardization of TBI research, this study used specific guidelines for pediatric TBI research set by the NINDS TBI work group. The CDE guideline procedures are outlined elsewhere (Duhaime et al., 2010) and were followed by a neuroradiologist (Michael McLaughlin, MD) as outlined for training guidelines for the present study. Of the 28 findings outlined and operationalized by the CDE work group, eight findings (See Table 3) are relevant in the chronic phase of a TBI and were used in this project. Each scan was reviewed and scored using the above-mentioned criteria by a neuroradiologist to ensure effective execution of the CDEs for the current study. The results of the analyses are outlined in Table 3, including the core requirement (i.e., identification of the presence or absence of a lesion) and supplementary requirement (i.e., identification of lesion type).

In addition, The Schelten's Visual Ratings Scale protocol were reviewed. Previously, these guidelines have been used to rate the white matter hyperintensities located specifically in the medial temporal lobes. The steps for this clinical rating protocol are outlined elsewhere (Kapeller et al., 2003) and require excellent inter-rater agreement ( $\kappa > .9$ ) with a trained professional (e.g., Erin D. Bigler, Ph.D., ABPP) before analysis can begin. Lesion identification and location with the Schelten's protocol both for the medial temporal lobes and generalized to the entire brain were previously sufficiently completed for participants of the SOBIK cohort, although this data is not yet published. Qualitatively, there were very few participants with findings from the Schelten's Ratings with lesions located within the medial temporal lobes and relevant for the three networks of interest in this study ( $n = 3$ ). The Schelten's ratings conducted

to identify white matter hyperintensities in the whole brain would also have been captured by the CDE analyses; therefore, they were not explicitly reviewed for the current project and were not specifically used for any formal analyses in the current project. Instead, the radiological findings from the CDE method was the primary clinical rating method used to identify lesion type and lesion location for the present study.

Table 3

*Common Data Elements (CDE) of Neuroimaging: Number of Radiological Findings by Group*

	TBI (N = 99)	OI (N = 82)
Subacute or chronic subdural hematoma	7	
Traumatic aneurysm	0	
Contusion/contusion findings	27	2
Diffuse axonal injury/DAI anatomic sites	11	
Penetrating injury	4	
Cervicomedullary junction or brainstem injury	0	
Ischemia or infarction or hypoxic-ischemic injury	2	1
Brain atrophy or encephalomalacia	18	
Total Patients with CDE Findings	n = 45 (45%)	n = 3 (4%)
Non-CDE findings	skull fracture subarachnoid blood epidural hematoma	perivascular space

*Notes.* Descriptions of findings provided where relevant; Some patients had multiple findings; Non-CDE findings were not included in any analyses. TBI = traumatic brain injury; OI = orthopedic injury.

The investigators then went on to specify if the injuries were located within any of the neural networks explored in this study (i.e., DMN, SN, and MN). If so, we included where

within the network. Of those individuals with a TBI with identified lesions on a brain scan, 17 participants had lesions that were not within the neural networks investigated in this study.

Interestingly, only two of these participants had any overlapping lesions with a network under investigation. On the other hand, participants with lesions in one of the networks also had overlapping injuries in one or more of the other networks. These details are provided in Table 4.

Regarding the four individuals in the OI group with identified lesions as noted in Table 3, the first participant had a contusion in the right TPJ within the MN. The second participant had a contusion in the right superior frontal gyrus not within a neural network investigated in this study. The third participant had a nonspecific ischemic injury in the left thalamus. Finally, the last participant with the non-CDE injury had a perivascular space in the left basal ganglia. These participants were not included in any analyses.

Table 4

*Location of Lesions by Neural Network in Participants with TBI*

TBI Participants with a Finding (N = 45)	
	N (%)
<b>Default Mode Network (DMN)</b>	<b>24 (53%)</b>
Ventromedial prefrontal cortex (vmPFC)	17
Posterior cingulate cortex (PCC)	0
Inferior parietal lobule (IPL)	8
Hippocampal formation (HF)	2
<b>Saliience Network (SN)</b>	<b>14 (31%)</b>
Ventrolateral prefrontal cortex (vlPFC)	13
Insula (I)	1
Anterior cingulate cortex (ACC)	1
Amygdala (A)	2
<b>Mentalizing Network (MN)</b>	<b>19 (42%)</b>
Dorsomedial prefrontal cortex (dmPFC)	14
Superior temporal sulcus (STS)	5
Temporo-parietal junction (TPJ)	2
Temporal pole (TP)	7
<b>Not in an identified network</b>	<b>17 (38%)</b>

**Volumetric Analyses**

All scans completed on the participants in this study underwent volumetric analysis via FreeSurfer software Version 5.3 (<http://surfer.nrm.harvard.edu/>). The technical details for the mostly automated procedures used can be found elsewhere (Dale, Fischl, & Sereno, 1999).

FreeSurfer procedures have shown good test-retest reliability across both scanner manufacturers

and varying field strengths (Han et al., 2006; Reuter, Schmansky, Rosas, & Fischl, 2012). The volume of each region of interest (ROI) was derived via FreeSurfer's automatic cortical parcellation or subcortical automatic segmentation method (Desikan et al., 2006; Fischl et al., 2004). The volumes of the relevant ROIs that make up specific networks (e.g., DMN, SN, MN) were summed to constitute the volume for the networks under review (see Table 5).

Table 5

*Neural Network Volumes by Group, Unadjusted for Covariates*

	TBI		OI	
	M (SD)	Range	M (SD)	Range
TICV	1464 (142.40)	1150 – 1726	1497 (160.26)	1078 – 1991
DMN	101 (12.05)	73 – 130	100 (13.15)	69 – 140
SN	33 (3.57)	25 – 42	34 (3.75)	26 – 43
MN	144 (15.61)	110 – 179	145 (17.42)	110 – 196

*Notes.* M = mean; SD = standard deviation; Volumes are presented in cm<sup>3</sup>; TICV = total intracranial volume; Networks volumes are unadjusted for covariates; DMN = Default Mode Network; SN = Salience network; MN = Mentalizing network.

**Social Outcome Measure**

This study examined the social behavioral outcome for children following TBI using the Behavior Assessment System for Children, Second Edition (BASC-2; (Reynolds & Kamphaus, 2004). This measure was a common behavioral measure available between the two separate data sets; thus, this behavioral measure was utilized for the current study. The BASC-2 is a psychometrically sound social outcome measure that has previously been used in a pediatric TBI population (Barney et al., 2011; Schultz et al., 2016; Starkey et al., 2018; Thaler et al., 2012). The BASC-2 can be triangulated to obtain a thorough picture of the child's social function in the

past several months using a self-report form for children ages 2-21 years, a teacher report form, and a parent report form. The measure creates a composite made up of subscales, which vary slightly among the forms. The Externalizing Problems Composite is composed of the hyperactivity, aggression, and conduct problems subscales. The Internalizing Problems Composite includes the anxiety, depression, feelings of inadequacy, somatization, locus of control, social stress, and atypicality subscales. Other composites include the School Problems Composite on the teacher rating form that is comprised of attitude to school, attitude to teachers, and sensation seeking. The Adaptive Skills Composite is made up of adaptability to change, social skills, leadership skills, activities of daily living, study skills, and functional communication. Finally, the Behavior Symptoms Index (BSI) is comprised of atypical behavior, social withdrawal, school problems, learning problems, and the attention problems subscale. The results are presented as norm referenced T scores (mean = 50, SD = 10) with scores below 60 considered to be within the “normal” range, scores between 60-69 to be in the “at-risk” range, and scores greater than or equal to 70 are considered to be in the “clinical” range. Scores for the participants in the current study are included in Table 6.

For the focus of the current study, we will evaluate social outcome in children following TBI using the Internalizing Behaviors Composite and the Externalizing Behaviors Composite. Practically speaking, these two composites were the only common composites available amongst the two larger datasets providing the subsample for the current study. The subscales within these composites have been used in previous research to assess different aspects of social function in children following TBI and we believe many of the same symptoms captured by these subscales directly relate to the DMN, SN, and the MN.

Table 6

*BASC-2 Social Outcome Scores by Group*

	TBI		OI		T (df)	p
	N	M (SD)	N	M (SD)		
Externalizing	72	52.33 (12.29)	69	48.91 (7.35)	-1.99 (139)	.05*
Internalizing	73	52.75 (12.92)	69	48.36 (9.27)	-2.32 (140)	.02*

*Notes.* M = mean, SD = standard deviation; T = result of the independent sample t-test; df = degrees of freedom; \* = significant findings of  $p < .05$ ; TBI = traumatic brain injury; OI = orthopedic injury; Outcome scores are T-scores (M = 50, SD = 10).

**Statistical Analyses**

All analyses controlled for total intracranial volume, age at scan, and sex of the participant (see Table 7). Total brain volume was derived automatically by the FreeSurfer software as a variable called estimated total intracranial volume (Schmansky, 2016). The age was defined as age at the time of MRI scan. For the Baylor dataset, age at the time of the scan was defined as 18 months after the child was enrolled into the study post injury. On average, children were enrolled into the study within 39 days of experiencing the brain injury.

Data screening and cleaning was conducted; one volumetric outlier was removed from the analyses. We attempted to fence this outlier within two and three standard deviations of the dataset's mean, but the fenced data remained an outlier and was ultimately removed. Statistical frequencies were run for the variables used in the current study. Missing data was found in both data sets, as each dataset was originally created for entirely separate purposes and a subsample was used for this study, and data were determined to be missing at random. Relatedly, the sample size was also different for each analysis. Assumptions of linearity, normality, homogeneity and multicollinearity were all tested and found satisfactory to proceed for the analyses. Once the data

screen was complete, the analyses were performed using SPSS version 25. The specific models used for the statistical analyses run for each hypothesis in this study can be found in Table 7.

Table 7

*Statistical Models for Proposed Hypotheses*

Hypothesis	Analysis	Model	
		Dependent Variable	Variable of Interest
Hypothesis 1 (covary age, sex, total brain volume)	MANCOVA	Network volume: DMN, SN, MN	TBI OI
Hypothesis 2 (covary age, sex, total brain volume)	ANCOVA	Network volume: DMN, SN, MN	TBI+ TBI- OI
Hypothesis 3	Multiple Regression	Externalizing Internalizing	DMN, SN, MN
3.1 (covary age, sex, total brain volume)	Regression	Externalizing Internalizing	DMN volume
3.2 (covary age, sex, total brain volume)	Regression	Externalizing Internalizing	SN volume
3.3 (covary age, sex, total brain volume)	Regression	Externalizing Internalizing	MN volume

*Notes.* MANCOVA = multivariate analysis of covariance; ANCOVA = analysis of covariance; DMN = default mode network; SN = salience network; MN = mentalizing network; TBI = traumatic brain injury; OI = orthopedic injury

## Results

### Participant Characteristics

The TBI and OI groups did not vary significantly by sex ( $\chi^2(1) = .03, p = .87$ ), race ( $\chi^2(4) = 3.15, p = .53$ ), age at injury ( $F(1, 180) = .002, p = .96$ ), age at scan ( $F(1, 180) = .20, p = .65$ ), or total intracranial volume ( $F(1, 143) = 1.68, p = .20$ ); details available in Table 2.

### Hypotheses

**Hypothesis 1.** The first aim of the study was to determine whether network volume differed based on group membership. Hypothesis one posited that the TBI group would have lower network volumes compared to the OI group while controlling for age, sex, and total brain volume. This hypothesis was generally supported (please see Table 8). The omnibus MANCOVA showed a weak effect, trending toward significance, of group on network volumes ( $\Lambda = .95, F(3, 137) = 2.62, p = .053$ ). Further exploration of group differences with univariate analyses revealed that the volume of the DMN was significantly larger in the TBI group ( $F(1, 139) = 4.79, p < .05, d = 2.05$ ); however, the effects were not present for the SN volume ( $F(1, 139) = .01, p > .05, d = .09$ ) and the MN volume ( $F(1, 139) = .58, p > .05, d = .71$ ), adjusting for the effects of the covariates. Still, the effect size for MN volume was also large and suggested greater volume in the TBI group compared to the OI group. Adjusted means, mean differences, and standard errors are presented in Table 8.

Table 8

*Results for MANCOVA, Hypothesis 1, Including Covariates*


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OMNIBUS Wilk's Lambda ( $\Lambda$ ) = .95,  $F(3, 137) = 2.62, p = .053$

Network	Group	Adj. Mean (Std. Err)	95% CI	$F$ (df)	$p$ value	$d$
DMN	TBI	102.54 (1.11)	100.35-104.74	4.79 (1,139)	.03*	2.05
	OI	98.99 (1.18)	96.67-101.32			
	Mean diff (Std Err)	3.55 (1.62)				
SN	TBI	33.90 (0.29)	33.33-34.47	0.01 (1,139)	.93	.09
	OI	33.86 (0.31)	33.26-34.47			
	Mean diff (Std Err)	0.04 (0.42)				
MN	TBI	144.89 (1.44)	142.04-147.74	0.58 (1,139)	.45	.71
	OI	143.30 (1.52)	140.29-146.31			
	Mean diff (Std Err)	1.59 (2.10)				

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*Notes.* All values (i.e., adjusted mean, standard error, confidence intervals) presented in  $\text{cm}^3$ ; CI = confidence interval presented as lower bound – upper bound;  $F$  = result of F-test; df = degrees of freedom; \* = significance level  $p < .05$ ;  $d$  = Cohen's  $d$ ; DMN = default mode network; SN = salience network; MN = mentalizing network; TBI = traumatic brain injury; OI = orthopedic injury.

**Hypothesis 2.** The second aim of the study was to determine if the presence of a lesion in a subcomponent of a network would subsequently result in total network volume loss. We hypothesized that children with a TBI and a lesion in one network would have a lower total network volume in that network compared to children with a TBI and a lesion anywhere else in the brain, without a lesion in the first network, and compared to children in the OI group. These analyses were run for all three networks.

The first analysis included seven children with a lesion exclusively in the DMN. There were no participants who had a lesion in other parts of the brain excluding the DMN and 68

children in the OI group ( $F(1, 70) = 2.29, p = .14, d = 1.37$ ; adjusted mean total DMN volume,  $\text{cm}^3$  (Std Err) = 106.09 (3.99); adjusted mean total OI volume,  $\text{cm}^3$  (Std Err) = 99.74 (1.23)). The second analysis included two children with an injury exclusively in the SN, no children with a lesion in other parts of the brain excluding the SN, and 68 children in the OI group. There were no main effects between the groups ( $F(1, 65) = 0.49, p = .49, d = .66$ , adjusted mean total SN volume,  $\text{cm}^3$  (Std Err) = 32.79 (1.92); adjusted mean total OI volume,  $\text{cm}^3$  (Std Err) = 34.16 (0.32)). Finally, there were five children with lesions exclusively in the MN compared to no children with injuries exclusively elsewhere in the brain excluding the regions in the MN, and 68 children in the OI group. There was a significant effect between the total MN network volumes of children with a lesion exclusive in the MN and the OI group ( $F(1, 68) = 5.30, p = .02, d = 2.11$ ; adjusted mean total volume MN,  $\text{cm}^3$  (Std Err) = 130.05 (6.15); adjusted mean total volume OI,  $\text{cm}^3$  (Std Err) = 144.72 (1.64)).

**Hypothesis 3.** The third aim of the study was to determine if network volume would predict social outcome. We made three hypotheses based on each network. We first hypothesized that lower DMN volume would predict higher externalizing scores, indicative of worse functioning, but not internalizing scores. This hypothesis was not supported as the DMN volume did not significantly predict scores on either the externalizing behaviors ( $R^2 = 0.32, F(4, 108) = .88, p = .23, \beta = -0.14, f^2 = .03$ ) or the internalizing behaviors composites ( $R^2 = 0.39, F(4, 109) = 1.12, p = .28, \beta = -0.12, f^2 = .04$ ). Our next hypothesis posited that lower SN volume would predict higher externalizing and internalizing scores. This hypothesis was not supported. SN volume did not significantly predict either externalizing ( $R^2 = 0.19, F(4, 108) = .53, p = .81, \beta = -0.03, f^2 = .02$ ) or internalizing behaviors ( $R^2 = 0.52, F(4, 109) = 1.50, p = .11, \beta = -0.21, f^2 = .05$ ). Thirdly, we hypothesized that lower MN volume would predict worse externalizing and

internalizing functioning (i.e., higher scores). This hypothesis was supported. Mentalizing network volume significantly predicted both externalizing ( $R^2 = 0.05$ ,  $F(4, 108) = 1.54$ ,  $p = .047$ ,  $\beta = -0.24$ ,  $f^2 = .06$ ) and internalizing behaviors ( $R^2 = 0.09$ ,  $F(4, 109) = 2.56$ ,  $p = .01$ ,  $\beta = -0.30$ ,  $f^2 = .09$ ).

## Discussion

The overarching aim of this study was to identify whether large brain networks are impacted by lesions located within the network as a result of traumatic brain injury. If there is an impact, to what degree, if at all, is there an effect on social function for children in the chronic stage of the brain injury. This study investigated the total volumes for three large scale brain networks (i.e., DMN, SN, and MN) between two groups (i.e., TBI compared with OI). We found significant differences in total DMN volume between the two groups. Additionally, participants with lesions solely in the MN had lower total MN volume and the lower volume was associated with worse functioning (i.e., higher T-scores) on measures of internalizing and externalizing behaviors.

## Findings

**Aim 1.** Total network volumes varied between the TBI and OI groups with a trend toward significance. However, the findings were in an unanticipated direction. After adjusting for the covariates, the volumes for the TBI group were consistently larger for all three networks, although the difference in the SN between groups did not appear to be meaningful (Table 8). The difference between the TBI and OI groups in the DMN was statistically significant and had a very large effect size representing approximately  $3.5 \text{ cm}^3$ . Finally, the difference between groups in the MN was not statistically significant but had a large effect size. Possible reasons for these findings will be discussed.

The larger TBI volumes, compared to the OI volumes, could be attributed to several factors. According to Bigler (2016), the common automated process to derive volumetrics is to fit the patient brain to a template of a healthy child brain and derive any volume reductions in the comparison. However, practically speaking, the results show not only the expected changes in volume from focal lesions, but also reflect widespread volumetric changes to other areas of the brain that are connected via white matter. Therefore, the resulting volumetric data includes information above and beyond the focal lesion and likely reflects the results of the white matter pathology resulting from the injury. In fact, Wilde and colleagues (2005) found that frontal gray matter loss was attributable to focal injury, while frontal and temporal white matter volume loss was related to both diffuse and focal injury. Interestingly, the same study found that preserved frontotemporal tissue was related to functional recovery. Thus, perhaps increased volume in these networks represents functional recovery or even some type of injury-related compensatory response. There is precedence to this idea as prior work has shown not only decreases in gray matter volume following stroke, but also gray matter increases in other regions, possibly as a compensatory mechanism (Diao et al., 2017). Given the chronic stage of the injury, the participants in the present study are well into their recovery. Moreover, the participants from the SOBIK subset were in some part required to be functional and present in a classroom by this stage. Thus, providing evidence of functional recovery and confirming the assumption that recovery may be a reason for higher volumes in the TBI group. Another possible reason for our counterintuitive findings may be related to imaging tissue misclassification. From a neuroinflammatory perspective, the presence of hemosiderin in neuroimaging has previously been indicative of localized neuroinflammation (Bigler, 2016) that can be misclassified in FreeSurfer. For example, T1 hypointensities can often be misclassified as gray matter,

inadvertently increasing volume in FreeSurfer (Zhu, 2013). Taken together, misclassification of volume may provide yet another explanation for the higher TBI volumes relative to OI group. Finally, a third possible reason for our findings may be related to the effects of injury in developing brains. Developmentally, children undergo synaptic pruning and an interruption in this process due to injury may explain higher volumes in the TBI group. According to Wen, Li, Shen, and Chen (2017), TBI-induced physiological changes introduce neuroinflammation and interrupt healthy proinflammatory cytokine production necessary for synaptic plasticity. The resulting excessive secretions and microglia cause an impairment in synaptic pruning and disrupt synaptic plasticity. According to the authors, no studies to date have investigated this phenomenon in the context of a TBI. Thus, decreased pruning post-injury may result in higher brain volume in children during the chronic phase of a TBI.

In regard to the significant difference in volume occurring solely in the DMN, the majority of the participants with identified lesions, had lesions located in the DMN (53%). Within the network, 63% of the lesions were in the vmPFC, which is comprised of the frontal pole and medial orbito-frontal cortex. Consistent with the literature, the frontal lobes are particularly vulnerable to injury following a TBI (Wilde et al., 2005). However, the SN and the MN both include various regions of the frontal lobe in the composition of both networks and the frequency of lesion presence also favors the PFC in both networks. Yet neither network was significantly different between the groups when we controlled for age, sex, and total brain volume.

Therefore, the next logical explanation for this finding, above and beyond the frequency of lesions present in the vmPFC, may be that a subcomponent region within the vmPFC (e.g., the frontal pole) is more prone to frontal injury than other areas within the PFC or other frontal

areas. The frontal pole has been shown to be vulnerable in acquired pediatric brain injury (Levan et al., 2016) and the white matter in this region undergoes prolonged development (Wilde et al., 2005). This prolonged process could have a unique impact on the long-term volume of this region, particularly in the chronic stage of the injury. Other considerations may include appreciating the location of the lesioned subcomponents. Previous research has identified brain regions located near a bone or in the watershed areas between white and gray matter are more vulnerable to acquired brain injury (Bigler, 2007); whereas components of a network safely located in lateral or posterior cortical areas may be less vulnerable to an acquired brain injury (Wilde et al., 2005). Other considerations beyond the scope of this study include an investigation of neurochemical processes that occur after a brain injury and the downstream effects of these processes on brain volume (Yeates et al., 2009), as well as late effects of a severe TBI on brain atrophy (Merkley et al., 2008). Finally, given the heterogeneity in brain lesions and levels of injury severity that result from TBI in children (Bigler, Abildskov, et al., 2013), it may be important to categorize the results of this finding by injury severity to elucidate nuanced differences within the TBI group.

***Developmental implications.*** As children with TBI develop into adults, the reduced DMN volume, particularly involving the prefrontal cortex, may have long term consequences. Historically, neuroscience research has clarified the relationship between specific brain regions and specific cognitive functions such that a lesion in this area would result in specific cognitive impairment. For example, the famous case of patient “Tan” demonstrated that lesions to the third frontal convolution of the left frontal lobe (now referred to as the Broca’s area) resulted in impaired articulated speech, outlining the role of the Broca’s area in speech (Broca, 1861). However, studying deficits as a consequence of an injury is broadly applicable to adults, after

brain maturation. Contemporary studies are beginning to show that early insult to the developing brain can result in damage to the development of entire brain networks. For example, Spencer-Smith and Anderson (2009) discuss brain development following an injury, stating this process often requires the allocation of additional resources recruited from healthy areas of the brain. In particular, the PFC has an extended developmental trajectory that has long term implications if injured during the maturation process. If a brain injury were to occur during the maturation process and prematurely prevent full development of the PFC, the child may have to compensate by allocating additional resources from healthy brain regions to function at levels similar to their typically developing peers for a long period of time. The long-term use of additional resources could result in future cognitive inefficiencies and these types of problems can place a child at risk to fall behind in the classroom, a location for major social development. Difficulties in this milieu as a result of inefficient cognitive function (e.g., poor grades) can result in social difficulties (e.g., being isolated as the one with poor grades) and related behavioral problems (e.g., depression related to poor self-concept and/or acting out of frustration).

**Aim 2.** Although approximately half of the participants with a brain injury had an observable lesion on a brain scan, nearly all participants had lesions in more than one network (lesions location is outlined in Table 4). However, a few TBI participants (n=5) had injuries exclusively in the MN resulting in lower total MN volume. Per our previous discussion, the composition of the MN (please see Table 1) includes areas of the brain most commonly impacted in acquired brain injury due to proximity to bony areas and brain regions prone to shearing injury.

While lesions located within a network may in fact cause decreased total network volume, there may be alternative explanations. For example, the subcomponent regions of the

MN may be more substantial in size relative to the subcomponents of other brain networks. Although this was not formally assessed in this study, qualitatively, regions expanding an entire gyrus or sulcus, such as the superior temporal sulcus in the MN, may be larger in size compared to individual subcomponent regions of the PFC that is included in each of the three large scale networks (i.e., dmPFC in the MN, vlPFC in the SN, and vmPFC in the DMN). Thus, an injury to one subcomponent area of the MN may have a drastic or more direct impact on the total network volume because one region may contribute more to the total network volume, relative to the composition of the other networks. Additionally, as previously stated, it may be important to analyze these results by injury severity to understand any other meaningful differences relevant for this finding. Bigler, Abildskov, et al. (2013) suggested that injury severity can serve as a correlate for the size of the lesion, particularly with severe brain injuries; therefore, appreciating injury severity in conjunction with lesion type and location may be necessary for a richer understanding of these findings.

A closer look at the TBI participants with lesions in the MN showed that the majority of these participants (n=4 out of 5) had only one lesion in the network (see Table 9), rather than multiple lesions. Therefore, this finding implies underlying connectivity unique to the subcomponent areas of the MN such that an injury to one subcomponent area could cause a significantly reduced overall network volume. The likely etiology may be multifocal, including potential Wallerian degeneration or neurochemical or neurometabolic changes, both previously considered and continue to remain beyond the scope of the current study. Unfortunately, robust conclusions are difficult to draw given the limited number of participants driving this finding.

Table 9

*Lesions in Subcomponent Regions of the Mentalizing Network*

Participants	dmPFC	STS	TPJ	TP	Total Lesions
1			x		1
2		x		x	2
3	x				1
4		x			1
5	x				1
Total	2	2	1	1	6

*Notes.* Participants included are those with TBI and lesions exclusively in the mentalizing network; dmPFC = dorsomedial prefrontal cortex; STS = superior temporal sulcus; TPJ = temporo-parietal junction; TP = temporal pole; The makeup of these subcomponents can be found in Table 1.

**Aim 3.** Within the three networks investigated in this study, only the low MN volume significantly predicted worse internalizing (mood and somatization symptoms) and externalizing (hyperactivity and aggression) behaviors. The MN is associated with the ability to think about the mental state of oneself and of other people (Dennis et al., 2013). It is also associated with perspective taking, “the ability to understand the intentions, desire, [and] beliefs of another person, resulting from (cognitively) reasoning about the other’s state” (Hein & Singer, 2008, p. 154). On the social outcome measure, the internalizing composite included the anxiety, depression, and somatization subscales which represent internal experiences or over-controlled behaviors. The externalizing composite includes the hyperactivity and aggression subscales characterized by disruptive behaviors. Furthermore, both composites are related to complications

with developing healthy peer relationships (Reynolds & Kamphaus, 2004). Therefore, the results suggest not only that low MN network volume, with perspective taking as a predominant feature of the network, could be related to difficulties with mood (anxiety and depression) and reactivity (disruptive behaviors), but injury to the Mentalizing Network may also affect the development of healthy peer relationships.

***Social implications.*** This finding is in line with the current literature when assessing the subcomponent regions of the MN and the relation to social function. Wagner, Kelley, Haxby, and Heatherton found the dmPFC (a subcomponent of the MN, see table 1), historically implicated in social cognition, also has a “dominant function in everyday situations to support reasoning about the thoughts and intentions of conspecifics” (2016, p. 6917). Nelson, Jarcho, and Guyer (2016) summarized that regions such as the fusiform face area, superior temporal sulcus (STS), and the temporo-parietal junction (TPJ; both the STS and TPJ are subcomponent regions of the MN) are selectively sensitive to social stimuli at least by early childhood and are fine tuned for social responses through childhood development. Similarly, Simon, Gomez, Nadel, and Scalf (2017) recently confirmed the historical notion that the (TPJ) is critical to determining the degree to which situations or personal actions vary from expectation in college aged adults.

On the one hand, in the context of the main function of the network (i.e., assessing the mental state of oneself and of other people), this finding is unsurprising (Dennis et al., 2013). On the other hand, this finding is novel and has important implications for social development. When considering the link between low MN volume and impaired ability to accurately detect changes in social communication or the intention of others, it is conceivable that this could impact the person’s emotional state. For example, incorrectly interpreting nuanced social information could create self-doubt and impact mood. Alternatively, difficulty appreciating the

nuance in social information could lead to frustration (reactivity; disruptive behaviors). These types of social experiences over time could certainly lend themselves to difficulties with initiating or maintaining healthy peer relationships.

Previous social cognitive neuroscience studies, outlined by Yeates et al. (2007), describe the relationship between taking on more complex social behavior and the development of brain regions implicated in social behavior. Furthermore, the PFC is particularly slow to mature and undergoes synaptogenesis as part of its maturation process during this critical period. Therefore, the implication of the findings could vary significantly depending on the location of the injury, the age at which the injury is incurred, and the developmental phase of the child at the time of injury. That is to say, the association between network volume and a child's potential to manage complex social interactions may also depend on the developmental stage at the time of injury.

Additional considerations to interpret the finding includes a review of the statistical analyses. The analyses in hypothesis three did not distinguish between the TBI and OI groups, rather the results included all of the participants. Although this allows for the generalizability of the conclusions regardless of injury type, it may also explain why the first finding (i.e., DMN volume varied between the two groups) did not carry forward into the final analysis where the DMN volume was not related to social function. The DMN, for all intents and purposes should have been linked to internalizing and externalizing behaviors because not only is this network involved in self-related cognitive activity, it was also trending toward significance and different between the two groups in Specific aim 1. It was curious that the differences did not carry over into Specific aim 3; however, the group differences were not considered. An additional positive consideration for the relevance of the finding is that while there is a plethora of data on the DMN, there is very little known about the practical social functions of the MN, particularly

during development and in a brain injured population. Therefore, these findings add to the literature in defining the core features of the MN.

### **Limitations**

The current study has a number of limitations including the use of a subsample from two larger archival datasets. Each of the original datasets had varying aims, thus the available measures between the two sets also varied significantly. As a result, we were unable to prospectively select behavioral measures to assess social outcomes. Despite this limitation, the internalizing and externalizing composites of the BASC-2 remain a valid source of behavioral and emotional functioning; thus, these composites represent core components of social interactions. That said, the BASC-2 is a broad-based questionnaire with data collected based on parent report. As a result, the data may not be as sensitive in representing the difficulties experienced by the participants (i.e. internalizing symptoms) compared to outward manifestations of problematic behavior (i.e. externalizing symptoms). Also, the parent report of child function may be colored by the parent's mental health and ability to manage their post-injury experience (Catroppa et al., 2017). In addition, the varied data collection methods led to data missing at random, resulting in uneven observations in variables investigated this study. These datasets also included an orthopedic injury group as a control group. Historically there has been some controversy as to the difference between those with a mild TBI and an extracranial orthopedic injury. Wilde et al. (2018) recently conducted a longitudinal study of DTI metrics (i.e., FA and MD) between children with a mild TBI, an extracranial OI group, and a non-injured typically developing control group. Comparing DTI metrics shortly after an injury and 3 months post-injury, the study largely found similarities in the FA and MD of the mild TBI and OI groups both in the subacute and longitudinal stage of the injury. However, significant differences were

consistently found between the mild TBI and TD group, even over time. Therefore, whenever possible, studies including participants with a mild TBI should include a TD and an OI control group for a more nuanced and accurate interpretation of results.

Although statistical analyses accounted for uneven observations, additional participants in each of the proposed analyses may have improved statistical power and provided more robust results. Despite the use of two datasets and an overall participation of more than 180 subjects, additional participants could have mitigated the significant heterogeneity in lesion type and lesion location. That said, our analyses were also fairly restrictive. First, the exclusions in Specific aim 2/second hypothesis resulted in very few cases for each analysis. Second, the analyses conducted between the TBI and OI groups did not differentiate between TBI severity, instead we grouped all of the TBI participants together. Previously, TBI participants with a complicated mild TBI have shown different lesion patterns and smaller lesion size compared to participants with a severe TBI (Bigler, Abildskov, et al., 2013). Therefore, considering injury severity could have allowed for more robust and meaningful results. A potential confound that was not considered explicitly in this project was age at injury; given the remarkable developmental patterns present for this age group, controlling for age at injury may account for some of the variance in the results and allow for more meaningful assertions.

Neuroimaging data was collected for both original datasets using the most advanced neuroimaging technology available at the time. However, imaging has advanced significantly and advanced imaging (i.e., higher magnetic field strength) may have improved detection of more subtle injuries, which may have been unappreciated in the lesion analysis for the present study. That said, each scan in this study was reviewed individually by a trained neuroradiologist. The volumetric data in this study was gathered using an automated procedure within FreeSurfer,

which has its own limitations (Gronenschild et al., 2012). However, all efforts were made to conduct analyses on one operating system, separately for each dataset (defined elsewhere for the SOBIK study Bigler, Abildskov, et al., 2013). Finally, structural imaging protocols in both original datasets did not include diffusion tensor imaging sequences, which may have provided additional information about network connectivity.

## **Conclusions**

This study sought to understand the long-term impact of TBI on large scale brain networks. Indeed, the DMN volume was reduced in children with a TBI relative to the OI group in the chronic stage of an injury. In fact, various types of lesions located within the MN decreased total MN volume. Further, low MN volume was related to worse internalizing and externalizing behaviors in children.

Our findings have developmental implications for injuries incurred early in life. Children with a TBI and low DMN volume due to lesions in areas of the brain that still require additional development to be fully functional may need ongoing allocation of cognitive resources from healthy brain regions to compensate and function at similar levels to their peers. Furthermore, this need for additional resources could cause cognitive inefficiencies in the long run and contribute to concomitant behavioral difficulties.

In addition, the present study added clarity to the core functions of the MN network. First, the study highlighted a potential underlying connectivity unique to the MN as total MN volume loss resulted from a lesion located in a single region within the network. The study also found that low MN volume was related to behaviors reflective of internal experiences such as anxiety and depression, as well as aggressive or hyperactive behaviors. More interestingly, low MN volume was related with a difficulty to maintain healthy peer-relationships. Finally, the

weaknesses in this study emphasize the importance of considering injury severity when investigating TBI, as the lesion patterns are heterogeneous and vary significantly between TBI severity.

### **Future Directions**

Going forward, studies investigating networks impacted by TBI should, at least in part, incorporate some of the nuances described above (i.e., subdivide the TBI group by injury severity, consider unique maturation patterns, etc.) to allow for more generalizable and robust results. Furthermore, when studying networks, it is important to consider the white matter associations in addition to the gray matter regions of the large scale brain network. Therefore, future studies should also incorporate white matter volumes and/or sophisticated neuroimaging sequences specific to white matter connectivity (i.e., diffusion tensor imaging), where possible, for a clearer understanding of the underlying network connectivity.

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