Objective: Magnetic resonance imaging (MRI) provides a method to identify and quantify abnormalities resulting from traumatic brain injury (TBI). MRI abnormalities in children with TBI have not been fully characterized according to the frequency, location, and quantitative measurement of a range of pathologies critical for studies of neuropsychological outcome. Here, we report MRI findings from a large, multicenter study of childhood TBI, the Social Outcomes of Brain Injury in Kids (SOBIK) study, which compared qualitative and quantitative neuroimaging findings in 72 children with complicated mild-to-severe TBI to 52 children with orthopedic injury (OI). Method: Qualitative analyses of MRI scans coded white matter hyperintensities (WMHs), hemosiderin deposits reflecting prior hemorrhagic lesions, regions of encephalomalacia and/or atrophy, and corpus callosum atrophy and traumatic shear lesions. Two automated quantitative analyses were conducted: (a) FreeSurfer methods computed volumes for total brain, white matter (WM), gray matter (GM), corpus callosum, ventricles, amygdala, hippocampus, basal ganglia, and thalamus along with a ventricle-to-brain ratio (VBR); and (b) voxel-based morphometry (VBM) to identify WM, GM, and cerebrospinal fluid. We also examined performance on the Processing Speed Index (PSI) from the Wechsler Intelligence Scale for Children, Fourth Edition, in relation to the above-mentioned neuroimaging variables. Results: WMHs, hemosiderin deposits, and focal areas of encephalomalacia or atrophy were common in children with TBI, were related to injury severity, and were mostly observed within a frontotemporal distribution. Quantitative analyses showed volumetric changes...
related to injury severity, especially ventricular enlargement and reduced corpus callosum volume. VBM demonstrated similar findings, but, in addition, GM reductions in the inferior frontal, basal forebrain region, especially in the severe TBI group. The complicated mild TBI group showed few differences from the OI group. PFI was significantly associated with global atrophy, as measured by VBR. Conclusion: MRI findings after childhood TBI are diverse and particularly influenced by injury severity, and they involve common features, group heterogeneity, and individual variability.

**Keywords:** pediatric, traumatic brain injury, magnetic resonance imaging, heterogeneity, hemosiderin, white matter hyperintensities, atrophy

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One of the challenges in understanding how pediatric traumatic brain injury (TBI) affects the brain is how to interpret variability in different lesion types and locations. Lesion heterogeneity represents a major problem in relating lesion types and location to TBI outcomes because trauma has the potential to induce scattered patterns of damage, even within the same level of injury severity (Saatman et al., 2008). Although some patterns of brain injury are common after childhood TBI (e.g., petechial hemorrhages in white matter [WM] tracts; see Maxwell, 2011), considerable heterogeneity exists in the presence and location of traumatic insults detected by magnetic resonance imaging (MRI). A key question is whether heterogeneity is error variance or principled patterns of brain insult.

Because each TBI occurs in unique and highly individualized circumstances, neither the impact biomechanics nor individual genetic and experiential background of any two injured individuals is ever identical (Saatman et al., 2008). Nevertheless, some causes of injury involve similar mechanisms, and some brain regions are more vulnerable than others to injury, and therefore more commonly damaged. Given the shape of the skull and how the brain is held in situ, focal contusions occur often in frontotemporal regions and produce a frontotemporal distribution of cortical atrophy (Bigler, 2007a; Levine et al., 2008). WM tracts are also more vulnerable to injury because of the influence of acceleration–deceleration and rotational forces and their direct exposure to shear and strain forces (McAllister et al., 2012; Ropper & Gorson, 2007).

Multiple lesion types may be identified in MRI studies depending on the sequence used and time postinjury (Bigler, 2007b; Bigler & Maxwell, 2011). The child depicted in Figure 1 sustained a severe TBI associated with a depressed skull fracture and underlying contusion. Localized frontal encephalomalacia is readily identifiable, but how should this abnormality be described and quantified? Damaged tissue degenerates in response to injury, leaving areas of reduced parenchymal volume within the general region of interest (ROI), associated with a focal increase in the amount of cerebrospinal fluid (CSF), and often accompanied by residuals of the original hemorrhagic contusion as by-products of degraded blood, referred to as hemosiderin, which appears as a hypointense or dark signal in what should otherwise be normal appearing parenchyma (Bigler & Maxwell, 2012).

Although hemosiderin may be detected by several different types of MRI sequences, those that employ a gradient recalled echo (GRE) or variant thereof (see Figure 1) are most sensitive. Signal differences in WM are particularly evident in TBI, and the fluid attenuated inversion recovery (FLAIR) sequence is especially sensitive in detecting trauma-related WM signal abnormalities (see

![Figure 1](image-url). Types of abnormalities in a single subject in the Social Outcomes of Brain Injury in Kids study. Axial images at similar levels of T2 (left), fluid attenuated inversion recovery (middle), and gradient recalled echo (right) depicting various types of abnormalities (top and middle rows). Top right arrow points to hemosiderin deposition at the site of a previous contusion from a frontal impact associated with a depressed skull fracture in that region. Middle arrow left points to focal regions of increased cerebrospinal fluid and also detectable are signal intensity differences in the white matter, especially the prominent periventricular hyperintensity (middle arrow). Bottom row shows T1 images with arrow pointing to the region of encephalomalacia. Bottom middle shows slice orientation for the T1 image to the left (red arrow) and coronal image through the lateralized frontal encephalomalacia (blue arrow).
signal in the frontal WM surrounds the divot that resulted from the original frontal skull fracture and contusion. A focal hyperintense signal is shown in the periventricular region as well, adjacent to the right anterior horn of the lateral ventricle and the entire right frontal WM signal intensity is different compared to the left. The T1 anatomical MR sequence is well suited for identifying surface areas of encephalomalacia and focal atrophy, especially when viewed in conjunction with the T2 sequence, which highlights CSF (compare the T1, FLAIR, and T2 sequences in Figure 1). Thin-slice T1-weighted images with no gaps between slices provide the basis for volumetric computation of any ROI facilitated by the development of computer-assisted methods (Bigler et al., 2010).

A variety of qualitative rating methods can be used reliably to identify the type, size, and location of MRI abnormalities (Bigler, 2007b). Although sophisticated quantitative image analysis methods have rigid acquisition parameters and formatting requirements, even artifact or distortion problems caused by movement, dental braces, or postsurgical implants or defects often do not preclude qualitative ratings of pediatric TBI scans. A simple qualitative coding involves the presence or absence of any brain abnormality and its general location (Max et al., 2011).

Voxel-based morphometry (VBM; Ashburner & Friston, 2001), which assesses quantitative changes after TBI, involves segmenting the image into WM, gray matter (GM), and CSF space, followed by image smoothing and normalization within a uniform three-dimensional space, typically within what is referred to as Talairach or Montreal Neurological Institute space. Whole brain and regional differences in pixel density provide the basis for comparing a TBI group to a comparison group. Because VBM comparisons depend on the number and consistency of voxel differences occurring within an ROI, the VBM averaging method is not likely to detect subtle, widely distributed, or regionally infrequent abnormalities (Bruggemann et al., 2009); however, VBM techniques will identify distinct pathological differences when a sufficient number of individuals have similar changes occurring within a particular ROI (Gale, Baxter, Roundy, & Johnson, 2005).

The Social Outcomes of Brain Injury in Kids (SOBIK) investigation (Dennis et al., 2012; Yeates et al., 2013) provides an ideal dataset to investigate patterns of qualitative and quantitative lesion heterogeneity in children with TBI. This multicenter pediatric sample of 8–13-year-old children consists of 143 participants, 127 of whom underwent MRI scanning with usable scan data from 72 children with complicated mild-to-severe TBI, as well as 52 children with orthopedic injuries (OI), group-matched for demographic features. This study describes the nature, location, and type of brain pathologies in a large sample of children with TBI from the SOBIK study and how different neuroimaging analysis methods characterize the damage.

This report had two objectives. The first was to investigate lesion patterns in this diverse, multisite pediatric sample to address the following key questions. How frequent are different forms of MRI pathology in a large pediatric TBI sample compared to a control group with OI? Do these lesions consistently occur in similar locations, and do they overlap? How is injury pathology related to lesion severity as defined by clinical presentation, for example, Glasgow Coma Scale (GCS) score (Teasdale & Jennett, 1974)? What do volumetric and VBM studies reveal about pathological changes after pediatric TBI? We predicted that pediatric TBI would produce a variety of lesion types, but that, as documented in adults (Bigler, 2007a; Levine et al., 2008), lesion location would most commonly involve frontal and temporal lobes. We also predicted that volume loss and VBM findings would be most prominent in children with GCS-defined severe TBI.

The second objective—given the different ways that TBI-related neuropathology can be expressed—was to determine how neuropsychological studies of pediatric TBI outcome should use neuroimaging variables. For example, processing speed is often reduced in pediatric TBI with the deficits thought to reflect, in part, WM integrity (Anderson, Godfrey, Rosenfeld, & Catroppa, 2012; Kourtidou et al., 2012; Wozniak et al., 2007). Similarly, the presence of hemosiderin in TBI is considered a marker of shear injury and diffuse axonal damage (Beauchamp et al., 2013). Thus, although numerous neuroimaging indicators of brain pathology are now identifiable, which indicator should be used to examine neuropsychological outcome? To keep the second objective narrow and focused, for the current study, we used just the Processing Speed Index (PSI) from the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003) and examined PSI performance in relation to various quantitative and qualitative neuroimaging indicators.

**Method**

**Participants**

From 2006–2010, a total of 143 participants were recruited into a multisite (Toronto, Canada, Columbus, Ohio, and Cleveland, Ohio) study of social outcomes in children with TBI, 124 of whom underwent MRI scanning at a minimum of 6 months postinjury (see Figure 2). The study was conducted in accordance with established ethical guidelines, and received institutional ethics approval from all three neuroimaging sites (The Hospital for Sick Children and the University of Toronto, Rainbow Babies & Children’s Hospital and Case Western Reserve University, and The Research Institute at Nationwide Children’s Hospital and The

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Diagram depicting distribution of traumatic brain injury subjects by injury classification and severity and those with orthopedic injury as well as sample sizes used for qualitative and quantitative image analysis. SOKIK = Social Outcomes of Brain Injury in Kids; TBI = traumatic brain injury; OI = orthopedic injury.
Ohio State University) and the neuroimaging analysis site (Brigham Young University); written informed consent was obtained from all participants. The TBI group was composed of 82 children who experienced TBIs resulting in hospitalization and who had a recorded day-of-injury (DOI) postresuscitation GCS score of 12 or less, or a score of 13–15 with positive imaging for brain insult or skull fracture. Sample sizes per injury severity are given in Figure 2; TBI severity was based on GCS score, with severe level of injury identified as 8 or less, moderate as 9–12, and complicated mild as 13–15; the presence of skull fracture and/or some form of acute intracranial hemorrhage or identifiable edema on the computed tomography (CT) scan was required in conjunction with a GCS score greater than 12 to meet inclusion criteria for the complicated mild TBI group. All children had DOI clinical neuroimaging, but presence of acute abnormality was only a criterion for the mild-complicated group. Dennis et al. (2012) have summarized the CT findings in this sample and the method of rating for coding radiologist reported pathology for CT-focal injury (maximum score = 6) and CT-diffuse ratings (maximum score = 7). For the 61 children with OI (n = 52 scanned), some form of OI had occurred, but the GCS score had to be recorded as 15 with no diagnosis of TBI or facial fractures or other indications of possible head injury. Participant and demographic information is provided in Table 1, including Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) scores, WISC-IV PSI scores, age at injury, and age at time of testing (MRI and neurobehavioral assessments).

Usable clinical rating data were available from most scans (TBI: n = 72; OI: n = 52; see Figure 2). Reasons for exclusion were poor scan quality as a result of movement (five subjects) or artifact (seven subjects, most often postsurgical for the TBI participants or from dental braces) or incomplete imaging sequences due to claustrophobia, equipment failure, or participant noncompliance (seven subjects; note that some participants had dual reasons for incomplete scanning). Because of the magnitude of prominent localized regions of encephalomalacia in severe TBI or postsurgical changes, parenchymal distortion can become so significant that it precludes automated image analysis, because defining boundaries for image parcellation are either absent and/or distorted, which was the case with two of the children with severe TBI. We were not aware of bias for those scanned versus not scanned, but this could not be explicitly tested.

## Magnetic Resonance Imaging

MRI was performed during the chronic phase of injury (minimum = 6 months postinjury; average = 2.7 years posttrauma), when lesion type and location have stabilized (Blatter et al., 1997; Ross, 2011; Warner et al., 2010). Magnetic field strength was 1.5 T for all studies. The Toronto and Columbus sites used GE Signa Excite scanners and the Cleveland site used a Siemens Symphony scanner. All sites acquired the following sequences on each participant: thin slice, volume acquisition T1-weighted ultrafast 3-dimensional gradient echo, commonly referred to as MPRAGE or FSPGR (depending on scanner manufacturer) for FreeSurfer and VBM analyses; a dual-echo proton density (PD)/T2-weighted sequence; FLAIR; and GRE. Identical phantom imaging was performed at the beginning to check the uniformity of image acquisition and image quality across the multiple sites.

Qualitative ratings to identify the presence or absence and location of lesion abnormalities (Bigler & Maxwell, 2011) were based on the methods outlined by Bigler (2007b) and Max et al. (2011) and conducted without knowledge of group membership or injury severity. Two of the authors (E. D. Bigler and T. J. Abildskov) were raters trained by clinical neurologists and neuroradiologists following standardization methods previously published (Bergeson et al., 2004; Hopkins et al., 2006). Although all scans were deidentified with no information whether OI or TBI, comp-

### Table 1

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Note. OI = orthopedic injury; TBI = traumatic brain injury; ANOVA = analysis of variance; VBM = voxel-based morphometry; GCS = Glasgow Coma Scale; WASI = Wechsler Abbreviated Scale of Intelligence; WISC-IV PSI = Wechsler Intelligence Scale for Children, 4th edition, Processing Speed Index.

*p ≤ .001.
plete masking of raters to group was not possible, because many
scans included obvious trauma-related pathology. Ratings of focal
tencephalomalacia and atrophy were based on any sequence, but
ratings of WM signal abnormalities were based on the PD/T2 and
FLAIR sequences, with hemosiderin identified on the PD/T2 and
GRE sequences. Clinical identification of FLAIR-identified signal
abnormalities, including presence of WM signal abnormalities and
WMHs and of GRE and PD/T2-identified hemosiderin deposits
and localized encephalomalacia and focal atrophy, was conducted
separately for frontal, temporal, and parieto-occipital regions and
plotted on standard axial images. Disagreement in rating was
resolved by consensus.

Large hemorrhagic lesions occurred in conjunction with focal
tencephalomalacia, and so they were not separately coded. Subcor-
tical hemosiderin deposits were also coded for the basal ganglia
and thalamus. Lesions of any type (i.e., WMH, hemosiderin, and
focal atrophy) were identified in the corpus callosum, together
with presence of corpus callosum thinning. The approximate cen-
ter point of WM findings of hyperintense signal (coded as WMHs,
blue dots in color plots in Figure 3) and hemosiderin deposition
(red dots) were identified and plotted on a conventional axial
T1-weighted image from an OI control. WMHs or hemosiderin
depositions were coded for presence and general location, but not
for size. For focal cortical atrophy, start and stop points were color
coded in green.

For volumetric analyses, the FreeSurfer method used Version
5.1 (surfer.nmr.mgh.harvard.edu) and followed the methods de-
tailed by (Bigler et al., 2010). For VBM, an extension of the
Statistical Parametric Mapping, Version 8 (SPM8), software
(www.fil.ion.ucl.ac.uk/spm), and the VBM8 toolbox (dbm.neur-
o.uni-jena.de/vbm8) was used. Images were corrected for any
bias-field inhomogeneity, registered using linear (12-parameter
affine) and nonlinear transformations along with GM and WM
tissue and CSF classification within the same generative model

Figure 3. Location of visually identifiable focal abnormalities in the Social Outcomes of Brain Injury in Kids
cohort plotted on a T1-weighted image from a control subject where blue dots signify location of distinct
white-matter hyperintensities, red dots reflect areas of hemosiderin deposition, and green depicts location and
extent of focal atrophy or encephalomalacia. Differences in shade of green reflect differences in overlapping
regions where lighter green indicates more than one participant had abnormalities in that region. Yellow outlines
some of the extensive focal pathology for the subject with severe traumatic brain injury with the most substantial
pathological changes. L = left; R = right; TBI = traumatic brain injury; WMH = white-matter hyperintensity.
Types of Lesions

Each scan was reviewed for distinct signal abnormalities identifiable within the WM on FLAIR or T2 sequences summarized as WMHs, focal encephalomalacia, or atrophy, using all image sequences, or hemosiderin deposits on the PD/T2 or GRE sequence, with lesion location graphically depicted in Figures 3 and 4. As predicted, the distribution of traumatic lesions in pediatric TBI was more frequent in frontal and temporal lobe regions and more frequently observed after moderate-to-severe than complicated mild TBI. Irrespective of injury severity, at least one type of the possible abnormalities was present in 49 of the 72 (68%) children with TBI. Comparing lobular location of pathology by injury severity, WMHs approached a significantly higher rate in the temporal lobe in severe TBI ($\chi^2 = 5.80, p = 0.06$) compared to other injury severities. More findings of focal frontal atrophy ($\chi^2 = 7.79, p = 0.02$) were observed in the severe TBI group. Distribution of hemosiderin deposits by lobe did not vary significantly by TBI severity.

Lesion Distribution and Overlap

Figure 3 shows focal encephalomalacia, hemosiderin deposits, and WMHs across the participants with TBI, as plotted on axial images from a control OI subject without identifiable pathology. Lesions were widely distributed, with few overlapping lesions across participants. Distinct areas of focal encephalomalacia overlapped in the frontal region in five participants and the temporal poles in four participants with TBI, and in the right medial temporal lobe in three participants. Regions of overlap are shown in lighter green in Figure 3. Notably, this illustration demonstrates the diversity of traumatic lesions and their dispersion across the brain in a pediatric TBI group.

Lesions by Injury Severity Grouping

Heterogeneity marked the size, location, and distribution of lesions at all levels of injury. Figure 5 characterizes this heterogeneity by showing five complicated mild TBI children, all with different lesion patterns. No child with complicated mild TBI had a large lesion, and, as a group, they most commonly had only one type of pathology. Of the 41 complicated mild TBI children scanned, only four (9.8%) had all three abnormalities, in contrast to five of 20 (25.0%) with severe TBI and one of 11 (9.1%) with moderate TBI. Although lesions were more likely to occur within the frontotemporal lobe distribution, little regional overlap was observed.
apparent (see Figure 5), and no two subjects in any TBI group had completely overlapping lesions. Figure 5 also depicts a solitary WMH in a child with OI, in a characteristic region often observed with TBI (see arrow in Figure 5f and compare to 5d). In terms of lesion size, the largest lesion, of any lesion type, in the complicated mild TBI group was located in the frontal lobe (see Figures 1–4 in the supplemental materials).

Qualitatively, focal lesions in children with moderate or severe TBI were larger than those in children with complicated mild TBI, albeit scattered in a similar manner with the same type of inter- and intraindividual differences (see Figures 1–4 in the supplemental materials). Even after severe TBI, abnormalities ranged from no identifiable abnormalities to small hemosiderin deposits in the thalamus as the only identifiable abnormality to the massive structural damage reflective of multiple types of pathology. When multifocal and/or multiple types of lesions were present in the same child, they were distributed across diverse locations, often quite distal to other types or focal pathology (see Figures 1–4 in the supplemental materials).

Corpus Callosum Quantitative and Clinical Findings

Figure 6 shows the relationship between injury severity and total as well as regional corpus callosum volume. Based on planned comparisons examining the OI and three TBI groups, the severe TBI group had the smallest corpus callosum volume, with all regions significantly reduced in size compared to the OI group. The typical pattern of corpus callosum atrophy was a stair-step decrease in volume with increasing injury severity; when total corpus callosum was examined, the OI group differed significantly from each TBI group.

Eleven children (15.3% of all TBI cases) had some type of visible abnormality of the corpus callosum (see Figure 7) in the form of either generalized thinning, focal lesion (tear-shear lesion and/or hemosiderin deposit) with localized atrophy, and/or focal regional atrophy without identifiable lesion. Eight of the 11 children with clinical ratings of corpus callosum abnormality had sustained a severe TBI (40.0% of all those with severe TBI), whereas only one had moderate TBI (9.0% of all with moderate TBI) and two had complicated mild TBI (4.9% of all with mild TBI).

Deep Hemorrhagic Lesions

Three children, all with severe TBI, had deep hemorrhagic lesions, two in the thalamus and one in the midbrain (see Figure 2 in the supplemental materials).

Quantitative MRI Analyses

Volumetric analyses. Because total intracranial volume (TICV) did not differ significantly in the three TBI and OI groups,
and because VBR automatically adjusts for head size differences, we did not further control for head size in the planned statistical comparisons involving parenchymal volume measurements. Histograms reflecting mean group volume differences are presented in Figure 8 for TBV, VBR, total ventricle, WM, GM, hippocampus, amygdala, thalamus, and basal ganglia, all of which differed significantly in the severe TBI group relative to the complicated mild TBI and OI groups. Group average volume loss or VBR expansion

Figure 6. Quantitative volumetric comparisons of total and regional corpus callosum by injury severity in the Social Outcomes of Brain Injury in Kids sample. Corpus callosum volumes in all regions were smallest in the severe traumatic brain injury group, and all group differences remained significant after correcting for age, sex, and intracranial volume. Note that the y axis differs for each plot, due to variance in volume measures for each corpus callosum region of interest. For each significant planned comparison, the p value is shown on the horizontal line at the top of each histogram, where vertical bars represent 95% confidence intervals. CC = corpus callosum.

Figure 7. Three types of corpus callosum pathology were identified in the Social Outcomes of Brain Injury in Kids sample: generalized corpus callosum atrophy with shear lesions combined with focal regional atrophy (on the left, there is overall thinning of the corpus callosum with multiple shear lesions in the posterior midbody and isthmus and distinct atrophy of the splenium; note the signal-intensity differences in the posterior corpus callosum, reflecting both focal pathology and nonspecific thinning effects observed elsewhere) (a); generalized corpus callosum thinning without identifiable shear lesions (in the middle scan, the corpus callosum is thinned in appearance from the genu to the splenium) (b); and generalized atrophy of the corpus callosum with focal lesions (c).
was conservative, because the massive structural damage in two severe TBI cases (one shown in the yellow lesion outline in Figure 3) could not be quantified in FreeSurfer (the automated program was unable to follow the surface geometry of the brain).

**VBM analyses.** Multiple VBM analyses explored group differences in regional WM, GM, and CSF pixel concentration. Largest group differences ($p < .001$) were between the severe TBI and both complicated mild TBI and OI groups. The largest regional differences were in the lateral ventricles for CSF analyses, corpus callosum for WM analyses, and ventral frontal and basal forebrain regions for GM analyses (see Figure 9).

**Figure 8.** Quantitative volumetric comparisons for total brain volume, gray matter, white matter, ventricular, amygdala, hippocampus, basal ganglia, and thalamus in the Social Outcomes of Brain Injury in Kids sample. Planned comparisons demonstrated that the severe traumatic brain injury group had significantly lower volume on all volumetric measures. For each significant planned comparison, the $p$ value is shown on the horizontal line at the top of each histogram, where vertical bars represent 95% confidence intervals. TBV = total brain volume; VBR = ventricle-to-brain ratio; WBTGM = whole brain total gray matter; WBTWM = whole brain total white matter.

**PSI and Neuroimaging Relationships**

WISC-IV PSI performance did not differ significantly across the three injury severity levels examined and OI children as shown in Table 1. WISC-V PSI performance was not related to DOI CT findings (see Figure 5 in the supplemental materials). Figure 10 compares WISC-V PSI performance across several volumetric measures (i.e., TBV, VBR, total WM and GM volume, and total and posterior corpus callosum volume) with the moderate-to-severe TBI groups combined into a single group. As visibly shown in Figure 10, regardless of which metric was used, while greater
ary axotomy (Bigler & Maxwell, 2012). Similarly regions of focal traumatic axonal injury resulting from primary as well as second-order, especially in conjunction with WMH in TBI, is thought to reflect mostly nonoverlapping (see Figure 3). Hemosiderin deposition, Marquez de la Plata et al., 2007), but were widely distributed and temporal lobe regions (consistent with observations in adult TBI; Consistent white matter (WM) loss was present within the anterior and posterior aspects of the corpus callosum, and also includes part of the fornix, gray matter (GM) loss within the basal forebrain, and generalized ventricular cerebrospinal fluid (CSF). For CSF and WM VBM findings, all voxels displayed remained significant after multiple comparison corrections at a false-discovery rate (FDR) of 0.05. However, only those reflected in white remained significant after FDR correction for GM. Similar results were obtained when the complicated mild TBI subjects were compared to the severe TBI group (results not shown). Comparisons of the complicated mild TBI and OI groups were not significant.

Figure 9. Voxel-based morphometry (VBM) comparisons between all participants with severe traumatic brain injury (TBI) versus all orthopedic injury (OI) controls in the Social Outcomes of Brain Injury in Kids sample. Consistent white matter (WM) loss was present within the anterior and posterior aspects of the corpus callosum, and also includes part of the fornix, gray matter (GM) loss within the basal forebrain, and generalized ventricular cerebrospinal fluid (CSF). For CSF and WM VBM findings, all voxels displayed remained significant after multiple comparison corrections at a false-discovery rate (FDR) of 0.05. However, only those reflected in white remained significant after FDR correction for GM. Similar results were obtained when the complicated mild TBI subjects were compared to the severe TBI group (results not shown). Comparisons of the complicated mild TBI and OI groups were not significant.

Discussion

Using a range of MRI-derived metrics, we identified a variety of heterogeneous lesion patterns and parenchymal volume loss in children with TBI. Injury severity predicted lesions and volume loss where more severe injuries were associated with larger lesions, more generalized WM and GM volume loss, and increased CSF, as well as greater whole brain volume loss. For severe TBI, the most robust volume difference involved concomitant reductions in corpus callosum and increase in ventricular volume. The VBR measure, which indexes TBV loss combined with ventricular expansion and adjusts for head size differences, was a particularly robust indicator of whole-brain trauma-induced changes related to severity of injury (see Figure 8). The complicated mild TBI group showed few differences from the OI group, aside from volume loss in the corpus callosum.

Focal WM signal abnormalities and WMHs, along with areas of hemosiderin deposition, were located predominantly in frontal and temporal lobe regions (consistent with observations in adult TBI; Marquez de la Plata et al., 2007), but were widely distributed and mostly nonoverlapping (see Figure 3). Hemosiderin deposition, especially in conjunction with WMH in TBI, is thought to reflect traumatic axonal injury resulting from primary as well as secondary axotomy (Bigler & Maxwell, 2012). Similarly regions of focal encephalomalacia were generally in a frontotemporal distribution. It should be emphasized that inclusion criteria required either a GCS score below 12 or a positive DOI CT image in those with GCS scores of 13–15, thus no children with uncomplicated mild TBI were included.

Volumetrically, all parenchymal ROIs exhibited volume loss related to injury severity particularly notable in the severe TBI group. This pattern of general ROI volume loss in pediatric TBI is similar to that reported in adults (see Blatter et al., 1997; Levine et al., 2008). Overall CSF increased, especially prominent as lateral ventricular enlargement. Ventricular expansion in TBI, assuming that ventricular foramina are not obstructed, is termed hydrocephalus ex vacuo and reflects parenchymal volume loss, especially WM (Bigler & Maxwell, 2011, 2012). The concurrent increase in ventricular size with WM volume loss, especially in the corpus callosum, has been attributed to greater selectivity of WM damage in TBI. In addition, the corpus callosum is the WM structure most vulnerable to TBI (McAllister et al., 2012). As our VBM analyses demonstrate (see Figure 9), periventricular WM volume loss likely results in disproportionate ventricular dilation (Bigler & Maxwell, 2011, 2012), not surprising given that WM surrounds most of the lateral ventricle, with the base of the corpus callosum forming the upper boundary of the lateral ventricular cavity. Ventricular expansion, therefore, represents a proxy marker of WM loss. Given these markers of extensive WM damage in TBI related to severity of injury, such damage likely results in widespread disruption of inter- as well as intrahemispheric connectivity (see Pannek et al., 2011).

VBM differences in the severe TBI group occurred in predicted areas, and included reduced WM of the corpus callosum and GM loss within the basal forebrain, along with ventricular dilation (see Figure 9), as in adult studies (Levine et al., 2008; Rao et al., 2010). VBM analyses between the moderate TBI and other groups was limited by a lack of statistical power, with only nine children
having usable scans meeting criteria for moderate TBI, three of whom had no visible intracranial abnormalities. Nonetheless, the distribution of affected areas was similar to that in the severe TBI group, but did not remain significant after FDR correction.

Aside from loss of corpus callosum volume, the complicated mild TBI group was generally similar to the OI group, not surprising because almost half of the children with complicated mild TBI had no visible intracranial abnormality at the time of the study and those with abnormalities showed widely distributed findings with little overlap. The presence of CT-identified skull fracture and/or some form of acute intracranial hemorrhage or identifiable edema was required in conjunction with a GCS score greater than 12 to meet inclusion criteria for the complicated mild TBI group; however, such acute DOI pathology did not guarantee that chronic MRI abnormalities could be detected with the VBM or FreeSurfer volumetric methods. The lack of significant VBM findings in the mild-complicated TBI group is not surprising, given the basically nonsignificant ROI volumetric findings.

Aside from TBI severity effects, TBI-specific MRI abnormalities were identified where hemosiderin deposits or areas of focal encephalomalacia were observed only after TBI and not after OI. Also, some nonspecific findings were noted: WMHs in three OI children; small arachnoid cysts (two children with OI and one child with TBI), presumably congenital (Al-Holou et al., 2010); cavum septum pellucidum (one child with TBI); and congenital abnormality of posterior corpus callosum (one child with TBI). Control groups often show incidental MRI findings, including WMHs (Hartwigsen, Siebner, Deuschl, Jansen, & Ulmer, 2010; Hopkins et al., 2006), and isolated WMHs because the only MRI signal abnormality in TBI is not a definitive indicator of WM injury. Greater confidence in the traumatic origin of WMHs can be made in TBI when associated with an adjacent hemosiderin deposit or focal encephalomalacia (Gean & Fischbein, 2010).

Turning to neuropsychological outcome, PSI relationships with neuroimaging variables depended on the metric and group. As shown in Figure 10, only one general metric of brain integrity, the VBR, related robustly with PSI and only in the combined group with moderate-to-severe injury. In TBI, the VBR metric represents a nice summary measure of global brain atrophy, as well as concomitant WM loss (see Tate et al., 2011). Because most of the periventricular

Figure 10. The relationship between processing speed and various morphometric measures shows in general slower processing speed associated with less volume, and the only significant correlation was within the moderate-to-severe traumatic brain injury combined group and ventricle-to-brain ratio (VBR). Processing speed was based on the Wechsler Intelligence Scale for Children, 4th Edition (Wechsler, 2003). The y axis reflects volume in cubic millimeters, except for the VBR, where the y axis reflects the ratio (total ventricular volume/total brain volume × 100). WISC = Wechsler Intelligence Scale for Children; CC = corpus callosum; mTBI = mild traumatic brain injury; Mod/Sev = moderate to severe.
WM surrounds the lateral ventricle, which makes up the major aspect of ventricular volume (the numerator in the VBR equation), increased VBR is particularly influenced by WM volume loss. Although statistical significance was only reached with VBR, as depicted in Figure 10, generally the various volumetric measures showed that slower PSI performance was associated with greater volume loss. It should be noted that, on average, children were scanned and neuropsychologically assessed approximately two-and-a-half years postinjury. Often, PSI deficits are most prominent closer to the time of the initial injury, and so the PSI relationships described above might be different if assessed during earlier postinjury timeframes. Lastly, we could not complete MRI quantification in several of the most severely injured TBI children because of cranial defects and massive structural damage that precluded image registration for the automated volumetric analyses.

The range of brain insult in childhood TBI is broad; nevertheless, our study shows that aspects of TBI damage are readily identifiable. Taking this diversity of neuropathology into account may be part of a more comprehensive approach to establishing structure–function relationships in this population when studying neuropathological outcome. Clearly evident in this analysis is that any singular quantitative or qualitative measurement of structural damage from TBI is likely to underestimate parenchymal pathology due to trauma. Approaches involving the integration of quantitative and qualitative analyses to more comprehensively describe abnormalities, when used in conjunction with neuroimaging methods that identify neural networks with hubs, nodes, and connectors, may be particularly beneficial in defining neuropathological relationships with neuropsychological outcome given the degree of WM damage in TBI (van den Heuvel & Sporns, 2011).

Study Limitations

The current investigation has several limitations. Neuroimaging methods have rapidly improved over the time frame of this investigation. Hemosiderin deposition is now best detected by use of a susceptibility-weighted sequence and not the standard GRE sequence used in the current investigation (Beauchamp et al., 2013; Nandigam et al., 2009). Diffusion tensor imaging (DTI) is now a standard for investigating WM integrity in TBI, but was not available during the SOBIK investigation. Furthermore, all MRI studies in this investigation were performed at 1.5 T; a higher magnetic field strength might have improved detection of not only hemosiderin but also WM pathology. It is likely that our methods failed to detect more subtle pathologies, which may be most important in identifying neuropathology within the complicated mild TBI group.

The SOBIK study was a multisite investigation that combined MRI scan findings across different scanners and platforms, which introduces additional variability (Focke et al., 2011). Some of the lack of VBM findings may also be related to corrections used in controlling for scan site differences as well as the normalization and smoothing techniques that potentially obscure subtle findings. For example, Eriksson et al. (2009) found that, even in epilepsy surgery patients with cortical neuronal loss and hippocampal sclerosis, the VBM technique may not detect parenchymal differences. Because the majority of SOBIK cases involved complicated mild TBI, with few distinct abnormalities and minimal overlap in the location of abnormalities, the absence of VBM findings may be largely attributable to the insensitivity of the VBM technique.

FreeSurfer also has limitations associated with automated algorithms used for image quantification (Gronenschild et al., 2012); however, to minimize such differences, all analyses used a single type of hardware and operating system (Linux CentOS, Version 5.4). Finally, the SOBIK imaging protocols used only structural imaging techniques and did not include DTI or any functional neuroimaging sequences (e.g., resting state connectivity) that may have provided additional information about location and type of damage (Toledo et al., 2012). No children with uncomplicated mild TBI were included in the study, and therefore quantitative and qualitative neuroimaging comparisons with the most common form of brain injury were not possible.

Conclusion

Studies of the neuropsychological outcomes of brain injury typically view TBI as an independent variable that defines an event that injures the brain. Studies relating neuropathological changes to neurobehavioral outcome in neurological disorders often attempt to use some singular index of “lesion burden.” However, defining lesions and measuring their aggregate effects in pediatric TBI remain elusive goals, as reflected in Figure 1 and summarized in the SOBIK findings presented here. The major contribution of this study is to demonstrate that lesion burden is complex but knowable if combinations of TBI-specific and general abnormalities are identified, if both group heterogeneity and individual variation and heterogeneity are described, and if multiple MRI measurement approaches are used. This information provides the basis for investigations of neuropsychological outcomes and their relations with MRI neuroimaging abnormalities after pediatric TBI.

References

BRAIN LESIONS IN PEDIATRIC TRAUMATIC BRAIN INJURY


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