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Day of Injury CT and Late MRI Findings: Cognitive Outcome in a Pediatric Sample with Complicated Mild Traumatic Brain Injury

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Abstract

Objectives—Complicated mild traumatic brain injury (mTBI) or cmTBI is based on the presence of visibly identifiable brain pathology on the day-of-injury computed tomography (CT) scan. In a pediatric sample the relation of DOI CT to late MRI findings and neuropsychological outcome was examined.

Methods—MRI (> 12 months) was obtained in pediatric cmTBI patients and a sample of orthopedically injured (OI) children. Those children with positive imaging findings (MRI+) were quantitatively compared to those without (MRI-) or with the OI sample. Groups were also compared in neurocognitive outcome from WASI subtests and the WISC-IV Processing Speed Index (PSI), along with the Test of Everyday Attention for Children (TEA-Ch) and a parent-rated behavioral functioning measure (ABAS-II).

Results—Despite the MRI+ group having significantly more DOI CT findings than the MRI- group, no quantitative differences were found. WASI Vocabulary and Matrix Reasoning scores were significantly lower, but not PSI, TEA-Ch or ABAS-II scores. MRI+ and MRI-groups did not differ on these measures.

Conclusions—Heterogeneity in the occurrence of MRI-identified focal pathology was not associated with uniform changes in quantitative analyses of brain structure in cmTBI. Increased number of DOI CT abnormalities was associated with lowered neuropsychological performance.

Keywords

pediatric; complicated mild traumatic brain injury; magnetic resonance imaging; neuropsychological outcome

Introduction

As defined by Glasgow Coma Scale (GCS) scores that range from 13-15, mild traumatic brain injury (mTBI) is the most common acquired injury across all ages [1–3].

If day-of-injury (DOI) neuroimaging findings, most typically based on computed tomography (CT), indicate an abnormality such as contusion or petechial hemorrhage with GCS in the 13-15 range, the injury is often classified as “complicated” or cmTBI. In contrast, with negative DOI CT findings but GCS still in the 13-15 range, the injury has been referred to as un- or non-complicated mTBI [4–6]. As a broad cmTBI classification, the range of DOI CT abnormalities may include skull fracture, cerebral contusion, intracranial hemorrhage of any kind (subdural, epidural, subarachnoid and/or petechial) and/or edema including midline shift [5, 7]. All of these abnormalities represent objective findings on CT thereby minimizing classification error as to the occurrence of a brain injury. Since skull fractures and epidural hemorrhage occur outside the brain proper, the inference is that the mechanical forces from head injury are sufficient to injure the underlying brain parenchyma [see 8]. More narrow definitions of cmTBI have been restricted only to intraparenchymal pathology [9–11] identified on DOI scans. Regardless, based on DOI neuroimaging, the presence of a visually identifiable abnormality has been presumed a marker of greater neuropathology and therefore increased likelihood for residual

neurocognitive and neurobehavioral deficits [12], although not all studies demonstrate worse outcome associated with cmTBI [11].

A major limitation of cmTBI outcome studies is that they rely on DOI CT findings. CT is less sensitive in detecting abnormalities than magnetic resonance imaging (MRI) [4, 13, 14]. Thus, a DOI intracranial abnormality may in fact be present, but simply below the threshold of CT detection [4, 15]. Likewise, the presence of skull fracture or epidural hematoma, as already mentioned are abnormalities that may reflect head trauma but not necessarily specify injury to the brain. Further complicating the meaning of DOI CT findings in cmTBI outcome is that intraparenchymal pathology such as petechial hemorrhage or edema may take time to evolve [4, 16] and, therefore not detectable on the DOI CT. With the DOI CT being emergently performed—often within the first hour of injury—subtle pathology that requires time to develop may not be expressed at the time of initial CT imaging. As such, the DOI CT represents just a single snapshot of possible pathology in the mTBI patient. Alternatively, cmTBI pathology may be better characterized with follow-up neuroimaging utilizing MRI because of its greater sensitivity to and multiple methods for detecting pathology [15, 17].

The Social Outcomes of Brain Injury in Kids (SOBIK) [18, 19] is a large multisite pediatric TBI study that includes 41 children meeting the broad criteria for cmTBI, all of whom had some type of DOI CT abnormality with follow-up MRI and neuropsychological testing. Follow-up MRI was obtained during the chronic phase (> 6 months) along with cognitive and behavioral testing. For comparison purposes, a large orthopedically injured (OI) group (n = 52 with MRI) generally matched in age, grade level and sex were also scanned and completed outcome testing. None of the OI children had a DOI head CT scan. In the current investigation, DOI CT findings from the children with TBI were examined in terms of their relation to quantitative and qualitative MRI findings obtained on average more than 2 years post injury. Cognitive outcome variables were based on the Wechsler Abbreviated Scale of Intelligence (WASI) [20] and Processing Speed Index (PSI) from the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) [21]. Also included were three subtests from the Test of Everyday Attention for Children (TEA-Ch) [22], which were combined to provide a composite measure of attention/executive function. To assess behavioral competence, the Adaptive Behavior Assessment Scale, Second Edition (ABAS-II) [23], was completed by the parent.

DOI CT rating schemes typically classify findings within three broad categories: intracranial pathology, edema, and skull fracture [24, 25]. These pathologies clearly overlap. For example, traumatically induced intraparenchymal hemorrhage often leads to swelling and parenchymal displacement just from edema and certain types of hemorrhages frequently occur in association with skull fracture. A variety of clinical rating methods exist for classifying visibly identifiable MRI abnormalities associated with TBI [26], typically described in the form of encephalomalacia, regional atrophy, white matter hyperintensity (WMH), and/or residual hemorrhage (hemosiderin deposition as an indication of prior hemorrhage). In a previous study, applying such clinical ratings to the MRI findings from the cmTBI SOBIK children revealed that more than half had some form of clearly identifiable MRI abnormality (MRI+) at least 6 months post-injury [see 27]. Quantitatively,

the children in the cmTBI group did not differ from OI controls in overall brain volume, ventricle-to-brain ratio (VBR) or total corpus callosum volume, although in the moderate to severe TBI groups robust differences were observed in all of these measures as compared to the OI controls. In regards to the children with cmTBI, the Bigler et al. [27] study raised the following questions: How do DOI CT findings relate to identifiable MRI abnormalities during the chronic stage in children with cmTBI? Quantitatively, does the cmTBI MRI+ group exhibit greater structural changes reflected volumetrically or when assessed with voxel-based morphometry (VBM) or cortical thickness techniques when compared to those without MRI findings (MRI- group)? Do cmTBI MRI+ children as a group differ on cognitive and behavioral outcome measures with cmTBI MRI- children or from OI Controls?

In the current investigation, the follow-up MRI from SOBIK participants with cmTBI was examined for qualitative indicators of pathology such as focal encephalomalacia, WMH, and prior hemorrhage in the form of hemosiderin deposition reflective of contusion and/or petechial hemorrhage. Presence of any one of these findings constituted inclusion within the MRI+ group. Those with absent or equivocal MRI findings constituted the MRI- group. MRI+ and MRI- groups were separately analyzed and compared to the OI group in terms of VBM, cortical thickness and volumetric comparisons. Because the SOBIK study was focused on social outcomes only a limited number of cognitive tests were administered, but included the Matrix Reasoning (MR) and Vocabulary (VOC) subtests from the WASI [20] the Processing Speed Index (PSI) from the WISC-IV [21] and three TEA-Ch [22] subtests. We hypothesized that the cmTBI MRI+ group would exhibit greater volumetric and quantitative differences along with poorer cognitive performance and behavioral competence as compared to the cmTBI MRI- group

Method

Participants

Details of the SOBIK study have been previously published [see 18, 19]. The current investigation included only the cmTBI and OI children recruited from three metropolitan areas [Toronto (Canada), Columbus (US) and Cleveland (US)]. The cmTBI group consisted of those children who received a GCS of 13-15 with positive (broadly determined) DOI CT imaging [see 19]. Forty-four children met these criteria although only 41 underwent MRI. MRI scanning was not performed on children with braces or those who declined to participate. For the 61 children with OI (n = 52 scanned), some form of orthopedic injury had occurred but a GCS had to be recorded as 15 with no diagnosis of TBI, facial fractures, or other indications of possible head injury. For those with MRI scans, not all could be included in some of the analyses due to motion and post-surgical artifact which precluded automated image analysis methods. Groups did not significantly differ in age, or age at injury for the MR+ or MRI- participants or GCS, or percent of males in any group. Likewise, ethnicity was generally similar across groups. However, SES was lower in the MRI+ group. SES was derived based on the methods outlined by Yeates and Taylor [28]. Participant and demographic information is provided in Table 1 for all subjects included in the MRI quantitative and neuropsychological outcome analyses.

Neuropsychological Measures

Details on the administration of the neuropsychological variables have been previously published [19, 27]. As previously mentioned the WASI [20] VOC and MR subtests were administered from which a WASI Full Scale IQ (WASI IQ) score was derived. PSI was obtained from the WISC-IV [21]. Inhibitory control, working memory, and cognitive flexibility were assessed using the Walk/Don't Walk, Code Transmission, and Creature Counting subtests of the TEA-Ch [22], respectively. The TEA-Ch is a norm-referenced measure with high reliability and construct validity in assessing various aspects of attention and executive functions [29, 30]. In the Walk/Don't Walk subtest, children take one step along a path each time they hear a tone ("go tone"), at regular intervals. Different tones occur occasionally to signal the child not to take a step ("no-go tones"). The total score reflects the number of correct responses to both tones. The Code Transmission subtest is akin to an n-back task, and requires children to monitor a stream of monotonous digits for a particular target; the total score reflects the number of correctly identified targets. In the Creature Counting subtest, children must count creatures depicted in a burrow, switching between counting forwards and backwards when they encounter arrows pointing up or down. The total score reflects speed as well as accuracy. Because they were significantly correlated with one another, the scaled scores for the three measures were averaged together to create an attention/executive function composite for analyses. The General Adaptive Composite (GAC) from the ABAS-II [23] was used as the omnibus measure of behavioral competence.

MRI

In this study, MRI was performed during the chronic phase (i.e., a minimum of 12 months post-injury but with an average of 2.62 years post-trauma; range = 1-5.2 years). This timeframe was used to insure that lesion type and location were generally stabilized [31–33]. Magnetic field strength was 1.5 Tesla for all studies with each site participating in scan acquisition for both cmTBI and OI children, details of which may be found in Bigler et al. [27]. Briefly, the Toronto and Columbus sites used GE Signa Excite scanners whereas scanning in Cleveland was performed on a Siemens Symphony scanner. The basic platform across all sites was thin-sliced 1.2mm section thickness whole brain T1 weighted MPRAGE or FSPGR sequences (depending on scanner manufacture) acquired in the sagittal plane ear to ear (T1/TE/TR = 1000/1.47 – 3.80/3000 ms). Native voxel dimensions (in millimeters) differed by site as follows: Cleveland – 0.625X0.625X1.2; Columbus – 0.938X0.938X1.2; Toronto – 0.469X0.469X1.2 with uniform pre-processing and formatting applied to all scans for FreeSurfer and VBM analyses. There were no systematic differences across the sites in terms of demographic factors for the participants who sustained brain or orthopedic injuries. For clinical interpretation and rating the following sequences were obtained but not quantitatively analyzed: a dual-echo proton density (PD)/T2-weighted sequence; fluid attenuated inversion recovery (FLAIR); and gradient recalled echo (GRE). Identical phantom imaging was performed at the beginning to check the uniformity of image acquisition and image quality across the multiple sites.

Qualitative MRI ratings, which identified the presence or absence and location of lesion abnormalities, were based on the methods outlined by Max et al. [34] and conducted without

knowledge of group membership (OI versus cmTBI) or injury severity. Blinding was not entirely possible, however, because many scans included obvious trauma-related pathology. Ratings of focal encephalomalacia and atrophy were based on any sequence, whereas white matter (WM) signal ratings were based only upon the proton density T2 (PD/T2) and fluid attenuated inversion recovery (FLAIR) sequences, with hemosiderin identified on the PD/T2 and gradient recalled echo (GRE) sequences. Clinical ratings were performed by two independent raters (EDB and TJA), with disagreements resolved by unanimity as to classification.

FreeSurfer analyses used version 5.1 (<http://surfer.nmr.mgh.harvard.edu/>) and followed the methods detailed by Bigler et al. [35]. For voxel-based morphometry (VBM), an extension of the statistical parametric mapping (SPM8) software (Wellcome Trust Center for Neuroimaging, Oxford, England; <http://www.fil.ion.ucl.ac.uk/spm>) and the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm8>) was used. Images were corrected for bias-field inhomogeneities, registered using linear (12-parameter affine) and nonlinear transformations along with gray matter (GM) and WM tissue, and cerebrospinal fluid (CSF) classification within the same generative model [36]. Segmentation was further refined using the “DARTTEL” method, which is an algorithm for diffeomorphic image registration [37], which better accounts for partial volume effects. As a final stage of image processing, images were smoothed with a Gaussian kernel of 8 mm at full width half maximum (FWHM). Because of the differences across sites in terms of some of the scan parameters as well as being different sites, acquisition site was controlled for in all statistical analyses.

FreeSurfer was used to determine volumes for total brain (TBV), as well as ventricular and corpus callosum volume. By dividing ventricular volume by TBV and multiplying by 100 (to insure using whole numbers) a ventricle-to-brain ratio (VBR) may be calculated, that reflects overall brain integrity [38]. Cortical thickness studies utilized the Query, Design, Estimate and Contrast (QDEC <https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/QdecGroupAnalysis>) FreeSurfer function [see 39]. Eleven children had MRIs that were of sufficient quality to obtain clinical ratings, but could not be analyzed by FreeSurfer or VBM techniques. The reasons for non-inclusion included a combination of factors including motion artifact, dental artifact, or early termination of the scan sequence mostly from claustrophobia or non-compliance resulting in incomplete data. All scans with abnormalities are shown in Figure 1 (asterisks denote those not included in quantitative analyses). Comparing as a group those who could not be included in the FreeSurfer or VBM analyses with those who could, showed no difference in age or sex. Accordingly, the FreeSurfer and VBM analyses are felt to be representative of all participants included in the study.

DOI CT Rating

Although the three children’s hospitals where this investigation was undertaken were Level I trauma centers, a number of the children were initially evaluated, stabilized, and scanned at a tertiary facility and then transferred to the level I center. For the majority of those children actual scan images for review were not available. Since no uniformity existed in which CT protocol was used and given that not all scans could be reviewed, the clinical CT report interpreted by a radiologist was used for identification of acute pathology and

independently scored by two of the authors (KY and MD), as has been previously described (see 19). The rating scheme identified four general categories, as outlined and defined in Table 2. Each radiological report was independently reviewed to identify key words reflective of DOI pathology (total CT rating scale = 16).

Statistical Analyses

Using a Spearman rank correlation coefficient, the relation between clinical CT rating of the DOI scan was examined for each cognitive and neurobehavioral measure. MRI clinical ratings were based on the Max et al. [34] methods that used a binary classification for all cmTBI cases, dividing subjects into MRI+ (clearly identifiable abnormalities) and MRI- (absent or indistinct findings) regardless of lesion type or location. Much of this investigation provides descriptive scan information about abnormalities identified on MRI. For all MRI and neuropsychological outcome variables, analysis of variance (ANOVA) with planned comparisons that examined the OI, MRI+ and MRI- groups was undertaken using the IBM SPSS Statistics package [40]. VBM analyses used a voxel-wise general linear model (GLM) as implemented in SPM8 [see 41]. Only significant clusters surviving a statistical threshold of $p < 0.05$ after false-discovery rate (FDR) correction were included. In setting up the contrasts for VBM, site of scan acquisition was controlled in all comparisons.

Results

DOI CT Findings

For the WASI IQ ($r_s = -.31, p = 0.001$), VOC ($r_s = .28, p = 0.002$), and MR ($r_s = .27, p = 0.003$) as well as the TEA-Ch ($r_s = -.25, p = 0.006$), clinical DOI CT ratings in the cmTBI group (head CT imaging was not done in the OI children) were modestly but significantly related, but not for WISC-IV PSI ($r_s = -.15, p = 0.104$) or ABAS-II GAC ($r_s = -.01, p = .96$). Combined, the cmTBI children had a mean of 4.6 (S.D. = 2.1) DOI CT abnormalities where the MRI+ group had significantly ($p = .001$) more than the MRI- group (see Table 3).

Quantitative MRI Findings Comparing cmTBI Participants to OI Controls

As shown in Table 3, controlling for age and sex, volumetric and VBR findings comparing cmTBI participants to OI controls, regardless of whether they were MRI+ or MRI-, resulted in no significant difference for any variable.

MRI Classification

Figure 1 depicts a single level image that captures for each cmTBI participant distinctly visible pathology that demonstrates the variability and range of abnormalities identified in the MRI+ group. Abbreviations beneath each scan image summarize the reported general DOI CT findings. In Figure 1, scans are organized by the number of scored (see Table 2) DOI CT abnormalities identified. Since the basis for the MRI- cmTBI group was no identifiable gross pathology, MRI scans from the MRI- group are not shown. For the MRI+ group, almost half had 3-4 positive DOI CT findings (47.8%), with 39.1% with 1-2 DOI CT findings and only 13% with 5 or more. The majority of children within the MRI- group had only 1-2 positive CT findings (68.7%), with 18.7% having 3-4 positive DOI CT findings and only 2 with ratings 5 or higher (12.5%).

Only one child each in the MRI+ and MRI- groups had skull fracture as the solitary positive DOI CT scan finding, with all other fractures in both groups being associated with subdural and epidural hematomas. Volumetric and VBR differences between the MRI+ and MRI- groups were not significant.

Cognitive Performance

Table 3 also provides mean scores for WASI, WISC-IV PSI, TEA-Ch and ABAS-II findings for OI, MRI+, and MRI- groups. Full Scale IQ (FSIQ), VOC, and MR index scores from the WASI were significantly lower in the cmTBI group, regardless of whether MRI+ or MRI-, compared to OI controls, but PSI, TEA-Ch and ABAS-II scores did not significantly differ, although performance on the TEA-Ch approached significance. Scores for the MRI+ and MRI- subsets of the cmTBI group did not differ significantly for any of the measures.

Voxel-Based Morphometry (VBM) and Cortical Thickness

VBM results, as shown in Figure 2 depict a region of reduced corpus callosum volume in the posterior corpus callosum when all cmTBI participants were compared to the OI group; however, this finding did not remain significant after correction for family-wise error and multisite scan acquisition. Likewise, no significant VBM differences were observed when MRI+ participants were compared to MRI-. No differences in cortical thickness were observed for any OI or cmTBI (either MRI+ or MRI-) comparisons.

Discussion

Increased number of DOI CT scan findings negatively related to neuropsychological performance on the WASI IQ, VOC and MR subtests as well as the TEA-Ch. Although from a GCS and clinical classification standpoint, all subjects were mild in terms of injury severity, increasing number of DOI CT findings would suggest that those with a greater number of scan abnormalities biomechanically likely experienced more significant trauma. As such, more DOI pathology did relate modestly to poorer neuropsychological outcome. However, even though all TBI participants had DOI identified CT abnormalities, as described in Table 2, a substantial number had no grossly identifiable pathology on follow-up MRI more than a year post-injury. Approximately one-third of the children meeting cmTBI criteria did not exhibit visually identifiable pathology on follow-up MRI. The assumption that MRI+ would be reflective of greater pathological change within the mild TBI spectrum by showing significantly greater volume loss was not supported. As such the MRI+ group did not exhibit greater quantitative differences on neuroimaging compared to the MRI- group. The cmTBI group did perform significantly below the OI group on WASI variables (FSIQ, VOC and MR) but not on WISC-IV PSI, regardless of whether residual TBI pathology could be identified on follow-up MRI. The MRI- group did have significantly fewer abnormal DOI CT findings than the MRI+ group, but the MRI+ and MRI- cmTBI groups did not differ on any quantitative volumetric MRI measure, including VBM and analyses of cortical thickness findings that withstood adjustments for FDR.

The diversity of abnormalities associated with cmTBI is clearly evident in reviewing Figure 1. The heterogeneity of the DOI CT findings combined with the non-overlapping locations

of cmTBI lesions may help account for why the cmTBI subjects differed from the OI group on some neurocognitive measures but not on volumetric, VBR, VBM or findings of cortical thickness. Also evident in reviewing Figure 1 is that *none* of the visible pathology was identical in any of the children with MRI+ findings. The absence of any overlapping lesions makes it unlikely that any uniform pathology would emerge that would be reflected in systematic changes in regional differences detectable by quantitative techniques, including cortical thickness. VBM showed reduced WM density in the posterior corpus callosum in the cmTBI participants (see Figure 2), but this finding did not withstand statistical correction for multiple comparisons and different acquisition sites. With such diversity of pathology combined with the subtleness of pathology, little uniformity can be expected in the underlying pathology associated with cmTBI in this cohort.

Cognitively, although overall performance was within the average range, the cmTBI participants had significantly lower VOC and MR scores on WASI testing than the OI controls, although WISC-IV processing speed did not differ. Heretofore, the WISC-IV PSI has been one of the neuropsychological assessment measures thought to be sensitive in detecting residual effects from pediatric TBI, including mTBI [42]. However, in the current study no differences in PSI were observed regardless of whether MRI was positive or negative. At the mild end of the TBI spectrum, PSI may be sensitive to the acute effects of injury, but with time the sensitivity wanes, especially when no gross WM abnormality occurs in a consistent, overlapping fashion to chronically affect processing speed [43].

Four critical limitations of the current study may relate to why pathology was not detected in this cmTBI sample: (1) magnetic field strength, wherein the current study was 1.5 Tesla, and higher field strength may detect subtler pathology [44], (2) susceptibility weighted imaging (SWI) was not used for hemosiderin detection, and is more sensitive than the conventional GRE sequence used in the current study [45], (3) different scanners and multi-site acquisition of the imaging data increases error and because of required statistical correction reduces the likelihood of detecting significance and (4) other MRI metrics like diffusion tensor imaging (DTI) and magnetic resonance spectroscopy were not used, which may have greater sensitivity in detecting subtle pathology [45]. Figure 3 shows a cmTBI child with DOI CT demonstrating a distinct epidural hematoma, which was surgically drained. Follow-up MRI appears to reflect no gross abnormality. Substantial head impact dynamics were likely at play to produce such DOI pathology, but without more sophisticated neuroimaging studies, conclusions about the absence of residual neuropathology in this child should be avoided because of the limitations of current technology.

This investigation points out several limitations to the cmTBI classification in pediatric TBI. First, a DOI CT abnormality may not be a stable abnormality in terms of brain imaging, even though it appears to have predictive value for some indices of functional outcome. As depicted in Figure 3, while an epidural hematoma may potentially result in displacement and mass effect, the hemorrhage occurs externally to the brain. Although such deformations may compromise blood flow and stimulate edema [46], good outcome may occur [47]. In contrast, focal parenchymal damage such as shear injury with hemosiderin as a marker of diffuse axonal injury may have more permanent sequelae [48]. However, the acute effects of these injuries, by definition in cmTBI, would have to be minimal so as to not lower GCS

beyond the mild range [49, 50], to remain a participant in the cmTBI group. Thus, while parenchymal injury occurs in cmTBI, at the level of gross morphology it is not necessarily manifested in a consistent fashion over time post-injury. Another limitation of the current investigation is that follow-up MRI was done during the chronic phase, which undoubtedly is influenced by maturation and plasticity. Future study designs would be aided by using the DOI CT findings as baseline and then monitoring at specific time periods to account for change in lesion characteristics and maturational effects as well. Furthermore, this investigation focused exclusively on cmTBI and it would certainly be informative to compare outcome variables in those who meet mTBI criteria without positive DOI findings to those who show such findings, as well as to pediatric cases involving moderate and severe TBI.

These results provide some practical direction for future mTBI investigations. Neither DOI CT findings nor follow-up conventional MRI sufficiently capture all of the potential brain pathology that may underlie mTBI. The variability in what occurs on the DOI CT with eventual demonstrable MRI-identifiable pathology is considerable and this presents a major challenge on how best to analyze neuroimaging findings. A substantial number of pediatric cmTBI patients have no identifiable gross pathology on follow-up conventional MRI despite having DOI abnormalities. Acute lesions such as petechial hemorrhage or focal edema, as well as substantial hematomas as shown in Figure 3, may not result in detectable findings on follow-up MRI. Even though, as can be visually observed in Figure 1, distinct residual lesions occur in cmTBI, they are not uniform enough in this sample to produce global changes in brain, WM, GM or corpus callosum volume. Additionally, in review of Figure 1, although frontal lesion sites dominate, none overlap. The current investigation demonstrates that future studies that examine mTBI sequelae will need to have much larger sample sizes because of the diversity in lesion distribution. With a larger sample, participants could be partitioned into general region of interest categories and also apply newer methods of network analysis.

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References

- [1]. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet*. 1974; 2:81–84. [PubMed: 4136544]
- [2]. Bigler, ED.; Maxwell, WL. Understanding mild traumatic brain injury: neuropathology and Neuroimaging. In: Vasterling, J.; Bryant, R.; Keane, T., editors. PTSD and mild traumatic brain injury. Guilford Press; New York: 2012. p. 15-36.
- [3]. Ruff RM. Mild traumatic brain injury and neural recovery: rethinking the debate. *NeuroRehabilitation*. 2011; 28:167–180. [PubMed: 21558623]
- [4]. Bigler ED. Neuroimaging biomarkers in mild traumatic brain injury (mTBI). *Neuropsychol Rev*. 2013; 23:169–209. [PubMed: 23974873]

- [5]. Iverson, GL.; Lange, RT. Concussion versus mild traumatic brain injury: is there a difference?. In: Zollman, FS., editor. Manual of traumatic brain injury management. Demos Medical Publishing; New York: 2011. p. 35-43.
- [6]. Maestas, KL.; Sander, AM.; Clark, AN.; vanVeldhoven, LM.; Struchen, MA.; Sherer, M.; Hannay, HJ. Preinjury coping, emotional functioning, and quality of life following complicated mild traumatic brain injury; J Head Trauma Rehabil. Mar. 2013 p. 26[Epub ahead of print], Available from: www.headtraumarehab.com DOI: 10.1097/HTR.0b013e31828654b4
- [7]. Bassin, SL. The neurointensive care unit: intracranial pressure and cerebral oxygenation. In: Zollman, FS., editor. Manual of traumatic brain injury management. Demos Medical Publishing; New York: 2011. p. 174-79.
- [8]. Roth TL, Nayak D, Atanasiyevic T, Koretsky AP, Latour LL, McGavern DB. Transcranial amelioration of inflammation and cell death after brain injury. Nature. Jan 9; 2014 505(7482): 223–8. [PubMed: 24317693]
- [9]. Fayol P, Carriere H, Habonimana D, Dmond JJ. Preliminary questions before studying mild traumatic brain injury outcome. Ann Phys Rehabil Med. 2009; 52:497–509. [PubMed: 19760806]
- [10]. Gean, AD. Imaging of Head Trauma. Raven Press; New York: 1994.
- [11]. Iverson GL, Lange RT, Waljas M, Liimatainen S, Dastidar P, Hartikainen KM, Soimakallio S, Ohman J. Outcome from complicated versus uncomplicated mild traumatic brain injury. Rehabil Res Pract. 2012; 415740:1–7.
- [12]. Wilde EA, Hunter, Bigler ED. Pediatric traumatic brain injury: neuroimaging and neurorehabilitation outcome. NeuroRehabilitation. 2012; 31(3):245–60. [PubMed: 23093453]
- [13]. Hanten G, Li X, Ibarra A, Wilde EA, Barnes AF, McCauley SR, McCarthy J, Hoxhaj S, Mendez D, Hunter JV, others. Updating memory after mild tbi and orthopedic injuries. J Neurotrauma. Apr 15; 2013 30(8):618–24. [PubMed: 23227898]
- [14]. Provenzale JM. Imaging traumatic brain injury: a review of the recent medical literature. AJR Am J Roentgenol. Jan; 2010 194(1):16–9. [PubMed: 20028899]
- [15]. Yuh EL, Mukherjee P, Lingsma HF, Yue JK, Ferguson AR, Gordon WA, Valadka AB, Schnyer DM, Okonkwo DO, Maas AIR, others; TRACK-TBI Investigators. Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. Ann Neurol. 2013; 2013; 73:224–35. [PubMed: 23224915]
- [16]. Kim JJ, Gean AD. Imaging for the diagnosis and management of traumatic brain injury. Neurotherapeutics. 2011; 8:39–53. [PubMed: 21274684]
- [17]. Ortega-Carnicer J, Ambros A, Diarte JI. Reversible posterior leukoencephalopathy syndrome in a young trauma patient. Resuscitation. 2005; 64(1):119–20. [PubMed: 15629565]
- [18]. Yeates KO, Gerhardt CA, Bigler ED, Abildskov T, Dennis M, Rubin KH, Stancin T, Taylor HG, Vannatta K. Peer relationships of children with traumatic brain injury. J Int Neuropsychol Soc. 2013; 19(5):518–27. [PubMed: 23340166]
- [19]. Dennis M, Simic N, Taylor H, Bigler ED, Rubin K, Vannatta K, Gerhardt CA, Stancin T, Roncadin C, Yeates KO. Theory of mind in children with traumatic brain injury. J Int Neuropsychol Soc. 2013; 18(5):908–16. [PubMed: 22846440]
- [20]. The Psychological Corporation. Wechsler Abbreviated Scale of Intelligence. Psychological Corp; San Antonio, TX: 1999.
- [21]. Wechsler, D. Wechsler Intelligence Scale for Children. 4th. PsychCorp; San Antonio, TX: 2003.
- [22]. Manly, T.; Robertson, IH.; Anderson, V.; Nimmo-Smith, I. The Test of Everyday Attention for Children (TEA-CH). Pearson; San Antonio, TX: 1998.
- [23]. Harrison, PL.; Oakland, T. Adaptive Behavior Assessment System–Second Edition. The Psychological Corporation; San Antonio, TX: 2003.
- [24]. Gene, AD. Imaging of head trauma. Raven Press; New York: 1994.
- [25]. Marshall LF, Toole BM, Bowers SA. The National Traumatic Coma Data Bank. Part 2: patients who talk and deteriorate: implications for treatment. J Neurosurg. 1983; 59(2):285–8. [PubMed: 6864295]

- [26]. Bigler, ED. Neuroimaging correlates of functional outcome. In: Zasler, ND.; Katz, DI.; Zafonte, RD., editors. Brain injury medicine: principles and practice. Demos Medical Publishing; New York: 2007. p. 201–24.
- [27]. Bigler ED, Abildskov TJ, Petrie J, Farrer TJ, Dennis M, Simic N, Taylor HG, Rubin KH, Vannatta K, Gerhardt CA, others. Heterogeneity of brain lesions in pediatric traumatic brain injury. *Neuropsychology*. 2013; 27:438–51. [PubMed: 23876117]
- [28]. Yeates KO, Taylor HG. Predicting premorbid neuropsychological functioning following pediatric traumatic brain injury. *J Clin Exp Neuropsychol*. Dec; 1997 19(6):825–37. [PubMed: 9524877]
- [29]. Manly T, Anderson V, Nimmo-Smith I, Turner A, Watson P, Robertson IH. The differential assessment of children's attention: the Test of Everyday Attention for Children (TEA-Ch), normative sample and ADHD performance. *J Child Psychol Psychiatry*. Nov; 2001 42(8):1065–81. [PubMed: 11806689]
- [30]. Heaton SC, Reader SK, Preston AS, Fennell EB, Puyana OE, Gill N, Johnson JH. The Test of Everyday Attention for Children (TEA-Ch): patterns of performance in children with ADHD and clinical controls. *Child Neuropsychol*. Dec; 2001 7(4):251–64. [PubMed: 16210214]
- [31]. Blatter DD, Bigler ED, Gale SD, Johnson SD, Anderson SC, Burnett CV, Ryser D, Macnamara SE, Bailey GJ. MR-based brain and cerebrospinal fluid measurement after traumatic brain injury: correlation with neuropsychological outcome. *AJNR Am J Neuroradiol*. 199718(1):1–10. [PubMed: 9010514]
- [32]. Ross DE. Review of longitudinal studies of MRI brain volumetry in patients with traumatic brain injury. *Brain Inj*. 2011; 25:1271–78. [PubMed: 22077533]
- [33]. Warner MA, Youn TS, Davis T, Chandra A, Marquez de la Plata C, Moore C, Harper C, Madden CJ, Spence J, McColl R, others. Regionally selective atrophy after traumatic axonal injury. *Arch Neurol*. 201067(11):1336–44. [PubMed: 20625067]
- [34]. Max JE, Keatley E, Wilde EA, Bigler ED, Levin HS, Schachar RJ, Saunders A, Ewing-Cobbs L, Chapman SB, Dennis M, others. Anxiety disorders in children and adolescents in the first six months after traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2011; 23:29–39. 1. [PubMed: 21304136]
- [35]. Bigler ED, Abildskov TJ, Wilde EA, McCauley SR, Li X, Merkley TL, Fearing MA, Newsome MR, Scheibel RS, Hunter JV, others. Diffuse damage in pediatric traumatic brain injury: a comparison of automated versus operator-controlled quantification methods. *Neuroimage*. 201050(3):1017–26. [PubMed: 20060915]
- [36]. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage*. 2005; 26:839–851. [PubMed: 15955494]
- [37]. Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage*. Oct 15; 2007 38(1):95–113. [PubMed: 17761438]
- [38]. Tate DF, Khedraki R, Neeley ES, Ryser DK, Bigler ED. Cerebral volume loss, cognitive deficit, and neuropsychological performance: comparative measures of brain atrophy: II. traumatic brain injury. *J Int Neuropsychol Soc*. 201117(2):308–16. [PubMed: 21352625]
- [39]. Spitz G, Bigler ED, Abildskov T, Maller JJ, O'Sullivan R, Ponsford JL. Regional cortical volume and cognitive functioning following traumatic brain injury. *Brain Cogn*. 201383(1):34–44. [PubMed: 23872098]
- [40]. 2009. IBM SPSS Statistics
- [41]. Muhlau M, Winkelmann J, Rujescu D, Giegling I, Koutsouleris N, Gaser C, Arsic M, Weindl A, Reiser M, Meisenzahl EM. Variations within the Huntington's Disease gene influences normal brain structure. *PLoS ONE*. 2012; 7(1):e29809. 1–5. [PubMed: 22235343]
- [42]. Donders J, Janke K. Criterion validity of the Wechsler Intelligence Scale for Children-Fourth Edition after pediatric traumatic brain injury. *J Int Neuropsychol Soc*. 200814(4):651–5. [PubMed: 18577295]
- [43]. Wu TC, Wilde EA, Bigler ED, Li X, Merkley TL, Yallampalli R, McCauley SR, Schnelle KP, Vasquez AC, Chu Z, others. Longitudinal changes in the corpus callosum following pediatric traumatic brain injury. *Dev Neurosci*. 2010; 2(5-6):361–73. [PubMed: 20948181]
- [44]. Luccichenti G, Giugni E, Peran P, Cherubini A, Barba C, Bivona U, Formisano R, Sabatini U. 3 Tesla is twice as sensitive as 1.5 Tesla magnetic resonance imaging in the assessment of diffuse

- axonal injury in traumatic brain injury patients. *Funct Neurol*. 2010;25(2):109–114. [PubMed: 20923609]
- [45]. Benson RR, Gattu R, Sewick B, Kou Z, Sakariah N, Cavanaugh JM, Haacke EM. Detection of hemorrhagic and axonal pathology in mild traumatic brain injury using advanced MRI: implications for neurorehabilitation. *NeuroRehabilitation*. 2012;31(261):261–279. [PubMed: 23093454]
- [46]. Ulrich PT, Fuessler H, Januschek E. Acute epidural hematoma with infarction of the right hemisphere in a 5-month-old child: case report with a long-term follow-up and a review of the literature. *J Child Neurol*. 2008;23(9):1066–9. [PubMed: 18827272]
- [47]. Leitgeb J, Mauritz W, Brazinova A, Majdan M, Wilbacher I. Outcome after severe brain trauma associated with epidural hematoma. *Archives of Orthop Trauma Surg*. 2013;133(2):199–207.
- [48]. Smits M, Hunink MG, van Rijssel DA, Dekker HM, Vos PE, Kool DR, Nederkoorn PJ, Hofman PA, Twijnstra A, Tanghe HL, others. Outcome after complicated minor head injury. *AJNR Am J Neuroradiol*. 2008;29(3):506–13. [PubMed: 18065509]
- [49]. Jamous MA, Abdel Aziz H, Al Kaisy F, Eloqayli H, Azab M, Al-Jarrah M. Conservative management of acute epidural hematoma in a pediatric age group. *Pediatr Neurosurg*. 2009;45(3):181–4. [PubMed: 19440005]
- [50]. Gerlach R, Dittrich S, Schneider W, Ackermann H, Seifert V, Kieslich M. Traumatic epidural hematomas in children and adolescents: outcome analysis in 39 consecutive unselected cases. *Pediatr Emerg Care*. 2009;25(3):164–9. [PubMed: 19262419]

Figure 1.

MRI performed at a minimum of 6 months post-injury in cmTBI subjects with identifiable pathology. Red arrows point to at least one visibly identifiable abnormality. The rows are organized by the number of DOI CT findings from 1-2 to the last row with greater than 5.

Figure 2.

VBM results depict a region of reduced corpus callosum volume in the posterior corpus callosum when all cmTBI participants were compared to OI, however, this did not remain significant after correction for family wise error and the multisite acquisition.

Figure 3.
DOI CT scan with prominent epidural with no gross pathology identified in follow-up MRI

Table 1

Demographic information for participants included in quantitative neuroimaging and neuropsychological outcome analyses.

Variables	OI Control (48)	MRI Positive (22)	MRI Negative (14)	$F(\chi^2)$
Age at Testing M(SD)	10.5(1.63)	10.7(1.34)	10.8(1.67)	0.18
Age at Injury M(SD)	N/A	8.0(1.99)	8.2(1.83)	0.41
Percent Male	63%	64%	71%	(.382)
SES	.3383 (1.05)	-.4677 (.84)	-.1107 (.92)	5.29***
Race	41 Caucasian, 3 African/Caribbean descent, 3 Multicultural, 1 Unspecified	19 Caucasian, 1 African/Caribbean descent, 1 Multicultural, 1 Unspecified	11 Caucasian, 0 African/Caribbean descent, 3 Multicultural, 0 Unspecified	-
GCS	15 (0)	14.6 (.66)	15 (0)	

Notes: OI = orthopedic injury,

 $p < 0.01$

Table 2

Keywords used to score day-of-injury (DOI) CT findings.

A. INTRACRANIAL DAMAGE (from presurgical CT; if multiple CTs, take first DOI scan)	Rating
Focal intracranial injury/contusion	1
Intraparenchymal/intracerebral/intraventricular bleed	1
Subarachnoid	1
Subdural	1
Epidural	1
None/not reported	0
B. BRAIN SWELLING (from presurgical CT; if multiple CTs, take first DI scan)	
Generalized, bilateral	1
Generalized, unilateral	1
Focal, bilateral	1
Focal, unilateral	1
None/not reported	0
C. DIFFUSE AXONAL INJURY/ROTATIONAL- ACCELERATION FORCES (from presurgical CT; if multiple CTs, take first DOI scan)	
Gray-white abnormal; punctate gray-white hemorrhages	1
Ventricles abnormal or compressed	1
Basal cisterns abnormal or obliterated	1
Midline shift present	1
None/not reported	0
D. SKULL FRACTURE/TRANSLATIONAL FORCES (code from x-ray or imaging, not clinical signs)	
Basal skull fracture/fluid in mastoids	1
Depressed fracture	1
Linear fracture	1
None/not reported	0
TOTAL:	16

Table 3

DOI CT findings.

Variable	MRI + M(SD)	MRI – M(SD)	OI Control	Sig.
DOI CT Rating	5.72(2.20)	3.38(1.44)	--	.000*
TBV	1206.91(85.26)	1264.88(104.47)	1228.12(122.58)	.513
VBR	.79(.36)	.91(.42)	.91(.31)	.641
Total CC	2.75(.37)	2.88(.42)	2.95(.47)	.315
Total GM	728.16(48.25)	759.82(59.93)	736.91(.67.23)	.458
Total WM	360.52(35.87)	379.38(39.02)	367.32(46.04)	.701
WASI IQ	100.00(15.09)	98.57(14.20)	110.66(13.72)	.001
WASI VOC	49.54(9.36)	50.35(9.03)	56.29 (9.54)	.006
WASI MR	49.55(11.76)	47.14(12.39)	55.72(7.55)	.004
WISC PSI	101.91(11.32)	100.92(12.60)	104.61(14.79)	.651
ABAS GAC	99.37(15.33)	104.72(17.22)	99.54(15.21)	.764
TEA-Ch (Total Correct)	7.47 (2.9)	8.23 (3.8)	9.33 (3.0)	.066

**Significance is just between MRI+ and MRI– groups, compared to OI but not between MRI+ or MRI–, OI= Orthopedically Injured

* Significance is just between MRI+ and MRI– groups,