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Structural neuroimaging findings in mild traumatic brain injury

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Abstract

Common neuroimaging findings in mild traumatic brain injury (mTBI), including sport-related concussion (SRC), are reviewed based on computed tomography (CT) and magnetic resonance imaging (MRI). Common abnormalities radiologically identified on the day-of-injury, typically a CT scan, are in the form of contusions, small subarachnoid or intraparenchymal hemorrhages as well as subdural and epidural collections, edema and skull fractures. Common follow-up neuroimaging findings with MRI include white matter hyperintensities (WMHs), hypointense signal abnormalities that reflect prior hemorrhage, focal encephalomalacia, presence of atrophy and/or dilated Virchow-Robins peri-vascular space. The MRI findings from a large pediatric mTBI study show low frequency of positive MRI findings at 6 months post-injury. The review concludes with an examination of some of the advanced MRI-based image analysis methods that can be performed in the patient who has sustained an mTBI.

Defined by a Glasgow Coma Scale score ≥ 13 , the most common traumatic brain injury (TBI) is a mild injury, including sports-related concussion or SRC[1]. An important part of clinical SRC management and research is neuroimaging. In fact the 2012 Zurich consensus statement on concussion in sport (see McCrory et al. [2] explicitly states in its “Definition” section that “*Concussion may result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury and as such, no abnormality is seen on standard structural neuroimaging studies.*” Given this consensus statement, neuroimaging findings have been used to define what constitutes SRC explicitly by the absence of any abnormality using conventional neuroimaging techniques, with the designation of “mild” TBI or mTBI often meaning something more. The arbitrariness of using neuroimaging in this manner is obvious, however, because of differences in imaging methods, analysis and sensitivity of various neuroimaging techniques to detect pathology [3].

To address some of the issues in the mTBI debate, this review examines current conventional neuroimaging findings in evaluating mTBI focusing on three objectives: First, an overview of the most common radiologically defined abnormalities as visualized with computed tomography (CT) and magnetic resonance imaging (MRI). Second, from a large ongoing neuroimaging investigation in pediatric mTBI that includes children with SRC, the frequency of clinically defined neuroimaging abnormalities in mTBI in 8 to 15 year olds evaluated at a Level I Trauma Center will be summarized. The third objective will introduce some of the advanced neuroimaging methods that remain research tools at this time but with considerable potential to further inform the clinician and researcher about the effects of mTBI and SRC.

Computed Tomography (CT) and Magnetic Resonance Imaging Findings in mTBI

Day of injury (DOI) CT is typically the first type of brain scan performed in head injury [4]. However, since CT exposes the patient to ionizing radiation, its use is limited to cases that meet clinical criteria, especially in the pediatric population. Scanning with magnetic resonance (MR) is typically done as a follow-up procedure, especially during the chronic post-injury phase of TBI[5], although there are established and emerging MR imaging (MRI) technologies used during acute assessment as well [6]. Because CT imaging can be completed quickly and is capable of detecting a broad spectrum of medically significant pathologies, it is the standard for acute TBI assessment. However, the majority of those who sustain a mTBI, including SRC do not undergo CT imaging, as they do not meet established clinical guidelines for CT utilization [7]. When CT findings are identified, they generally relate to severity of the TBI, where the majority of those with mTBI exhibit no gross abnormalities [7]. In mTBI when the DOI CT is positive, common abnormalities are in the form of contusions, small subarachnoid or intraparenchymal hemorrhages as well as subdural and epidural collections, edema and skull fractures.

Figures 1–4 provide examples of these types of CT findings as the initial DOI assessment in mTBI compared to follow-up MRI during the chronic phase. The Table insert provides brief definitions of various terms to be used in this review. Since MRI has superior capability over CT in detecting subtle pathology, it is preferred for follow-up. There are two important factors associated with DOI CT scanning in mTBI: (1) presence of an abnormality in mTBI constitutes what is referred to as a ‘complicated’ mTBI [8] and (2) DOI imaging establishes a baseline, including where transient pathologies (i.e. edema) may not be visualized with follow-up MRI. If symptoms/problems persist after mTBI, it is clinically appropriate to follow-up with MRI as MR techniques better define parenchymal abnormalities, such as those involving the white matter[5]. Additionally, as will be discussed at the end, numerous quantitative image analysis techniques can be applied to MR scans that cannot be done with CT.

Figure 1 is from a child who at 10 years of age sustained a mTBI (GCS = 15) without documented loss of consciousness (LOC) as the result of a bicycle accident. DOI CT imaging demonstrated a skull fracture (black arrow in A) with a small amount of underlying

hemorrhage (white arrow in A). Two years later when MRI studies were done, residual evidence of the prior hemorrhage and likely prior contusion were evident on the standard MR sequences; note, however that each sequence depicts a different feature of the original injury. The gradient recalled echo (GRE) is particularly sensitive in detecting residual blood by-products (hemosiderin) characterized as a hypointense (dark) signal (white arrow in B). Additionally, the T2 sequence is sensitive to intraparenchymal pathologies as well as characterizing the location and boundaries of cerebrospinal fluid (CSF). The fluid attenuated inversion recovery (FLAIR) sequence is sensitive to white matter pathologies that show up as regions of hyperintense or bright white signal differences. Within the FLAIR MR sequence it is not uncommon to have some increased signal intensity within peri-ventricular regions, but what is likely abnormal in this child is the size and asymmetry of the white matter hyperintensity (WMH) to the left of the anterior horn of the lateral ventricle (white arrow in F). Presence of WMH in mTBI may be a marker of residual shear-strain injury to white matter, although there are various other factors associated with WMHs as well that are not specific to TBI.

Figure 2 is from a 30-year-old patient who was struck by a falling object resulting in occipital skull fracture and epidural hematoma (EDH) as demonstrated in the DOI CT (left image, white arrow). GCS was 15 at the scene of the incident as well as initially within the emergency department (ED). However, in the ED mental status began to deteriorate and the patient underwent emergent neurosurgical evacuation of the EDH. MRI studies performed a year post-injury revealed no identifiable areas of parenchymal damage in the left occipital region where the skull fracture and EDH had occurred but residual encephalomalacia in the middle temporal gyrus. Presence of intracranial hemorrhage and edema, even though initially defined as an mTBI, may become a life threatening injury that require careful clinical assessment [4].

The case in Figure 3 is from a 27-year-old patient who sustained a mTBI in a two-vehicle high-speed collision with an initial GCS of 14 at the scene as low as a 13 during transportation, where CT imaging revealed a solitary small hemorrhage in the left basal ganglia (see Figure 3). However, when assessed a year later with MRI, multiple regions of hemosiderin deposition were noted where only one overlapped with the original traumatic hemorrhage. In this patient, susceptibility-weighted MRI was performed, which is superior in detecting hemosiderin to the prior GRE standard done in the case described in Figure 1[9].

Figure 4 is from a 7 1/2 child injured as a passenger in a motor vehicle accident. GCS was never lower than 14 as assessed in the ED, but the DOI CT revealed multiple small hemorrhagic lesions in the left inferior frontal region. Interestingly the DOI hemorrhagic lesions identified on CT do not necessarily tract to where follow-up MRI pathology (hemosiderin) was found as shown in Figure 4. DOI CT or MRI identified hemorrhagic lesions are consistent with shearing forces that resulted in diffuse axonal injury or DAI [see description by 7]; also consistent with NIH common data element [CDE, for discussion see 9] of hemorrhagic axonal injury.

While these four mTBI cases demonstrate some of the common pathology potentially observed in CT and MR imaging of mTBI, it should also be obvious that the lesions and abnormalities observed were unique to each individual and did not overlap in these four cases where there was considerable diversity in size and distribution of radiologically defined abnormalities. Accordingly, there is substantial heterogeneity in where mTBI-related abnormalities may occur as well as their frequency of occurrence.

As to the frequency of these kinds of findings in mTBI, the NIH funded Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) investigation has begun to address [7, 10]. In the TRACK-TBI study all mTBI patients examined had documented head trauma sufficient to triage to non-contrast head CT using the American College of Emergency Physicians/CDC guidelines[11]. Follow-up neuroimaging was done with MRI. Of the 135 mTBI patients examined the majority of study participants had suffered brain trauma from some type of vehicular accident with 80% having positive LOC. Accordingly, this was not a sample of individuals with SRC, but with more serious brain injuries although still within the mTBI range of severity. CT and follow-up MRI were interpreted by CDE standards [see 12]. Approximately 44% of mTBI patients met criteria for having at least one abnormality, mostly singular in nature.

Since by definition, the Yuh et al. investigation did not specifically assess SRC, those investigations that have examined frequency of positive neuroimaging findings in SRC observe a much lower yield of identifiable abnormalities. Specific to sports participants and DOI CT imaging, the largest to date ED based study is the Pediatric Emergency Care Applied Research Network (PECARN) study by Glass et al. [13], which identified only 4% with abnormalities of 3289 individuals seen within the ED for evaluation of SRC. Although MRI follow-up was not part of the PECARN investigation, in a smaller sample that did involve follow-up with MRI, Ellis et al. [14] examined 151 SRC patients referred to a pediatric concussion clinic where all subjects were 19 years of age or younger. Thirty-six individuals did meet clinical criteria for undergoing neuroimaging. Two were found to have skull fracture with CT and one with suspect intracranial hemorrhage. For those who underwent MRI one patient was identified as having had a non-hemorrhagic contusion, one with non-specific white matter abnormality and several with incidental findings. Similarly, but of an even more limited sample size is a retrospective study by Morgan et al. [15] that examined 52 pediatric patients with mTBI, many of whom had sustained their injury during sport or recreational activities. Only 23 met criteria for follow-up neuroimaging where only one MRI and one CT were identified as demonstrating an abnormality.

To provide a more comprehensive statement on frequencies of structural MRI abnormalities in mTBI, including SRC in a large on-going prospectively recruited cohort of 251 children ranging in age from 8 to 15, a brief description of the study titled 'A Psychiatric and Imaging Study of Pediatric Mild Traumatic Brain Injury' will be presented. For the sake of brevity, hereafter this investigation will be referred to as the 'Pediatric mTBI Study'.

Frequency of positive CT and MRI findings in children 8 to 15 years of age assessed in a Level I Trauma Center and assessed to have sustained a mTBI

The 'Pediatric mTBI study' has prospectively assessed within the same Level I Trauma Center a group of children 8 to 15 years of age with a GCS score ≥ 13 who met American Congress of Rehabilitation Medicine [16] criteria for mTBI. For purposes of an imaging control group, MRI was also obtained on children of both sexes and similar age range seen in the ED but only for an orthopedic Injury (OI), meeting no criteria for head injury. Initial behavioral, neuropsychiatric and symptom reporting was established in the acute, sub-acute and chronic timeframe with the research MRI at 6 months post-injury. Only the MRI clinical findings will be reported herein. As part of the recruitment criteria, if the child's head injury met clinical standards for undergoing a CT scan, that was noted; however, all CT imaging solely was based on clinical decision making[17, 18]. In the first 251 cases initially reviewed for study inclusion, 37.4 % had sports related injury, 28.6% with fall related injuries, 28.2% had experienced some type of recreational injury, with 5.8 % of the injuries related to some type of vehicular accident (none in OI children). While falls were a common mechanism of injury within the category of "recreational injuries", they occurred during some form of recreational activity as opposed to a simple fall. The most common recreational injury was skateboarding, followed by trampoline accidents, roller skating/blading, horseback riding, rock climbing and falls from monkey bars. Falls not associated with a recreational activity were reported to be from tripping, falling off of some object, "horse-play", running and tripping, falls in the house or yard (i.e. a tree), etc. The majority of the sports-related injuries came from football and soccer, but all of the major contact sports were represented including basketball, cheerleading, wrestling, volleyball, baseball, hockey and karate.

Follow-up MRI studies were performed at 6 months post-injury, wherein the same board certified neuroradiologist (JRH), blind to patient history, independently viewed each scan with specific reference for trauma-related features of whether focal encephalomalacia, hemosiderin deposition, WMH and/or dilated Virchow-Robin (V-R) space could be identified. Although not previously mentioned, prominent V-R space(s) within the deep white matter may occur in mTBI potentially related to shear/strain influence on the vasculature[19] but also may be a normal variant or associated with non-traumatic pathology. As such V-R findings are not a specific indicator of prior TBI.

In the initial cohort of 251 children seen in the ED with either mTBI or OI, 197 underwent a research MRI at 6 months (66 OI, 131 mTBI children), wherein 25 (9.9%) were identified with some type of neuroradiological finding. Hemosiderin deposition was observed in only 3 mTBI individuals, two of whom sustained brain injuries involving vehicular accidents. The other child with MRI-identified hemosiderin deposition was injured from a fall at school. Similarly, focal encephalomalacia was observed in only those with a history of mTBI and just in two cases. One was a significant fall from a height with observed positive LOC and the other a bicycle-truck collision with no helmet being worn. CT studies were negative. Twelve children were observed to have FLAIR identified WMHs, but only four with mTBI and only one injured playing sports. Of the eight OI children with WMHs only one child had

sustained the injury playing sports. Five children, all of whom had sustained mTBI, were identified with prominent VR spaces. The head injury in two of the children with prominent V-R spaces were vehicular, with one associated with CT-identified parietal skull fracture and SAH and the other positive LOC but negative CT. The others were associated with fall. Non-traumatic incidental findings were found in 7 percent.

A three-dimensional representation of the brain along with the distribution of clinical neuroimaging findings from the 'Pediatric mTBI study' is presented in Figure 5. WMHs, hemosiderin deposition and focal atrophy/encephalomalacia clearly have a frontotemporal distribution of pathology.

Consistent with what has been discussed with the PECARN findings with DOI CT scanning and related studies, there were few structural neuroimaging abnormalities clinically identified in the 'Pediatric mTBI Study' with uniform high-field MRI. However, such findings were based on just the conventional neuroimaging performed. Next, several advanced MRI quantification techniques that can be applied in assessing mTBI will be discussed.

Advanced Neuroimaging Methods

During the last decade significant advances in automated image analysis techniques have been made that permit a variety of quantitative methods in the study of mTBI[9, 20–22]. While not ready for clinical application at this time, these techniques have potential for advancing our understanding of mTBI and will be briefly reviewed herein.

Automated image analysis techniques capitalize on MR signal intensity differences between white matter, gray matter and CSF, where algorithms applied to those differences can extract and classify anatomical borders and regions of interest (ROI) as shown in Figure 6. FreeSurfer is one of the pioneering programs to achieve this goal [see 23] from which the volume of major ROIs can be calculated, cortical surface determined as degree of gyrification (surface area) along with gray matter cortical thickness or volume (see Figure 6). For example, the scatter plots shown in Figure 6 show the classic age-dependent gray matter volume reductions thought to reflect neuronal pruning that increases with age, [24] where no difference between OI and mTBI children in the 'Pediatric mTBI study' was observed. The FreeSurfer technique also permits exploration of a dependent variable like a cognitive or TBI outcome score in relation to a ROI anatomical variable like cortical thickness. What is shown in Figure 7 is that initial symptom rating derived from the Post-Concussion Symptom Inventory (PCSI) [25] in the 'Pediatric mTBI Study' was related to cortical thickness, but this applied to both OI and mTBI groups. In viewing Figure 7, reduced cortical thickness within the insular cortex on the right and bilaterally in areas that included the cingulate gyrus were associated with higher symptom reporting. These regions are known to relate to pain and interoceptive processing, and within the 'Pediatric mTBI study' were associated with more symptom reporting in both OI and mTBI participants. Since this was found with the groups combined, it could not be attributed to TBI but to symptom perception and potentially the anatomical constitution of the brain at the time of injury regardless of whether a mTBI occurred. What has been shown in Figures 6 and 7

demonstrate some of the potential applications of quantitative neuroimaging in the study of mTBI.

Another major benefit of using quantitative methods like FreeSurfer is that after establishing a representative normal sample, the individual quantitative data can be compared to a normative sample for any structure or region of interest (ROI). As a case study example of this from the 'Pediatric mTBI Study' is shown in Figure 8. While playing this child fell from several feet striking a concrete surface, sustaining a witness-documented LOC followed by nausea and vomiting. CT was abnormal with frontal lobe contusion noted, but not requiring neurosurgical intervention. MRI identified "... focal encephalomalacia in the anterior-inferior frontal lobes, bilaterally (left >>right)," as shown in Figure 8. Although there is no focal pathology involving other brain regions, FreeSurfer volumetric analyses demonstrated reduced volumes in several ROIs, including the hippocampus (see Figure 8).

To better view in 3-D where anatomical differences are in this child's brain compared to a non-brain injured sample, another semi-automated structural image analysis method is to compare the individual brain to a normative atlas or template generated from OI participants. Using the method referred to as advanced normalization tools [ANTs, see 26], the individual brain can be compared to a control template brain by "stretching" or warping the image contours of the patient brain to fit the template. Applying this technique to the case in Figure 8, a 3-D graphic image of the brain can be rendered that simultaneously demonstrates not just where the focal lesion is located but where other cortical volume losses have occurred (warm colors, yellow to red) beyond those visually detected by just viewing the images.

The last method to be discussed is diffusion tensor imaging (DTI) which provides exquisite information about white matter integrity[27]. As already shown in Figure 8, the T1 weighted image depicts a prominent region of focal encephalomalacia. The color DTI map shown in Figure 8B reflects directionality of water diffusion, which in turn permits inferences about directionality of white matter tracts. Green indicates tracts coursing in the anterior-posterior direction, warm colors (orange-to-red) reflect side to side or laterally oriented tracts and blue hues reflect vertically oriented tracts. There is "less" appearance of green (white arrow in B) with overall reduced tract volume. Additionally, DTI permits application of diffusion metrics as well as actually deriving tract bundles from this area. The most common DTI diffusion metric is fractional anisotropy (FA), which can be used as an index of white matter tract integrity. Figure 8C depicts FA across the corpus callosum within the forceps minor. Because of its distinct location, the forceps minor can be automatically identified using an open-source software package, Automated Fiber Quantification (<https://github.com/jyeatman/AFQ>). After completing whole-brain tractography using a deterministic streamline tracking algorithm (STT), individual fibers assigned to the forceps minor fiber tract can be identified if they passed through two waypoint ROIs. Using DTI techniques like this permit quantification of FA along every component of the white matter tract.

Knowing where there are quantitative changes in brain structure may facilitate the clinician in establishing relevant clinical correlations. The 'Pediatric mTBI Study' is ongoing, so we are not in a position to report on neurobehavioral correlates with neuroimaging findings in this cohort. Nonetheless, in the case presented in Figure 8, documented frontal pathology

with reduced white matter integrity combined with smaller hippocampal volume may put this child at higher risk for experiencing deficits in emotional regulation, cognitive and executive functioning.

Discussion

The common structural neuroimaging findings in mTBI were summarized in Figures 1–4. In the ‘Pediatric mTBI Study’ at six months post-mTBI including SRC, a uniformly applied research MRI with standard clinical MR sequences identified few children with reportable neuroradiological findings. Identifiable abnormalities of focal atrophy/encephalomalacia were observed only in accidental falls and vehicular accidents. No participant with SRC was identified with either abnormality. WMHs were observed in both mTBI and OI cases and lacked specificity as a marker of brain injury. Advanced quantitative imaging techniques hold promise to further identify potential abnormalities associated with SRC and mTBI but require further research.

In one sense in the ‘Pediatric mTBI Study’, given that all cases were scanned with the same high-field 3 Tesla MRI with a uniform protocol, it is reassuring in this pediatric sample that serious structural pathology was not observed in over 90% of the cases. Although the absence of clinical findings may just be a limitation of current technology, it does suggest that any residual SRC pathology to be detected by neuroimaging will be subtle. Also, the limitation in detecting pathology associated with SRC may simply reflect the limits of technology. As a demonstration of this issue, Moenninghoff et al. [28] used a MR field strength of 7 Tesla in a TBI patient which detected microhemorrhages not visible at 3 Tesla. The combination of improved MR technology with image analysis tools for post-processing hold great promise for more effective neuroimaging methods to assess brain integrity in the assessment of the SRC or mTBI patient [27].

In conclusion, findings from the ‘Pediatric mTBI Study’ confirm that conventional MRI sequences used in the clinical management of mTBI yield few abnormalities that can be clinically defined. If subtler abnormalities are to be reliably detected, they will need to come from “advanced neuroimaging” methods, some of which were discussed in this review.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

This mTBI case depicts the most common findings observed in CT and MRI. (A) The DOI CT shows soft-tissue swelling (black star) and the point of contact, beneath the location of a skull fracture (black arrow). White arrow points to the location of what was assessed to be a hemorrhagic contusion. Follow-up MRI studies depict the different ways that old contusion sites may appear on different MR sequences. (B) The GRE is sensitive to blood byproducts (hemosiderin) and shows a hypointense (dark) ring around a liquid center (white arrow). (C) T2-weighted imaging demonstrates increased CSF associated with this lesion site (white arrow) with a small region of parenchymal damage (white arrow in D) identified in the T1-weighted anatomical image. In E, the FLAIR image depicts hypointense signal where the prior hemorrhage occurred. However, F also demonstrates the appearance of a very prominent hyperintense (bright white) signal in the left peri-ventricular region (white arrow).

Figure 2.

The image on the left is from the DOI CT where the white arrow points to an epidural hematoma, with underlying occipital skull fracture (not shown in this image). Also, note the right Sylvian fissure (SF) on the DOI CT is readily visualized but is not identifiable on the left. This reflects localized edema from the trauma involving frontotemporal regions of the brain where a year later follow-up MRI depicts a small region of encephalomalacia (arrows).

Figure 3.

The upper left image is the DOI CT which demonstrates focal hemorrhage in the region of the left internal capsule-globus pallidus however, on follow-up MRI more than a year post-injury susceptibility weighted imaging (SWI) reflects multiple areas of residual prior hemorrhage from the trauma (white arrows). The two bottom images are FLAIR sequences that show not only some of the hypointense signal changes from the prior hemorrhagic shear injuries, but also multiple regions of hyperintense signal (white arrows), some directly associated with where hemorrhagic lesions occurred and some independent.

Figure 4.

(A) The DOI CT depicts multiple foci of traumatic hemorrhagic injury in the inferior left frontal lobe (punctate white dots). However, on follow-up MRI hemosiderin deposition is also identified in multiple other frontal regions more superior to where it was originally observed in the DOI scan. Also, the T2-weighted image in D, T1-weighted images in E and F depict where regions of focal encephalomalacia developed in the frontal polar, gyrus rectus region of the brain.

Figure 5.

Three cases from the ‘Pediatric mTBI Study’ highlight the blinded as to group independently identified MRI abnormalities observed in the first 251 patients screened for participant inclusion. Research MRI studies were obtained all from the same GE 3 Tesla scanner and included a sagittal plane volume acquisition T1 IR-SPGR sequence (TR: 7.15 ms, TE 2.90 ms, 1.2 mm slice thickness), T2-fluid attenuated inversion recovery (FLAIR) sequence (TR: 8000 ms, TE: 140.58 ms, 3.0 mm slice thickness) and a 3-D susceptibility weighted imaging (SWI) sequence (TR: 30 ms, TE: 23 ms, 1.0 mm slice thickness). Each abnormality as neuroradiologically defined was identified as a region of interest (ROI) generated by hand tracing the lesion boundaries onto a template image using Mango (<http://ric.uthscsa.edu/mango/>). Then, a surface model was generated to represent each lesion area in 3-D space. The ROI’s represent the relative location where lesions were located. Small WMHs and regions of hemosiderin deposition were slightly enlarged to improve visualization.

A **B** **Figure 6.**

A: Quantitative neuroimaging steps to segment and classify region of interest (ROI) features using FreeSurfer begin with the anatomical T1-weighted image (Top Left). The upper image is the original, native space T1 image sectioned in the coronal plane. (Bottom Left) Skull stripped and intensity normalized coronal T1 weighted image derived from the original image, as shown in the top left. (Top middle) The segmented white matter estimate *wm.mgz* file created during the FreeSurfer pipeline. (Bottom middle) Subcortical and cortical segmentations overlaid onto a T1 weighted image. Note that through this method the major regions of interest and brain nuclei may be identified and quantified. (Top Right) Enlargement of a cortical ROI with (Bottom Right) depiction of how cortical thickness, cortical volume and surface area may be derived from FreeSurfer. **B:** (Bottom Left Scatter-

Plot) Using the total gray matter volume computation from FreeSurfer the scatterplots on the left depict age-mediated changes in gray matter volume for mTBI participants in the 'Pediatric mild TBI' study comparing the regression line trajectories of children with mTBI versus those with OI, reflecting no significant difference. (Bottom Right Scatter Plot) Similarly, the scatterplot of white matter volume, shows no significant difference in whole-brain white matter volume by age between those with mTBI versus OI.

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Figure 7.

Using FreeSurfer to compute cortical gray matter volume (see upper right hand images of Figure 6) when mTBI and OI groups are combined smaller cortical volume (blue hues reflect less volume) as shown in the inflated surface maps. Since in the typical gyral surface pattern, the depths of the cortical surface are embedded within a sulcus, the inflated surface maps depict the location of a gyrus by darker gray.

Figure 8.

All of the images in this Figure are derived from the same subject (A) In the axial T1-weighted image in the upper left, the white arrow points to a region of focal encephalomalacia. In the T1-weighted image it is challenging to identify how significant white matter changes are, but from the diffusion tensor imaging (DTI) scan in B actual tract integrity can be assessed which is shown in C and F based on fractional anisotropy (FA) values derived from the DTI scan. Reduced FA values are shown on the left in F with in the gray zone which occurs in the region of encephalomalacia. Accordingly, these findings implicate damaged white matter associated with the encephalomalacic changes shown in A. (D). Coronal image in the lower left cut through the hippocampus depicts some prominence of the temporal horn of the lateral ventricle where FreeSurfer shows hippocampal volume that is approximately 1.5 standard deviations below the OI comparison group with temporal horn volume almost 2.0 standard deviations above the norm. (E) (Frontal View) Using the Advanced Normalization Tools (ANTs) this patient's 3-D rendered image was 'warped' to a typical developing control (TDC) template, that shows the frontal polar atrophy (bright yellow-orange) involves more than just the focal encephalomalacia as depicted in 'A'. Quantitative 3-D imaging contrasted to a TDC template permits the simultaneous

visualization of where other brain regions are less in volume, and not just where clinically identifiable pathology is noted.

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