White Matter Tract Integrity: An Indicator of Axonal Pathology after Mild Traumatic Brain Injury

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Abstract

We seek to elucidate the underlying pathophysiology of injury sustained after mild traumatic brain injury (mTBI) using multi-shell diffusion magnetic resonance imaging, deriving compartment-specific white matter tract integrity (WMTI) metrics. WMTI allows a more biophysical interpretation of white matter (WM) changes by describing microstructural characteristics in both intra- and extra-axonal environments. Thirty-two patients with mTBI within 30 days of injury and 21 age- and sex-matched controls were imaged on a 3 Tesla magnetic resonance scanner. Multi-shell diffusion acquisition was performed with five b-values (250–2500 sec/mm²) along 6–60 diffusion encoding directions. Tract-based spatial statistics (TBSS) was used with family-wise error (FWE) correction for multiple comparisons. TBSS results demonstrated focally lower intra-axonal diffusivity (D_{axon}) in mTBI patients in the splenium of the corpus callosum (sCC; $p < 0.05$, FWE-corrected). The area under the curve value for D_{axon} was 0.76 with a low sensitivity of 46.9% but 100% specificity. These results indicate that D_{axon} may be a useful imaging biomarker highly specific for mTBI-related WM injury. The observed decrease in D_{axon} suggests restriction of the diffusion along the axons occurring shortly after injury.

Keywords: diffusion; kurtosis; mild traumatic brain injury; MRI; white matter tract integrity

Introduction

MILD TRAUMATIC BRAIN INJURY (mTBI) IS A MAJOR PUBLIC health problem, representing about 80% of the 2.8 million traumatic brain injuries sustained each year in the U.S.^{1,2} Up to 22% of patients report persistent symptoms.³ White matter (WM) injury has been widely implicated as playing a key role after mTBI⁴; however, the specific pathophysiology of WM injury remains controversial.

The exploration of non-invasive methodologies for the detection of WM injury using diffusion magnetic resonance imaging (MRI) is extremely promising. Diffusion tensor imaging (DTI) shows areas of abnormal WM fractional anisotropy (FA) and mean diffusivity (MD) in mTBI^{5–7}; more recently, diffusion kurtosis imaging (DKI) has been employed to characterize non-Gaussian diffusion (e.g., mean kurtosis [MK]) in mTBI patients showing altered brain tissue microstructural complexity.^{8–10} FA and MK are nonspecific measures. However, building on this previous work, imaging biomarkers more specific to the biophysical injury sustained in mTBI are sought.

Compartment-specific WM tract integrity (WMTI) metrics¹¹ derived from multi-shell diffusion imaging have been proposed to describe microstructural characteristics in intra- and extra-axonal environments of WM, including: 1) the axonal water fraction (AWF); 2) intra-axonal diffusivity along axons [D_{axon}]; 3) extra-axonal axial [$D_{e,\parallel}$] and 4) extra-axonal radial [$D_{e,\perp}$] diffusivities; and 5) the derived tortuosity¹² [$\alpha = D_{e,\parallel}/D_{e,\perp}$] of the extra-axonal space. The benefit of this two-compartment model is the limited number of assumptions incorporated: 1) there is no significant inter-compartment water exchange and 2) the inherent parameter estimation duality is resolved by assuming lower diffusivity in the intra-axonal compared to the extra-axonal environment. WMTI metrics have been studied in several animal validation works.^{13–15} They also have been shown to be of use in understanding microstructural changes in normal development,¹⁶ as well as a host of central nervous system disorders, including stroke,¹⁷ multiple sclerosis,¹⁸ Alzheimer's disease,^{19,20} mild cognitive impairment,¹⁹ autism,²¹ and mTBI.²²

Here, we investigate WM microstructural changes after mTBI in terms of compartment-specific WMTI metrics within 30 days of injury, representing a reasonable interval to capture a majority of

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acutely symptomatic concussion patients. Our investigation moves beyond empiric depictions of WM (e.g., DTI or DKI measures of diffusion signal) in an attempt to uncover underlying microstructural changes that occur after mTBI.

Methods

Study population

This study has been approved by our Institutional Review Board, and all experiments were performed in accordance with relevant guidelines and regulations. All subjects provided written informed consent before the procedure. Subjects were prospectively recruited in a consecutive fashion who were seen for clinical care in the emergency department or institutional concussion center who fulfilled the following inclusion criteria: 1) adult patients between the ages of 18 and 65 years old; 2) diagnostic criteria of mTBI defined by the American Congress of Rehabilitation Medicine (ACRM²³; established either by emergency department medical record or standardized self-report survey obtained at the time of assessment at the concussion center), including either loss of consciousness of less than 30 min or altered consciousness at time of accident and a Glasgow Coma Scale score of 13–15; and 3) injury within 30 days. Patients were excluded for previous history of significant TBI, other neurological illness or psychiatric disorder, history of participation in organized contact sports, and contraindication to MRI. We studied 32 patients with mTBI (mean age, 35 ± 12 years [range, 21–64]; median age, 32 years old [interquartile range, 25–45]; average time since injury, 17 days [range, 4–29]; 14 male). Twenty-one age- and sex-matched normal controls (NC) with no history of TBI or neuropsychiatric disease also were studied (mean age, 34 ± 9 years old [range, 19–51]; median, 31 years old [interquartile range, 28–41]; 11 male). Full participant demographic and injury characteristics are shown in Table 1. This is the first report including these subject cohorts.

MRI acquisition

MRI experiments were performed on a 3 Tesla magnetic resonance scanner (Skyra; Siemens Medical Solutions, Erlangen, Germany). Diffusion imaging was performed at multiple shells: 5 b-values (250, 1000, 1500, 2000, 2500 sec/mm²) along with multiple diffusion en-

coding directions (6, 20, 20, 30, 60, respectively) using multiband (factor of two) echo-planar imaging (EPI) for accelerated acquisitions with anterior-posterior (AP) phase encoding direction. Three non-weighted diffusion images (b = 0 sec/mm²) also were acquired. Other imaging parameters were: field of view = 220 mm × 220 mm, acquisition matrix = 88 × 88, image resolution = 2.5 × 2.5 × 2.5 mm³, number of slices = 56, repetition time/echo time = 4900/95 msec, bandwidth = 2104 Hz/pixel, and a generalized autocalibrating partially parallel acquisitions factor of two. For geometric distortion correction, an additional image with b = 0 sec/mm² was acquired with the same imaging parameters but with reversed (PA) phase encoding direction. The total acquisition time is about 12 min.

Image analysis

Diffusion image processing. The pre-processing steps for the diffusion images include Marchenko-Pastur principal component analysis denoising,²⁴ Gibbs correction,²⁵ geometric EPI distortion correction (FSL's function, 'topup'), eddy current distortion and motion correction (FSL's function, 'eddy'), and outliers detection.²⁶ In-house image processing software developed in MATLAB R2016a (The Mathworks, Inc., Natick, MA) was used to calculate maps of the WMTI metrics (AWF, D_{axon} , $D_{\text{e,||}}$, $D_{\text{e,⊥}}$, tortuosity α), as well as both DTI metrics (FA, MD, axial diffusivity [AD], radial diffusivity [RD]) and DKI metrics (MK, axial kurtosis [AK], radial kurtosis [RK]).

Tract-based spatial statistics

Voxel-wise analyses were performed using standard procedures of tract-based spatial statistics (TBSS).²⁷ Subject FA maps were registered to the FA template (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FMRIB58_FA) and voxel-wise statistics were performed on FA values projected onto the WM skeleton by looking for local maximum values perpendicular to the skeleton. All other parametric maps underwent the same transformations and processes. The tract skeleton was thresholded to FA ≥ 0.4 to restrict analysis to WM regions, as recommended.¹¹ Statistical tests were conducted using the permutation-based nonparametric analysis routine "randomize" with 5000 iterations, using threshold free cluster enhancement.

Statistical analysis

Subject groups were compared in terms of sex using a Fisher's exact test and in terms of age using an exact Mann-Whitney *U* test. For TBSS analysis, age and sex were included as covariates, and the significance level was set at $p < 0.05$ with the family-wise error (FWE) correction for multiple comparisons using the TBSS package.²⁷ A receiver operating characteristic (ROC) curve analysis was conducted using MedCalc version 17.5.3 (MedCalc Software bvba, Ostend, Belgium) to identify a threshold value for a significant diffusion metric to discriminate mTBI patients from controls. The threshold was identified by maximizing the Youden index, implying that characterizing subjects as test positive or negative for mTBI according to the threshold maximized the average of sensitivity and specificity. Corresponding areas under the ROC curve (AUCs), sensitivities, and specificities were calculated.

Results

The groups were not significantly different in terms of sex ($p = 0.58$, Fisher's exact test) and age ($p = 0.98$, Mann-Whitney *U* test). The mechanisms of injury include fall (40.6%), hit by object (18.8%), motor vehicle accident (15.6%), assault (6.3%), sports-related (6.3%), and others (12.5%; Table 1). Review of conventional MRI demonstrated one mTBI subject with a possible injury-related finding (i.e., single punctate focus of susceptibility in the left parietal lobe) and one mTBI subject with incidental finding of a 1.2 cm pineal cyst without complication.

TABLE 1. DEMOGRAPHIC AND INJURY CHARACTERISTICS OF STUDY PARTICIPANTS

Variables	mTBI (n = 32)	Control (n = 21)
Age, years (mean ± SD)	35.4 ± 11.9	33.7 ± 9.3
Gender, M/F	14/18	11/10
Race, n (%)		
Caucasian	24 (75.0 %)	14 (66.7 %)
African American	4 (12.5 %)	1 (4.8 %)
Asian	1 (3.1 %)	6 (28.6 %)
Other	3 (9.4 %)	0 (0 %)
Education, years (mean ± SD)	16.6 ± 2.0	16.0 ± 1.8
Hand preference, right, n (%)	26 (81.3 %)	19 (90.5 %)
Cause of injury, n (%)		
Fall	13 (40.6 %)	N/A
Hit by object	6 (18.8 %)	
Motor vehicle accident	5 (15.6 %)	
Assault	2 (6.3 %)	
Sports-related	2 (6.3 %)	
Others	4 (12.5 %)	
Days post-injury (mean ± SD)	17.2 ± 7.1	N/A

mTBI, mild traumatic brain injury; SD, standard deviation; M, male; F, female.

Intra-axonal diffusivity (D_{axon})

FIG. 1. Tract-based spatial statistics results for “ D_{axon} ” comparing subjects with mild traumatic brain injury (mTBI) and healthy controls: Clusters of voxels demonstrating significantly decreased D_{axon} in mTBI ($p < 0.05$, family-wise error corrected) are present in the splenium of the corpus callosum (sCC; red-yellow). Heat map showing differences between cohorts is overlaid on the MNI152 T1 template and mean white matter skeleton (green).

FIG. 2. Tract-based spatial statistics (TBSS) results towards significant at the 90% confidence level after family-wise error (FEW) correction: Statistical trends in the TBSS results ($p < 0.1$, FWE corrected) though not reaching $p = 0.05$ threshold for significance, comparing mild traumatic brain injury (mTBI) subjects and controls with respect to axial diffusion (AD) and axial kurtosis (AK). Clusters showing a trend towards lower AD (top) in mTBI patients are present in the right anterior body of the corpus callosum (bCC; red-yellow; $p < 0.1$, FWE corrected). Clusters showing a trend towards higher axial kurtosis (AK) are present in the bCC and genu of the corpus callosum (gCC; blue).

FIG. 3. Receiver operating characteristic curve showed the performance of D_{axon} . The area under the receiver operating characteristic curve (AUC) was 0.76 for D_{axon} alone.

TBSS analysis demonstrated significantly lower D_{axon} ($p < 0.05$, FWE-corrected) in mTBI patients (1.33 ± 0.12), compared with controls (1.45 ± 0.10), most notably in the splenium of the corpus callosum (sCC; Fig. 1). No other diffusion metrics showed areas of significant difference surviving correction for multiple comparisons. Figure 2 shows the spatial distribution of WM diffusion differences between groups that trended toward significance ($p < 0.1$, FWE-corrected) demonstrating decreased AD and increased AK also localizing to regions in the CC.

The ROC curve for D_{axon} yields an area under the curve (AUC) of 0.76 (Fig. 3). The cut-off value was $D_{\text{axon}} = 1.31 \text{ mm}^2/\text{sec}$ with a sensitivity of 46.9%, a specificity of 100%, and an overall accuracy of 67.9%.

Discussion

In this study using WMTI diffusion MRI, D_{axon} was significantly lower in mTBI subjects compared with controls in a localized fashion in the posterior CC (Fig. 1), and this splenial intra-axonal restriction of diffusion was found to be highly specific for injury within 30 days.

The CC is known to be susceptible to shear strain forces of mTBI. Biomechanical models show quantitative stress measures²⁸ and von Mises stress²⁹ to be highest in and around the CC and *in vivo* diffusion data corroborate this, including specifically implicating the splenium.³⁰ A range of potential WM injuries have been postulated after mTBI from primary axotomy to demyelination to kinking and malalignment of otherwise intact fibers, or perhaps a combination of these. Based on mechanical stretch injury models, sub-lethal axonal injury results in irregularity of the axon such as beading, varicosity, or undulation of the axon.^{31,32} In principle, all such geometric distortions of axonal fibers may cause reduced diffusion coefficients in intra- and extra-axonal spaces, along the main direction of the fiber tract. While it is not possible to completely disentangle their relative contribution to the observed diffusivity result, based on prior works, lower D_{axon} has been observed in ischemia,¹⁷ believed to relate to axonal beading.³³

The presence of measurable differences in D_{axon} and no differences in AWF or $D_{\perp}$ further militates against axotomy and de-

myelination, respectively, as dominant pathologies in this case as prior works show alterations of these measures.^{15,22} Our results are in keeping with histologic studies showing primary axotomy to be an uncommon primary mechanism of injury in TBI.³⁴ Therefore, some other longitudinal pathology along the main axonal axis, such as beading, varicosity, or undulation (known to occur in axon stretch injury models), is believed to be dominant. Thus, we see that WMTI metrics, based on multi-shell diffusion acquisition, provide additional insight into the biophysical meaning of WM injury after mTBI with information beyond traditional empiric diffusion metrics such as FA, and help further elucidate the pathophysiology of underlying tissue damage.

FA alterations following mTBI have been previously reported in DTI studies, although results of the literature are inconsistent: Some studies show lower FA in mTBI subjects compared with controls,³⁰ some higher,³⁵ and others variable³⁶ or no difference.³⁷ Here, we found no differences in FA, which is in keeping with prior reports in the acute to subacute period; the variability of FA is believed to relate to differences in time since injury as FA can be affected by myriad, perhaps overlapping, pathophysiologic changes including edema, axon injury, and demyelination. As such, FA is known to be a nonspecific measure of WM injury after mTBI that can undergo a period of pseudonormalization.^{38,39}

Several trends also were present, which, while not reaching statistical significance after FWE correction, are nevertheless worth noting: lower AD and higher AK in the mTBI group, also localizing to regions in the CC (Fig. 2). It is of interest that both of these metrics again point to microstructural alterations along the long axis of the axon, perhaps indicating more complex, subtle injury present throughout the CC. Though these trends observed in AD and AK between mTBI and controls are compelling, statistical significance will require a greater sample size to confirm.

In the present study, D_{axon} was found to have overall low sensitivity of 46.9% (15 of 32 mTBI) and high specificity of 100% (21 of 21 NC). For diagnosis and patient stratification in mTBI, thus far there is no single biomarker demonstrating concurrent high sensitivity and specificity. A highly specific marker such as D_{axon} could be used in conjunction with other more sensitive tests to accurately

detect injury. Of note, specific imaging biomarkers are especially lacking in mTBI.

The WMTI model¹¹ used in this study characterizes a bi-compartment (intra- and extra-axonal) diffusion model in keeping with observed diffusion behavior within areas of highly aligned WM bundles. It models the intra-axonal space as a collection of zero-radius cylinders (or sticks) and incorporates the following two main assumptions: 1) there is no significant inter-compartment water exchange and 2) the inherent parameter estimation duality is resolved by assuming lower diffusivity in the intra-axonal compared with the extra-axonal environment. Histopathologic validation studies in rodents support these choices.¹⁵ In addition, while the original WMTI choice implies $D_{\text{axon}} < D_{\text{e},\parallel}$ for selecting the “branch” of the solutions of the inherent duality in estimating WMTI compartment diffusivities in the longitudinal direction for model parameters, there exist arguments for the alternative branch selection.⁴⁰ In this work, we do not attempt to resolve this inherent duality and keep for now the original WMTI branch selection $D_{\text{axon}} < D_{\text{e},\parallel}$. In any case, the branch choice is limited to the longitudinal metrics and irrespective of this choice, our study shows that at least one of the compartment diffusivities along the WM tracts is affected in MTBI, which also is supported by the trend of reduced overall longitudinal diffusivity from the diffusion tensor. Importantly, significant differences are not observed in diffusivity $D_{\text{e},\perp}$ transverse to the tracts or AWF.

An additional limitation of the present study includes the somewhat broad range in time since injury. The goal was to capture the majority of acutely symptomatic patients. Although some mTBI patients present at the time of injury, many others present days to weeks after injury for the first time and some patients' symptoms emerge over the initial days after injury.⁴¹ Note that because of the range in time since injury that was included, these results may be generalizable across subjects within 30 days of injury and D_{axon} may be a useful imaging marker specifically in a cohort where FA can be variable. Further, examining findings within this period may provide a basis for investigations aimed at identifying the subset of patients who go on to have persistent post-concussion symptoms several months following injury. This is a cross-sectional study and future work is underway to follow patients in a longitudinal manner to provide insight into how WMTI metrics evolve over time and what they suggest with regard to underlying pathophysiology during injury recovery.

This study recruits from both the emergency department and institutional concussion center, broadly reflecting patients with recent concussion. This may represent a subset of more symptomatic patients. In addition, upper age limit for inclusion in this study was set at 65 years, excluding geriatric patients with mTBI who may have potentially confounding disease states such as ischemia, hemorrhage, and amyloid that might be difficult to separate from injury-related changes. The slightly greater number of females in the mTBI group (14 males and 18 females) is representative of the population seen at this urban academic medical center's Institutional Concussion Center. Though there may be a higher incidence of mTBI in males relating to participation in contact sports, new evidence suggests females may be at greater risk of concussion, suffer worse outcome, and be more likely to report symptoms which may influence rate of self-referral.⁴² The study groups were not significantly different in terms of sex ($p=0.58$) and age ($p=0.98$), and both sex and age effects were adjusted as covariates during the analyses.

In conclusion, WMTI reveals microstructural changes in WM highly specific to mTBI even during a period after injury when FA

changes may be obscured or pseudo-normalized. These changes affect the splenium of the CC, revealing lower than expected D_{axon} in mTBI patients within 30 days of injury. Compared with previous findings from WMTI validation studies, the combination of results showing differences in D_{axon} and no measurable difference in AWF or $D_{\text{e},\perp}$, militates against demyelination and axotomy as dominant pathologies and supports some other type of pathology along the longitudinal axis of the axon such as beading, varicosity or undulation, seen to occur in axon stretch injury models.

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Author Disclosure Statement

No competing financial interests exist.

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