White Matter Abnormalities in Acute Mild Traumatic Brain Injury: A Diffusion Kurtosis MRI Study

Sohae Chung[1,2], Els Fieremans[1,2], Jelle Veraart[1,2], Dmitry S. Novikov[1,2], Jacqueline Smith[1,2], Steven R. Flanagan[3], and Yvonne W. Lui[1,2]

[1]*Center for Advanced Imaging Innovation and Research (CAI2R), Department of Radiology, New York University School of Medicine, New York, NY, United States,*
[2]*Bernard and Irene Schwartz Center for Biomedical Imaging, Department of Radiology, New York University School of Medicine, New York, NY, United States,*
[3]*Department of Rehabilitation Medicine, New York University Langone Medical Center, New York, NY, United States*

Target audience: Scientists/Clinicians interested in quantifying microstructural changes in white matter (WM) using diffusion MRI-based tissue models.

Purpose: Mild traumatic brain injury (mTBI) is a growing public health problem, which represents more than 80% of all traumatic brain injury[1]. It is known that white matter injury can occur in mTBI and contribute to long-term behavioral and cognitive symptoms[2]; however, our overall sensitivity to white matter injury and understanding of the underlying pathophysiology is limited. Here, we investigate white matter abnormalities in mTBI in terms of compartment specific WM tract integrity (WMTI) metrics[3,4] derived from diffusion kurtosis imaging (DKI), such as intra-axonal diffusivity (D_{axon}), extra-axonal axial and radial diffusivities ($D_{e,\parallel}$ and $D_{e,\perp}$) and axonal water fraction (AWF).

Methods: Seven patients (mean age 34±11, range 24-51 yrs; 4 male) with mTBI within two weeks of injury and seven age and sex matched normal controls (NC) (mean age 31±9, range 22-50 yrs; 4 male) were scanned on a 3T MR scanner (Skyra, Siemens). DKI acquisition was performed with 6 b-values (0,0.25,1,1.5,2,2.5 $\mathrm{ms}/\mu\mathrm{m}^2$) along with 3,6,20,20,30,60 diffusion encoding directions using multiband (factor of 2) echo-planar imaging for accelerated acquisitions. Other imaging parameters were: acquisition matrix = 88×88, image resolution = 2.5×2.5×2.5mm^3, number of slices = 56, TR/TE = 4.9s/95ms, BW/pixel = 2104Hz, FOV = 220×220mm^2, a GRAPPA factor of 2. Both diffusion and kurtosis parametric maps of mean, axial and radial diffusion coefficients (MD, $D_\parallel$ and $D_\perp$), fractional anisotropy (FA), and mean, axial and radial kurtosis (MK, $K_\parallel$ and $K_\perp$) were calculated, and then used to derive WM tract integrity of D_{axon}, , $D_{e,\parallel}$, $D_{e,\perp}$ and AWF. We tested for differences between NC and mTBI groups using tract-based spatial statistics (TBSS)[5] and region-of-interest (ROI) analysis of 27 WM regions. Using FSL (Analysis Group, FMRIB), we nonlinearly registered the individual FA maps to the FA template on the basis of the John Hopkins University WM label atlas[6]. The tract skeleton and WM ROIs were thresholded to $FA \geq 0.4$ to restrict analysis to WM regions consisting of single-fiber orientations[4]. The resulting statistical maps from TBSS were thresholded ($P < 0.05$). Means and SDs were extracted for each metric.

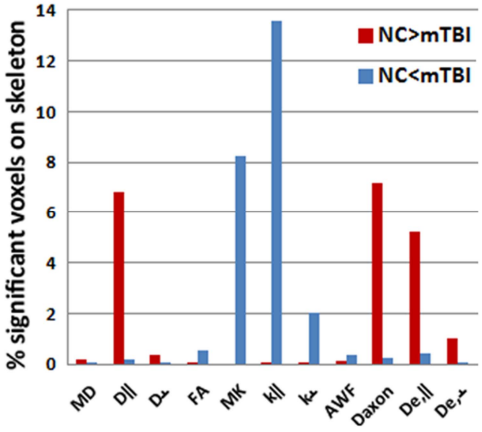

Figure 1. Bar graphs showing the percentage of significantly different voxels on the skeleton for each standard diffusivity, kurtosis, and WMTI metrics using TBSS.

Results: Fig. 1 shows the percentage of significantly different voxels ($P<0.05$) between NC and mTBI from the TBSS analysis, revealing that the most sensitive metrics, i.e., with the highest number of significantly different voxels between groups were the $D_\parallel$, $K_\parallel$, D_{axon} and $D_{e,\parallel}$. Fig. 2 shows the corresponding spatial distribution of the TBSS analysis for these four metrics, particularly in the splenium of corpus callosum (sCC) ($D_\parallel$, D_{axon} , $D_{e,\parallel}$) and anterior coronal radiata (ACR) ($K_\parallel$). The results from the ROI analysis were consistent with the TBSS results. In the sCC, significantly decreased values in the mTBI group were found in $D_\parallel = 2.13 \pm 0.46$, $2.07 \pm 0.43\ \mathrm{mm}^2/\mathrm{s}$; $D_{axon} = 1.23 \pm 0.24, 1.17 \pm 0.22\ \mathrm{mm}^2/\mathrm{s}$; $D_{e,\parallel} = 2.87 \pm 0.88, 2.76 \pm 0.51\ \mathrm{mm}^2/\mathrm{s}$; NC vs mTBI, respectively. In the ACR, $K_\parallel$ was significantly increased in the mTBI group ($K_\parallel = 0.67 \pm 0.07$ (NC), 0.70 ± 0.07 (mTBI)).

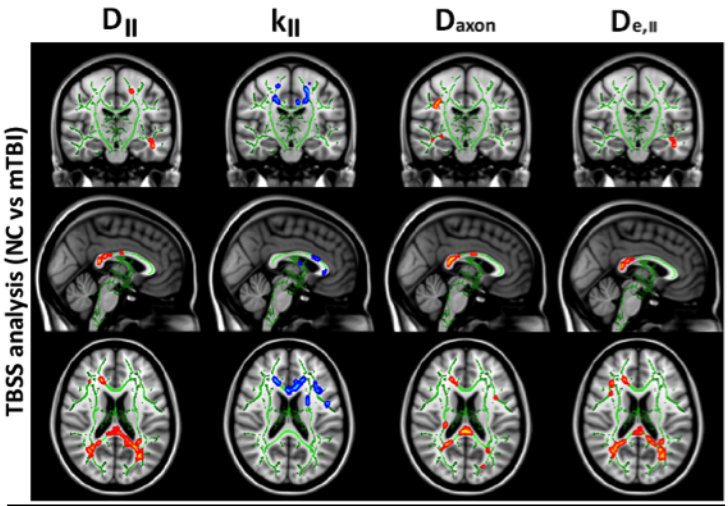

Figure 2. TBSS results showing comparisons between NC and mTBI for selected metrics. Clusters of significantly increased voxels ($P \leq .05$) are shown in red, significantly decreased in blue, and overlaid on the FMRIB FA template, together with the mean skeleton (green).

Discussion: In this study, which used both TBSS and the ROI analyses, we demonstrate that both empirical DKI, as well as WMTI metrics can detect widespread WM alterations after mTBI. Furthermore, the WMTI metrics provides unique insight into the underlying mechanisms of WM alterations after mTBI. We observed decreased $D_\parallel$, D_{axon} and $D_{e,\parallel}$, and increased $K_\parallel$ in mTBI subjects. These changes are all in line with acute axonal injury, with axonal beading[7] as a possible mechanism providing main restrictions to the diffusion in the intra-axonal space, thereby modulating the diffusivity mainly inside, but also outside along axons in the acute phase after mTBI.

Conclusion: This study indicates that WMTI metrics, as derived from DKI using a two-compartment model, may be useful as early biomarkers of injury after mTBI. The observed decreases in $D_\parallel$, D_{axon} and $D_{e,\parallel}$ suggest that increased restrictions along the axons, both inside and outside, such as possibly axonal beading, could occur acutely after injury. Detecting and understanding WM injury after mTBI is critical for further investigating the mechanisms that underlie tissue damage and recovery. Longitudinal follow-up may provide insight in the different acute and chronic processes altering WM after mTBI.

References: [1] Langlois et al., J head Trauma Rehabil 21, 375 (2006). [2] Scheild et al. Arch Neurol 63, 418 (2006). [3] Fieremans et al. NMR Biomed 23, 711 (2011). [4] Fieremans et al. Neuroimage 58, 177 (2011). [5] Smith, et al. Neuroimage 31, 1487 (2006). [6] Mori et al. Amsterdam, the Netherlands:Elsevier (2005). [7] Li et al, J Neurosci 28, 11970 (2008).