Title: Insights of Contemporary Diffusion MRI Modeling Techniques in Mild Traumatic Brain Injury: A TRACK-TBI Study

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Introduction

The majority of traumatic brain injuries are categorized as mild (mTBI), and in up to 82% of cases, neuroimaging is ordered, with only ~9% of studies revealing intracranial pathology. Novel advanced neuroimaging techniques such as diffusion-weighted magnetic resonance imaging (DWI) are sensitive to subtle white matter changes following injury, but the natural history of these changes in recovery have yet to be fully defined. Inconsistencies in observed patterns of change with the common modeling technique diffusion tensor imaging (DTI) may be due to limitations of the model, and in this study, we explore novel modeling techniques that take advantage of high angular resolution multishell data collected during the TRACK-TBI study at UCSF.

Methods

DWI data at b-values of 1300 mm/s² and 3000 mm/s² from two-weeks and six-months post-injury were analyzed with MRtrix3's constrained spherical deconvolution and fixel-based analysis. Post-Hoc comparisons were conducted on white matter tracts constructed with TractSeg a deep learning algorithm trained on human connectome project data. Tract average metrics computed with DTI, diffusion kurtosis imaging (DKI), and neurite orientation dispersion and density imaging (NODDI) for projection fibers, long association fibers and commissural fibers were compared with fixel-based analysis metrics. The analysis scheme is summarized in Figure 1. **Results**

Significant differences in all fixed-based metrics observed at the two-week timepoint remained at the six-month timepoint Figure 2. Differences between mTBI and control means decreased between timepoints, but a greater number of significant fixels were present for fiber density (FD), fiber cross-section (FC), and fiber density cross-section (FDC) at the six-month timepoint. There were no significant differences in any change images. Initially, a decrease in FD drove differences, whereas, at later time points, there was a greater contribution of decreased FC as well.

Conclusion

Fixel-based analysis revealed damage to white matter that was observed at two-weeks post mTBI remained at six-months post injury. This would suggest there is a difference in the time course of biological recovery and resolution of symptoms that should be the target of future study and interventions. Fixel-based analysis and NODDI metrics demonstrated similarities in sensitivity to white matter change, and there were no differences observed for the DTI metric FA. This adds further evidence it should not be used as the sole modeling technique when studying mTBI.



Acknowledgements: Sponsored by the U.S. National Institutes of Health, National Institute of Neurologic Disorders and Stroke (Grant # TRACK-TBI NINDS Grant# U01 NS1365885), and our public and private partners. The opinions or assertions contained here are the private views of the authors and are not to be construed as official or as reflecting the views of any sponsor.

Data used in the preparation of this abstract/poster were obtained and analyzed from the controlled access datasets distributed from the DOD- and NIH-supported Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics Systems. FITBIR is a collaborative biomedical informatics system created by the Department of Defense and the National Institutes of Health to provide a national resource to support and accelerate research in TBI.

Dataset identifier(s): [10.23718/FITBIR/1419836]. This abstract/poster reflects the views of the authors and may not reflect the opinions or views of the DOD, NIH, or of the Submitters submitting original data to FITBIR Informatics System.

	Standard Preprocessing		Modified Preprocessing	Begin FBA	
Preprocessing	Denoising Gibb's ringing artifact removal	Motion and eddy current distortion correction Bias field correction	<u>No</u> susceptibility field correction Signal Intensity Normalization for Concatenation	Compute individual subject three tissue response functions. Create average three tissue response functions from control subjects	and an and a second sec
Fixel-Based Analysis & Statistical Comparisons	WM FODs in the region of the Cen	trum Semiovale	Perform Constrained Spherical Deconvolution (CSD) to Estimate Fiber Orientation Distributions (FODs)	Upsample to 1.25mm isotropic voxels	Compute group average tissue response functions.
	Generate FOD templates 1) intra-subject template (intersection of two week and six-month images)	Registration of all subject FOD images and masks to intrasubject template	Input all intra-subject templates 2) inter-subject template (intersection of all subject intra-subject templates)	 A A	Warp all subjects to the template study specific template
	Hypothesis testing with Connectivity-based fixel enhanced	C S	Generate whole brain tractogram. Reduce streamlines with spherical informed filtering of tractograms (SIFT).	Reorient and assign fixels to template Compute Fiber Cross section (FC) and Fiber Density and Cross Section. Log transform FC.	Segment FODs and Compute Fiber Density
Post Hoc analysis	Extract spherical harmonic peaks from WMFOD template	TractSeg Compute Ending Segmentations, Bundle Segmentations and Track Orientation Mapping. → Generate Tracks	TractSrg 72 Image: Corritorspinal Tracts Image: Corritorspinal Tracts Image: Corritorspinal Corritorspinal Tracts Image: Corritorspinal Tracts Image: Corritorspinal Corritorspinal Corritorspinal Tracts	Binarize tracts and compute fixel and voxel means within them for all diffusion models	Comparison of mTBI and Controls at two weeks and six months post injury

Figure 1. Graphical Representation of Fixel-Based Analysis Pipeline

Figure 2. Fixel-Based Analysis Results for Fiber Density Cross-Section



