

## 3T Diffusion Tensor Imaging of Mild Traumatic Brain Injury: A Prospective Longitudinal Study

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**Introduction:** Traumatic brain injuries (TBI) are suffered by approximately 1.4 million Americans each year, leading to 50,000 deaths, 235,000 hospitalizations, and over \$60 billion dollars of medical costs and lost productivity according to a CDC report<sup>1</sup>. Over 70% of cases are classified as mild TBI. Diffuse axonal injury (DAI) of white matter is thought to be the key mechanism of the cognitive impairment caused by TBI. Conventional CT and MR imaging, the latter even at 3T, have been unable to adequately assess DAI in mild TBI, as findings on CT and 3T MR imaging do not correlate with the patients' neurocognitive outcome<sup>2</sup>. Diffusion tensor imaging (DTI) has recently been used to detect serial microstructural white matter changes in moderate or severe TBI<sup>3,4</sup>. Since it is not yet known whether DTI has sufficient sensitivity to detect such changes in mild TBI, we applied highly reproducible quantitative DTI tractography methods<sup>5</sup> to measure microstructural white matter integrity longitudinally during the first year after mild head injury.

**Methods:** DTI was performed on thirty-one patients with mild TBI (Glasgow Coma Scale 13-15 at presentation in the Emergency Dept.) and nineteen control subjects. Subjects and controls were matched for age, gender, and educational level. Each TBI patient was scanned at less than 2 weeks, at 1 month, and at 1 year following head injury using a 3T GE Signa EXCITE scanner with 8-channel phased array head coil. Each control subject was scanned once only. Whole-brain DTI was performed using a multislice 2D single-shot echo planar sequence with interleaved 1.8-mm axial sections with no gap, in-plane resolution of 1.8 x 1.8 mm with a FOV of 230 mm and 128x128 matrix, and 55 diffusion-encoding directions at  $b = 1000 \text{ s/mm}^2$ . Scan data were analyzed using DTI Studio (<http://www.mristudio.org>), and color-coded FA maps were created. Tractography was performed with Fiber Assignment by Continuous Tracking, using the brute-force method in which tracks were seeded from all voxels in the brain with an FA value larger than 0.3. Fibers were tracked while voxel FA values exceeded 0.2 and turning angles between the primary eigenvectors of neighboring voxels were less than  $50^\circ$ . Individual tracts were then selected by requiring fibers to pass through manually placed Regions of Interest (ROIs) on DTI color maps, according to protocols specific for each tract, as described by Wakana et al.<sup>5</sup> Quantitative three-dimensional fiber tracking was used to measure the average fractional anisotropy (FA) over whole fiber tracts bilaterally, including the cingulum bundle (CB), arcuate fasciculus (AF), inferior fronto-occipital fasciculus (IFO), uncinate fasciculus (UF), corticospinal tract (CST), and the genu and splenium of the corpus callosum (CC) which include the forceps minor and major, respectively. Group comparisons were made using the nonparametric Wilcoxon signed-rank test, with group differences considered significant at  $p < 0.05$ . Longitudinal changes in FA were examined using the generalized linear model with correction for repeated measures.

**Results:** Compared to controls, patients with mild TBI demonstrated reduced FA values ( $p < .05$ ) within the IFO, UF, CB, and the genu and splenium of the corpus callosum. The greatest differences between patients and controls were observed in the UF and the CC genu, seen as early as 2 weeks after injury. No statistically significant differences were observed within the AF or the CST at any time point (Table). FA values trended lower between 1 month and 1 year in all tracts except the AF, although the statistical power of this study was not adequate to establish that these longitudinal changes were statistically significant.

**Discussion:** In adult mild TBI patients, quantitative DTI tractography detected reduced microstructural white matter integrity compared to matched controls within the UF, IFO, CB and callosal genu and splenium. Interestingly, almost all of these tracts have prefrontal connectivity, and are also those most commonly affected in chronic symptomatic mild TBI, as we have reported previously<sup>6,7</sup>. Reduced FA in the UF and CC genu were apparent as early as 2 weeks after mild head injury. The longitudinal trends towards decreasing FA between one month and one year after injury in all investigated white matter tracts except for the AF will need to be confirmed by a larger-scale investigation of mild TBI.

**Conclusions:** DTI reveals microstructural white matter damage in specific tracts during the first year after mild TBI, including the acute and sub-acute stages of injury. DTI tractography deserves further investigation as a quantitative biomarker for mild TBI, which may be useful for predicting which patients will go on to suffer from persistent post-concussive syndrome.

Tract	Tract FA				P-values		
	Controls (n=19)	Mild TBI <2 weeks (n=31)	Mild TBI 1 month (n=29)	Mild TBI 1 year (n=23)	Control vs. <2 weeks	Control vs. 1 month	Control Vs. 1 year
<b>CB</b>							
Left	0.562±0.033	0.549±0.028	0.551±0.036	0.542±0.031	0.099	0.092	<b>0.025</b>
Right	0.520±0.022	0.512±0.025	0.512±0.030	0.510±0.023	0.238	0.132	0.120
Average	0.541±0.026	0.531±0.025	0.532±0.031	0.526±0.023	0.132	0.070	<b>0.046</b>
<b>AF</b>							
Left	0.516±0.022	0.517±0.019	0.513±0.023	0.516±0.018	0.948	0.768	0.905
Right	0.491±0.022	0.484±0.027	0.480±0.026	0.482±0.025	0.341	0.146	0.150
Average	0.504±0.018	0.505±0.021	0.500±0.021	0.503±0.019	0.702	0.518	0.885
<b>IFO</b>							
Left	0.550±0.024	0.539±0.023	0.542±0.026	0.536±0.021	0.107	0.292	0.083
Right	0.533±0.022	0.524±0.023	0.520±0.024	0.518±0.023	0.083	<b>0.029</b>	<b>0.032</b>
Average	0.542±0.022	0.531±0.020	0.531±0.023	0.527±0.019	0.079	0.083	<b>0.020</b>
<b>UF</b>							
Left	0.492±0.022	0.474±0.21	0.475±0.020	0.472±0.021	<b>0.005</b>	<b>0.008</b>	<b>0.005</b>
Right	0.470±0.022	0.455±0.24	0.458±0.020	0.457±0.024	0.055	0.098	0.085
Average	0.481±0.020	0.465±0.020	0.467±0.018	0.464±0.018	<b>0.008</b>	<b>0.012</b>	<b>0.008</b>
<b>CST</b>							
Left	0.587±0.28	0.589±0.022	0.584±0.024	0.581±0.024	0.956	0.727	0.338
Right	0.573±0.023	0.571±0.027	0.567±0.026	0.561±0.022	0.948	0.694	0.134
Average	0.580±0.024	0.580±0.022	0.576±0.024	0.571±0.022	0.930	0.830	0.221
<b>CC</b>							
Genu	0.556±0.022	0.542±0.022	0.544±0.026	0.542±0.019	<b>0.012</b>	0.052	<b>0.018</b>
Splenium	0.669±0.025	0.658±0.027	0.654±0.031	0.653±0.027	0.142	0.109	<b>0.037</b>

**References and Acknowledgements:** [1] <http://www.cdc.gov/ncipc/tbi/TBI.htm>. [2] Lee H et al. J Neurotrauma 2008; 25:1049-1056. [3] Bendlin BB et al. NeuroImage 2008; 42:503-14. [4] Sidaros A et al. Brain 2008; 131:559-572. [5] Wakana S et al. NeuroImage 2007; 36:630-644. [6] Niogi SN et al. AJNR 2008; 29:967-73. [7] Niogi SN et al. Brain 2008; doi:10.1093/brain/awn247. This study was funded by a collaborative grant from the James S. McDonnell Foundation to the Cognitive and Neurobiological Research Consortium in Traumatic Brain Injury (CNRC-TBI).