A longitudinal study of microstructural white matter changes after mild traumatic brain injury

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Introduction

Mild traumatic brain injury (TBI) is difficult to diagnose by conventional neuroimaging, yet it can cause significant long-term cognitive impairments. Diffusion tensor imaging (DTI) shows promise in mild TBI patients as a biomarker for neurocognitive outcome. However, using diffusion tensor imaging for prognosis remains controversial because recent studies of the early phase of mild traumatic brain injury have shown conflicting results, with some reporting elevations in fractional anisotropy (FA) whereas others demonstrate reductions [*1, 2*]. Furthermore, there is a lack of prior longitudinal DTI studies of mild head trauma. We used tract-based spatial statistics (TBSS), a whole-brain data-driven diffusion tensor analysis method, to examine microstructural white matter changes measured within 2 weeks, at 1 month, and at 1 year after mild head trauma with loss of consciousness and post-traumatic amnesia, with correlation to performance on tests of verbal memory and visuospatial attention.

Methods

Subjects: Thirty adult patients were compared with 29 controls matched for age, gender, and level of education. Mean age: 29.9 ± 6.9 years for controls and 29.3 ± 9.6 years for patients; Gender: 22 male + 7 female for controls and 30 male + 6 female for patients. Handedness: 26 right-handed and 3 left-handed for controls and 30 right-handed for patients. Years of education: 15.4 ± 2.1 for controls and 15.2 ± 2.8 for patients.

Imaging: The 3T DTI data were collected using a spin echo single-shot EPI sequence (TE=63 ms, TR=14 seconds , NEX=1, Matrix=128x128, FOV=230mm , 72 interleaved axial slices with slice thickness of 1.8 mm and no gaps) with 55 diffusion-encoding directions isotropically distributed over the surface of a sphere with electrostatic repulsion (b values 0 and 1000 s/mm^2). The total acquisition time was 13.07 minutes.

Processing: Following brain extraction, motion correction, and generation of DTI parametric maps using the tools provided in FSL (http://www.fmrib.ox.ac.uk/fsl), the voxel-wise statistical analysis of DTI parameter maps was conducted with TBSS [*3*]. Direct registration of individual FA volumes to the FMRIB58 template was applied, and the mean FA image and mean FA skeleton were created. After registration, nonparametric permutation testing was performed using Randomise. Voxel-wise cross-subject statistical analysis was conducted with group comparison (controls>patients and patients>controls). Multiple comparison correction was conducted with Threshold-Free Cluster Enhancement (TFCE) in Randomise [*4*].

Neurocognitive Testing: Verbal memory was assessed at all three time points after head injury with the California Verbal Learning Test, 2nd edition (CVLT-II). Visuospatial attention was measured at all three time points using the Attention Network Task (ANT), including measures of alerting, orienting, and conflict [*5*].

Results

Widespread decreases of FA and increases of mean diffusivity and radial diffusivity were found in patients versus controls at the early time point. The loss of white matter FA was progressive over time, worsening both in magnitude and spatial extent across the three time points (Fig. 1). The left and right anterior corona radiata showed the greatest early reduction in FA, with values in the right anterior corona radiata strongly correlating with verbal memory performance. We also demonstrate that early FA measurements in the right superior longitudinal fasciculus predict long-term outcome on visuospatial attention testing (Fig. 2). Finally, those patients whose verbal memory did not improve during the first year after injury showed greater and more widespread decreases compared to controls in white matter FA, measured at the early time point, than did those patients whose verbal memory did improve over the three time points (Fig. 3).

Discussion

These findings of (a) altered diffusivity early after mild head trauma, (b) progressive deterioration of microstructural white matter integrity over time, (c) correlation of white matter microstructure at baseline with behavior at late follow-up, and (d) early microstructural differences between patients with long-term improvement in cognition and those with worsening cognition, all support a role for diffusion tensor imaging as a quantitative dynamic biomarker of neurocognitive outcome in persistent post-concussive syndrome.

References: [1] Lipton ML et al., Radiology 2009; 252:816-24 [2] Mayer AR et al., Neurology 2010, Epub before print [3] Smith SM et al., Neuroimage 2006; 31:14871505, [4] Smith SM, Nichols TE. Neuroimage 2009; 44:83-98, [5] Fan et al., Neuroimage 2005; 26: 471-9.

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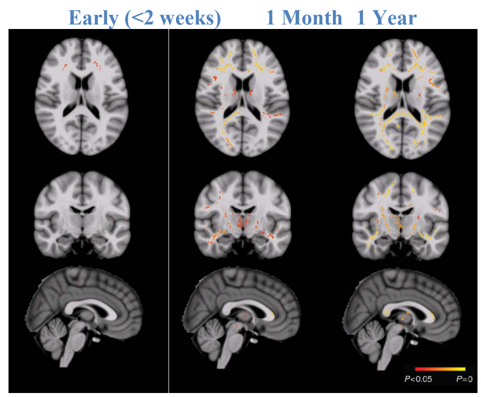

Figure 1: FA (controls > TBIs), at the threshold of p < 0.01 corrected for multiple comparisons, serially across 3 time points after injury

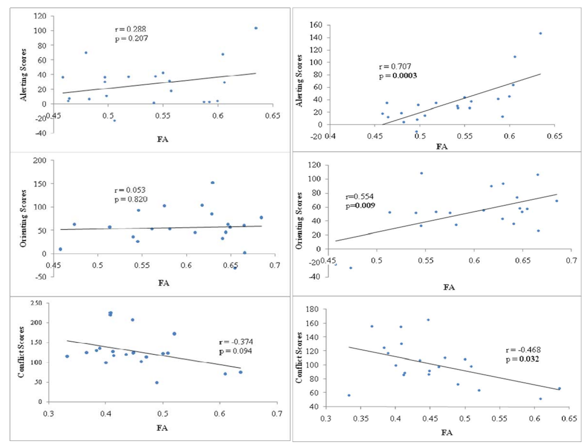

Figure 2: FA of the right superior longitudinal fasciculus measured within 2 weeks of injury predicts visuospatial attention at one year post-mTBI, but not at the early time point

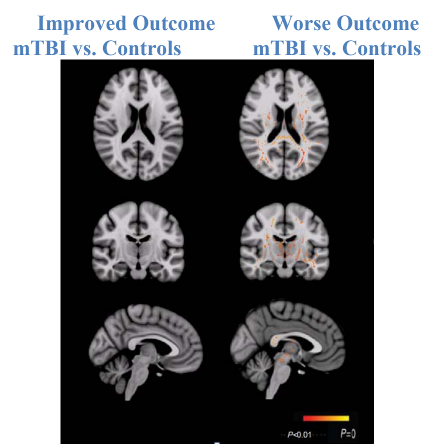

Figure 3: Reductions in early FA versus controls are greater in mTBI patients with stable to worsened performance on the Total Trials 1-5 subtest of the CVLT over the first year after mTBI compared to those with improved performance