Progressive White Matter Microstructural Changes Following Mild Traumatic Brain Injury Revealed by Bootstrap Analysis of Serial 3T Diffusion Tensor MRI

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Introduction: Traumatic brain injury (TBI) is a leading cause of mortality and morbidity in the US, especially in young people under age 45. Conventional MRI and CT are limited in the accurate evaluation of TBI due to their tendency to underestimate the extent of injury, especially diffuse axonal injury (DAI), and absence of quantitative pathophysiological information. Diffusion tensor MRI (DTI) is emerging as a powerful tool to overcome these limitations. The extensive spatial heterogeneity of fractional anisotropy (FA) presents a challenge for detecting changes in anisotropy. Hence, manual ROI analysis has been the most commonly used method for quantitative DTI analysis despite being labor-intensive and operator-dependent. In this study, we applied automated voxel-wise longitudinal analysis of serial 3T DTI for robust and sensitive detection of progressive microstructural white matter changes in TBI.

Methods: Six patients with mild TBI (Glasgow Coma Scale 13-15 at presentation in the Emergency Dept.) and two trauma control subjects who suffered leg injury but not head injury underwent conventional MRI and DTI at three separate time points (acute stage < 2 weeks, 1 month and 1 year post injury) on a 3T GE Signa EXCITE scanner with an 8-channel phased array head coil, using ASSET parallel imaging at an acceleration factor of two. Whole-brain DTI was performed with single-shot multislice axial spin-echo EPI (TR/TE = 14s/64ms, NEX=1) at 1.8-mm isotropic voxel resolution using 55 diffusion-encoding directions at b=1000 s/mm^2, as well as one b=10 s/mm^2 acquisition. For the detection of focal FA changes over time, we used Bootstrap-based Longitudinal Analysis of DTI Estimates (BLADE: Chung, 2006b). This technique can be briefly described as a difference map scaled by uncertainty such that thresholding and/or clustering can be used to select groups of voxels with statistically significant FA changes over time. The residual bootstrap (Chung, 2006a) is used because it is non-parametric and can be used to calculate uncertainty of FA or other DTI metrics in individual voxels from only a single DTI dataset. Utilizing data redundancy from the 55 distinct diffusion measurements at each voxel, we can perform voxel-wise statistical testing in each subject separately, without performing multiple DTI acquisitions, pooling data from multiple subjects, or making assumptions about the underlying noise properties. First, FA maps were created for each time point to be used as templates for inter-session non-linear registration. This information was used to resample all raw diffusion data such that data from all the time points are registered to a common space. Second, residual bootstrap with 200 iterations was used to create the standard error map of FA as well as the FA map itself, and these were combined for each pair of time points to calculate the T-statistic map. Finally, only 3D clusters larger than 15 voxels, where each voxel showed statistically significant FA changes over time ($p<0.01$), were overlaid in color on the average FA map. These quantitative FA changes over time were confirmed with ROI and/or fiber tracking analysis.

Results: 3T MRI findings were normal in the two leg injury control subjects, whereas contusions and/or axonal shearing injuries were found in all six mild TBI patients. No statistically significant white matter FA changes were detected by BLADE in the two leg injury control subjects. In both of the two TBI patients with focal cortical contusions, BLADE showed recovery of FA values between the acute and 1-month time points in white matter subjacent to the contusions. Of the four mild TBI patients with evidence of axonal shearing injury on conventional MRI, the patient with the most severe DAI showed recovery of FA values within the lesions (Figure, *arrow*), but decreases of FA in adjacent normal-appearing white matter (NAWM) (Figure, *arrowheads*). The greatest component of this progressive FA decrease in NAWM occurred between the acute and 1-month time points, but further decreases were seen by 1 year following trauma. Fiber tractography confirmed that this NAWM was connected to the lesion.

Discussion: This is the first study demonstrating automated, subject-specific, voxel-wise longitudinal analysis of whole-brain DTI in TBI, localizing progressive microstructural changes, including in NAWM. Improvement of FA in white matter subjacent to contusions and within axonal shearing lesions may represent resolution of vasogenic edema and other local inflammatory changes. The progressive decrease of FA in NAWM adjacent to shearing lesions may represent Wallerian degeneration along white matter pathways. Combined with traditional ROI analysis and/or fiber tracking, BLADE can be a powerful detection and analysis tool for DTI, enhancing longitudinal imaging studies in TBI as well as other white matter diseases.

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References:

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