

Evaluation of Anatomical and Functional Connections Following Traumatic Brain Injury in Humans by Diffusion Tensor Imaging and Resting-State Functional Connectivity

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Introduction: One of the major contributors to cognitive dysfunction following traumatic brain injury (TBI) is thought to be axonal injury. Current clinical imaging modalities have been optimized to assess hemorrhage and ischemia but are inadequate for the direct assessment of axonal injury. Diffusion tensor imaging (DTI) has shown promise but it has yet to be fully validated for its potential role as a diagnostic tool in the evaluation of brain injury. This imaging technique has been shown to be sensitive to changes seen in white matter pathology in experimental animal models of TBI (Mac Donald et al, *Exp Neurol*, 2007; Mac Donald et al, *J Neurosci*, 2007). Additionally, resting-state functional MRI (fMRI) correlation analysis has been proposed as a useful tool in the evaluation of brain functional connectivity (fcMRI). The basis of this method is that anatomically connected regions in the brain show correlated fluctuations in the blood oxygen level dependent (BOLD) signal. (Biswal et al, *MRM*, 1995; Fox et al, *PNAS*, 2005, Vincent et al, *Nature*, 2007, He Neuron 2007). Here, we investigated whether changes observed in directional diffusivity using DTI and functional connectivity would correlate with known clinical deficits in patients following TBI as seen in our initial case study (Mac Donald et al, *Neurology*, 2008).

Methods: Twenty individuals clinically diagnosed with TBI ages 18-30, 1-7 years post-injury and 12 controls matched for age and handedness were scanned on a 3T Allegra MRI scanner (Siemens, Erlangen, Germany). Following the methods of Shimony et al, (*Cereb Cortex*, 2006), patients were scanned with 25 direction DTI (TR=6400ms, TE=87ms, 1.5 x 1.5 x 1.5 mm voxels) and fcMRI sequence (TE=25ms, 90° flip, 4 x 4 x 4 mm voxel size) as previously described by Fox et al (*PNAS* 2005). Standard anatomical scans (MPRAGE, T2-weighted fast spin echo, and FLAIR) were also employed. Post-processing was performed to align each set of scans into standardized Talairach coordinate system using cross modal affine transformations. DTI parameters (relative anisotropy, axial diffusivity, and radial diffusivity) along with the functional connectivity maps were analyzed for each subject and compared to controls. A battery of neuropsychological assessments was also performed the day of the scan. Rigorous correction for multiple comparisons was employed using the Bonferroni method.

Results: Reductions in anisotropy as well as functional connectivity were noted in regions appearing normal on the standard anatomical scans. These reductions correlated with behavioral measures obtained during the neuropsychological assessment. fcMRI abnormalities in networks implicated in attention and decision making (Brodmann 11) correlated with Connor's Continuous Performance (CPT) scores obtained during the assessment for reaction and sustained attention. Similarly, changes in anisotropy within left cingulum bundle connecting the left hippocampal network correlated with the Long Delay Free Recall Score assessing verbal memory during the California Verbal Learning Test (CVLT). In contrast there was no correlation between the CVLT performance and Brodmann area 11 connectivity nor was there correlation between the left cingulum anisotropy and the CPT performance, indicating the specificity of our findings. Several other significant correlations between imaging abnormalities and cognitive performance deficits were found. The results of this study give further insight into the structural and functional changes occurring following injury and add additional information that was not apparent from conventional MR imaging.

Discussion: These findings provide an example of how modern MRI-based lesion-deficit studies may shed new light on the perplexing cognitive and behavioral deficits that appear after traumatic brain injury, and perhaps other neurological and psychiatric conditions as well. This approach may be promising for diagnosis, prognosis, rehabilitative planning, and therapeutic trial stratification.

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Figure: DTI and fcMRI Results Correlate with Neuropsychological Assessments.

(A) Diffusion tensor imaging regions of interest (ROI). ROI's were sketched over multiple slices throughout each region. Examples of five ROIs are denoted in the figure comparing control to a TBI patient. The top images are transverse slices and the bottom images are coronal. Regions of interest shown include genu (1), splenium (2), anterior (3) and posterior (4) limb of the internal capsule and the left cingulum bundle (5). (B) Resting-state fMRI Correlation Analysis. Exemplar figures show the decreases in functional connectivity observed following trauma in two of the 11 neural networks of interest. Images are correlation maps overlaid on the subjects MPRAGE and are in anatomical space. Single slices from each network are shown for comparison. (C-D) Comparison of Neuropsychological Assessments with DTI and fcMRI Results. (C) The left cingulum bundle anisotropy significantly correlated to the long delay free recall standard score (SS) of the CVLT. (D) Comparison of the extent of correlation between each subject and group control was determined by the Pearson Product Moment correlation coefficient (ppm). This measure in Brodmann area 11 was found to be significantly correlated to reaction time from the CPT. Worse performance is indicated by lower standard score on CVLT but higher reaction time on the CPT.

