

# Diffusion tensor imaging abnormalities associated with cognitive decline in relapsing-remitting multiple sclerosis

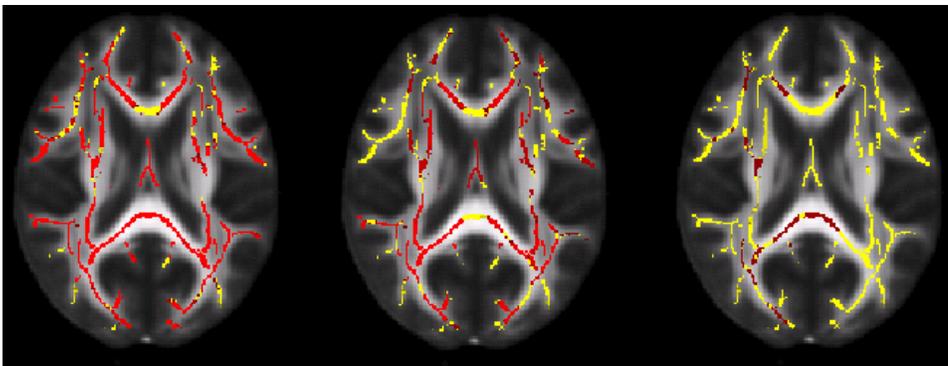
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**Introduction:** Axonal injury is a major component in the pathophysiology of multiple sclerosis (MS), therefore a technique that can noninvasively capture axonal fiber architecture would be useful in understanding the disease progression and potentially in predicting outcome. Diffusion tensor imaging (DTI) is a sensitive tool for detecting and quantifying microstructural tissue damage *in vivo* and it is being used increasingly in MS research. Tissue pathology in MS can result in motor, cognitive, and neuropsychiatric symptoms. Disruption of critical white matter tracts might lead to reduced functional connectivity between cortical-cortical or cortical-subcortical regions, resulting in impairment of motor and cognitive functions. The majority of DTI studies in MS thus far have included patients with mixed subtypes (1, 2); this study focused on the most common subtype only, relapsing-remitting MS (RRMS), to avoid differential effects due to pathological heterogeneity and cumulative effects of disability progression. The goal of the study was to explore DTI abnormalities in RRMS, and to investigate whether such evidence of tissue damage is associated with the presence and severity of cognitive impairment or depression.

**Methods:** Thirty-seven RRMS patients (40.9±10.1 yr) and twenty healthy controls (34.0±10.3 yr) were included in the study. All MS patients underwent neurological assessment using the Expanded Disability Status Scale (EDSS) at the time of participation. Patients also underwent neurocognitive assessments exploring commonly affected cognitive domains in MS, including: the Rey Auditory Verbal Learning Test (RAVLT) to assess short term auditory-verbal memory and learning, the Single Digit Modality Test (SDMT) to assess sustained concentration, and visual information processing speed, and the 3 second-Paced Auditory Serial Attention Test (PASAT) to assess sustained attention, working memory, and auditory information processing speed. Depression was assessed in 25 of the patients with the Chicago Multiscale Depression Inventory, consisting of vegetative (CMDIV), mood (CMDIM), and evaluative (CMDIE) subscales. All DTI scans were conducted on a 3T Phillips Achieva MR Scanner using an echo planar imaging spin echo sequence with a SENSE factor of 2.4 (TE/TR: 62/5400 ms, 2x2x3 mm resolution), a b factor of 800s/mm<sup>2</sup> and 15 encoding directions. To analyze DTI data in a voxelwise fashion, TBSS was used to minimize multi-subject registration errors. All images were processed following the TBSS pipeline, part of FSL (<http://www.fmrib.ox.ac.uk/fsl>). Briefly, images were preprocessed to correct for motion and eddy current distortion, and the diffusion tensor then fitted to each voxel. The four primary quantitative DTI measures, fractional anisotropy (FA), mean, axial, and radial diffusivity, are then derived voxelwise. The TBSS registration then transforms the FA images into a standard space, and a tract skeleton is then produced, using a lower threshold of FA of 0.2 to include only WM voxels. The final WM skeleton is a representation of the WM tract geometry common to the entire group of subjects, including both patients and controls. Correlations with neurocognition and depression within the MS group were only explored in regions with significant differences from controls. Statistical analysis was performed using FSL *randomise* tool, and corrected for multiple comparisons using threshold free cluster enhancement (TFCE) (3).

**Results:** Lower FA was found in RRMS patients compared to control subjects across the tract skeleton (0.40±0.03 vs. 0.43±0.01, p<0.01). In areas with reduced FA, increased mean diffusion was found, and was dominated by increased radial diffusivity with no significant change in axial diffusivity. Significant correlations were found between mean abnormal skeletal FA values in patients with cognitive scores including SDMT (r=0.62, p<0.01), RAVLT (r=0.45, p<0.01), and PASAT (r=0.35, p<0.05), but no significant correlations were found with depression index including CMDIM (r=-0.25, p=0.22), CMDIE (r=-0.35, p=0.08), and CMDIV (r=0.12, p=0.59).



**Figure 1.** One slice from the TBSS result (TFCE,  $p < 0.05$ ) displayed on mean FA image showing skeletal voxels with significantly reduced FA (yellow) in MS patients compared to controls that also significantly correlated with cognitive scores (red): SDMT (left), RAVLT (middle), and PASAT (right).

**Discussion:** DTI using TBSS and TCFE analysis enables the detection of disruptions in microstructural white matter integrity. The reduced anisotropy was shown to be primarily due to an increase in radial diffusivity (across the fibers) due to demyelination, as opposed to axonal loss. The most significant correlations of abnormal FA and neurocognitive impairment were found with SDMT suggest that it may be more sensitive to global white matter degeneration. Depression measures, on the other hand, were not correlated with DTI abnormalities in any region but may be due to the smaller number of patients with depression measures.

## References:

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2. R. A. Dineen *et al.*, *Brain* 132, 239 (Jan, 2009).
3. S. M. Smith, T. E. Nichols, *Neuroimage* 44, 83 (Jan 1, 2009).