

# Functional Relevance of White Matter Degradation in Multiple Sclerosis: A Tract-Based Spatial Meta-Analysis

Thomas Welton<sup>1</sup>, Dorothee Auer<sup>1</sup>, and Rob Dineen<sup>1</sup>

<sup>1</sup>Radiological Sciences Group, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom

**Target audience:** Those with an interest in multiple sclerosis (MS) or in the impact of white matter degradation on cognition and disability; in particular, with regard to diffusion-tensor imaging (DTI) or tract-based spatial statistics (TBSS).

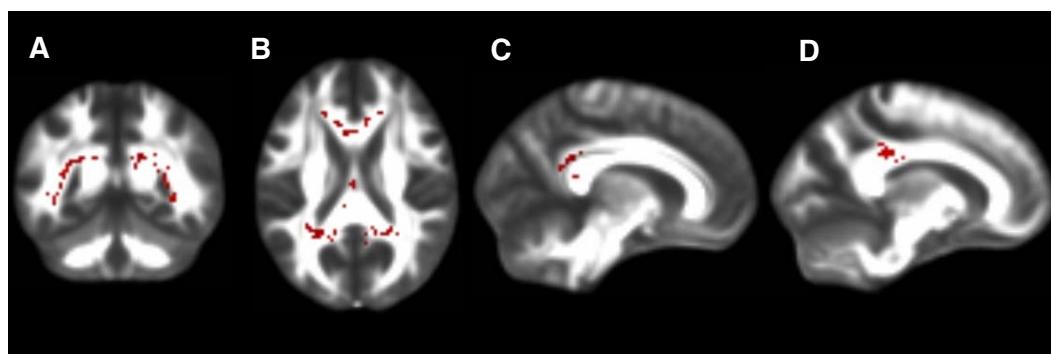
**Purpose:** Since the description of the TBSS<sup>1</sup> method in 2006, various studies have reported patterns of tract-based white matter degradation in MS patients compared to healthy controls, and distributions of white matter degradation that correlate with disability and cognitive performance in MS patients. We perform a spatial meta-analysis aiming to identify consensus between published studies for distribution and functional relevance of white matter degeneration in MS.

**Methods:** A literature search was performed in PubMed, Web of Knowledge and Google Scholar using the term: ““multiple sclerosis” AND (TBSS OR “tract-based spatial statistics”””. Articles were included if they performed TBSS analysis of DTI data and made one or more of the following analyses: (1) group difference in fractional anisotropy (FA) between MS patients and healthy controls; (2) correlation FA in MS patients to scores on the Expanded Disability Status Scale (EDSS); (3) FA in MS patients to scores in the Paced Auditory Serial Addition Task (PASAT) or other comparable test of cognition. Primary authors were contacted by e-mail to request the statistical maps required for meta-analysis. For each of the three voxelwise meta-analyses, the Effect Size-Signed Differential Mapping software<sup>2,3</sup> (ES-SDM; <http://www.sdmproject.com>) was used, which implements a random-effects model to calculate a weighted mean of the maps. A voxel-based permutation test determined statistical significance. Standard thresholds were used ( $p < 0.005$  and cluster extent  $\geq 10$  voxels).

**Results:** 13 papers were identified from 91 unique search results, of which data from 8 was available for analysis and data from the remaining 5 studies could not be accessed. The resulting dataset comprised 358 MS patients (mean age 35.7 years; mean EDSS score 2.0; 331 relapsing-remitting, 11 secondary-progressive and 8 primary-progressive) and 167 healthy controls (mean age 33.6 years) across 8 countries. Voxelwise meta-analysis revealed widespread supra-threshold white matter abnormalities in MS patients compared to controls ( $n=298$ ; fig. 1A & 1B), including the corpus callosum, periventricular parietal and temporal white matter and fornices. For the FA-to-disability comparison ( $n=138$ ), more severe disability was associated with reduced FA in the splenium of the corpus callosum and posterior cingulum (fig. 1C). For the FA-to-cognition comparison ( $n=235$ ), more impaired cognition was associated with reduced FA in the left posterior callosum (fig. 1D).

**Discussion:** We present the first meta-analysis of TBSS studies in MS. We have determined comprehensive maps showing specific patterns of reduced tract FA associated with MS, and report regional reductions in FA associated with disability and cognitive dysfunction. The results support the notion that disconnection resulting from white matter damage is one of the contributory mechanisms by which functional impairment occurs in MS.

**Conclusion:** Our meta-analytic approach confirms widespread FA reduction in white matter of MS patients compared to controls, and confirms the relevance of white matter pathways in the corpus callosum and posterior cingulum for both clinical and cognitive functional status.



**Figure 1.** Significant voxels (red) overlaid on the FMRIB58 FA average brain. (A & B) Widespread significant FA reductions were associated with MS involving corpus callosum, periventricular white matter and fornix. (C) Disability scores were associated with reduced FA in callosal splenium and posterior cingulum. (D) Cognitive dysfunction was associated with reduced FA in left posterior callosum.

**References:** [1] Smith SM et al, 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31(4):1487-505. [2] Radua J & Mataix-Cols D, 2012. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *Br J Psychiatry* 195:393-402. [3] Peters et al, 2012. White matter development in adolescence: diffusion-tensor imaging and meta-analytic results. *Schizophrenia Bull* 38:1308-17.