Tract-Based Spatial Statistics shows lower FA in the fornices of early MS patients

S. D. Roosendaal[1], J. J. Geurts[1,2], H. Vrenken[1,3], K. S. Cover[3], J. A. Castelijns[1], P. J. Pouwels[3], and F. Barkhof[1]

[1]Radiology, MS Center, Amsterdam, Netherlands, [2]Pathology, MS Center, [3]Physics & Medical Technology, MS Center

Introduction: Diffusion tensor imaging (DTI) measures have been related to pathological processes occuring in Multiple Sclerosis (MS). In animal models, changes in radial diffusivity (mean of lambda 2 and 3) were found to be related to demyelination, whereas axial diffusivity (lambda 1) could be related to axonal damage[1]. With the recently developed method Tract-Based Spatial Statistics, DTI measures of the white matter (WM) can be compared voxelwise[2]. We used this tool to investigate differences between a group of healthy controls and a group of MS patients.

Patients and Methods: MR imaging was performed on a 1.5T whole body scanner (Siemens Sonata, Erlangen, Germany). Diffusion-weighted echoplanar images (TR 8500 ms, TE 86 ms; 58 contiguous axial slices with a slice thickness of 2 mm and an in-plane resolution of 4 mm^2) with 60 diffusion gradients (*b*-value: 900 s mm^{-2}) and 10 volumes without directional weighting were acquired. Thirty-one patients (mean age 40.8 ± 9.0 years; 19 females) and 31 age-matched healthy controls (mean age 40.6 ± 9.9 years; 21 females) were included. The patient group could be divided in a subgroup of 16 patients with short disease duration (2.2 ± 2.1 years; mean age 35.0 ± 6.6 years; mean EDSS 2.2 ± 1.2) and a second subgroup of 15 patients with longer disease duration (9.3 ± 1.9 years; mean age 47.0 ± 7.0 years; mean EDSS 4.2 ± 1.6). FMRIB's Diffusion Toolbox was used to correct motion and eddy current distortion, and to locally fit diffusion tensors. Using the TBSS pipeline on a computer cluster, a target image was found and the FA images were nonlinearly registered to standard space via this image. A mean FA image was created and skeletonised, the registered FA data was projected onto this skeleton. The registration and projection vectors were also applied on radial and axial diffusivity, and mean diffusivity (MD) data. Differences between the patients, patient subgroups and controls were analyzed voxelwise using FSL's *randomise* (which combines General Linear Model testing with permutation inference statistics). A cluster-forming threshold of t=3 and a corrected cluster size significance level of p<0.05 was used. The data analysis required around 1,800 computing hours and was therefor performed in the grid infrastructure provided by the Virtual Laboratory for e-Sciences project.

Results: Patients were found to have a lower FA compared to controls in the left superior longitudinal fasciculus, parts of the corpus callosum, the fornices, the dorsal parts of both hippocampi, both optic radiations and the right inferior longitudinal fasciculus (fig. 1). The axial diffusivity was significantly higher in patients in all of these areas, except for the hippocampi. The radial diffusivity was elevated in patients, also outside the areas where lower FA was found (fig. 2). Most of these lower FA areas, including the fornices (fig. 3), continued to show a significantly lower FA when the subgroup of patients with a short disease duration was compared to controls.

Conclusion:
This study, which is one of the first to use the TBSS method in MS, shows that MS patients have areas of lower FA, not only in the WM commonly affected by lesions, but also more specifically in structures involved in memory processing, like the fornices and the hippocampus. These areas were found to be already affected in the early stages of the disease. The axial diffusivity was found to be higher in patients than controls in some areas of the WM. This opposites the lower axial diffusivity found in animal models of axonal pathology, but is in line with other (post-mortem) studies[3].

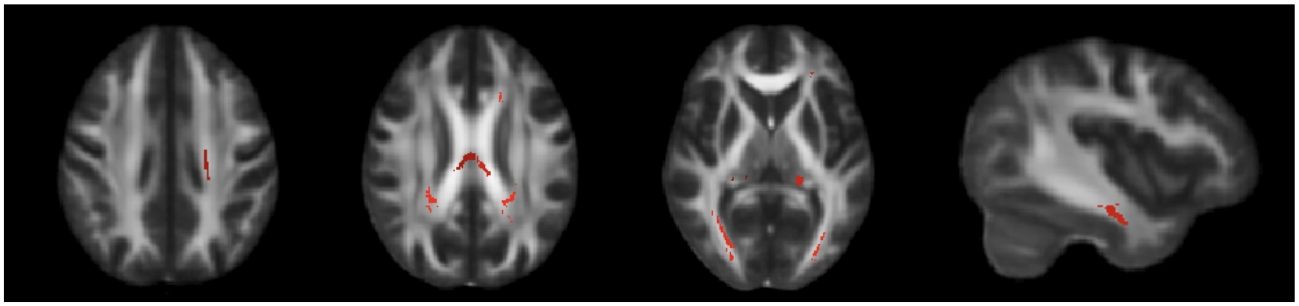

Fig. 1: Axial and sagittal images, showing a standard space mean FA image with lower FA (red) at several areas of the WM of the whole patient group.

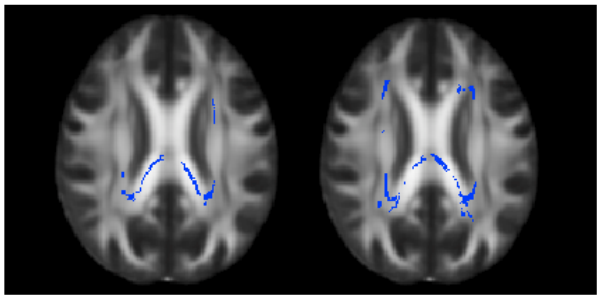

Fig 2. Left: Image showing a number of areas where axial diffusivity is higher in patients. Right: Same slice, showing areas of higher radial diffusivity in patients.

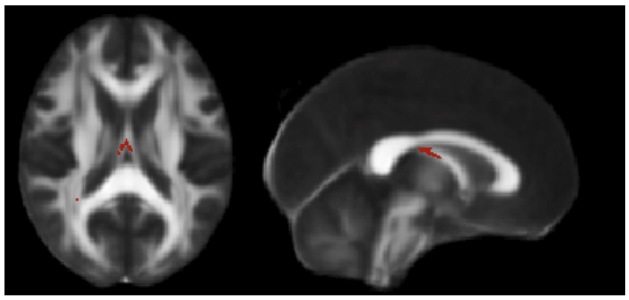

Fig. 3: Axial and sagittal images, lower FA (red) in the fornices of the patient group with a short disease duration.

References:
1. Song SK et al. NeuroImage 2003; 20:1714-1722.
2. Smith S et al. NeuroImage 2006; 31:1487-1505.
3. Schmierer K et al. NeuroImage 2007; 35:467-477.

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