Tract-Based spatial statistics: application to the study of multiple sclerosis

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Introduction Diffusion tensor imaging (DTI) has been widely applied in the study of white matter (WM) changes in multiple sclerosis (MS) with the potential to provide more specific pathologic information than T_2-weighted MRI. Typically, DTI studies in MS have investigated diffusion tissue properties within T_2-visible lesions and in areas of the WM appearing normal (NAWM) to visual examination [1]. This approach has potential limitations due to the difficulty in manually identifying in an accurate manner T_2 lesions and NAWM, especially in areas of high lesion density, and leukoaraiosis. Additionally, lesion number and volume are subjective to magnet field strength. Whole brain DTI histograms represent an alternative approach to quantify disease burden but lack of specificity on the spatial information of the measured changes.

Using whole brain high-resolution DTI we performed a voxel-wise Tract-Based Spatial Statistics (TBSS) [2] to investigate the nature and distribution of fractional anisotropy (FA), mean diffusivity (MD) and T_2 changes in patients with different phenotypes of MS versus age-matched healthy controls.

Methods Whole-head, high-resolution diffusion tensor images (TR=4.056 s, TE= 80ms, 2.5 mm isotropic voxels, b=700s/mm^2, 32 directions plus one volume with no diffusion weighting) were acquired in 35 patients with MS (mean±SD age: 40.8±12.3 years) and 17 healthy controls (mean±SD age: 36.5±12.9) on a 1.5 Tesla Philips scanner (Best, The Netherlands). DTI data were first corrected for motion and eddy current distortions, and FA maps were then calculated from the corrected volumes as previously described [3]. Alignment of FA images from all study participants was obtained using TBSS. First all images were aligned to a 1x1x1mm standard space using a non linear registration; a mean of all aligned FA images was then created and "thinning" (non-maximum suppression perpendicular to the local tract structure) was applied to create a skeletonised mean FA image. Each subject's (aligned) FA image was projected into the skeleton by filling the skeleton with FA values from the nearest relevant tract center. This was achieved, for each skeleton voxel, by searching perpendicular to the local skeleton structure for the maximum value in the subject's FA image. TBSS was then applied to other derived-diffusion data including MD and T_2-weighted "lowb" images. All aligned FA, MD, and T_2 images were spatially smoothed with a 3-D filter with a full width at half maximum of 1 mm and whole-brain voxel-wise comparisons were performed in the following subgroups: 10 patients with a single clinical episode indicative of MS (8F/2M; mean±SD age: 35.8±8.9) and 10 patients with relapsing-remitting (RR) MS (8F/2M; mean±SD age: 32.1±5.5) vs 10 sex- and age-matched healthy subjects (8F/2M; mean±SD age: 31.6±5.1 years); 15 patients with chronic-progressive MS (10F/5M; mean±SD age: 50±11.7 years) and 9 age-matched controls (10F/5M; mean±SD age: 45.6±9.8 years).

Results Voxel-wise analyses demonstrated distinct changes of diffusion WM properties in different phenotypes of MS. In patients at the earliest phase of the disease WM changes were discrete and consisted of three main patterns compared to matched controls: 1) areas characterized by significantly increased T_2, decreased FA, and increased MD; 2) areas with no significant changes in the T_2 images but significantly reduced FA and increased MD; and 3) areas characterized by significantly increased lowb, decreased FA but no significant MD changes (Fig. 1, A-B).

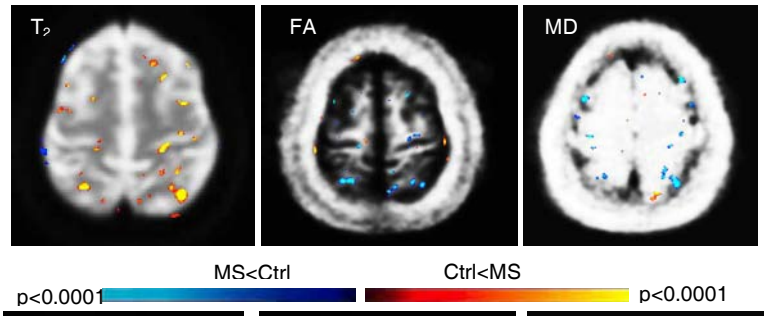

Fig. 1-A. T_2 (left), FA (middle), and MD (right) voxel-based statistical difference maps between 10 patients with a single clinical episode of MS vs matched healthy controls. Significant T_2 increases in patients are associated with significant FA decreases in the corresponding brain regions and increases or decreases in MD. Maps are shown in the axial view, radiological convention.

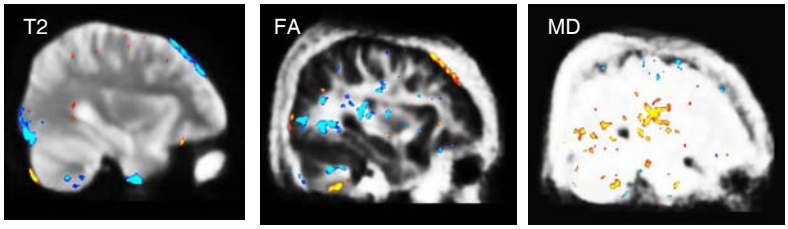

Fig. 1-B. Sagittal view of T_2 (left), FA (middle), and MD (right) voxel-based statistical difference maps between 10 patients with a single clinical episode of MS vs matched healthy controls.
Areas with no significant T_2 in patients are associated with significant FA decreases in the corresponding brain regions and increases in MD.

Patients with a RR disease course showed, with respect to healthy subjects, a predominant pattern of WM diffusion changes consisting of significantly increased T_2 changes associated with decreased FA and increased MD. Increase in T_2 signal was diffuse and involved most of the WM (Fig.2.).

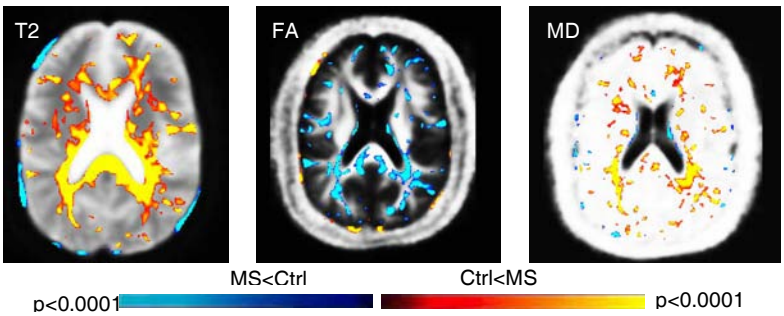

Fig. 2. T_2 (left), FA (middle), and MD (right) voxel-based statistical difference maps between 10 patients with RRMS vs matched healthy controls.
These patients show significant diffuse T_2 increases vs controls and corresponding significant FA decreases and increases in MD.
Maps are shown in the axial view, radiological convention.

Finally patients with a more advanced and chronic-progressive disease course showed, in addition to the WM pattern described in RRMS patients, areas of WM degeneration characterized by significantly increased T_2 changes associated with reduced FA and MD. This is probably because a marked glial proliferation might potentially decrease both MD and FA.

Conclusions This preliminary study shows that TBSS voxel-wise based analysis can identify distinct patterns of WM degeneration at different stages of MS, being potentially more sensitive and objective than methods that rely on manual intervention in defining and outlining T_2 lesions and areas of NAWM. Future directions include relating these findings to measures of neurological and cognitive outcome.

References

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