

Longitudinal Tract-Based Spatial Statistics Analysis Reveals Left and Right Asymmetric DTI Alterations in Relapsing Remitting Multiple Sclerosis

S. Hannoun¹, F. Durand-Dubief^{1,2}, C. Confavreux², F. Cotton¹, and D. Sappey-Marini^{1,3}

¹CREATIS, University of Lyon, Lyon, Rhone-Alpes, France, ²Neurological Hospital, Lyon, Rhone-Alpes, France, ³CERMEP-Imagerie du Vivant, Lyon, Rhone-Alpes, France

Introduction: Multiple Sclerosis (MS) patients are classified in three clinical forms of disease progression: relapsing-remitting (RR), secondary progressive (SP) and primary progressive (PP). If this classification allowed cross-sectional characterization of MS pathological processes, their evolution over time is still unclear. Diffusion tensor imaging (DTI) has proven to be a very sensitive tool for assessing microstructural alterations occurring in white matter (WM) [1]. More recently, tract-based spatial statistics (TBSS) [2] analysis of DTI metrics provided an objective (non-operator dependant) and sensitive mean to monitor brain damage first, between MS forms and second, over a period of time. Therefore, we present here a longitudinal DTI study investigating the evolution of WM alterations in different clinical forms of MS over a period of two years.

Materials and methods: Twenty-nine control subjects and fifty-nine MS patients (24 RR, 23 SP and 12 PP) were examined on a 1.5 T MR Siemens Sonata system. DTI protocol included a spin-echo EPI sequence (TR=3800 ms, TE=96 ms) with 96 x 96 phase-encodings over a field of view of 240 x 240 mm and 51 axial slices of 2.5 mm thickness. Post-processing of DTI data was performed using FSL [4]. Eddy-current correction using the FMRIB's Diffusion Toolbox (FDT) was performed before the extraction procedure of non-brain voxels using a factor of 0.35. Fractional anisotropy (FA) and eigen-values (λ_1 , λ_2 and λ_3) maps were generated using the FDT module. TBSS technique is based on creating first, a mean skeleton from FA images by using an initial approximate nonlinear registration. Second, FA images of each subject are projected onto the skeleton by filling it with FA values from the nearest relevant tract centre. Third, voxel-wise statistics are carried out across subject groups. DTI maps obtained at the initial time point (t1) in RR, SP and PP patients were compared to those of control subjects. They were then compared to the corresponding maps acquired 2 years later at the second time point (t2). As TBSS analysis of FA maps resulted in significant alterations of the external capsule (EC) in RR patients, the EC region was selected as a ROI for further quantification. Right and left ROIs of the external capsule were delineated on the WM skeleton and processed to obtain DTI metrics values. Statistical analysis of these values was performed using STATA software to compare patients of each MS form between first, t1 and t2 and second, right and left ROIs. Third, the slopes calculated over the 2 years period for each DTI metric were compared between right and left EC ROIs.

Results: TBSS analysis of MS patients at t1 showed significant differences between RR, SP and PP patients and control subjects (Fig. 1). Longitudinal TBSS analysis of each clinical form over a period of 2 years (Fig. 2) showed significant FA and λ_1 alterations in the right hemisphere while λ_2 and λ_3 maps were significantly modified in both hemispheres of RR patients. SP and PP patients showed no significant changes. ROI analysis of the EC comparing DTI values between time points in RR patients showed significant reduction of FA values ($p<0.001$) and increases of λ_2 ($p<0.01$) and λ_3 values ($p<0.001$) in right EC while only a significant decrease of λ_2 ($p<0.05$) was observed in left EC. No differences were detected in SP and PP patients. Comparing FA values of right and left EC, they were significantly higher in the right EC of RR and SP patients at t1 ($p<0.01$) and t2 ($p<0.05$) while no changes were detected in PP patients. λ_1 , λ_2 and λ_3 values were lower in the right than in the left EC of RR (Table 1), SP and PP patients at each time point. The variation (expressed as a slope) of DTI metrics between time points (t2-t1) showed significant differences between right and left ROIs of RR patients while no changes were found in SP and PP patients. No changes were also detected between MS clinical forms when comparing DTI metrics slopes.

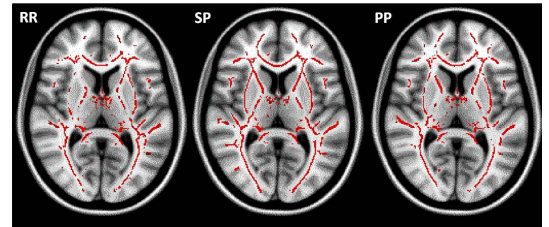


Figure 1: TBSS analysis of FA maps in RR, SP and PP patients compared to control subjects

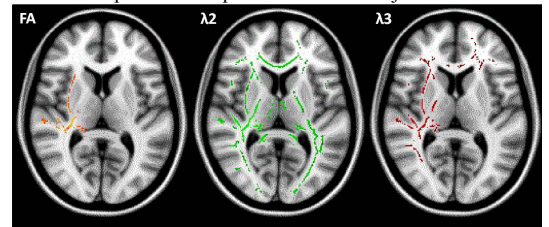


Figure 2: TBSS analysis of DTI metrics showing significant alterations in RR patients during a 2 years period of time

	Right External Capsule				Left External Capsule			
	FA	λ_1 ($\times 10^{-3}$)	λ_2 ($\times 10^{-3}$)	λ_3 ($\times 10^{-3}$)	FA	λ_1 ($\times 10^{-3}$)	λ_2 ($\times 10^{-3}$)	λ_3 ($\times 10^{-3}$)
Controls	0.355±0.020	1.031±0.032	0.730±0.032	0.491±0.030	0.347±0.023	1.083±0.050	0.760±0.042	0.529±0.043
RR-t1	0.350±0.019#	1.061±0.036#	0.765±0.028#	0.505±0.032#	0.324±0.026	1.136±0.053	0.829±0.053	0.581±0.055
RR-t2	0.338±0.021#	1.070±0.034#	0.792±0.043	0.527±0.036#	0.320±0.024	1.122±0.069	0.805±0.076	0.581±0.063
Slope ($\times 10^{-3}$)	-6.4±6.5*	4.6±13.2*	13.0±18.7**	11.0±10.3*	-2.4±9.3	-6.9±29.1	-12.3±31.2	0.1±23.8

Table 1: DTI metrics at both time points and slopes obtained in right and left external capsule ROIs (right vs. left: * $p<0.05$; ** $p<0.01$; # $p<0.001$)

Discussion: Firstly, the longitudinal TBSS analysis of three MS clinical forms showed a significant evolution of WM alterations in RR patients, particularly in the right external capsule, whereas no changes were detected in SP and PP patients. Secondly, the longitudinal ROI analysis of this region confirmed a significant change in the right EC of RR patients. Since FA values were more significantly decreased in the left EC, at both t1 and t2, these results suggest the occurrence of an evolving process spreading from the left to the right hemisphere that becomes more damaged over time. In contrast to the increasing λ_2 values observed over time in the right EC, reflecting probably demyelinating processes [5], a significant decrease was observed in the left EC. This finding may reflect the presence of a self-repair mechanism such as remyelination in the initially damaged left hemisphere. The lack of longitudinal changes in DTI metrics of SP and PP patients probably resulted from the more advanced disease progression of these forms, as shown in Fig. 1. Further investigations will include the effect of disease duration, age and clinical scores such as EDSS and MSFC, on disease evolution as characterized by their DTI markers of WM abnormalities. Finally, DTI has proved its effectiveness in monitoring the progression of the disease by detecting evolving microstructural damages in WM of RR MS patients.

References: 1) Ciccarello O, et al. J. Neurol. 2003, 250:287-292. 2) Smith SM et al. Neuroimage. 2006, 31:1487-1505. 3) Ge Y, et al. Ann. N. Y. Acad. Sci. 2005, 1064:202-219. 4) Smith SM, et al. Neuroimage. 2004, 23:S208-219. 5) Lowe MJ, et al. Neuroimage, 2006 32:1127-1133.