Differentiation of Pathological Processes and Clinical Forms in Multiple Sclerosis: a Tract Based Spatial Statistics Study.

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Introduction

Multiple Sclerosis (MS) is characterized by demyelination, axonal damage, gliosis and often remyelination processes and can clinically appear either as relapsing-remitting (RR) phases of inflammation, sooner or later, followed by a secondary progressive (SP) period or directly as a primary progressive (PP) evolution which may constitute the clinical expression of a neurodegenerative process [1]. Diffusion tensor imaging (DTI) has proven to be very sensitive for detecting and quantifying pathological changes in lesions and normal appearing white matter (NAWM) [2], but is constrained by an operator-dependant selection of brain regions of interest [3]. Recently, a statistic analysis technique of DTI measurements has been developed under the name "Tract-Based Spatial Statistics" (TBSS) [4]. This technique is first based on creating from FA images a mean skeleton 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. Therefore, the goal of this study is to apply TBSS on different patient groups to characterize and differentiate their clinical forms.

Methods

This study included 62 patients of different clinical forms: 24 RR (36.4 ± 7.9 y), 24 SP (42.9 ± 4.7 y) and 14 PP patients (44.3 ± 3.8 y) along with 19 control subjects (37.2 ± 10.5 y). All patients were diagnosed with definite MS according to McDonald's criteria and their expanded disability status scale ratings (EDSS) measured. MR exams were performed on a 1.5 T Siemens Sonata system and DTI protocol included a spin-echo EPI sequence (TR=3800 ms, TE=96 ms) with 96 x 96 phases-encoding over a FOV of 240 x 240 mm and 51 axial slices of 2.5 mm thickness. Post-processing of diffusion tensor data was performed using FSL [5]. An eddy current correction using the FMRIB's Diffusion Toolbox (FDT) was performed followed by the extraction of non-brain voxels using the Brain Extraction Tool [6] with a brain extraction factor of 0.35. FA maps were then generated using FDT module. TBSS registration and tract skeletonisation process was performed before voxel-wise cross-subject statistical analysis (Fig. 1).

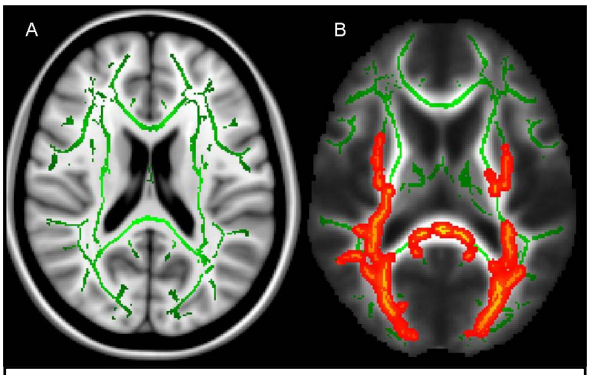

Figure 1: Mean FA skeleton (green) overlaid on the mean FA image (A). Colour scale shows skeletal voxels with lower FA (red) in the PP *vs* RR test (B).

Results

Decreased FA Regions	RR *vs* C	SP *vs* C	PP *vs* C	SP *vs* RR	PP *vs* RR
Inferior longitudinal fasciculus L&R	p<0.01	p<0.01	p<0.01	p<0.01	p<0.05
Superior longitudinal fasciculus L	p<0.01	p<0.01	p<0.01	p<0.01	-
Superior longitudinal fasciculus R	-	p<0.01	p<0.01	p<0.01	p<0.05
Inferior fronto-occipital fasciculus L&R	p<0.01	p<0.01	p<0.01	p<0.01	p<0.05
Anterior thalamic radiation L	p<0.01	p<0.01	p<0.01	p<0.01	-
Anterior thalamic radiation R	p<0.01	p<0.01	p<0.01	p<0.01	p<0.05
Corticospinal tract L	p<0.01	p<0.01	p<0.01	p<0.01	p<0.05
Corticospinal tract R	-	p<0.01	p<0.01	p<0.01	p<0.05
Anterior limb of the internal capsule L&R	p<0.01	p<0.01	p<0.01	p<0.01	-
Posterior limb of the internal capsule L	-	p<0.01	p<0.01	p<0.01	-
Posterior limb of the internal capsule R	-	p<0.01	-	p<0.01	-
External capsule L	p<0.01	p<0.01	p<0.01	P<0.01	p<0.05
External capsule R	-	p<0.01	p<0.01	P<0.01	p<0.05
Corpus callosum genu	p<0.01	p<0.01	p<0.01	P<0.01	-
Corpus callosum body	p<0.01	p<0.01	p<0.01	P<0.01	p<0.05
Corpus callosum splenium	p<0.01	p<0.01	p<0.01	P<0.01	p<0.05
Forceps Minor	p<0.01	p<0.01	p<0.01	P<0.01	-
Forceps Major	p<0.01	p<0.01	p<0.01	P<0.01	p<0.05
Cingulum L&R	p<0.01	p<0.01	p<0.01	P<0.01	-
Uncinate fasciculus L&R	-	p<0.01	p<0.01	P<0.01	-

Table 1: WM regions with significant FA decreases in patients (RR, SP or PP) compared to control (C) subjects and RR patients.

As reported in Table 1, FA values were significantly decreased in numerous white matter regions when comparing first, RR, SP and PP patients to controls and second when comparing SP and PP with RR patients.

However, the alterations were significantly less in PP patients than in SP patients as shown by their comparison to RR patients.

No significant changes were observed between PP and SP forms.

Discussion

This new statistical approach using TBSS allowed us to compare all brain regions from different groups of patients. These findings demonstrated extensive decreases of FA values in numerous white matter regions. These pathological changes were further increased with the gravity of the patient clinical status. SP patients showed more significant region alterations than PP and RR patients and equal changes between left and right hemispheres in contrast with RR (more changes in left than in right hemisphere) demonstrating the extensive and progressive damages occurring in the SP form. Furthermore, the large differences found between PP and RR patients and the lack of significant changes between SP and PP patients suggest that the PP form may reveal a primary progressive neurodegenerative process.

In conclusion, TBSS is an important tool to objective global brain changes. This statistical approach may help us to better understand the cerebral progression of the disease and differentiate the inflammatory processes occurring between first (RR) and second advanced (SP) forms or neurodegenerative processes underlying primary progressive form (PP).

References

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