White matter abnormalities are associated with cognitive dysfunction in secondary progressive multiple sclerosis

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TARGET AUDIENCE: Clinicians with an interest in multiple sclerosis and white matter neurological diseases, neuropsychologists with an interest in the mechanisms of cognitive dysfunction, and physicists/imaging analysts working with diffusion weighted imaging and voxel based analyses.

PURPOSE: To investigate whether microstructural abnormalities along white matter (WM) tracts are associated with cognitive dysfunction in secondary progressive multiple sclerosis (SPMS) patients.

INTRODUCTION: Cognitive dysfunction is common in patients with SPMS and has been associated with loss of WM integrity[1,2]. However, no study has yet examined the contribution of tract-specific WM injury to dysfunction in different cognitive domains in patients with SPMS. In this study we investigated WM matter abnormalities in SPMS patients with and without cognitive impairment. Furthermore, the correlation between tract-specific loss of WM integrity and cognitive function in patients was examined.

METHOD: Thirty SPMS patients (20 women, mean age 54 yrs, range 36-65) and thirty-two healthy controls (HCs) (20 women, mean age 41 yrs, range 21-65) underwent a whole-brain imaging protocol on a 3T scanner, including diffusion weighted imaging. After correction of motion and eddy current distortions, a diffusion tensor model was fitted on a voxel-by-voxel basis using DTIFIT from the FMRIB's Diffusion Toolbox. Tract-based spatial statistics (TBSS) was used to perform voxel-based diffusion tensor MRI analyses across subjects. Cognitive assessment included comprehensive testing spanning five cognitive domains that are commonly affected in MS patients. Twelve patients were defined as cognitively impaired, since their cognitive test score was at least 2 SD below the mean of the HCs on a minimum of 2 out of 5 tested cognitive domains; 18 patients were defined as cognitively preserved. Group differences for diffusion measures were analysed using a permutation algorithm (FSL's randomise) using threshold-free cluster enhancement (TFCE), to adjust for multiple comparisons. Lesional voxels where 10% or more patients showed T2 lesions were calculated and mapped onto the TBSS skeleton. In patients, correlations between DTI-metrics and cognition were explored in regions demonstrating significant differences between the SPMS patients and the control group using the same statistics. The alpha level was set at $p<0.05$, corrected for age and gender.

RESULTS: All SPMS patients together showed a widespread loss of WM integrity, reflected by reduced fractional anisotropy (FA) and elevated axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD), when compared with controls; in particular, patients showed reduced tract integrity in the corpus callosum, fornix and inferior longitudinal fasciculus, both within and outside hyperintense T2 WM lesions. Furthermore, more extensive and severe loss of WM integrity was observed in cognitively impaired patients relative to cognitively preserved patients; most pronounced differences were observed in the fornix, corpus callosum, forceps major, right inferior longitudinal fasciculus and right uncinate fasciculus. In patients, DTI metrics of many of these tracts showed significant correlations with processing speed (**Fig. 1A**) and visual memory. FA values of the corpus callosum ($r = 0.405$, $p = 0.03$), forceps major ($r = 0.478$, $p = 0.01$) (**Fig. 1B**), fornix ($r = 0.468$, $p = 0.01$), right superior longitudinal fasciculus ($r = 0.517$, $p = 0.005$) and right inferior fronto-occipital fasciculus ($r = 0.615$, $p = 0.001$) (**Fig. 1C**) were correlated with processing speed. Visual memory was correlated with FA values in fewer tracts, including the corpus callosum ($r = 0.469$, $p = 0.01$) and forceps major ($r = 0.518$, $p = 0.01$).

DISCUSSION: Damage to WM tracts that connect grey matter regions involved in cognitive function may be a potential mechanism for cognitive impairment in SPMS, possibly through a "disconnection syndrome". In fact, the WM tracts that were more severely affected in cognitively impaired patients are critical for cognitive processing, and the extent of damage in the interhemispheric callosal pathways and association pathways was greater in patients with worse speed of information processing and visual memory.

CONCLUSION: Loss of WM integrity assessed using TBSS is a powerful tool to monitor cognitive decline in SPMS patients. Cognitively preserved patients can be distinguished from cognitively impaired patients based on the degree of WM impairment.

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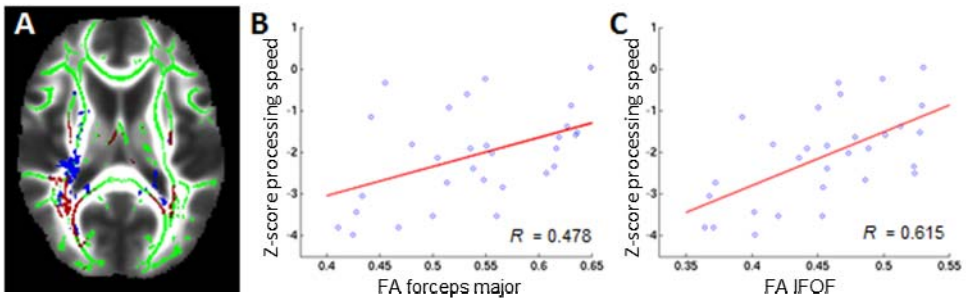

Fig. 1 | Decreased FA correlated significantly with a decline in cognitive performance in SPMS patients. (A) Processing speed correlated with reduced FA in several WM tracts, shown in red (lesions are in blue and the TBSS skeleton in green), including the forceps major (B) and right inferior fronto-occipital fasciculus (IFOF) (C).