Relationship of high-resolution diffusion tensor MRI measures of the cingulum bundle with cognitive function in multiple sclerosis

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Target Audience: This work is of interest to researchers studying Multiple Sclerosis, DTI, and cognitive decline.

Purpose: Over 40% of Multiple Sclerosis (MS) patients suffer from cognitive dysfunction, with frequent impairment of episodic memory [1]. The neural basis of episodic memory loss is unclear owing to the diffuse nature of the disease. The current work uses high-resolution DTI to examine the white matter pathway that connects the posterior cingulate cortex and the entorhinal cortex (PCC-EC), implicated in spatial processing and memory [2].Previous work has shown that diffusion tensor imaging (DTI) provides a measure of white matter pathology [3-5].In MS, DTI measures correlate with disease duration, relapse rate, and measures of cognition [6-7]. We hypothesize that DTI measures in subjects with MS will show an increase in mean, transverse, and longitudinal diffusivity (MD, TD, and LD, respectively) and a decrease in fractional anisotropy (FA) in the PCC-EC track as compared to controls, and that DTI measures will correlate with measures of episodic memory, but not with a measure of working memory.

	MS	Controls	p
Cognitive Variables			
CVLT	46.7 (11.2)	57.7 (9.4)	0.0004
BVMT	45.9 (13.3)	56.6 (7.9)	0.0024
SDMT	51.5 (13.6)	67.4 (11.6)	$4x10^{-5}$
PASAT	-0.42 (1.3)	0.34 (0.68)	0.0193

Table 1: Mean and standard deviation and Student's t-test p-value for each group comparison.

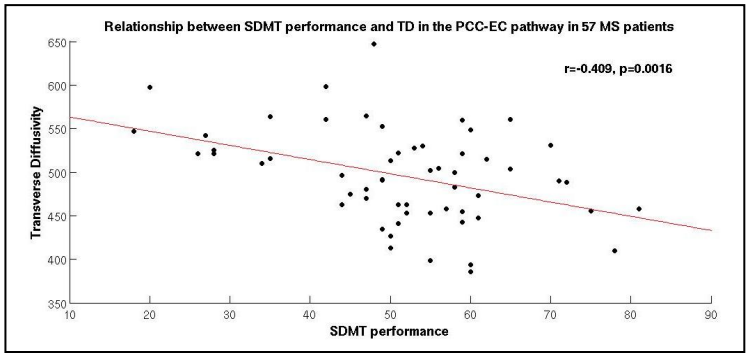
Methods: 57 patients with MS and 17 age-, sex-, and education-matched healthy controls (MS: mean age 44.6 ± 8.4, 18 males, mean EDSS 3.0 ± 2.0; Control: mean age 42.7 ± 10.1, 4 males) were scanned at 3T, in a 12-ch receive head coil. Scans included a T1-MPRAGE (1x1x1.2mm) and a HARDI scan (FOV=192×192 mm^2; matrix=192×192; 45 1-mm thick slices; TE/TR=90/7700 ms) 71 directions; 2 averages; 8 b=0 acquisitions per average.

The PCC was defined by a 6mm sphere, similar to the region used in Grecius et al. [8]. The EC was defined by an anatomic ROI manually drawn on the T1 anatomic image. Probabilistic tracking between pairs of seeds was performed using the calculated FODs to determine white matter pathways. FA, MD, TD, and LD averaged values were created for each subject by dividing the sum of track density weighted diffusivity values by the sum of track density for the pathway.

To investigate episodic memory the subjects were administered the California Verbal Learning Test (CVLT-II) and the Brief Visual Memory Test (BVMT-R). Additionally, subjects were administered the Symbol Digit Modalities Test (SDMT), a measure of information processing speed with elements of episodic memory, and the Paced Auditory Serial Addition Test (PASAT), a measure of speed of processing, attention, calculation ability, and working memory. The SDMT is sensitive to cognitive decline in MS [9], and we previously found a relationship between PASAT performance and DTI measures in the PCC-EC [10].

Results: Subjects with MS did not differ from controls on age or education, but did score significantly lower on all cognitive tests (Table 1). The patient group showed higher MD, LD and TD and lower FA in bilateral PCC-EC pathways ($p<0.031$). In controls, left PCC-EC TD was significantly correlated with performance on the BVMT, even after controlling for the effects of age ($r=0.576$, $p=0.019$). In patients, age and education were not related to DTI measures, and all DTI measures were related to performance on BVMT and SDMT. Neither PASAT nor CVLT performance were related to DTI measures.

Discussion: We found a strong relationship between bilateral DTI measures and performance on a measure of information processing speed and a measure of visual spatial episodic recall. Interestingly, we found no relationship with verbal episodic recall or PASAT scores. The relationship between DTI and visual spatial episodic recall was found in both patients and controls, suggesting specific involvement of the PCC-EC pathway. The strong relationship of SDMT and DTI measures in patients may not be specific to the PCC-EC pathway, but may reflect the critical role of processing speed in overall cognitive decline in MS.



Conclusion: Our findings show that DTI is a useful measure of disease progression in a cognitive pathway, and has potential to be refined and developed into a marker of disease progression.

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