White matter microstructural alterations and their correlations to neuropsychological measures

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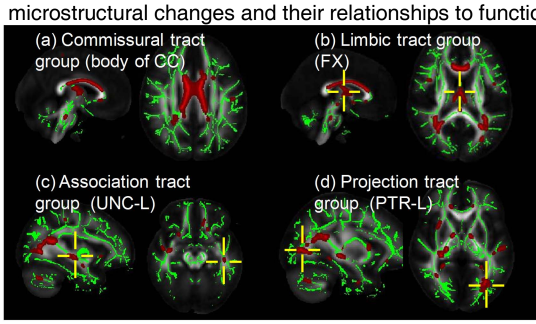
Target audience: Clinicians and MR physicists who are interested in predicting functional consequences with categorized tract-level white matter disruption detected from measurements of DTI-derived metrics in study of multiple sclerosis.

Introduction and Purpose: Diffusion Tensor Imaging (DTI) is capable of quantifying white-matter (WM) microstructural changes of patients with neurological diseases such as Multiple Sclerosis (MS). The four DTI-derived metrics, fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) capture different aspects of white matter microstructural alterations (1) and were applied in this study. The WM can be generally categorized into four tract groups, commissural, limbic, association and projection tracts, based on their functions (2). Whereas extensive previous work has documented MS-related WM changes, there has been minimal work investigating the functional consequences of these changes. In this study we assessed the sensitivity of the four DTI metrics in these four tract groups to MS WM pathology and performance changes, assessed by neuropsychological measures.

Methods*:* *Participants:* 13 patients (age=47±6.6) diagnosed with MS and 12 age-matched healthy controls (age=42±9.7) performed a neuropsychological tests battery including Selective Reminding Task Long Term Storage (SRT-LTS) and Symbol-digit modalities Task (SDMT). *DTI acquisition:* Data were acquired using a single-shot EPI with SENSE on a 3T Philips Achieva MR system. DWI parameters: FOV=224/224/143mm, in-plane imaging matrix=112×112, axial slice thickness=2.2 mm, no gap, slice number=65, 30 independent diffusion-weighted directions with b-value=1000 sec/mm^2, repetitions=2. *Voxelwise analysis:* TBSS from FMRIB software library was used for voxel-wise comparison. The single subject template used for nonlinear registration process in TBSS (3) is identical to that used for establishing JHU ICBM-DTI-81 (4). After statistical analysis from TBSS, significant clusters ($p < .001$; uncorrected) in the skeleton voxels of WM were identified. To avoid false positives due to noise, only clusters with continuous voxels larger than 10 were retained for the four DTI metrics FA, RD, AD and MD. *Tract-level comparison:* Tract-level analysis was based on FA values at the skeleton voxels after TBSS registration, projection and skeletonization steps. Average DTI metrics were calculated in each tract before student's t-test. *Correlation to neuropsychological measures:* DTI metrics averaged at the significant clusters were correlated with SRT-LTS and SDMT.

Results*:* *Voxelwise comparison:* Widespread WM disruptions were found in MS patients from voxelwise analysis. A representative case of WM disruption in each tract group detected with FA and RD are shown in Figs. 1 and 2 respectively. *Tract level comparisons:* The affected white matter tracts with significantly decreased FA and increased RD are listed in Tables 1 and 2 respectively. Tract level analysis indicated that a majority of the WM tracts were affected with the entire tract considered as a unit. Among the four DTI-derived metrics, RD results showed most severe microstructural changes than those from the other three, possibly because RD is most sensitive to demyelination, a hallmark of MS. It also revealed that more association tracts than projection or limbic tracts were disrupted in the MS group. *Correlations to neuropsychological measures:* As summarized in Table 3, significant correlations were found between FA and RD at disrupted clusters with SRT and SDMT.

Discussion: Results support the hypothesis that RD is the most sensitive measure of WM microstructural pathology in association tracts. However, FA showed greater sensitivity to WM integrity-performance relationships most notably in CC. These results have implication for measurement of MS-related microstructural changes and their relationships to functional consequences.



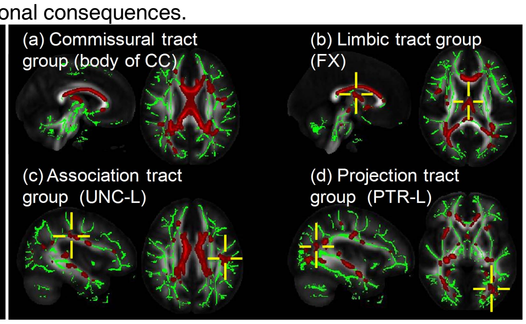


Figure 1 (left): The voxelwise WM disruptions with clusters (highlighted by yellow crosshairs) of a representative tract in each tract group featured in each panel. Underlying gray scale images are the MNI152 FA maps. Green indicates the core white matter skeleton. Red clusters indicate the locations of statistically significant WM microstructural differences with FA measurements between the MS and control group. Most tract abbreviations can be found in the Methods section. PTR: posterior thalamic radiation. Abbreviations: ATR/PTR: anterior/posterior thalamic radiation; CC: corpus callosum; CGC: cingulum bundle in cingulate gyrus; EC: external capsule; Fmajor/Fminor: forceps major/minor of CC; FX: fornix; IC: internal capsule; IFO-inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; SLF: superior longitudinal fasciculus; UNC: uncinate fasciculus (UNC-L/R). L and R indicates left and right, respectively.

Figure 2 (right): The red clusters indicate the locations of statistically significant microstructural differences with RD measurements between the MS and control group. See legend of Figure 1 for other specifications and abbreviations.

Tract group	Commissural	Association				Limbic		Projection	
Tract	Fmajor	IFO-L	IFO-R	ILF-L	ILF-R	CGC-L	CGC-R	ATR-L	ATR-R
FA (Ctr)	0.529	0.516	0.497	0.484	0.474	0.571	0.459	0.465	0.464
FA (MS)	0.489	0.468	0.454	0.435	0.429	0.51	0.406	0.433	0.436

Table 1: The tract level FA white matter disruptions (P<0.0025). For all tables, different colors indicate different tract groups which are involved in distinct brain functions. See legend of Figure 1 for abbreviations.

Tract group	Commissural	Association									Limbic		Projection	
Tract	Fmajor	IFO-L	IFO-R	ILF-L	ILF-R	SLF-L	SLF-R	SLF-temp-L	UNC-L	UNC-R	CGC-L	CGC-R	ATR-L	ATR-R
RD (MS)	0.56	0.55	0.57	0.57	0.58	0.54	0.56	0.53	0.55	0.55	0.52	0.59	0.6	0.6
RD (Ctr)	0.48	0.49	0.5	0.51	0.51	0.49	0.51	0.47	0.5	0.51	0.45	0.52	0.53	0.52

Table 2: The tract level white matter disruptions with RD measurements (P<0.0025). See legend of Figure 1 for abbreviations.

	Correlated with SRT		Correlated with SDMT					
Tract group	Commissural	Projection	Commissural			Projection		
Tract	FX-R	EC-R	Genu of CC	Body of CC	Splenium of CC	Anterior limb of IC-L	Posterior limb of IC-L	EC-L
FA	0.479	N/S	0.44281	0.43658	0.48419	0.60594	0.57734	0.48814
RD	-0.45	-0.484	N/S	N/S	N/S	N/S	-0.44264	-0.42565

Table 3: Correlation between FA and RD with the neuropsychological values in MS patients. See legend of Figure 1 for abbreviations.

References: [1] Song, SK et al (2002) Neuroimage 17: 1429. [2] Wakana, S et al (2004) Radiology 230: 77. [3] Smith, SM et al (2006) NeroImage 31:1487; [4]. Mori, S et al (2008) NeuroImage 40: 572.

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