Diffusion Tensor Imaging correlates of cognitive impairment and fatigue in Multiple Sclerosis

G. P. Parikh[1], M. Bester[1,2], M. Lazar[1], J. S. Babb[1], H. Jaggi[1], L. Miles[1], R. Grossman[1], and M. Inglese[1,3]
[1]Radiology, New York University, New York, NY, United States, [2]Neuroradiology, Eppendorf-Hamburg University, Hamburg, Germany, [3]Neurology, New York University, New York, NY, United States

Introduction: Cognitive impairment and fatigue are common symptoms in multiple sclerosis (MS) including patients with benign MS (BMS)[1] and clinically isolated syndrome (CIS) suggestive of MS[2]. Despite their impact on the quality of life[3], very little is known about the pathophysiology of these symptoms. Diffusion Tensor Imaging (DTI) has shown promising results in detecting subtle tissue damage in normal-appearing white matter (NAWM). In addition, the potential to reconstruct major white matter fiber bundles with diffusion tensor tractography provides the possibility to focus exclusively on structures that might play a major role in cognitive performance and fatigue development. In this study, we used DTI tractography to determine whether tissue damage in the corpus callosum (CC)[4] and in the anterior-thalamic tracts (AT)[5] is associated with cognitive dysfunction and presence of fatigue in patients with BMS and CIS.

Material and methods: 25 patients with BMS, (mean age 53.4 ± 7.1 yrs), and 11 patients with CIS (mean age 41.6 ± 9.0 yrs) and 24 healthy controls (CTRL, mean age 51.6 ± 11.2 yrs) underwent DTI imaging on a 3T whole body imager (Siemens Medical Solutions, Erlangen, Germany). Approval was obtained from the NYU IRB and informed consent was obtained from all subjects. The MRI protocol included the following sequences: axial T2 TSE, 3D T1 MPRAGE, and single shot EPI for DTI. The DTI sequence's parameters were: 6 diffusion encoding directions, b values: 0, 1000 s/mm$^{2)}$, TR/TE: 2000/2.6 ms., TI: 800ms, 4 averages, FOV: 230 × 230 mm^2, matrix size: 128×128, in-plane resolution 1.8*1.8 mm^2 , 48, 3 mm-tick contiguous axial slices. The Diffusion Tensor (DT) was estimated by linear regression and fractional anisotropy (FA), and mean diffusivity (MD) maps were calculated. Using DT MRI tractography (in-house developed software) the callosal genu (CCG), body (CCB) and splenium (CCS) tracts and the anterior-thalamic tract (AT) bilaterally were computed for every healthy subject[6]. Probability maps of the tracts were created in standard space using the Montreal Neurological Institute (MNI) template and transformed into each single subject space. Then, values of the DT derived maps were calculated inside each tracts[7,8] (**Figure 1**). Fatigue was assessed by a psychologist blind to the MRI findings using the multidimensional fatigue inventory (MFI). A comprehensive neuropsychological (NP) test-battery was administered to all patients. Mann-Whitney (MW) test to compare subject groups in terms of each DTI metric and Pearson correlations were used to describe the association of DTI metrics with NP Z-scores.

					p-values		
	Region	CTRL	CIS	BMS	CTRL vs. CIS	CTRL vs. BMS	CIS vs. BMS
FA	CCG	0.53 ± 0.02	0.52 ± 0.03	0.48 ± 0.04	0,43	<0.01	0,04
	CCB	0.53 ± 0.03	0.51 ± 0.03	0.48 ± 0.03	0,17	<0.01	0,01
	CCS	0.59 ± 0.03	0.55 ± 0.03	0.53 ± 0.04	<0.01	<0.01	0,16
	AT-R	0.39 ± 0.02	0.39 ± 0.01	0.35 ± 0.02	0,69	<0.01	<0.01
	AT-L	0.39 ± 0.03	0.36 ± 0.02	0.34 ± 0.03	0,24	<0.01	<0.01
MD	CCG	0.83 ± 0.07	0.84 ± 0.03	0.88 ± 0.08	0,69	<0.01	0,02
	CCB	0.84 ± 0.05	0.83 ± 0.03	0.90 ± 0.08	0,12	<0.01	<0.01
	CCS	0.85 ± 0.05	0.86 ± 0.05	0.94 ± 0.10	0,67	<0.01	<0.01
	AT-R	0.77 ± 0.05	0.76 ± 0.03	0.83 ± 0.06	0,04	<0.01	0,06
	AT-L	0.79 ± 0.05	0.81 ± 0.03	0.85 ± 0.05	0,08	<0.01	0,05

Figure 1. Mean± SD for FA and MD (x10^{-3}mm^{2}s^{-1}) measured in the callosum genu (CCG), body (CCB), splenium (CCS), right and left anterior thalamic tracts (AT-R and AT-L) in patients with BMS and CIS.

Results: DTI-derived metrics in the CC and AT tracts are presented in **Table 1.** Compared to controls patients with BMS showed significantly decreased FA and increased MD in both the CC and the AT tracts whereas patients with CIS showed decreased FA in the splenium of the cc and increased MD in the right AT. Compared to patients with CIS, patients with BMS showed decreased FA and increased MD of the examined tracts. A significant association was found between the FA and MD (r=0.4, p=0.01; r=-0.34, p=0.04) in the CC and the single digit modality test which measures processing speed and working memory. The association between FA of the AT with general (r=0.3, p=0.1) and mental fatigue (r=0.4, p=0.1) did not reach the level of statistical significance.

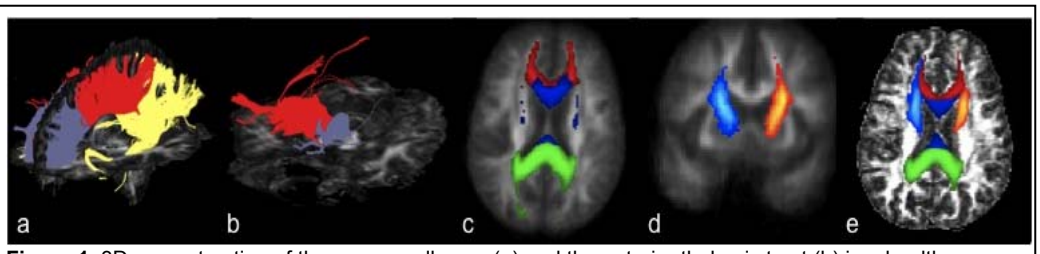

Figure 1. 3D reconstruction of the corpus callosum (a) and the anterior thalamic tract (b) in a healthy subject. CC (c) and AT (d) tract probability maps in MNI space and in the corresponding single subject space (e) after transformation.

Conclusion: Our study suggests that DTI tractography may help understand the role of selected brain region damage in the development of clinical symptoms such as cognitive impairment and fatigue in patients with BMS and CIS.

References: 1) Amato M *et al*., J. of Neurology 2006. **2**) Potagas C *et al.,* J Neurol Sci 2008. **3**) Rao SM *et al.,* Neurology ,1991. ***4)*** Hines M *et al.,* Behav Neurosci, 1992. ***5)*** Sepulcre J *et al*., Multiple Sclerosis, 2009. **6**) Wakana S *et al*., Neuroimage 2007. **7**) Pagani E *et al*., Neuroimage 2005. **8**) Mesaros E *et al*., HBM, 2009.**Acknowledgments:** This study was supported by NIH grants 5R01NS051623-04 and R01NS029029-16.