Identification of quantitative differences in normal-appearing white matter of multiple sclerotic patients vs. healthy controls using a novel Bloch-simulation-based T_2 mapping technique

Noam Ben-Eliezer[1,2], Veronica Cosi[1], Akio Yoshimoto[1], Daniel K Sodickson[1,2], Mary Bruno[1], Kai Tobias Block[1,2], and Timothy M Shepherd[1,2]

[1]*Center for Biomedical Imaging, Department of Radiology, New York University Medical Center, New York, NY, United States,* [2]*Center for Advanced Imaging Innovation and Research (CAI2R), Department of Radiology, New York University School of Medicine, New York, NY, United States*

Target audience Clinicians and researchers interested in rapid, accurate quantification of T_2 relaxation for the diagnosis and monitoring of progression in patients with Multiple Sclerosis.

Introduction Multiple sclerosis (**MS**) is a common neurological disorder affecting young adults, and characterized by episodes of inflammation and/or neurological symptoms with insidious progression of cumulative disability. Bright lesions in the brain and spinal cord can be used to detect inflammatory lesions, but are not specific, while T_2 lesion-burden or volumes alone do not always correlate well with disability. Accurate in vivo quantification of T_2 values has long been hampered by the inherent bias of rapid multi spin-echo (**MSE**) sequences due to stimulated and indirect echoes, non-rectangular slice profile, and transmit-field ($\mathbf{B_1^+}$) inhomogeneities[1,2]. This bias, moreover, is pulse sequence and parameter dependent, causing T_2 values in the same subject to vary between scanners and protocols. A new method for mapping T_2 – the EMC algorithm[3] – is able to overcome these limitations and deliver accurate and reliable maps of the true tissue T_2 values, independently from the scan settings[4]. Here we present initial results of applying the EMC algorithm for rapid and accurate T_2 mapping in the brains of healthy controls, and patients with multiple sclerosis. It is shown that, owing to its high accuracy, the EMC approach is able to uncover significant differences in normal-appearing white matter which cannot be discerned using traditional techniques.

Methods EMC algorithm: Bloch simulations of the prospective MSE protocol were performed using the exact RF pulse shapes and other experimental parameters. Simulations were repeated for a range of T_2 and B_1^+ values (T_2=1…1000ms, B_1^+ = 50…130 % deviation from nominal value), producing a database of EMCs, each associated with a unique $[B_1^+,T_2]$ value pair. Data acquisition: 30 healthy volunteers (16 males) and 9 patients (3 males) with clinically diagnosed relapsing-remitting MS were imaged on a whole-body 3 T scanner (Siemens Skyra) using a standard MSE protocol. Scan parameters were {TR=2500 ms, Echo-spacing=12 ms, N_{echoes}=10, res=1.7x1.7mm^2, slice=3 mm, bandwidth=200 [Hz/Px], T_{acq}=2:44min using 2x GRAPPA acceleration}. Reconstruction: T_2 maps were generated for an axial slice using the EMC algorithm in [12] by matching the experimental EMCs derived from DICOM image sets voxel by voxel to the EMC database via l_2-norm minimization of the difference between experimental and pre-calculated EMCs. Post processing: Mean and standard-deviation (**SD**) were calculated for 7 regions of interest (**ROIs**): genu and splenium of corpus callosum, caudate nucleus, putamen, thalamus, frontal white matter and, periventricular white matter (**GNU**, **SPL**, **CDN**, **PTM**, **TLM**, **FWM**, **PWM**).

Results Table 1 summarizes the average T_2 values for 7 brain ROIs in a group of 30 healthy controls (**HC**) versus matching ROIs in normal appearing (**NA**) tissue for 9 MS patients. Statistically significant T_2 elevation was detected in white matter (**WM**), corpus callosum and thalamus of MS patients *vs.* healthy controls. Figure 1 (and Table 1 bottom row) illustrates the average T_2 increase in normal appearing frontal white matter of the MS group, together with the expected sharp elevation inside visible lesions ROI (Figure 1b).

SPL	Healthy Controls	MS Patients	t-test P-value
GNU	47.4 ± 3.1	50.1 ± 3.5	0.062
SPL	56.1 ± 3.3	61.1 ± 3.3	0.001
CDN	55.0 ± 1.9	54.3 ± 3.3	0.565
PTM	49.6 ± 1.7	51.9 ± 4.2	0.145
TLM	54.6 ± 2.3	58.1 ± 2.9	0.007
FWM	51.2 ± 2.0	56.6 ± 2.5	< 0.001

Table 1: T_2 values (Mean ± SD) for 30 healthy controls *vs.* normal appearing tissue in 9 MS patients, calculated for 7 brain regions. Right column: statistical significance of the separation between the two groups.

Discussion Fitting techniques which do not account for the numerous coherence pathways occurring in MSE protocols suffer from inherent bias and increased spread of the measured T_2 values. This limitation is further exacerbated because the bias (accuracy) and its spread (precision) will depend on the protocol implementation and parameter set. By incorporating these factors into the library of expected spin evolutions, the EMC algorithm overcomes these limiting factors, thereby measuring statistically significant differences which would otherwise be buried beneath the inherent scanner- or protocol-dependent variability of traditional T_2 mapping approaches. As demonstrated here, the MSE acquisition remains fast and clinically feasible in MS patients. The EMC framework can be accelerated using radial sampling strategies[5], and extended to model other contrasts (e.g. T_1, diffusion, T_2^*), to derive multi-component T_2 distributions, or to support arbitrary acquisition schemes. Future studies will investigate whether quantitative T_2 can improve tracking of MS diffusivity in the brain, or add specificity to diagnosis and monitoring of response to pharmacologic therapies.

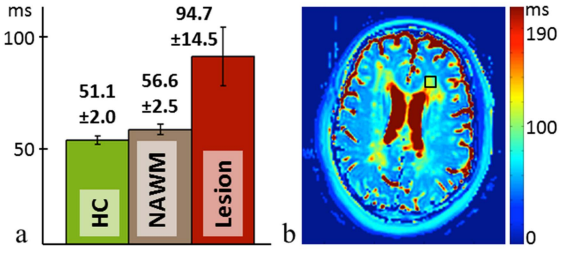

Figure 1: (**a**) Comparison of T_2 values between frontal white matter in 30 healthy controls (**HC**), normal appearing white matter (**NAWM**) ROI in 9 MS patients and, FWM lesion in 6 MS patients (**Lesion**). [HC & NAWM] and [NAWM & Lesion] are statistically different with p-val = 1.6e-3 and 7e-5 respectively. (**b**) Sample T_2 map of an MS patient with ROI drawn in a FWM lesion.

References **[1]** Deoni SC et al. MRM 2003; 49(3):515-26. **[2]** Lebel RM, et al. *MRM*. 2010; 64(4):1005-14. **[3]** Ben-Eliezer N et al. *MRM* 2014, doi: 10.1002/mrm.25156. **[4]** Cosi V. et al. 23rd ISMRM 2015, submitted. **[5]** Ben-Eliezer N et al. 22nd ISMRM 2014; p.4274.

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