Multivariate combination of magnetization transfer ratio and quantitative T_2* to detect subpial demyelination in multiple sclerosis

Gabriel Mangeat[1,2], Sindhuja Tirumalai Govindarajan[2], Revere Philip Kinkel[3], Caterina Mainero[2,4], and Julien Cohen-Adad[1,5]

[1]*Institute of Biomedical Engineering, Polytechnique Montreal, Montreal, Qc, Canada,* [2]*Martinos Center for Biomedical Imaging, MGH, Charlestown, MA, United States,* [3]*Clinical Neurosciences, University of California San Diego, La Jolla, CA, United States,* [4]*Harvard Medical School, Boston, MA, United States,* [5]*Functional Neuroimaging Unit, CRIUGM, Université de Montréal, Montreal, Qc, Canada*

Target audience. Scientists and clinicians interested in mapping cortical myelin content and in investigating subpial demyelination in multiple sclerosis.

Purpose. The ability to assess subpial demyelination *in vivo* in multiple sclerosis (MS) is motivated by improved correlation with functional deficits and for understanding the pathophysiology of the disease[1,2]. In vivo detection of cortical subpial lesions, however, is challenging due to the thin aspect of the cortex (2-4 mm) and to the low contrast in standard clinical MR imaging modalities. Recently, T_2* at 7 Tesla was shown to be a sensitive biomarker of pathology and disease progression associated with demyelination in the cortex of MS patients[1,3]. However, several physiological and technical confounds (i.e. iron content, blood vessels and poor shimming) may hamper the specificity of T_2* measures. Magnetization Transfer Ratio (MTR) imaging was demonstrated to be sensitive to myelin content[4] and cortical myelin changes in MS[5,6], potentially being an excellent complementary measure to T_2* estimation even more given that its underlying contrast mechanisms are different than those from T_2*. Additional confounds exist that can affect cortical mapping studies, including (i) the effect of cortical thickness, which can introduce variable amount of partial volume effect, and (ii) the angle between coherently-oriented myelinated fibers in the cortex and the direction of the main magnetic field (B0)[7]. The goal of this study was to use multivariate statistics to combine cortical MTR (from 3T) and T_2* (from 7T) measurements, cortical thickness, and B0 orientation dependency measure using a surface-based analysis framework in order to gain specificity to subpial demyelination in MS.

Methods. *Data acquisition.* We recruited 6 healthy subjects (mean age=36 +/- 5 years, 3 females) and 11 MS patients (mean age 46 +/- 12 years, 8 females). Subjects were scanned with a 7T whole-body Siemens scanner to measure T_2* and on a 3T scanner (Siemens TIM Trio) to measure MTR. MTR was not acquired at 7T due to difficulties in obtaining homogeneous B1 profile and SAR limitations. Both scanners were equipped with a 32-channel head coil. Parameters at 7T were: TR = 2020 ms, TE = 6.34+3.2n [n=0,...,11] ms, resolution = 0.33x0.33x1 mm^3. Parameters at 3T were: 3D FLASH, TR/TE = 30/2.49 ms, matrix = 192x192, resolution = 1.2x1.2x1.2 mm^3, with and without Gaussian MT pulse (7:45 min each). *Data processing.* T_2* and MTR data were (*i*) registered to individual cortical surfaces (extracted from 3 T T1-weighted anatomical scans), (*ii*) sampled along the cortical ribbon at the mid distance between the pial surface and the white matter surface and (*iii*) registered to a common template surface (*fsaverage*). Cortical thickness and B0 orientation maps were computed from the cortical surface of each subject as previously detailed[7]. *Multivariate combination.* First, multilinear regressions were performed using predictors of myelin content (MTR and T_2*) and potentially confounding covariates (cortical thickness and B0 orientation). The outputs of this step were 2 normalized maps representing the myelin-related information contained in MTR and T_2*, and corrected for partial volume effect and B0 orientation. A spatial independent component analysis (ICA)[8] was subsequently used to extract the shared myelin-related signal between MTR and T_2*. The result was a Combined Myelin Estimation (CME) map that reflected the cortical myelin content of each subject with more specificity than MTR or T_2* maps taken separately. All steps are summarized in **Figure 1**. *Statistical analysis.* General Linear Models (GLM) were run on a vertex-by-vertex basis to assess regions of significant differences ($p<0.05$) between controls and MS patients, for each of the following metric: MTR, T_2* and CME. The following regressors were used: age, gender and mean cortical thickness. *Specificity/Sensitivity assessment using Receiver Operating Characteristics (ROC) curves.* Cortical regions that are known to be preferentially affected by subpial demyelination in MS[1,2,6] were selected out of the V1 atlas[9]: primary motor cortex (BA4a and BA4p), somatosensory cortex (BA1 and BA2), and pre-motor cortex (BA6). Then, from the inter-group distributions of each metric (MTR, T2* and CME), the ROC curves were computed.

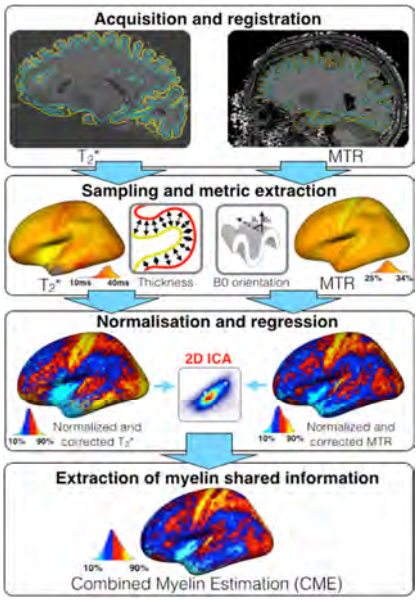

Figure 1. Processing steps applied to combine the cortical information of 7T T_2*, 3T MTR and B0 orientation in order to extract a metric more specific to myelin than other metric taken separately.

Results. Figure 2A shows the results of the GLM performed for T_2*, MTR and CME. Significant differences ($p<0.05$, not corrected) between both groups were detected in the motor cortex and in the frontal lobe. **Figure 2B** shows a zoom in the posterior primary motor cortex: BA4p (regions selected for the ROC analysis), illustrating the greater z-score for the CME metric (other regions exhibited similar large z-score in the CME map). **Figure 2C** represents the distributions of the metrics in BA4p for the controls group (blue) and the MS group (red). **Figure 2D** shows the resulting ROC curve for each metric, suggesting a potential gain in specificity and sensitivity for the CME map. For example, for a given sensitivity of 60%, the specificity of pathological-related change in this cortical region is 53%, 40% and 66% for MTR, T_2* and CME, respectively. **Figure 3** shows the gain in specificity for other cortical regions.

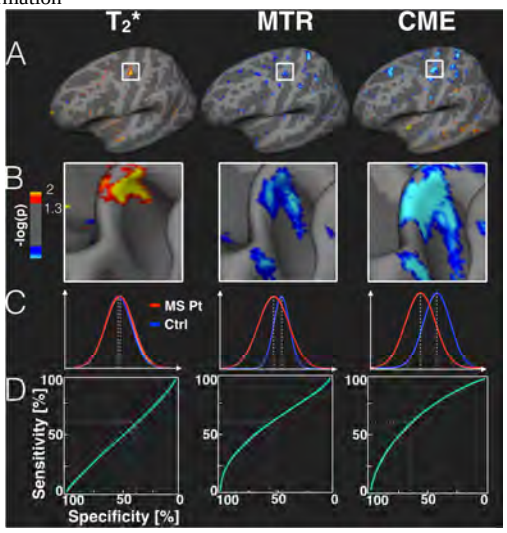

Figure 2. A. Overlay of GLM significance maps averaged on the mid-cortical surface. B. Zoom in the lower precentral gyrus (part of BA4). C. Distribution of both control and MS patient groups in BA4p. D. ROC curves of the distributions in C.

	T2*	MTR	CME		T2*	MTR	CME
BA4a	40%	53%	62%	BA1	40%	54%	60%
BA2	40%	59%	61%	BA6	40%	57%	60%

Figure 3. Specificity of the subject classification from the assessment of the subpial demyelination in the selected cortical regions, assuming a sensitivity of 60%.

Discussion. We introduced a multivariate statistical framework for combining MTR and T_2* measures in order to gain specificity to myelin content. We demonstrate its benefits for separating healthy controls from MS patients on the basis of cortical pathology. The framework is adaptable in that other relevant metrics such as T1 and diffusion-weighted measures can be added to the model.

References. [1]Cohen-Adad, *Neuroimage*, 2011; [2]Kutzelnigg, *Brain*, 2005; [3]Mainero, *Neurology*, 2009; [4]Schmierer, *Ann Neurol*, 2004; [5]Chen, *Neurology*, 2013; [6]Deraksan, *Hum Brain Mapp*, 2014; [7]Cohen-Adad, *Neuroimage*, 2012; [8]Hyvärinen, *Int J Neural Syst*, 2000; [9]Fischl, *Cereb Cortex*, 2008;

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