Technique development for accurate whole brain white matter and lesion myelin water fraction analysis for multiple sclerosis using multi-component T2 relaxometry

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Target audience: Clinicians and researchers studying white matter (WM) disorders.

Purpose: A major hurdle to conducting clinical trials for remyelinating agents in multiple sclerosis (MS) is the lack of a clinically feasible imaging method to assess myelin content. T2 relaxometry is a magnetic resonance (MR) imaging technique in which a series of T2-weighted images at different echo times are obtained and the contribution of water associated with myelin can be represented as myelin water fraction (MWF). Accurate registration and segmentation of whole brain MWF maps and anatomical images are critical for reliable quantification of regional brain changes. This is challenging due to differences in native voxel size, orientation, image contrast and artifacts provided by different imaging sequences. Here we demonstrate the technique to combine and analyze our previously developed and optimized whole brain MWF T2prep spiral gradient echo sequence [1,2] and our newly developed post-processing algorithm with WM segmentation utilizing FreeSurfer [3,4] and a semi-automated lesion mapping method.

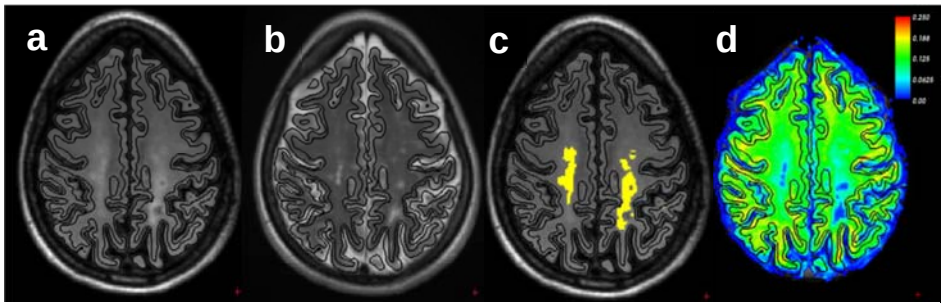

Fig. 1: T2 Flair Image (a), T2 Axial Image (b), T2 Flair Image with lesion segmentation (yellow label) (c), and MWF map (d) with black contours of FreeSurfer surface segmentations overlaid.

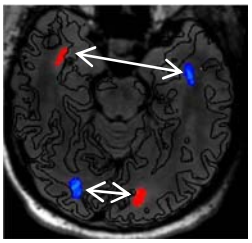

Fig. 2: lesion (red) and mirrored label (blue) overlaid on T2 Flair Image with FreeSurfer segmentation contours.

Methods: Eight patients with the diagnosis of MS participated after informed consent. Four data were acquired at 3T GE (HDxt 16.0) using 8-channel phased-array coil: T1-weighted SAG_3D_BRAVO (1.2x1.2x1.2mm), T2 (0.5x0.5x3mm), T2 Flair (1.2x0.6x0.6mm) and T2prep 3D spiral sequence (0.9x0.9x5mm, Tacq=10min). T2-prep 3D spiral sequence was optimized with the adiabatic pi/2 and refocusing RF pulses. The SPIRAL data was analyzed with our proposed post-processing algorithm, by restricting the relaxing T2 distribution to 2 Gaussian-shaped peaks corresponding to myelin water and intra/extra-cellular water. After WM segmentation with FreeSurfer on T1-weighted images, we co-registered all four images (Fig.1) on to patient's native T1 space which was conformed to 1mm isotropic during FreeSurfer process. T2 Flair image was bias-corrected and segmented into three distinct tissue types (WM, grey matter and others) with FSL tool [5, 6], and masked with FreeSurfer WM mask to create the automated lesion mask. The lesion mask was quality checked by overlaying T2 and T2 Flair images and manually edited. Unpaired t-test was performed to compare total WM MWF means to total lesion means as well as for the ROI analysis of selected lesion (L-MWF) compared to mirrored WM MWF (M_MWF) regions. Mirrored regions of WM were chosen to decrease the chance of normal anatomical variation within WM regions (Fig.2).

Results: We successfully merged four different images accurately to provide a framework for WM and lesion MWF comparison. Voxel-based comparative histogram analysis of whole brain WM MWF and lesions of the 8 patients is shown in Fig.3 and reveals a shift to lower MWF measurements in lesions. The mean whole-brain WM MWF (0.18 ± 0.02) among all patients was significantly higher compared to lesion MWF (0.12 ± 0.02), $p<0.00003$. Similarly, for the mirrored ROI analysis (Table), total mean M-MWF (0.18± 0.03) was significantly higher compared to L-MWF (0.14 ± 0.03), $p<0.018$.

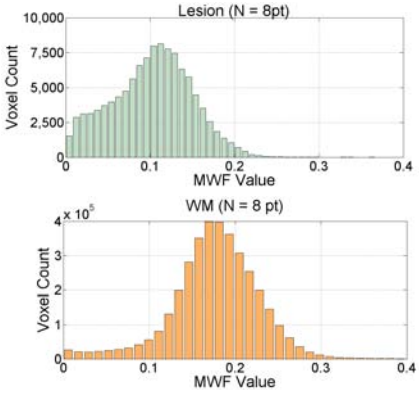

Fig. 3: histograms of total lesion and wm MWF values.

#	L-MWF	M-MWF
1	0.08± 0.02	0.16 ± 0.01
2	0.14 ± 0.025	0.18 ± 0.03
3	0.11 ± 0.02	0.15 ± 0.01
4	0.16 ± 0.02	0.24 ± 0.01
5	0.14 ± 0.01	0.15 ± 0.01
6	0.17 ± 0.05	0.22 ± 0.04
7	0.16 ± 0.03	0.18 ± 0.02
8	0.13 ± 0.03	0.18 ± 0.02

Table: Mean and SD of L-MWF and M-MWF for each ROI.

Discussion: Through this technique, we are able to integrate lesion and MWF maps for the efficient comparison of WM and lesion MWF. This statistical analysis shows that our acquisition and post-processing methodology can distinguish normal appearing WM from lesion. The directive comparative analysis of lesions vs. mirrored WM suggests that true pathological differences exist controlling for anatomical variability.

Conclusion: Given the ability to analyze a whole-brain MWF with accurate segmentation and detect lesion MWF changes with relatively low variability, this methodology can be applied to longitudinal studies to detect remyelination.

References: [1] Nguyen *et al*. (2012) *Magn Reson Med* **67** :614. [2] Nguyen *et al*. *Proc ISMRM* 2012:749 [3] Dale *et al*. (1999) *NeuroImage* **9**:179. [4] Fischl *et al*. (1999) *NeuroImage* **9**:195. [5] Zhang *et al*. (2001) *IEEE Trans Med Imag* **20**:45. [6] Jenkinson *et al*. (2002) *NeuroImage* **17**:825.

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