Describing the distribution of myelin water fraction change among early stage MS lesions

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Target audience: Researchers and clinicians interested in multiple sclerosis (MS)

PURPOSE Studies have demonstrated that remyelination can occur in multiple sclerosis patients, but the exact timing and duration of this reparative process is unclear (1,2). Acute MS lesions provide the opportunity to study lesion dynamics, as new lesions have been shown to have areas of demyelination, edema, and remyelination (3, 4). T2 relaxometry is a MRI technique in which the contribution of water associated with myelin can be represented as myelin water fraction (MWF) (5,6). An advantage of using T2 relaxometry for the study of new MS plaques is that the resultant intracellular/extracellular (IC/EC) peak, derived from the T2 spectrum, has been demonstrated to shift in the development and resolution of edema (7,8). Our group has optimized a 3D T2prep GRE sequence or FAST_T2 (9) and a novel post-processing approach to deriving myelin maps from T2 data (10). In this study we aimed to investigate how FAST-T2 can be utilized to describe early lesion dynamics in a large cohort of new enhancing and new non-enhancing MS lesions.

METHODS **Patient Population.** All patients in our ongoing MRI database who were identified as having longitudinal MWF scans with either enhancing lesions (EL) or new T2 non-enhancing lesions (NNEL) on baseline scans were included in our analysis. Clinical data collected included gender, age, disease duration (DD), Expanded Disability Status Score (EDSS), disease subtype, steroid use, and change in medication at the time of lesion development. **MRI data acquisition.** 3T GE scanner (HDxt 16.0) using 8-channel phased-array coil: T1-weighted sagittal 3D-BRAVO (1.2x1.2x1.2mm) with and without gadolinium enhancement, T2 (0.5x0.5x3mm), T2-FLAIR (1.2x0.6x0.6mm) and FAST-T2 (1x1x5mm). **MRI Post Processing.** FAST-T2 data was analyzed with our Multi-Gaussian post processing algorithm (10). Subject's T1 weighted images where automatically processed using FreeSurfer's longitudinal stream (11). T2 FLAIR, T2 weighted, and T1-contrast images were linearly aligned onto the T1 FreeSurfer volume. Specific lesion ROIs were manually defined by a trained neurologist based on FLAIR and T1-contrast images of the baseline time point. MWF maps were registered onto the T1 FreeSurfer volume using a boundary based registration method (12). **Statistics.** Change in myelin water fraction was calculated as average MWF at follow-up (MWF2) subtracted by average MWF at baseline (MWF1). The average change in the second moment of the IC/EC curve was used as a method of detecting subtle shifts in the T2 spectrum (12). A random effects model with the variable of interest indicated as MWF change was implemented and accounts for patient variability (random effect). Given the distinct differences in MWF change noted between EL and NNEL in the univariate analysis, lesions were dichotomized based on enhancement and treated as fixed effect groups with different variances (heteroscedastic model). Other fixed effects considered for the model included change in second moment of the IC/EC peak, and clinical variables listed above. A back-fitting procedure was used to determine the best model.

RESULTS 63 lesions (38 EL and 25 NNEL) were identified in 24 patients. MWF change, second moment change of the IC/EC peak, lesion size, and lesion age were significantly different in EL versus NEL ($p<.001$, Table 1). The best random effects model ($p<0.05$) calculated a coefficient of reliability (CR) for EL and NEL. The only fixed variable which remained in the model was lesion size ($p<0.03$). The distribution described by the model predicted that 95% of non-enhancing lesions would have a myelin water fraction change within the range of [-0.01 - 0.084] while non-enhancing lesions were would be a smaller range of [-0.021 - 0.030].

DISCUSSION Our study demonstrated the feasibility of FAST-T2 to study MWF within MS lesions. Furthermore, we exploited the T2 spectrum and utilized a novel approach to measure resolving edema (12) within new MS lesions. Our results demonstrate different patterns of MWF change within varying stages of MS lesions (EL and NNEL). EL showed a greater and more variable change in both MWF and second moment of the IC/EC peak. This implies that remyelination occurs within the earliest stages after initial lesion development, however, accurate assessment of this MWF change is challenged by the extent of edema resolution. Significantly less edema shift was appreciated in the slightly older lesions, yet MWF change was still detectable. Importantly, this work demonstrates the utility of MWF to study myelin dynamics in new MS lesions. Next steps are aimed at deriving an accurate assessment MWF change in new lesions while controlling for resolving edema.

REFERENCES 1. Patrikios et al. Brain. 2006;129:3165-72. 2. Patani et al. Neuropathol Appl Neurobiol. 2007;33(3):277-87. 3. Prineas et al. Ann Neurol 1993;33:137-151. 4. Barnett et al. Ann Neurol 2004;55:458-468. 5. MacKay et al. MRM 1994;31:674. 6. Deoni et al. MRM 2008; 60:1372. 7. Stanisz et al. Magn Reson Med 2004;51:473-479. 8. Webb et al. Magn Reson Med 2003;49:638-645. 9. Nguyen et al. MRM 2012;67:614 10. Raj A et al. PLoS One 2014 Jun 4;9(6). 11. Reuter et al. Neuroimage 2012;61(4), 1402-1418. 12. Greve et al. Neuroimage 2009;48:63-72.12 Pandya et al. ISMRM 2015 abstract ID: 6396.

Table 1: Patient Demographics and Lesion Statistics

Patient Demographics (n=24)	
Age, mean years (±SD)	32 (7.9)
Female gender, n (%)	16 (66.7)
Disease duration, mean years (±SD)	5.3 (5.1)
EDSS, mean (±SD)	1.5 (1.3)
Patients with RRMS, n (%)	20 (83.3)
Patients with multiple lesions, n (%)	12 (50)
Gd (+) T1 lesions, n (%)	38 (60.3)
Age, mean months (min-max)	1 (1-1)
Interval Follow up, mean months (min-max)	6.3 (3-12)
Size, mean voxels (±SD)	2164 (4408)
Myelin change, mean (±SD)	.0347 (.028)
Second Moment change, mean (±SD)	-1430 (1294)
Gd (-) T1 lesions, n (%)	25 (39.7)
Age (mo), mean months (min-max)	5.7 (1.5-12)
Interval follow up, mean months (min-max)	5.5 (2-12)
Size, mean voxels (±SD)	190 (121)
Myelin change, mean (±SD)	.006 (.017)
Second Moment change, mean (±SD)	-107 (378)

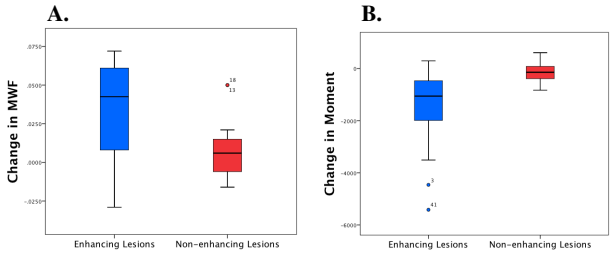

Figure 1: (A) This boxplot demonstrates the increased variance and increased magnitude of MWF change (MWF2-MWF1) appreciated in EL vs. NNEL. (B) This boxplot demonstrates the increased variance and magnitude of change for the second moment of the IC/EC curve in EL vs. NNEL

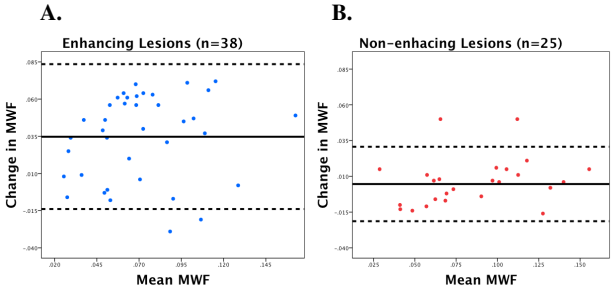

Figure 2: Plots A and B are Bland Altman difference plots using NNEL and EL average MWF values, respectively. Solid lines represent the fitted mean of the random effects model. Dotted lines indicate the 95% cofidence interval predicted by the random effects model.

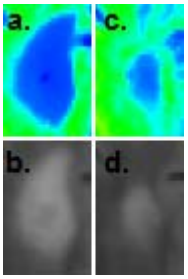

Figure 3: This is an example of an ehancing lesion that showed a large improvement in MWF (212% improvement) and a large shift in the second moment of the IC/EC peak (-19.45 %). **a**. Baseline MWF map and **b.** is its corresponding FLAIR image. **c.** and **d.** are the same lesion's MWF map and FLAIR at followup 6 months later. Partial resolution of the lesion can be appreciated on both the FLAIR and MWF images.