Clinical investigation of whole brain myelin water fraction imaging in patients with multiple sclerosis

Elizabeth Monohan[1], Sneha Pandya[2], Kyoko Fujimoto[1], Thanh D. Nguyen[2], Christopher Blackwell[1], Nancy Nealon[1], Jai S. Perumal[1], Ashish Raj[2], Tim Vartanian[1], and Susan A. Gauthier[1]

[1]Neurology and Neuroscience, Weill Cornell Medical College, New York, NY, United States, [2]Radiology, Weill Cornell Medical College, New York, NY, United States

Target Audience Researchers and clinicians interested in multiple sclerosis.

PURPOSE Multicomponent T2 relaxometry is a promising quantitative MRI technique to measure the contribution of water associated with myelin, called myelin water fraction (MWF), using T2 decay signal analysis (1,2). MWF has been shown to be a sensitive and specific biomarker of demyelination and remyelination in multiple sclerosis (MS) (3,4). A major impediment to a wider clinical acceptance has been long acquisition time and challenging MWF extraction (5). The aim of this study was to apply a fast whole brain T2 acquisition (T2prep 3D spiral) (6) and a novel post-processing algorithm (7) to a cohort of MS patients and assess its capability in demonstrating the variability in myelin content among lesions and normal appearing white matter (NAWM). The association of MWF and clinical measures was also investigated.

METHODS 141 patients with the diagnosis of MS (Table 1) had T1, T2, T2 FLAIR, and our optimized whole brain T2prep 3D spiral (24 cm FOV, 192x192x32 matrix, 15 echoes, 10 min acquisition time) images acquired at 3T (GE HDxt). The spiral data were analyzed with a robust spatially constrained non-linear multi-Gaussian T2 analysis method that can overcome the lower SNR and increased artifacts introduced by the fast spiral acquisition (7). All images were co-registered onto the subject's T1 image. T2 FLAIR images were bias-corrected and segmented into three distinct tissue types (WM, gray matter and others) with FSL and masked with FreeSurfer segmentation (8,9) to create semi-automated lesion masks.

RESULTS Our method produced high-resolution MWF maps with excellent lesion detection (Fig.1). Voxel-wise comparative analysis of NAWM and lesion MWF revealed a shift to lower MWF in lesions and demonstrated a range of MWF present within lesions. The mean NAWM MWF (0.123 ± 0.049) among all patients was significantly higher compared to lesion MWF (0.051 ± 0.036), p<0.0001. Voxel-based histogram demonstrates myelin heterogeneity within lesions (Fig.2). Lesion MWF decreased with both increasing disease duration and increasing age, whereas NAWM MWF was similar among groups (Fig.3). The association of lesion MWF with disease duration remained significant (p=0.006) after controlling for age (p<0.001), NAWM MWF (p=0.757) and T2 lesion volume (p=0.434).

DISCUSSION Through our fast acquisition method, which can cover whole brain in 10 minutes, we were able to compare whole brain NAWM and lesion MWF. The range of MWF among lesions suggests that this technique is pathologically more specific than T2W lesion detection. These results suggest that there is an association between disease duration and age with lesion myelin content. The multi-variate analysis proposes that lesion MWF, as a biomarker, is associated with the disease process. Further study is required to understand the independent influence of age and disease duration on lesion MWF. Importantly, given the ability to determine whole brain MWF, this methodology can be utilized to understand myelin dynamics in MS and applied to remyelination clinical trials.

CONCLUSION Fast whole brain myelin water mapping is feasible in routine clinical MRI of MS and can differentiate MWF changes in lesions and NAWM.

REFERENCES
1. MacKay et al. Magn Reson Med 1994; 31: 674.
2. Deoni et al. Magn Reson Med 2008; 60: 1372.
3. Laule et al. Neuroimage 2008; 40: 1575.
4. Kolind et al. Neuroimage 2012; 60: 263.
5. Kolind et al. Magn Reson Med 2009; 62: 106.
6. Nguyen et al. Mag Reson Med 2012; 67: 614.
7. Raj et al. Proc ISMRM 2013; 3617.
8. Dale et al. NeuroImage 1999; 9: 179.
9. Fischl et al. Neuroimage 1999; 9: 195.

Table 1. Patient demographics and disease characteristics.

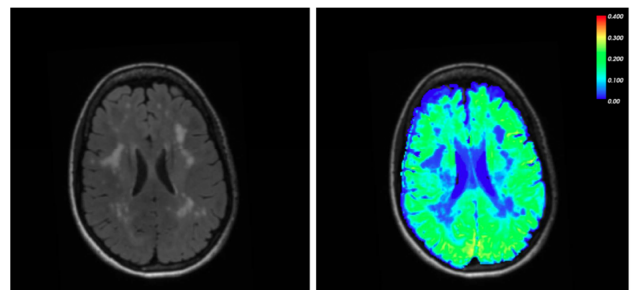| Characteristics	Values
Patients, n (%)	141
Males	48 (34)
Females	93 (66)
Age, mean ± SD (range)	42 ± 11 (24-73)
Diagnosis, n, (%)	
CIS	9 (6.4)
RRMS	123 (87.2)
PPMS	2 (1.4)
SPMS	7 (5.0)
Disease Duration, mean ± SD (range)	8.5 yrs ± 8.0 (0-40)
EDSS, mean ± SD (range)	1.6 ± 1.7 (0-6.5)
Treatment duration, mean ± SD (range)	4.5 yrs ± 4.5 (0-17)

Figure 1. Example of T2 FLAIR image and corresponding MWF map, demonstrating excellent lesion detection.
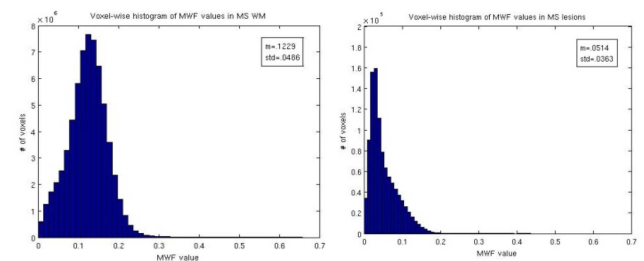

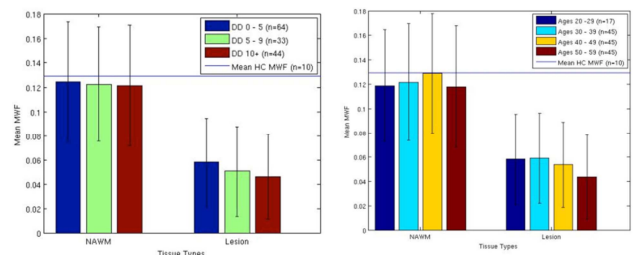**Figure 2**. Voxel-wise MWF histogram in NAWM and lesions.

Figure 3. NAWM and lesion MWF based on disease duration & age.