Quantification of normal-appearing white matter in Multiple Sclerosis (MS) by quantitative susceptibility mapping (QSM)

Weiwei Chen[1], Yan Zhang[1], Wenzhen Zhu[1], Ketao Mu[1], Chu Pan[1], Susan A. Gauthier[2], and Yi Wang[3]

[1]*Radiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science& Technology, Wuhan, Hubei, China,* [2]*Neurology, Weill Cornell Medical College, New York, United States,* [3]*Radiology, Weill Cornell Medical College, New York, United States*

Target Audience: Anyone interested in multiple sclerosis (MS)

Purpose: Normal appearing white matter (NAWM) in MS patients is reported to have subtle and diffuse abnormality pathologically, which may partly explains why MRI lesion burden correlates only moderately with disability. Recently, the susceptibility of MS lesions that is associated with iron deposition and demyelination is reported to be a new biomarker for revealing MS pathogenesis. However, whether the susceptibility of NAWM changes with the variation of MS lesions' susceptibilities is still unclear. Quantitative susceptibility mapping (QSM) is a novel MR technique for quantifying the tissue susceptibility. Therefore, we aim to quantify the susceptibility of NAWM by QSM to study its correlation with MS lesions' susceptibility variation and clinical features in MS patients.

Methods: A total of 70 consecutive clinical confirmed relapsing-remitting MS patients (23M/47F, 40.6 ± 10.6yrs, EDSS: 0 - 6 (median: 2); disease duration 0 - 43 (8.47 ± 8.94) yrs) and 26 age and gender matched healthy controls (HCs) (9M/15F, 21 - 59 (39.0 ± 11.42) yrs) were selected in this study. Both MS patients and HCs underwent QSM and a standard MRI (T2w, T2FLAIR, T1w, T1w+Gd). All MR images were co-registered for each patient. White matter regions without an abnormal signal on standard MRI were assumed to be NAWM for MS patients and normal white matter (NWM) for HCs. Hyperintense lesions on T2w images were assumed to be MS lesions. On T2w images, MS lesions were segmented and ROIs of NAWM/NWM and CSF were drawn in bilateral frontal and parietal white matter, in the genu and splenium of the corpus callosum, and in the body of lateral ventricle manually by two neuroradiologists (figure 1). The ROIs were overlaid onto QSM and the susceptibility values of MS lesions and NAWM/NWM were calculated using the subject's CSF susceptibility as the zero reference. The mean value of MS lesions and NAWM/NWM susceptibilities were calculated for each patient. The significance of difference in NAWM/NWM susceptibility was assessed by t-test and One-Way ANOVA with Bonferroni adjustment. The correlation between NAWM and MS lesions susceptibility was assessed by Pearson test.

Results: A total of 511 NAWM ROIs were drawn in 70 MS patients (excluding 49 regions contaminated by MS lesions) and 208 NWM ROIs in 26 HCs. Of 70 MS patients, 15 (21.4%) patients had one or more Gd-enhanced (Gd+) MS lesions, the remaining 55 (78.6%) had no Gadolium-enhanced MS lesion. The NAWM of MS patients showed significantly higher susceptibility than NWM of HCs (-19.96 ± 8.29ppb vs. -28.56 ± 5.44ppb, p<0.001). Sorting patients into 2 groups with and without Gd-enhanced lesions (Gd+ and Gd-), the NAWM of Gd+ patients showed a similar susceptibility to NWM of HCs (-25.97 ± 6.19ppb vs. -28.56 ± 5.44ppb, p=0.802), and the NAWM of Gd- patients showed significantly higher susceptibility than NWM of HCs (-18.29 ± 8.06ppb vs. -28.56 ± 5.44ppb, p<0.001) and the NAWM of Gd+ patients (-18.29 ± 8.06ppb vs. -25.97 ± 6.19ppb, p=0.001) (figure 2). The susceptibility of NAWM was positively correlated with the increase of MS lesions' susceptibilities (Pearson correlation: 0.439, P<0.001, figure 3).

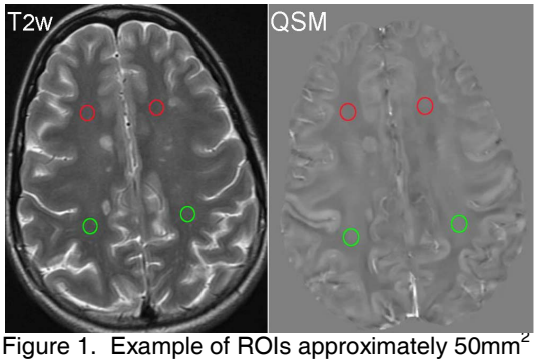

Figure 1. Example of ROIs approximately 50mm^2 placed over the NAWM in bilateral frontal (red circles) and parietal (green circles) white matter on T2-weighted and QSM images.

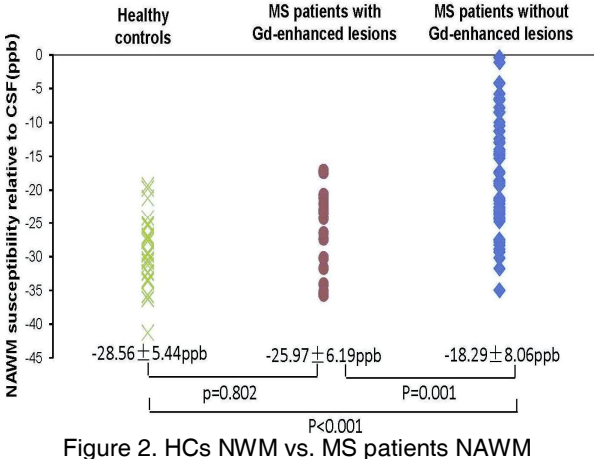

Figure 2. HCs NWM vs. MS patients NAWM

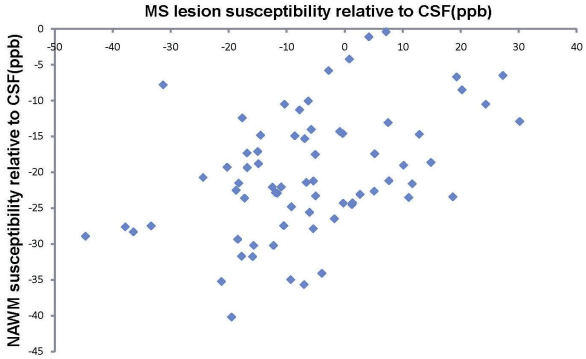

Figure 3. NAWM susceptibility is positively correlated with MS lesions susceptibilities.

Discussion and Conclusions: The susceptibility of NAWM increases only in inactive inflammation stage (patient without Gd-enhanced lesions), not in active inflammation stage (patient with Gd-enhanced lesions). The susceptibility of NAWM is positively correlated with the increase of MS lesions' susceptibilities. Our findings suggest that the susceptibility of NAWM in MS had a correlation with inflammation status, possibly reflecting the underlying iron redistribution or iron-load macrophage/microglia migration and diffuse demyelination in NAWM. The underlying pathogenic cause for the identified susceptibility change of NAWM in MS patients invites further investigation including comparing with pathological and longitudinal study.