Quantitative Susceptibility Mapping in Multiple Sclerosis

Ying Wu[1,2], Huan Tan[1], Ryan Hutten[1], Tian Liu[3], Hongyan Du[1,4], Hector Ferral[1,2], Matthew Walker[1,2], Joel Meyer[1,2], Yi Wang[3], and Robert R. Edelman[1,5]

[1]Department of Radiology, NorthShore University HealthSystem, Evanston, IL, United States, [2]Department of Radiology, The University of Chicago Pritzker School of Medicine, Chicago, IL, United States, [3]Weill Cornell Medical College, New York, New York, United States, [4]Center for Clinical and Research Informatics (CCRI), NorthShore University HealthSystem, Evanston, IL, United States, [5]Department of Radiology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States

INTRODUCTION: Multiple Sclerosis (**MS**) affects approximately 1 out of 1000 people in the United States. Patients suffer from a variety of neurologic symptoms including visual deficits, gait impairment, and muscle weakness leading to disabilities. The pathological hallmark of MS is the presence of demyelinating/inflammatory lesions in the brain and spinal cord. The appearance of lesions is best demonstrated in the living patient by magnetic resonance imaging (**MRI**). Conventional MR T2 hyperintense lesion number or lesion volume have not yielded satisfactory correlations and cannot adequately inform clinical diagnosis and decisions. The lack of pathological specificity of T2 hyperintense lesions ranging from edema, mild demyelination, and scar-like myelin gliosis may be responsible for the weak associations. Limited research has been done regarding the iron accumulation of the MS brain. Reports of both MR and histopathology have shown increased iron deposition, particularly in vessel walls of the veins in MS[1,2] and in basal ganglia areas[3,4,5,6]. Whether the study of iron property can afford more specific characterization of MS brain, function and treatment need to be further investigated. A new technique, quantitative susceptibility mapping (**QSM**), allows quantitative evaluations of iron deposition in the brain. A unique attribute of QSM is the ability of discriminating calcium induced susceptibility, thus it is more intrinsic to iron susceptibility. We performed QSM in patients with MS to characterize lesion burden and demonstrate the potential of QSM as a quantitative imaging marker for monitoring disease progression and/or responses to treatment.

METHODS AND MATERIALS: 3 MS patients (1 Male, 2 Females; mean age: 52.8 ± 6.0) and 2 normal control subjects (1 Male, 1 Female; mean age: 73 ± 1.8) were scanned at a 3 Tesla Siemens system (Siemens Verio, Germany). ***Image Acquisition:*** 1) For QSM: 3D multi-echo T2*-weighted spoiled gradient echo sequence (TR/TE {min, max} / FA =55 ms/ {3.6, 45} ms/ 15 ^{0}); Image resolution= 0.9x0.9x1.5 mm^3; Bandwidth = 240 Hz/Pixel; scan time= 7:40. 2) FLAIR: 2D FSE (TR/TE/TI/FA=9000ms/96ms/2500/150°/46, resolution=0.9 x 0.9 x 2 mm^3) scan time=4:14. 3) Pre- and post-contrast T1 weighted: High resolution none-selective SPGR T1-weighted image[7], scanning parameters (TR/TE/FA/slices=7.1ms/3.1ms/12°/512, resolution=1.0 x 1.0 x 0.4 mm^3) scan time=5:28. QSM images were reconstructed using a morphology-enabled dipole inversion (MEDI) algorithm offline[8]. Images including QSM and SWI were sent to the PACS system where two neuroradiologists reviewed the images independently. ***Quantitative Measurements:*** 1) Autoregional quantification was conducted[9,10]. QSM were coregistered to the T1 structural image. Automated segmentation was performed on structural scan using FreeSurfer[11] for masking 3D volume of interests (VOIs) and used to extract mean regional susceptibility values. The VOIs used in this study include: MS lesions, corpus callosum (**CC**), caudate, putamen, and lateral ventricles. To compare with previous reported normal brain data, regions of interest were manually outlined[8]. Summary statistics mean and standard deviation were reported.

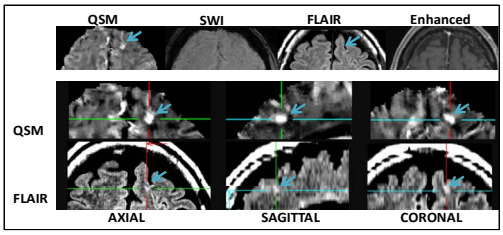

Fig. 1: One cortical MS lesion (blue arrows) shown on QSM and FLAIR, not visible on SWI and enhanced MR. The 3-plain view indicates superior conspicuity of QSM compared with FLAIR.

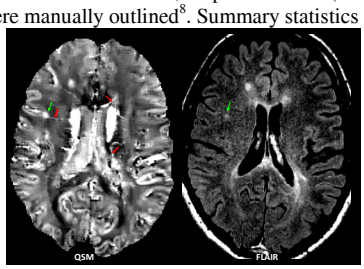

Fig. 2: One gray and white junction MS lesion (green arrows) shown on QSM and faintly on FLAIR. In addition, QSM is able to show lesion-vein connections (red arrows)

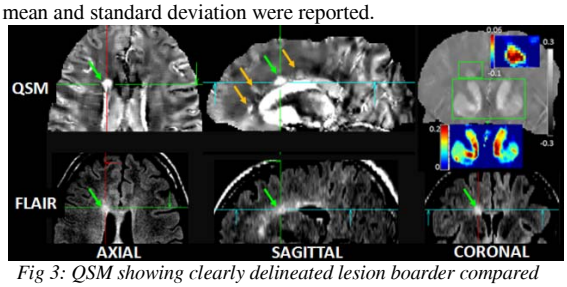

Fig 3: QSM showing clearly delineated lesion boarder compared with faint lesion shown on FLAIR, both on original axial and the reformatted sagittal views(green arrows) with additional lesions visible on the sagittal QSM (orange arrows). The susceptibility distribution with the lesion and basal ganglia are displayed on right.

Table 1: Regional Susceptibility of MS vs. Normal (Mean and SD)

Autoregional	Caudate	Globus Pallidus	Putamen	CC	CSF
Patients	0.086 ± 0.037	0.126 ± 0.125	0.097 ± 0.121	-0.014 ± 0.023	0.009 ± 0.007
Normal	0.039 ± 0.035	0.074 ± 0.047	0.032 ± 0.012	-0.016 ± 0.017	0.004 ± 0.018

Table 2. Regional of of MS VS. Normal (Mean and SD)

Manual	Caudate	Globus Pillidus	Putamen
Patients	0.123±0.036	0.214±0.037	0.150±0.054
Literature	0.089± 0.019	0.187±0.018	0.082±0.022

RESULTS: MS lesions appeared hyperintense on QSM. There were total of 49 lesions on QSM and 39 on FLAIR, 30 T1 lesions and 9 lesions visible on SWI, with QSM identifying the most and SWI identifying the least amount of lesions. In general, QSM showed more (25%) focal lesions than FLAIR with more distinctly delineated borders. In addition, QSM was able to show lesions near gray and white matter junctions that were missed or faintly shown by FLAIR (Fig. 1 and 2). On QSM, perivenularr lesions were observable with connection with veins (Fig. 2). The reformed Sagittal view based on this 3D QSM data, displayed additional lesions especially for the periventricular lesions above the ceiling of lateral ventricles (Fig. 3, orange arrows). There was no contrast enhanced lesions. Autoregional quantification: Susceptibility in MS lesions was increased by 200% fold compared to CC normal white matter regions. In basal ganglia regions, susceptibility of various structures increased between 70% - 200% fold with putamen altered the most. In normal white matter region CC, compared to the controls, there was also a 10% increase. Susceptibility was 100% higher in the CSF of patients compared to the normal. Quantification of basal ganglia (see table 2) was compared to previous report in healthy volunteers[8]. Susceptibility was increased between 20%-80% higher in MS patients using manually derived measurements on single 2D representative slice.

DISCUSSION: The findings of this small sample of MS patients demonstrated potential of QSM for both clinical practice and quantification. QSM identified more lesions than FLAIR, the current clinical gold-standard used to detect MS lesions. Previous reports of iron accumulation in MS lesions[1], normal appearing white matter[10] and basal ganglia[4] support our QSM findings. Interesting parallel to findings of elevated iron and iron-related proteins in CSF and blood[12], the susceptibility of the MS patients was increased about 100% in CSF. QSM has the ability to exclude calcium related contamination which the previous quantitative efforts, SWI, T2* and R2* lack.[13] QSM may be a very sensitive measure that is capable of detecting subtle iron accumulation (i.e. within MS lesion and CSF). In contrast, SWI seems to have limited value in MS lesion identification as well as being incapable of providing quantitative measure. The pathophysiology basis of QSM of MS lesion and the iron involvement of MS etiology are not clear. One theory may include the iron rich demyelinated debris responsible for the increased susceptibility reflected in this study[14]. In this investigation, QSM exhibited additional value identifying lesions in problematic areas such as the cortex and gray white junctions. The ability to identify MS lesions in these areas may be critical for patient management as these functional locations may have higher association with disability. Further studies with larger sample sizes are necessary to further confirm our findings. As the contrast of QSM is independent of field strength[15,16], it has the potential to be used across MR systems for multi-center trials. Compared to traditional manual two dimensional ROI analysis, this investigation further addresses the measurement consistency through improved automation and comprehensive estimation of disease burden including three dimensional lesion, basal ganglia, white matter and CSF assessment that may be critical for monitoring disease progression[9,10].

REFERENCES: [1] Craelius, W. et al. Archives of Pathology and Laboratory Medicine, 1982 [2]Zamboni P et al., J R Soc Med 2006}, [3] Bakshi R. et al. Arch Neurol 2001 [4]Drayer B et al. American Journal of Roentgenology, 1987 [5]Haacke M et al. JMRI, 2009 [6]Stankiewicz, J. et al. Neurotherapeutics, 2007 [7]Edelman RR et al., Invest Radiol. 2009 [8]Liu et al., Magn Reson Med, 2011 [9]Wu et al., JMRI 2010 [10]Wu et al., JMRI 2012 [11]Fischl, B. et al., Neuron 2002 [12]Petzold A et al., Brain, 2002 [13]Schweser et. al., Med Phys, 2010 [14]Fu L et al., Brain 1998 [15]De Rochefort L et al., MRM 2008 [16] Schweser F. et al., NeuroImage, 2011 [14]Tozer DJ et al., MRM 2005