Contributions to Susceptibility From Iron and Demyelination in Multiple Sclerosis Lesions

Cynthia Wisnieff[1,2], Sriram Ramanan[3], David Pitt[3], John Olesik[4], and Yi Wang[1,2]

[1]*Biomedical Engineering, Cornell University, Ithaca, New York, United States,* [2]*Radiology, Weill Cornell Medical College, New York, New York, United States,* [3]*Neurology, Yale University, New Haven, Connecticut, United States,* [4]*Ohio State University, Ohio, United States*

Target Audience: Those interested in a histological investigation of tissue content with quantitative susceptibility mapping

Introduction: Both iron deposition and demyelination in multiple sclerosis (MS) lesions can cause susceptibility changes that can be detected in T2* weighted MRI [1-3], but their relative contributions are unclear. Quantitative susceptibility mapping (QSM) can measure the magnetic susceptibility changes in MS lesions[4]. Laser Ablation Inductively Coupled Plasma Mass Spectrometry (LA-ICP-MS) [5] provides highly sensitive elemental analysis. Myelin basic protein (MBP) labeling detects the presence of myelin. Here we perform QSM, LA-ICP-MS and MBP labeling to assess major susceptibility contributions from iron and demyelination in white matter (WM) MS lesions.

Methods: *MRI acquisition:* A total of 7 formalin fixed MS brain specimens were imbedded in 1% agar. 16 unique GRE orientations evenly distributed over a sphere on a GE 3T MR750, acquired in oblique planes to reduce registration and acquisition time with similar imaging parameters TR/TE spacing/#Echoes: 53.8ms/ 4.15ms/12 echoes at a resolution of 0.75x0.75x0.8mm^3.*Histology and LA-ICP-MS* – LA-ICP-MS data generated an iron concentration [Fe] map (in ug/mL) with 106x250x50um^3 resolution over 2, 50um sections. A 50um section was used for MBP labeling. *Image Analysis:* QSM was generated with COSMOS[6]. Linear registration of orientations was performed with FLIRT [7, 8]. 2D [Fe] maps and histological slices were manually aligned to form a 3D volume. A non-rigid affine registration of the histology and QSM images was calculated from corresponding fiducial markers placed in the imaged volumes within and around the lesion. [Fe] maps were converted to susceptibility through an estimation of the molar susceptibility of iron at room temperature, with effective number of Bohr magnetons (3.78)[9] and a brain tissue density of 1.04g/cm^3[10]; yielding a susceptibility contribution of 1.4ppb*[Fe], where Fe is in ug/mL. The residual susceptibility map (RSM) was calculated as RSM = QSM – 1.4*[Fe].

Results: [Fe] iron contribution map, Fig. 1c, shows the interior of the lesion with similar heterogeneous appearance to the QSM, Fig. 1b. The RSM Fig.1d shows slightly paramagnetic susceptibility, and the MBP slide Fig.1e shows a substantial loss of MBP primarily in the interior of the lesion. Fig. 1f and g show significant changes in the local field of the lesion and surrounding WM in both strength and sign. Adjacent normal appearing WM showed a diamagnetic susceptibility of -31±3 ppb. The lesion interior showed total susceptibility 29±7.5ppb on QSM (Fig.1b), with 27±7.5ppb contribution from [Fe] (Fig.1c) and RSM 2.4±7.5ppb (Fig.1, d) possibly related to demyelination (Fig.1e). Other white matter lesions showed total susceptibility ranging between -2 to 9ppb.

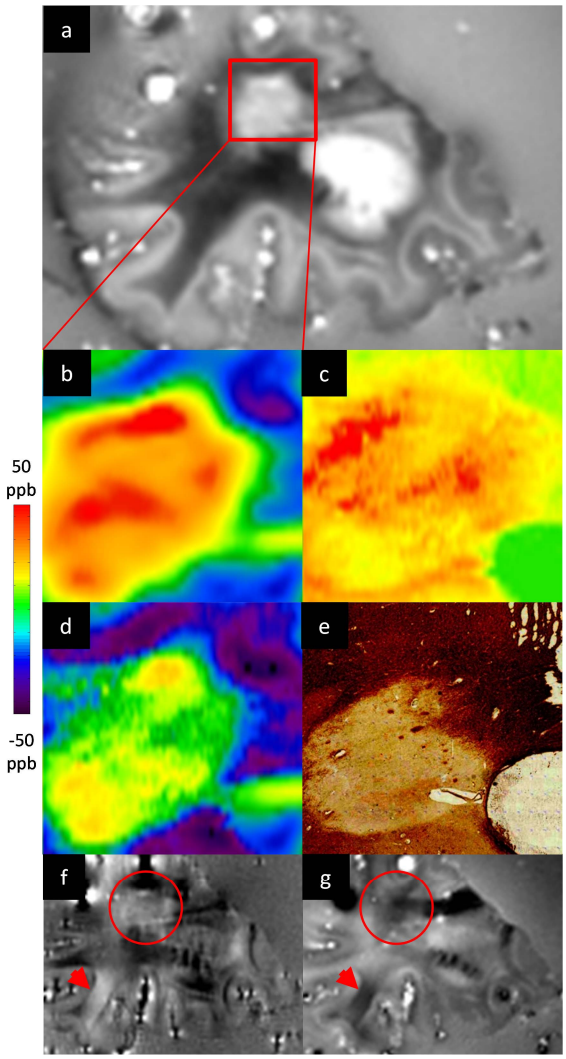

Figure 1: a) The QSM of the whole specimen (window ±50ppb), b) the QSM of the slice registered to the lesion, c) the susceptibility contribution from the [Fe] map, d) RSM, e) MBP labeled slide. f) and g) show the local phase images from two orientations (window: ±5Hz), the circle shows the location of the lesion and the arrow points to white matter.

Discussion and Conclusion: QSM and LA-ICP-MS demonstrated that both iron and demyelination contribute to susceptibility changes in this MS lesion. The residual susceptibility in the interior of the lesion is close to the susceptibility of agar in the QSM (1±7ppb) indicating that the relative change from normal appearing white matter from (-31ppb) is likely related to demyelination. This can be explained by the fact that iron is highly paramagnetic while myelin is weakly diamagnetic (or demyelination also causes an increase in susceptibility). The amount of demyelination was not quantified. Qualitatively the MBP labeling detected substantial demyelination within the lesion. Since there are few other significant susceptibility sources in WM, the paramagnetic residual susceptibility is attributed to demyelination. The phase images (Fig.1 f and g) demonstrate the problem of differentiating the susceptibility sources from the field shifts with QSM, where the measured field is highly dependent on the orientation of the applied field direction relative to the tissue making direct correlation of phase and the presence of iron difficult. Histological sections are from different physical locations in the lesion (within 1mm) and require nonrigid registration to the MR images, making it difficult to achieve a precise 1-to-1 correspondence among QSM, LA-ICP-MS and MBP.

References1. Hametner, S., et al., Ann Neurol, 2013.2. Pitt, D., et al., Arch Neurol, 2010. 67(7): p. 812-8.3. Mehta, V., et al., PLoS One, 2013. 8(3): p. e57573.4. Chen, W., et al. in ISMRM. 2013 Salt Lake City, USA.5. Becker, J., International Journal of Mass Spectrometry, 2010. 289(2-3): p. 65-75.6. Liu, T., et al., Magnetic Resonance in Medicine, 2009. 61: p. 196-204.7. Jenkinson, M. and S. Smith, Med Image Anal, 2001. 5(2): p. 143-56.8. Jenkinson, M., et al., Neuroimage, 2002. 17(2): p. 825-41.9. Schenk, J.F., Annals New York Academy of Sciences, 1992. 649: p. 285-301.10. Barber, T.W., et. Al., Acta Neurol Scand, 1970. 46(1): p. 85-92.