Probe Microstructure and Improve Contrast of Myelinated Axons Using Gd-Enhanced Susceptibility Mapping

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Purpose: Quantitative susceptibility mapping (QSM) produces MRI contrast that directly reflects the magnetic properties of tissue structures. For instance, loss of diamagnetic myelin in the central nervous system can be visualized using QSM[1]. Magnetic susceptibility contrast and SNR are greatly improved by the use of paramagnetic contrast agents at high field. Characterizing the dependence of apparent magnetic susceptibility on contrast agent and field strength aids in the effective use, comparability, and consistency of QSM to quantify myelination using MR histology. Compartmental uptake of these contrast agents may further allow us to probe the microstructure of white matter.

Methods: Six C57BL/6 mice were perfused[2] first with a mixture of 0.9% saline and one of six different concentrations of ProHance (Bracco Diagnostics, Princeton, NJ), and then formalin-fixed with 10% buffered formalin (Buffered Formalde-Fresh; Fisher Scientific). Skulls were removed from the body with the brain intact. Data for each brain specimen were acquired using a multi-gradient-echo sequence (TE_1/TE_{10} = 5.0/31.1ms, TR/FA/BW = 500ms/90°/62.5kHz, 86μm isotropic resolution) at field strengths of 2, 7, and 9.4 T. Four excitations were acquired at 2T to achieve adequate SNR. R_2* maps were calculated for each data set using the multi-echo signal information. The signal phase data underwent unwrapping, background phase removal[3], and a deconvolution operation[4] to invert the frequency map and calculate the magnetic susceptibility. The susceptibility maps were then normalized by the applied field. Note that the frequency offset and magnetic susceptibility are referenced to the carrier frequency of the excitation RF pulses set during the pre-scan—making both values relative measures. The adjacent cortical gray matter was used as an internal reference to allow for useful comparisons to be made between datasets. Three-dimensional region of interest (ROI) labels from the Waxholm Space (WHS) mouse brain atlas[5] were linearly registered to each data set, and then manually corrected using magnitude images and susceptibility maps. The labels were then registered to the image volumes to prevent interpolation of the original data from each specimen.

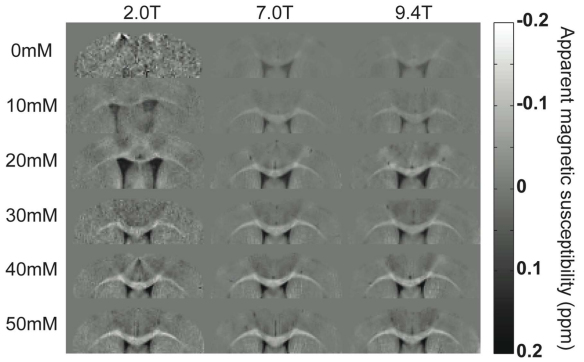

Fig. 1 Field-normalized susceptibility maps show the corpus callosum of mouse brain specimens perfused with six concentrations of Gd and scanned at three field strengths.

Results: Field-normalized susceptibility maps in Fig. 1 show the corpus callosum six Gd-perfused specimens scanned at each field strength. Despite substantial differences in SNR, there is very little difference in contrast among each set of three susceptibility maps for specimens perfused with the same Gd concentration. For each dataset, Fig. 2 charts the mean susceptibility of the ROIs representing the corpus callosum white matter (WM), ventricles (VE), and cortical gray matter reference (GM). Two other white matter regions and one other gray matter region (not shown) were also analyzed and yielded similar results as those shown. Fig. 3 is a plot of the mean relaxivity, R_2*, for each specimen at 7T. Linear trends were fitted to both the susceptibility and relaxation data using SNR-weighted least-squares regression.

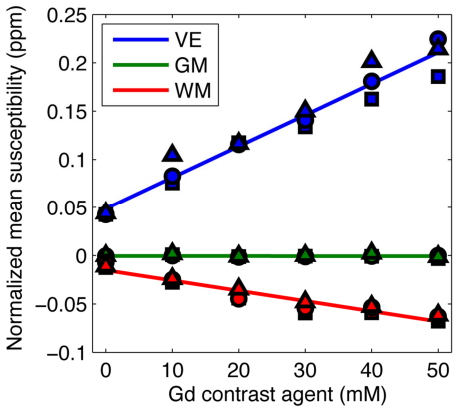

Fig. 2 Dependence of field-normalized susceptibility on Gd concentration at 2T (squares), 7T (circles) and 9.4T (triangles). The regions depicted are corpus callosum white matter (WM), ventricles (VE), and cortical gray matter reference (GM).

Discussion: WM-GM contrast is enhanced by the presence of Gd. As the Gd concentration increases, the *absolute* susceptibility of the GM is expected to increase linearly, as demonstrated by the linear increase in relaxivity (Fig. 3), though the *apparent* susceptibility remains unchanged at approximately zero ppm (Fig. 2). This is due to the carrier frequency of the RF fluctuating according to the resonance frequency of the specimen—thus GM is used as an internal reference in each scan. All WM regions in this study appear relatively more diamagnetic as the concentration of Gd increases, since the rate of susceptibility increase is smaller in WM than GM. A possible explanation for this rate difference is that Gd penetrates GM regions more extensively than WM regions. However, the data weaken this claim by showing that relaxivity increases substantially more in WM than in GM (Fig. 3). Alternatively, we propose that the root cause of the increased WM-GM contrast is found in the complex WM tissue structure. The three-pool model of white matter suggests that WM signal contributions arise from multiple, distinct water pools: a myelin pool, an extracellular "mixed" pool, and a myelinated axon pool[6]. The signal contribution from the myelin water pool quickly diminishes due to the high relaxivity of the diamagnetic myelin sheath. Likewise, in specimens perfused with Gd, R_2* increases significantly in the mixed water pool where Gd collects. The axon water pool, however, does not experience increased relaxivity because the myelin sheath acts as a diffusion-restricting barrier—preventing Gd from entering the axon. Thus, the overall relaxation of the WM tissue region increases, but the signal contribution from the more susceptibility-neutral axon water pool dominates because of its much lower relaxivity. Conversely, a paramagnetic signal contribution is most dominant in GM. As a result of homogeneous dispersion of Gd in GM, there is less likely to be a water pool with both low relaxivity and relatively neutral magnetic susceptibility, as seen in the WM axons.

Conclusion: Field-normalized magnetic susceptibility maps of the adult mouse brain verify that the susceptibility-field strength relationship is linear. Furthermore, Gd contrast agent has a linear effect on improving the susceptibility contrast between white and gray matter, likely due to the decaying signal contributions of a complex white matter water pool structure. Additional work is under way to characterize the time-dependent effects of WM structure on quantitative susceptibility mapping.

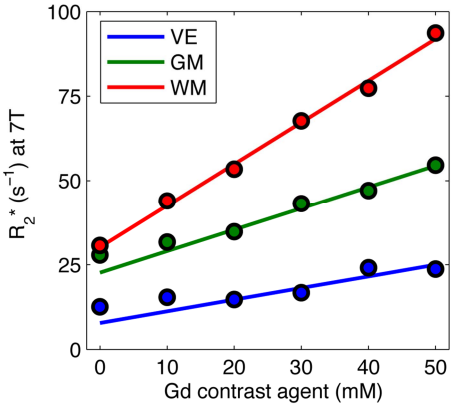

Fig. 3 Linear dependence of R_2* on Gd concentration in three brain regions at 7T.

References: [1] Liu C, et al. *NeuroImage.* 2011; 56(3):930-8. [2] Johnson GA, et al. *Radiology.* 2002; 222(3):789-793 [3] Schweser F, et al. *NeuroImage.* 2010; 54(4):2789-807. [4] Li W, et al. *NeuroImage.* 2011; 55(4):1645-56. [5] Johnson GA, et al. *NeuroImage.* 2010; 53(2):365-372. [6] Lancaster JL, et al. *J Magn Reson Imaging.* 2003; 17(1):1-10.

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