In vivo Quantitative Susceptibility Mapping of the Mouse Brain at 9.4T: A new contrast mechanism to investigate genetic models of neurodegeneration

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Target Audience Preclinical researchers with an interest in neurodegenerative diseases and neuroimaging of the mouse brain in vivo.

Purpose Pathological changes in brain tissue, including demyelination and iron accumulation are common to many neurodegenerative diseases[1, 2]. Transgenic mouse models are increasingly being used to further our knowledge of disease cause and progression, and identify new targets for therapeutic intervention. Quantitative Susceptibility Mapping (QSM) is an MRI technique that is sensitive to the bulk susceptibility of tissue and has been used to detect differences between grey matter structures in the human brain that correlate with iron content [7]. Myelin has been shown to be a predominant source of susceptibility contrast between white and grey matter in the mouse[3, 4] . Accurate and sensitive measures of white matter integrity and plaque-related iron load are powerful biomarkers of neurodegeneration and experimental treatment response. We present the first steps in a QSM protocol with the aim of generating an in vivo susceptibility atlas of the mouse brain that could be used as a reference for assessing white matter and grey matter changes in models of neurodegeneration.

Methods

Animals: 8 Male C57BL/6 mice were imaged in vivo at 10 weeks of age. Prior to imaging, mice were secured in a cradle under anaesthesia with 1-2% isofluorine in 100% oxygen using a custom-built head holder to reduce motion. Body temperature was maintained at 36 – 37.5 oC using a water-heating system and warm air fan. Core body temperature and respiratory rate were monitored using a temperature probe and pressure pad (SA Instruments, NY) *QSM acquisition:* All scans were performed on an Agilent 9.4 T VNMRS 20 cm horizontal-bore system (Agilent Inc. Palo Alto, CA, USA). A 72 mm birdcage radiofrequency (RF) coil was used for RF transmission and a quadrature mouse brain surface coil (RAPID, Germany) was used for signal detection. A Multi-Echo 3D Gradient recalled echo sequence was implemented with parameters : 12 echoes(TE1 =2.39 ms, ΔTE =2.64ms), TR =150ms , Flip Angle =15 degrees,FOV=15mmx15mmx15mm, Isotropic resolution =150µm , 5 averages.

QSM image processing: Phase difference maps, calculated through complex division of adjacent echoes, were spatially unwrapped using FSL prelude. Field maps were generated by dividing the unwrapped phase difference maps by ΔTE and then taking the mean across the whole set. Background field effects were removed through spatial high-pass filtering with a gaussian kernel (σ = 30 k-space voxels). Susceptibility maps were calculated by thresholded k-space division [5] with a threshold of 2. Regions of interest were drawn manually in the Corpus Callosum, Hippocampus, and Caudate Putamen, and mean values of susceptibility were calculated for comparison purposes.

DTI Acquisition: Diffusion-weighted images and a single B0 image were acquired using a 4-shot spin echo EPI sequence. Diffusion gradients were applied in 30 directions with parameters: G=0.25T/m, Δ=9.3ms, δ=5.5ms, and b=1050s/mm2,TR=2000ms.

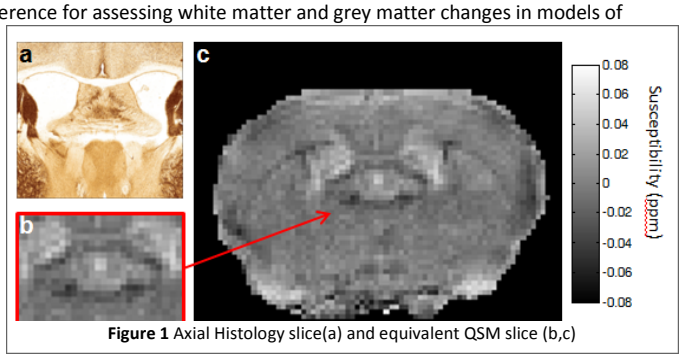

Figure 1 Axial Histology slice(a) and equivalent QSM slice (b,c)

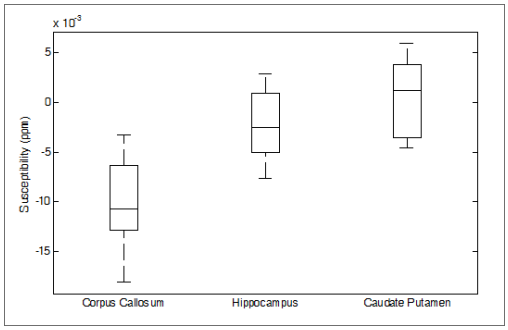

Figure 2 Mean ROI values of susceptibility in white matter and grey matter regions.

Results

An axial slice of the susceptibility map generated from a single representative mouse in the cohort is shown in Figure 1c where delineation of distinct anatomical features around the ventral hippocampal commissure are apparent (QSM Fig1b, Histology Fig1a). The mean susceptibility measured in the corpus callosum was -0.01±0.005ppm. This was significantly(P=.001) less than susceptibility measurements in the hippocampus(-0.002±0.004ppm). The Caudate Putamen (0.0005±0.004ppm) had a positive, significantly(P=.029) different measured susceptibility than the Hippocampus. Susceptibility values in the corpus callosum also showed a significant correlation(P<0.05, linear regression analysis) with Fractional Anisotropy values in the DTI data(Figure 3).

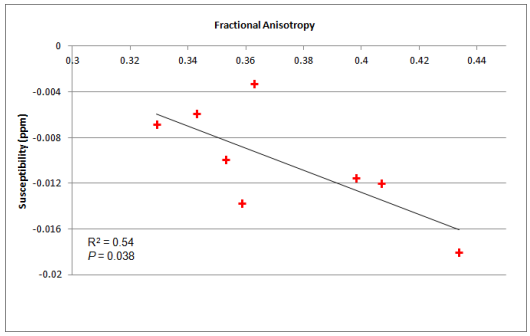

Figure 3 Plot of fractional anisotropy vs susceptibility in the corpus callosum

Discussion

The anatomical contrast surrounding the ventral hippocampal commissure was not observed in the magnitude or DTI images and may reflect iron and/or myelin concentration. We have presented in vivo QSM of the mouse brain generated from multi-echo gradient echo data and calculated susceptibility of white and grey matter structures. The white matter susceptibility values were negative and less than grey matter values in line with findings in the literature [4]. Increased fractional anisotropy was shown to correlate with increasingly negative susceptibility in the white matter, both measures have been shown to correlate with increased myelination of white matter previously[3, 6]. The aims of future work are to develop a robust non rigid registration pipeline for the gradient echo data to automatically segment brain structures without bias and also compare datasets from different mouse models of neurodegenerative disease.

References

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