

High-Field (9.4 T) MRI of Brain Dysmyelination by Quantitative Mapping of Magnetic Susceptibility

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INTRODUCTION: The multilayered myelin sheath wrapping around nerve axons is essential for proper functioning of the central nervous system. Abnormal myelination leads to a wide range of neurological diseases and developmental disorders. Non-invasive imaging of myelin content is of great clinical importance. The present work demonstrated that loss of myelin in the central nervous system of the shiverer mouse results in a dramatic reduction of magnetic susceptibility in white matter axons. The reduction resulted in a near extinction of susceptibility contrast between gray and white matter. Our data provides new evidences indicating that myelin is the predominant source of susceptibility differences between deep gray and white matter observed in magnetic resonance imaging. More importantly, the present study suggests that quantitative magnetic susceptibility is a potential endogenous biomarker for myelination.

METHODS: Quantitative magnetic susceptibility imaging (qMSI) and diffusion tensor imaging were conducted on a group of control and shiverer mice at 9.4 T. Shiverer is a mutation that adversely affect oligodendrocyte function and lead to dysmyelination in the CNS (1). Three pairs of adult (8 weeks) C3HeB/FeJ control mice and C3FeSWV-Mbp-Shi shiverer mice (The Jackson Laboratory, Bar Harbor, ME) were obtained and anesthetized with Nembutal. After perfusion fixation, the heads of the mice were stored in 20% buffered formalin overnight before imaging experiments in the following day. The perfused mouse brain was kept within the cranium to prevent any potential damage to the brain caused by surgical removal. The specimens were scanned using a 3D spoiled-gradient-recalled (SPGR) sequence with the following parameters: FOV = 22x22x11 mm³, matrix = 256x256x128, TE = 28 ms, TR = 400 ms, flip angle = 50°. To verify the axonal integrity, diffusion-weighted images were acquired with a 3D spin-echo sequence with the following parameters: FOV = 22x22x11 mm³, matrix = 256x256x128, TE = 12 ms, TR = 4s. Six diffusion encoding directions were used. The animal study was approved by the Institutional Animal Care and Use Committee (IACUC) of our institution.

Phase images were reconstructed from the SPGR images. Large background phase was removed with a sphere-mean-value (SMV) filter followed by a deconvolution operation (2). The advantage of this SMV filtering method over conventional high-pass filtering method is that the low frequency component of the local phase is also preserved. The resonance frequency map was calculated from the processed phase image. Quantitative magnetic susceptibility value was computed for each voxel iteratively using the LSQR algorithm (3).

RESULTS: Figure 1A shows a typical phase map computed directly from the complex images. The severe phase wraps completely obscure anatomical structures, for example, the corpus callosum (arrow). Even after unwrapping the phase, the presence of strong background phase overwhelms the tissue structures (Figure 1B). Figure 1C shows the background phase extracted with sphere mean value filtering, illustrating a smooth and unwrapped spatial profile. In the current study, a large filter radius of 9 voxels was employed so that the local phase information is minimally affected during the removal of background phase. Figure 1D shows the local phase obtained by subtracting the background phase (Figure 1C) from the total phase (Figure 1B). This local phase is used for subsequent calculation of frequency and susceptibility.

We further computed the magnetic susceptibility using the resulting frequency maps. The shiverer mice exhibited a near extinction of susceptibility contrast between gray and white matter (Fig. 2b). More importantly, because susceptibility is an intrinsic property of tissue and is reproducible, it provides a more reliable measurement for changes in brain tissues. On average, the relative susceptibility values changed from $-1.31 \sim -2.98 \times 10^{-8}$ in the control mice to $-0.09 \sim 0.04 \times 10^{-8}$ in the shiverer mice at the corpus callosum, the anterior commissure and the hippocampus. To rule out the possibility of axonal damage and its potential contribution to altered magnetic susceptibility, the control and shiverer mice were also characterized with DTI. As expected, the shiverer mice displayed similar fiber orientation as the controls. Quantitative analysis showed a decreased FA contrast in the shiverer mouse: a 26% reduction in the corpus callosum and 29% in the hippocampal commissure (Fig. 2c) consistent with previous findings (4). Nevertheless, the FA contrast between gray and white matter remains strong and visually similar, indicating that myelin is not the main source of the diffusion anisotropy.

DISCUSSIONS AND CONCLUSIONS: We have demonstrated that, while the phase and susceptibility maps exhibit a strong contrast between gray and white matter in the normal control mouse, this contrast essentially disappears in the myelin-deficient shiverer mouse. Our results indicate that myelin is the primary source of the phase contrast between gray and white matter in the deep brain regions observed at high field strength. More importantly, our findings suggest that the relative susceptibility value between white and gray matter may provide a sensitive endogenous biomarker for myelination. Given the critical importance of myelin to normal brain function, we anticipate that mapping magnetic susceptibility may become a useful tool for studying normal brain development and for assessing a wide range of white matter diseases associated with myelin. Imaging susceptibility may also provide a useful prognostic tool for assessing the effectiveness of treatment.

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REFERENCES: 1. Chernoff, G.F., Shiverer: an autosomal recessive mutant mouse with myelin deficiency. *J Hered* 1982 (72): 1281. Schweser, et al. A novel approach for separation of background phase in SWI phase data utilizing the harmonic function mean value property. *Proc of ISMRM 2010*, Stockholm, Sweden, p. 142. 3. Liu, C., Susceptibility tensor imaging, *Magn Reson Med* 2010: 1471-1477. (4) Ono, J, et al, Differentiation between dysmyelination and demyelination using magnetic resonance diffusion anisotropy. *Brain Res* 1995 (671): 141-148. (5) Song, S.K, et al, *Neuroimage* 2002 (17):1429-1436.

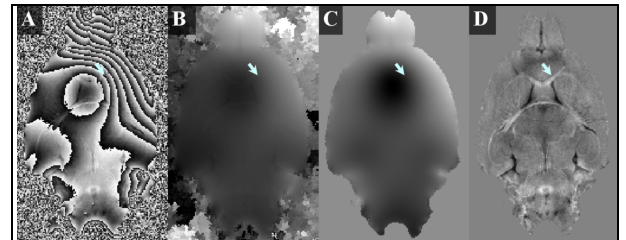


Figure 1. Processing of phase images. (A) raw phase map calculated directly from the complex image. (B) The corresponding phase map after unwrapping. Tissue contrast is overwhelmed by strong background phase. (C) The background phase map extracted with the sphere mean method. (D) The local phase map after background phase removal reveals high contrast (arrow).

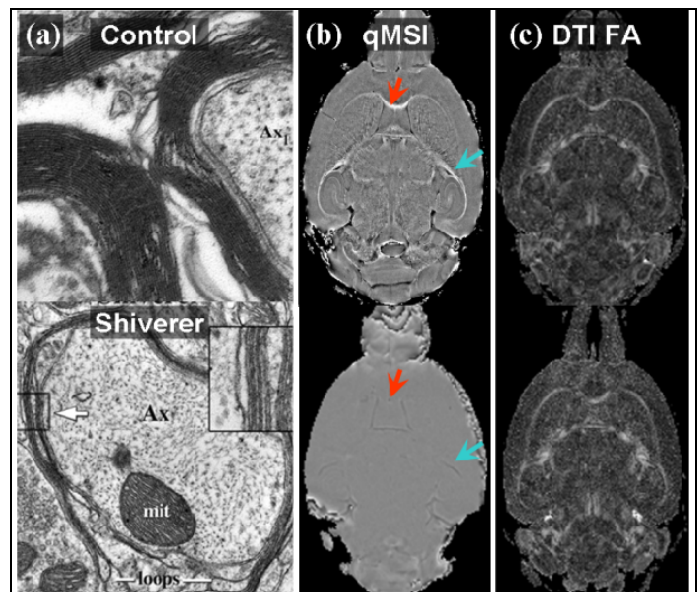


Figure 2. Control vs. shiverer mice. (a) Electron microscopy of myelin sheath shows dysmyelination in shiverer; (b) Loss of myelin results in an extinction of susceptibility contrast between gray and white matter. (c) DTI fractional anisotropy (FA) map does not show significant visual differences.