Sensitivity of magnetic susceptibility to white matter health in Cerebral Palsy

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Target Audience: Researchers interested in the use of quantitative susceptibility mapping (QSM) to study myelin specific white matter abnormalities.

Purpose: Recent work in quantitative susceptibility mapping (QSM) has indicated that magnetic susceptibility (χ) in white matter (WM) is sensitive to the integrity of the ordered lipids that constitute the myelin sheath, and is anisotropic with a $\sin^2\theta$ dependence on WM fiber orientation[1]. Here QSM is combined with Diffusion Tensor Imaging (DTI) to investigate the changes in magnetic susceptibility and its anisotropy in damaged WM in children with cerebral palsy (CP). The brain injuries associated with CP commonly result in the disrupted development of oligodendrocytes, and subsequent hypomyelination and necrosis of WM[2], making this disorder an appropriate testbed for the sensitivity of QSM to myelin health. We hypothesized that alterations in myelin content or health would be reflected in altered magnetic susceptibility anisotropy. Regions of myelin specific WM damage may be detectable using QSM by identifying voxels with magnetic susceptibilities that deviate from their expected values calculated from an empirically derived QSM anisotropy reference curve.

Methods: QSM images were acquired using a 3D FSPGR sequence (TE=40 ms, TR=50 ms, flip angle = 20°, 1 mm^3 isotropic resolution, FOV = 192 × 192 × 120 mm^3). DTI data were obtained (25 directions, b =1000 + 3b0, TE=70.5 ms, TR=12000 ms, 2 mm^3 isotropic resolution). The analyses presented here are focused on the WM associated with the cortico-spinal pathway, referred to here as the para-cerebral spinal tract (pCST), as damage to this WM is specifically relatable to clinical motor outcomes in CP. Creation of the pCST ROI for each subject was performed by warping the JHU-DTI-MNI "Eve" atlas template[3] into each subject's DTI image space via the Large Deformation Diffeomorphic Metric Mapping (LDDMM) algorithm[4], and combining the atlas regions labeled as the corticospinal tract, the inferior cerebellar peduncle, the medial leminiscus, superior cerebellar peduncle, the anterior limb of the internal capsule and the posterior limb of the internal capsule for each hemisphere separately. Mean susceptibility, (χ_θ), across all voxels with a primary diffusion direction at angle θ ranging from 0° – 90° in bins of 1° were plotted against the angles. The resulting data was fit to the equation $\chi_\theta = \chi_a \sin^2\theta + \chi_0$, where χ_θ is the mean apparent magnetic susceptibility for voxels at each angle, θ is the angle between the primary diffusion direction at that voxel and B_0 (main magnetic field), χ_a is the anisotropy of the magnetic susceptibility, and χ_0 is the baseline magnetic susceptibility of the tissue. We identified voxels with magnetic susceptibilities that deviated from their expected values based on an empirically-derived reference curve describing the relationship between magnetic susceptibility and fiber angle in WM. Voxels with aberrant QSM values are likely to have differences in myelin content and health than those with minimal deviation from their expected values. QSM measures were compared between the damaged and healthier hemispheres in a cohort of unilaterally impaired children (n=13) with CP, and between groups of individuals with severe (n=9) versus moderate (n=6) bilateral CP, where the severe and moderate designation was based on Gross Motor Function Classification Levels (GMFCS).

Results: In both groups of subjects, QSM anisotropy was significantly reduced in the more damaged tissue as compared to healthier WM. Further, in comparison to DTI measures, voxels with aberrant QSM anisotropy encompassed but also had a larger spatial extent than those voxels with elevated radial diffusivity (a potential measure for myelin integrity) in anatomical regions with hypothesized tissue damages. These new findings indicate that QSM may provide information that is complementary to DTI regarding WM tissue properties, as well as more sensitive measures on myelin integrity to help elucidate the neuropathology of CP.

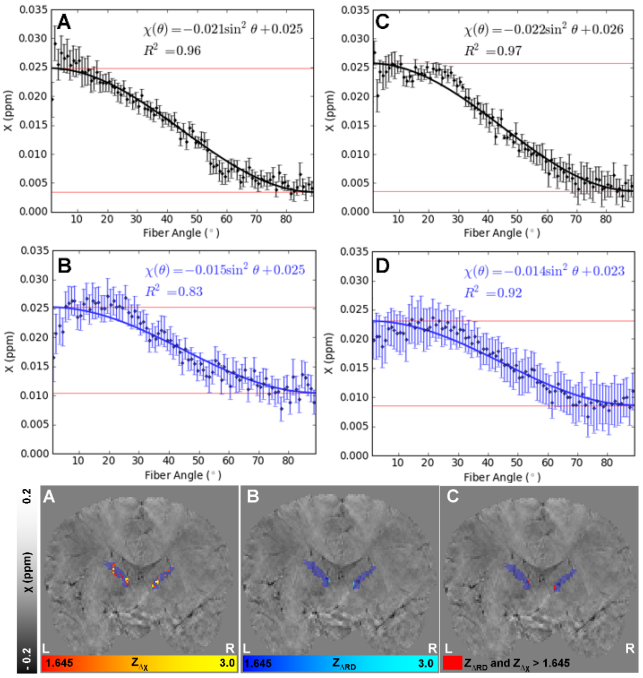

Fig 1. The mean magnetic susceptibility (χ_θ) across voxels with primary eigenvectors at angles ranging from 0° – 90° with respect to the main magnetic field (B_0) in bins of 1°, plotted as a function of angle to B_0. After fitting to the equation describing the theoretical angle dependence of magnetic susceptibility in the WM ($\chi_\theta = \chi_a \sin^2\theta + \chi_0$), the magnetic susceptibility anisotropy was shown to be reduced in the more damaged WM relative to the healthier WM. Specifically, QSM anisotropy was larger in the healthier hemisphere (A) versus the damaged hemisphere (B) in the unilaterally impaired subjects (n=13). Likewise, QSM anisotropy was larger in the less impaired individuals (n=6) (C) versus the more impaired individuals (n=9) (D). In both analyses, the magnetic susceptibility anisotropy (χ_a) and the accuracy of curve fitting (R^2) were reduced in the more damaged tissue, whereas the baseline susceptibility (χ_0) was similar. **Fig 2.** (A) Voxels with QSM values that deviated significantly from the expected anisotropy curve (red-yellow voxels, $Z_{\Delta RD} > 1.645$) and (B) voxels with significantly elevated RD (blue-cyan voxels, $Z_{\Delta\chi} > 1.645$), demonstrated in a bilaterally impaired subject (GMFCS = II, age = 2.1). (C) Red voxels indicate both $Z_{\Delta\chi} > 1.645$ and $Z_{\Delta RD} > 1.645$. $Z_{\Delta\chi}$ reflects significance of the difference between measured versus expected susceptibility at each voxel, which was calculated using an empirically derived reference curve quantifying the expected anisotropy of susceptibility. $Z_{\Delta RD}$ reflects the significance of the deviation in RD at each voxel from the mean RD in healthier WM. Both the reference curve used to derive $Z_{\Delta\chi}$ and the mean RD used to derive $Z_{\Delta RD}$ utilize the values from the group analysis of the healthier hemisphere in hemiplegic CP. The base image in (A) – (C) is the susceptibility map for this subject, with the outline of the bilateral para-cerebral spinal white matter ROI shown in purple.

Discussion: Consistent reductions in QSM anisotropy in the more damaged white matter relative to the healthier white matter are demonstrated. By identifying voxels with aberrant QSM anisotropy, it is demonstrated that QSM may be able to identify specific regions of WM damage within the ROI that may not be identifiable using diffusion-based metrics alone.

Conclusion: Significant changes in QSM anisotropy are demonstrated in damaged WM, likely indicative of hypomyelination caused by perinatal WM injury and characteristic of CP. While DTI measures are useful in elucidating the gross injury patterns of WM in CP, it cannot yet provide complete information regarding the underlying tissue properties, specifically myelin health. Here we present results suggesting that QSM can provide information beyond what can be measured by DTI alone, and may be a more specific and sensitive tool to assess changes in brain tissue that may be related to improvement or regression of functional abilities over time.

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