Molecular underpinnings of magnetic susceptibility anisotropy in the brain white matter

Wei Li[1], Bing Wu[1], Alexandru V. Avram[1], and Chunlei Liu[1,2]

[1]*Brain Imaging & Analysis Center, Duke University, Durham, North Carolina, United States,* [2]*Radiology, Duke University, Durham, North Carolina, United States*

INTRODUCTION: Frequency shift and susceptibility from gradient-echo MRI show excellent gray and white matter contrast, especially at high field (1). Both frequency and susceptibility contrast were shown to be dependent on white matter fiber orientation (2-4). However, the molecular underpinning of this orientation dependence is unclear. At the molecular level, most biomolecules are known to have anisotropic susceptibility (5). The potential importance of the molecular susceptibility on the macroscopic susceptibility anisotropy was realized only recently. Lee et al. showed that frequency shifts between white matter fibers with different orientations could be interpreted by susceptibility anisotropy, and suggested phospholipid bilayers as one possible source of this anisotropy (3). Liu also suggested structurally constrained macromolecules along axons as a potential source of susceptibility anisotropy (4). In this work, we further explored the molecular underpinnings of MRI-observed susceptibility anisotropy in brain white matter.

THEORY: Susceptibility anisotropy of the membrane lipids from human lipoproteins was estimated at 0.223 ppm by NMR spectroscopy (6), which is an order of magnitude larger than the gray-white matter susceptibility contrast of 0.013 to 0.029 ppm in normal mice (7). Given the strong anisotropy and the abundance of lipid molecules in the myelin, we hypothesize that myelin lipids is the main source of susceptibility anisotropy in white matter. An idealized model of the white matter with cylindrical lipid molecule distribution is proposed. Both an axon coordinate system (x, y, z) and a molecular coordinate system (x′, y′, z′) were defined (Fig. 1). The transformation matrix between these two coordinates is a rotation matrix around the z-axis, $\mathbf{R}_z$, with a rotation angle of φ. The ***fiber angle***, α, is defined as the angle between the z-axis and the H_0 direction. The magnetic moment $\vec{\mathbf{m}}_m$ of a molecule in response to $\vec{\mathbf{H}}$ is related to its rank-2 susceptibility tensor χ_m following $\vec{\mathbf{m}}_m = \mathbf{R}_z \chi_m \mathbf{R}_z^T \vec{\mathbf{H}}$, where $\chi_m = diag(\chi_m^{\parallel}, \chi_m^{\perp}, \chi_m^{\perp})$. Here, $\chi_m^{\perp}$ and $\chi_m^{\parallel}$ represent molecular susceptibility perpendicular (y′ or z′ direction) and parallel (x′ direction) to the lipid longitudinal direction, respectively. The induced magnetization density can be estimated as follows:

$$\vec{\mathbf{M}} = \int_V \vec{\mathbf{m}}_m \, dV = \frac{f_{lipid}}{2\pi} \int_{\varphi=0}^{2\pi} \mathbf{R}_z \chi_m \mathbf{R}_z^T \vec{\mathbf{H}} \, d\varphi \qquad [1]$$

In MRI, only magnetization along $\hat{\mathbf{H}}$ direction (M_z) can be measured, so the MRI-measured susceptibility can be derived as:

$$\chi = \frac{M_z}{H_0} = \frac{\vec{\mathbf{M}} \cdot \hat{\mathbf{H}}}{H_0} = f_{\text{lipid}} \left(\frac{\chi_m^{\parallel} - \chi_m^{\perp}}{2} \right) \sin^2 \alpha + \chi_0 \qquad [2]$$

Note that χ_0 includes baseline changes due to reference selection and isotropic susceptibility contribution in white matter. Eq. 2 suggested a sine-squared relationship between macroscopic susceptibility and the susceptibility anisotropy of an individual lipid molecule.

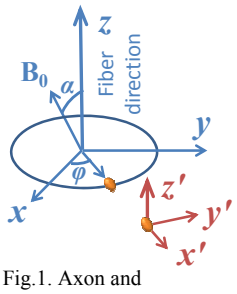

Fig.1. Axon and molecular coordinates

METHODS: Perfusion-fixed wild-type mouse brains (n = 2) were scanned at 9.4 T using a 3D spoiled-gradient-recalled (SPGR) sequence with matrix size = 256x128x128, FOV = 22x11x11 mm^3, FA = 40º, TE = 20 ms, TR = 200 ms. The number of orientations were 7 and 19, respectively. Diffusion tensor images (DTI) were acquired using a diffusion-weighted 3D spin-echo sequence. Human brain images of a healthy subject was acquired on a GE 3.0T scanner using a standard 3D SPGR sequence with TE = 40 ms, TR = 60 ms, FA = 20º, 2 mm resolution. 12 head orientations were acquired. DTI were acquired using a single-shot EPI sequence with 2x2x2 mm^3 resolution. The background phase was removed using the SHARP method (8) with modifications. Apparent magnetic susceptibility (AMS) was obtained using the LSQR method with the k-space derivative relationship (9). Susceptibility tensor images (STI) were obtained with a regularized approach (10).

RESULTS: In wild-type mice, the gray matter (GM)-white matter (WM) AMS contrast, calculated as $\chi_{WM} - \chi_{GM}$, increases with fiber angle (Fig.2), which could be fitted using Eq. 2. The susceptibility anisotropy of the white matter, estimated to be 0.026 ppm using least-square curve fitting. A similar susceptibility anisotropy value of 0.019 ppm was also estimated from the human brain using the same approach. Alternatively, the susceptibility anisotropy of the human white matter can also be estimated from the principal susceptibility as $\chi_1 - (\chi_2 + \chi_3)/2$ by assuming similar values perpendicular the lipid longitudinal directions, which is 0.022 ± 0.008 ppm. According to Eq. 2, assuming a susceptibility of 0.223 ppm for the myelin lipids (6), a lipid fraction of 0.16 in brain white matter (7), a susceptibility anisotropy value of 0.018ppm was obtained, which could explain most of the susceptibility anisotropy in *ex-vivo* mouse brains and *in-vivo* human brain. Further, the eigenvectors of STI agrees with that of DTI for large white matter fiber bundles.

CONCLUSION: In this study, a biophysical model is developed to link the molecular susceptibility anisotropy of myelin components to the bulk anisotropy observed by MRI. This model provides a consistent interpretation of the orientation dependence of macroscopic magnetic susceptibility in normal mouse brain *ex vivo* and human brain *in vivo* and the microscopic origin of anisotropic susceptibility. The results suggested that the cylindrically aligned lipid molecules in myelin are the main source of bulk susceptibility anisotropy.

REFERENCES: (1) Duyn et al, PNAS, 2007. (2) He and Yablonskiy, PNAS, 2009. (3) Lee et al, PNAS 2010. (4) Liu, MRM 2010. (5) Tjandra and Bax, Science, 1997. (6) Lounila, Phys Rev Lett, 1994. (7) Liu et al, Neoroimage, 2011. (8) Schweser et al, NeuroImage, 2011. (9) Li et al, Neoroimage, 2011. (10) Liu et al, Neoroimage, 2011.

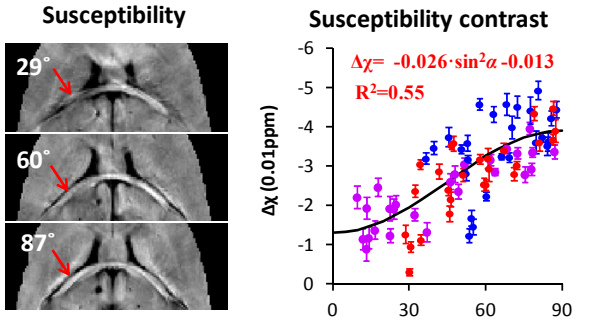

Fig.2. Orientation dependence of susceptibility contrast in normal mice

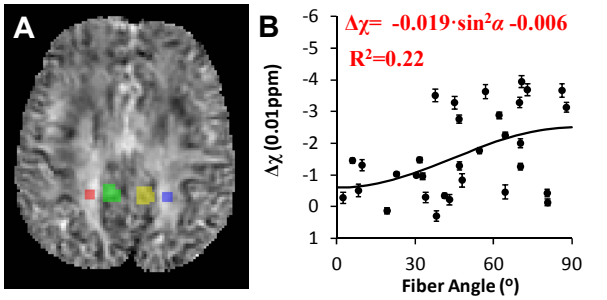

Fig.3. Orientation dependence of susceptibility contrast in human brain

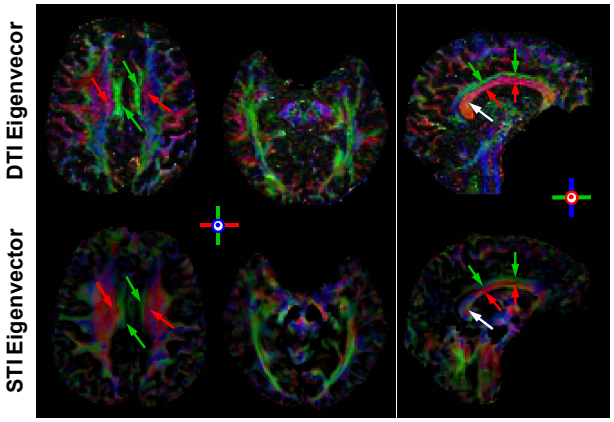

Fig.4. Comparison of the eigenvectors of diffusion and susceptibility tensors in the human brain.