Magnetic Susceptibility Anisotropy of Human Brain *in vivo* and its Molecular Underpinnings

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(Supplementary materials)

1. The detailed derivations from Eq. 2 to Eq. 4:

$\mathbf{R}_z$, $\vec{\mathbf{H}}$ and $\boldsymbol{\chi}_m$ is defined as follows:

$$\mathbf{R}_z = \begin{bmatrix} \cos\varphi & -\sin\varphi & 0 \\ \sin\varphi & \cos\varphi & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

$$\vec{\mathbf{H}} = \left[H_0 \sin\alpha, 0, H_0 \cos\alpha\right]^T$$

$$\boldsymbol{\chi}_m = diag(\chi_m^r, \chi_m^c, \chi_m^l)$$

The molecular magnetic moment ($\vec{\mathbf{m}}_m$) can be calculated as:

$$\vec{\mathbf{m}}_m = \mathbf{R}_z \boldsymbol{\chi}_m \mathbf{R}_z^T \vec{\mathbf{H}} = \begin{bmatrix} \sin\alpha(\chi_m^r \cos^2\varphi + \chi_m^c \sin^2\varphi) \\ -\sin\alpha(\chi_m^c - \chi_m^r)\cos\varphi\sin\varphi \\ \chi_m^l \cos\alpha \end{bmatrix} \quad [S1]$$

The induced magnetization density ($\vec{\mathbf{M}}$) is obtained from integration:

$$\vec{\mathbf{M}} = \int_V \vec{\mathbf{m}}_m dV = \frac{f_{lipid}}{2\pi} \int_{\varphi=0}^{2\pi} \mathbf{R}_z \chi_m \mathbf{R}_z^T \vec{\mathbf{H}} d\varphi = f_{lipid} \begin{bmatrix} \sin\alpha(\chi_m^c + \chi_m^r)/2 \\ 0 \\ \chi_m^l \cos\alpha \end{bmatrix} \quad [S2]$$

The MRI detectable magnetization (M_z) was derived by projecting $\vec{\mathbf{M}}$ in to $\hat{\mathbf{H}}$ direction:

$$M_z = \vec{\mathbf{M}} \cdot \hat{\mathbf{H}} = f_{lipid}\ H_0 \left[\left(\frac{\chi_m^r + \chi_m^c}{2} - \chi_m^l \right) \sin^2\alpha + \chi_m^l \right] \quad [S3]$$

The macroscopic susceptibility (χ) is then calculated as

$$\chi = M_z / H_0 = f_{lipid} \left(\frac{\chi_m^r + \chi_m^c}{2} - \chi_m^l \right) \sin^2\alpha + f_{lipid} \chi_m^l \quad [S4]$$

Eq.4 can be obtained by substituting $f_{lipid}\chi_m^l$ with χ_0. All these derivations are performed using Matlab symbolic toolbox (Mathworks, Natick, MA).

2. Susceptibility anisotropy of molecules not aligned with membrane surface norm

In deriving Eq. 3, the principal axes of the molecule, i.e. (x', y', z'), are assumed to be aligned with the radial, the circumferential and the longitudinal axis of the axon respectively. However, if additional degrees of freedom are allowed such that the principal axes are not aligned with the surface norm of the membrane (i.e. the radial direction), the macroscopic susceptibility tensor may be altered. We show here that, if limited degrees of freedom are allowed, the sine squared relationship still holds.

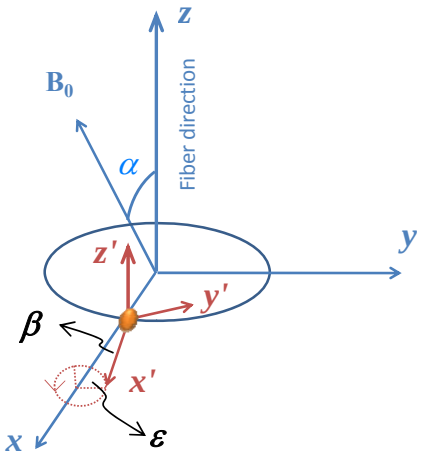

Fig. S1. The axon and molecular coordinate systems.

Specifically, suppose the principal axis, x', is tilted away from the surface norm (the radial direction) by an angle of β and is allowed to rotate freely about the radial direction by an angle of ε (Fig. S1). The tilting by an angle of β can be expressed as a rotation about the z-axis as $\mathbf{R}_z(\beta)$ and the rotation by an angle of ε can be expressed as $\mathbf{R}_x(\varepsilon)$. Under these conditions, the susceptibility tensor of a molecule located at the position shown in Fig. S1 can be expressed in the axon coordinate system as

$$\chi_m = \mathbf{R}_x(\varepsilon)\mathbf{R}_z(\beta)\chi_m^0\mathbf{R}_z^T(\beta)\mathbf{R}_x^T(\varepsilon) \qquad [S5]$$

Here, χ_m^0 is the susceptibility of the molecule expressed in its principal coordinate system (x', y', z') as $\chi_m^0 = diag(\chi_1, \chi_2, \chi_3)$. The induced total magnetization by molecules aligned on the surface of the axon is given by

$$\vec{\mathbf{M}} = \iiint_V \mathbf{R}_z(\varphi)\mathbf{R}_x[\varepsilon(x,y,z)]\mathbf{R}_z[\beta(x,y,z)]\chi_{mm}^0\mathbf{R}_z^T[\beta(x,y,z)]\mathbf{R}_x^T[\varepsilon(x,y,z)]\mathbf{R}_z^T(\varphi)\cdot\vec{\mathbf{H}}dV \qquad [S6]$$

For analytical simplicity, we assume that all molecules of a given type act coherently such that ε and β are location independent. Further, the angle ε is uniformly distributed with a probability distribution function of $p(\varepsilon) = 1/2\pi$. Eq. S6 can be simplified to

$$\vec{\mathbf{M}} = \frac{1}{2\pi}\int_{\varphi=0}^{2\pi}\int_{\varepsilon=0}^{2\pi} p(\varepsilon)\mathbf{R}_z(\varphi)\mathbf{R}_x(\varepsilon)\mathbf{R}_z(\beta)\chi_{mm}^0\mathbf{R}_z^T(\beta)\mathbf{R}_x^T(\varepsilon)\mathbf{R}_z^T(\varphi)\cdot\vec{\mathbf{H}}d\varepsilon d\varphi \qquad [S7]$$

The MRI detectable magnetization in the $\hat{\mathbf{H}}$ direction can be calculated as:

$$M_z = \vec{\mathbf{M}}\cdot\hat{\mathbf{H}} = H_0\left[\left(\frac{2\chi_1-\chi_2-\chi_3}{4}-\frac{3\chi_1-3\chi_2}{4}\sin^2\beta\right)\sin^2\alpha+\left(\frac{\chi_2+\chi_3}{2}+\frac{\chi_1-\chi_2}{2}\sin^2\beta\right)\right] \qquad [S8]$$

For a collection of molecules of different types (lipids and proteins), each with a different orientation angle (β^j) and a volume fraction of $f(j)$, the macroscopic magnetic susceptibility can be calculated as:

$$\chi = \left[\sum_j f(j)\left(\frac{2\chi_1^j-\chi_2^j-\chi_3^j}{4}-\frac{3\chi_1^j-3\chi_2^j}{4}\sin^2\beta^j\right)\right]\sin^2\alpha+\left[\sum_j f(j)\left(\frac{\chi_2^j+\chi_3^j}{2}+\frac{\chi_1^j-\chi_2^j}{2}\sin^2\beta^j\right)\right] \qquad [S9]$$

Eq. S9 shows that the sine squared relationship holds for any type of mulecules with different orientations, as long as they are aligned around the axon to a certain degree as described.

In the special case when β = 0, $\chi_1 = \chi_m^r = \chi^{\parallel}$, $\chi_2 = \chi_m^c = \chi^{\perp}$, $\chi_3 = \chi_m^l = \chi^{\perp}$ and for only phospholipids, Eq. S9 reduces to Eq. 5.

3. Orientation dependence of frequency shift

The orientation dependence of gray and white matter frequency contrast in selected ROIs (Fig. 2 A and D) was shown as follows:

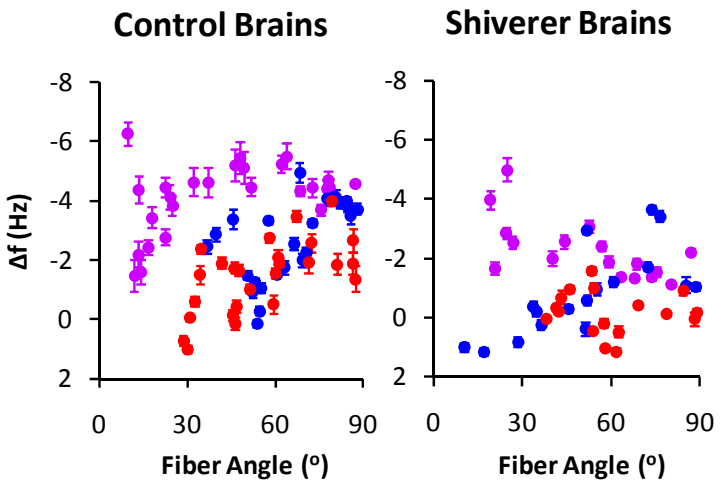

Fig. S2. Orientation dependence of frequency shift contrast. The ROIs are in Fig. 2A.

Different from the findings by Denk et al (Denk et al., 2011), no clear relationship was observed between the frequency shift and the fiber angle in both control mice and dysmyelinating shiverer mice (Fig. S1). This differing behavior could be attributed to the fact that phase is non-local and is dependent on surrounding susceptibility distributions. The effect of long-range dipole fields is more pronounced in the mouse brain where white matter structures are an order of magnitude smaller than those in the human brains. For example, the magnetic field generated by the cerebrospinal fluid in the ventricles can overwhelm the frequency shift in the nearby hippocampal commissure.

4. Orientation dependence of susceptibility contrast in mouse brains

This following figure plots the same data in Fig. 2 C and F, but is against $\sin^2(\alpha)$.

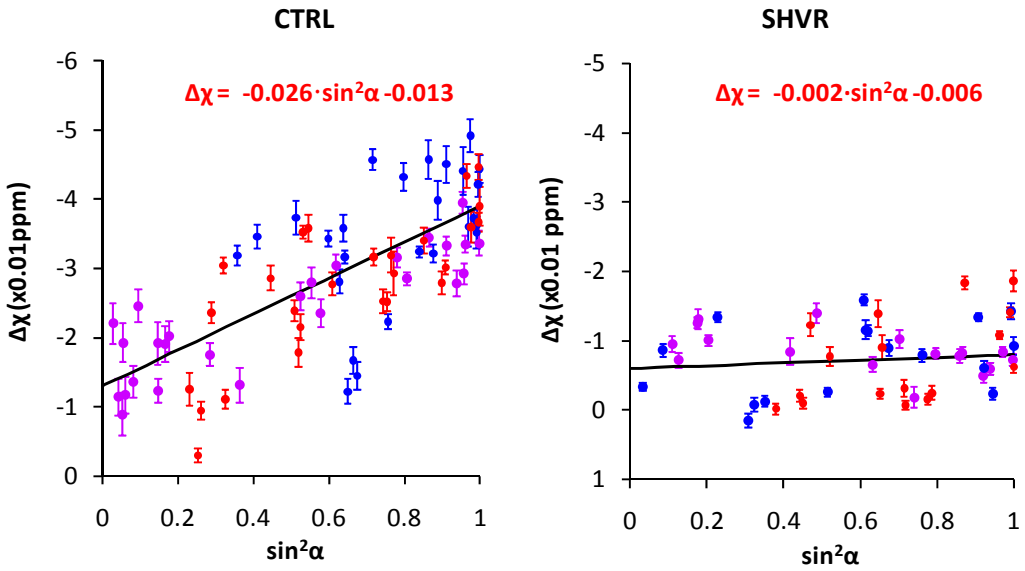

Fig. S3. Orientation dependence of susceptibility in normal and shiverer mice.

References:

Denk, C., Torres, E.H., MacKay, A., Rauscher, A., 2011. The influence of white matter fibre orientation on MR signal phase and decay. NMR in Biomedicine, 246-252.