Sensitivity of MRI resonance frequency to the orientation of brain tissue microstructure

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Introduction

High field (≥ 7 T) studies have demonstrated that contrast based on resonance frequency shifts (or phase in gradient-echo MRI) may substantially improve visualization of fine-scale structures in brain (1, 2). Several mechanisms including magnetic susceptibility and molecular exchange have been investigated as source for this frequency contrast (1-6). Recently, a new theoretical study (Generalized Lorentzian theory) suggests that frequency shifts may also report on tissue microstructure and its orientation relative to B_0 (7). This mechanism could explain some of the strong frequency shifts observed in the major fiber bundles and may have important implications for the application and interpretation of phase images. However, experimental evidence for this mechanism is sparse, and may be confounded by large-scale geometric effects inherent to a susceptibility contrast mechanism. Here, we aimed to directly observe the potential effect of brain microstructure on MRI resonance frequency.

Methods

The MRI experiment was designed to separate effects of tissue microstructure from well-known larger-scale geometric shape effects. A piece of human corpus callosum was sectioned from a fixed brain such that the main white matter fiber orientation was parallel to the long axis of the piece. The elongated piece was then cut into five sub-sections of two square prisms (C1 and C5) and three cubes (C2 to C4). Two experimental conditions were tested: one with the primary fiber orientation of all tissue pieces parallel to B_0 (condition A) and the other with the two cubes (C2 and C4) rotated by 90° such that their primary fiber orientation was perpendicular to B_0 (condition B). Images were acquired with a Bruker 7 T system. The fiber orientation was confirmed by a DTI scan (20 diffusion directions with b = 3000 s/mm^2, and 3 baseline). A 2D GRE sequence (FOV = 6 x 6 cm^2, voxels = 0.2 x 0.2 x 0.5 mm^3, TE = 10 ms, 4 slices) was then used to acquire phase images. After the first GRE scan, the C2 and C4 were rotated and another set of 2D GRE images was acquired. The DTI scan was also repeated. The phase images were unwrapped and background variations were removed by fitting 8th-order polynomials (2D) within a masked region (d = 32 mm). The frequency difference between the two conditions was calculated by subtracting the original unwrapped phase images and removing 2nd-order polynomials.

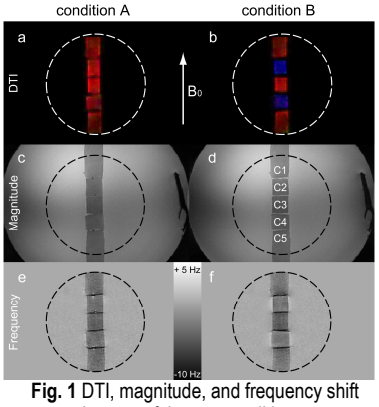

Fig. 1 DTI, magnitude, and frequency shift images of the two conditions.

Results

The DTI, GRE magnitude, and resonance frequency images from the two conditions are shown in Fig. 1. The mean resonance frequency of condition A was -3.89 ± 0.76 Hz relative to the saline. Under condition B, the resonance frequency of the rotated segments showed a significant positive shift of 0.56 ± 0.67 Hz (mean diff. ± pooled s.d., statistically significant with $p < 10^{-16}$ when averaged over all voxels) relative to condition A. The cross-sectional profile of the difference image (the central 4 mm of the tissues) shows the effect more clearly (Fig. 2). A slightly positive frequency shift is also seen in the fluid immediately lateral to the rotated tissue segments (Fig. 1f). The middle cube (C3), which was not rotated, shows decreased contrast in condition B. Inside of C1 and C5, the frequency gradually decreases close to the C1 side of the C1-C2 boundary and the C5 side of the C4-C5 boundary. This can be interpreted as the effect of C2 and C4 extending outside of those tissue sections with a frequency amplitude that decreases with distance. In summary, the results suggest that the orientation of microscopic structure affects the MRI resonance frequency both locally and remotely. In contrast, the generalized Lorentzian theory predicts only a local frequency shift.

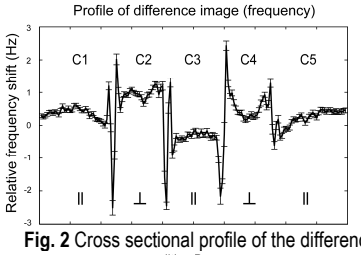

Fig. 2 Cross sectional profile of the difference

To explain both local and remote effects, we propose that tissue microstructure may result in an anisotropic magnetic susceptibility. A computer simulation was performed to investigate whether such an anisotropy could explain the observations. Cuboidal structures, similar to the tissue pieces used in the experiment, were modeled. The susceptibility for saline was assumed to be -9.05 ppm. Frequency maps were calculated by a Fourier-based method (8). An initial susceptibility model was set up for condition A assigning the same susceptibility value ($\chi_{\parallel}$) that gave the minimum difference between the simulation and experiment results. In a second model, C1, C3, and C5 were assigned $\chi_{\parallel}$ while the susceptibility of C2 and C4 ($\chi_{\perp}$) was determined by finding a value that matched the experimental results. The simulations show that anisotropic susceptibility leads to a pattern of frequency shifts that closely resembles the experimental observation including the effects outside the rotated segments (Fig. 3). Assuming the frequency shifts were caused entirely by susceptibility, the estimated susceptibility anisotropy ($\chi_{\parallel} - \chi_{\perp}$) was 0.012 ppm.

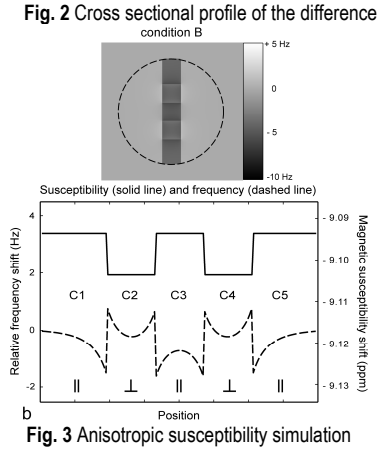

Fig. 3 Anisotropic susceptibility simulation results: (a) condition B, (b) cross sectional profile of estimated susceptibility in condition B (solid) and frequency of the difference (dashed)

Discussion and Conclusion

The tissue sample experiments suggest that MRI resonance frequency is dependent on tissue microstructure and its orientation relative to B_0. This phenomenon could be partly explained by tissue compartmentalization as suggested by theory (7, 9). However, this theory does not explain the non-local effects seen in the experiments. To explain these, we propose an orientation-dependent (anisotropic) magnetic susceptibility. Anisotropic susceptibility has been found in highly ordered structures including proteins (10-11) and lipid bilayers (12-13). Therefore, it is plausible that highly structured white matter fibers may show anisotropy.

The above findings represent the first direct experimental evidence for a dependence of MRI resonance frequency on the orientation of brain microstructure relative to B_0. The experimental design allowed separation between microscopic and macroscopic orientation effects that often coexist under general *in-vivo* imaging conditions and have complicated the interpretation of earlier studies. The observed sensitivity to orientation may result from anisotropic susceptibility that could provide important information about the cellular organization of the tissue.

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