Specialty area: Imaging Microstructure

Speaker: Chunlei Liu, PhD, chunlei.liu@duke.edu

Highlights: 1. Magnetic susceptibility quantifies magnetic properties of tissue;

2. Magnetic susceptibility is anisotropic;

3. MR signal is affected by susceptibility distribution and microstructure;

5. STI images tissue microstructure and fiber orientation.

Susceptibility Modelling: Relationship with Tissue Microstructure

[1, 2] Chunlei Liu, PhD,

Email: chunlei.liu@duke.edu

[1] Brain Imaging and Analysis Center, [2] Department of Radiology, Duke University, Durham, NC

Target audience: physicists, neuroscientists and clinicians interested in learning the principles and applications of magnetic susceptibility imaging.

PURPOSE

Phase and magnetic susceptibility maps derived from gradient-echo MRI reflect spatial variation of magnetic susceptibility sources within the tissue. This susceptibility variation originates from spatial variations of molecular or cellular components that are of different magnetic properties compared to bulk water. The objectives of the lecture are to explore the relationship between MRI measured susceptibility and the underlying tissue microstructure.

METHODS

Overview

There are several factors affecting the volume susceptibility measured by MRI (1). On the atomic level, paramagnetic susceptibility originates from spins of unpaired electrons which have higher tendency to align with an applied magnetic field and amplify the field. Diamagnetic susceptibility, on the other hand, originates from the induction currents of circulating electrons that generate fields opposing the applied field. On the molecular level, the availability of unpaired electrons, the distribution of electron cloud within the molecule and the competition between electron spins and induction currents will together determine the molecule's susceptibility and anisotropy. Finally, the microstructure of the brain tissue, i.e. the spatial arrangement of molecules and organelles within a voxel, will affect the microscopic magnetic field distribution within the voxel. As the water molecules are distributed within this heterogeneous magnetic field environment, what MRI phase measures is the averaged effect as seen by these molecules. As a result, the distribution (e.g. compartmentalization) and motion of the water molecules affect the perceived phase shift. In a healthy adult brain, the most striking feature of phase and susceptibility maps are that the gray matter largely appears paramagnetic and the white

matter largely diamagnetic (2-4). The emerging consensus is that the paramagnetic susceptibility of gray matter is mainly related to iron and the diamagnetic susceptibility of white matter is due to myelination.

Microstructure

Besides its chemical and molecular composition, brain tissue's microstructure (cellular and subcellular structures and arrangement of cells) also play a crucial role in affecting the MRI measured susceptibility. Compartmentalization of white matter (e.g. separation of axonal space, myelin space and extracellular space) plays a significant role in affecting the phase and T2* signal behavior (5-8). Protons in each compartment experience unique magnetic field and relaxation properties. The effect of microstructure can be generalized into two categories: orientation dependence and distribution of subvoxel magnetic field. These effects are especially prominent in the white matter due to its unique microstructure that cannot be treated as homogeneous even in a statistical sense.

Orientation effects include the angular dependence of magnetic fields generated by elongated structures (9) and the angular dependence due to underlying anisotropic susceptibility (10,11). For simplicity, we will refer to the former as "structural anisotropy" and the latter as "susceptibility anisotropy". Structural anisotropy can generate orientation-dependent phase even with only isotropic susceptibility simply due to the geometric shape. A classic example is the field shift of a vessel inside the magnet which is dependent on the relative angle between the vessel and the field (12). In an analysis of gray-white matter phase contrast, He and Yablonskiy predicted a dependence of white matter phase on the relative angle between axons and magnetic field due to the elongated shape of the axons similar to the vessels (9).

Susceptibility anisotropy describes that magnetic susceptibility is a tensor quantity rather than a scalar quantity (10). As a result, the interaction between susceptibility and magnetic field follows the rule of tensor-vector product rather than a simple scaling effect. In brain tissues, especially in the white matter, this anisotropy originates mainly from membrane lipids (13). Each lipid molecule has an anisotropic response to an external magnetic field due to its chain-like structure and non-spherical distribution of electron clouds. Li et al demonstrated that it was the anisotropic susceptibility of lipid molecules and the ordered arrangement of these lipids that gave rise to the bulk susceptibility anisotropy observed on the voxel level (13). Wharton et al simulated the field distribution within myelinated axons by modeling axons as hollow cylinders. They concluded that anisotropic susceptibility of myelin was needed to fully explain the behavior of the GRE phase (8).

For a given imaging voxel containing heterogeneous structures, magnetic field within the voxel is also heterogeneous while the total magnetization of the voxel is a summation of all spins within the voxel, each experiencing a slightly different local magnetic field. The phase angle of the resulting signal represents the strength of the mean field. The spatial heterogeneity is however lost during the ensemble averaging. Liu and Li proposed a spectral analysis technique in the Fourier spectrum space (p-space) that could recover the field distribution within the voxel thus allowed them to infer the underlying tissue microstructure (14). Specifically, this method measures the spatial variation of the magnetic field within a voxel that is induced by the underlying structural heterogeneity. The underlying principle is that, in the direction parallel to the axons, the field variation is expected to be minimal while the variation is the largest in the directions perpendicular to the axons. The ability to detect such spatial variations is enhanced at higher field strengths due to the increased susceptibility effect.

Susceptibility tensor imaging

A susceptibility tensor imaging (STI) technique was proposed to measure and quantify susceptibility as a rank-2 tensor (10). This technique relies on the measurement of frequency offsets at different orientations with respect to the main magnetic field. The orientation dependence of susceptibility is characterized by a tensor. In the brain's frame of reference, the relationship between frequency shift and susceptibility tensor is given by (10)

$$f(\mathbf{k}) = \gamma B_0 \left(\frac{1}{3} \hat{\mathbf{H}}^{\mathrm{T}} \boldsymbol{\chi}(\mathbf{k}) \hat{\mathbf{H}} - \hat{\mathbf{H}} \cdot \mathbf{k} \frac{\mathbf{k}^{\mathrm{T}} \boldsymbol{\chi}(\mathbf{k}) \hat{\mathbf{H}}}{k^2} \right) \quad [1]$$

Here, $\boldsymbol{\chi}$ is a second-order (or rank-2) susceptibility tensor; $\hat{\mathbf{H}}$ is the unit vector (unitless) of the applied magnetic field. Assuming that the susceptibility tensor is symmetric, then there are six independent variables to be determined for each tensor. In principle, a minimum of six independent measurements are necessary. A set of independent measurements can be obtained by rotating the imaging object, e.g. tilting the head, with respect to the main magnetic field. Given a set of such measurements, a susceptibility tensor can be estimated by inverting the system of linear equations formed by Eq. [1]. Fewer than six orientations are also feasible by incorporating fiber orientation estimated by diffusion tensor imaging (DTI) and assuming cylindrical symmetry of the susceptibility tensor (15,16).

Susceptibility tensor can be decomposed into three eigenvalues (principal susceptibilities) and associated eigenvectors. Similar to DTI fiber tractography, fiber tracts can be reconstructed based on STI (17,18).

Imaging tissue microstructure and connectivity

Magnetic susceptibility of white matter is also anisotropic (10,11). To measure the anisotropy of magnetic susceptibility, the method of susceptibility tensor imaging (STI) has been used (10). A recent study also explored the capability of STI for tracking neuronal fibers in 3D in the mouse brain ex vivo (17). In large fiber bundles, the orientation determined by STI was found to be comparable to that by diffusion tensor imaging (DTI) of diffusion anisotropy. A recent study suggested that the susceptibility anisotropy in brain tissue mainly originates from myelin, and the cylindrically aligned lipid molecules in myelin are likely the main source of the MRI-determined susceptibility anisotropy (13).

Similar relationship between also exists in other organs such as kidney and heart (18-20). STI has been successfully applied in these structures outside the central nervous system.

DISCUSSION

A critical obstacle in interpreting susceptibility values is the competing effects of multiple signal sources. Characterizing and imaging sub-voxel magnetic field distribution is another emerging area of interest, which may provide insights into tissue microstructure. The volume susceptibility measured by QSM reflects only the mean field shift of a given voxel, it does not portray the field heterogeneity within the voxel. A basic model for this field heterogeneity is the three-pool model of axonal water, myelin water, and extracellular water (5,8). A more systematic way to extract the sub-voxel field information is to perform a Fourier spectral analysis with the p-space technique which has been demonstrated in phantoms and mouse brains ex vivo (14). Another way is to measure diffusion attenuation caused by this internal heterogeneous magnetic field (21,22).

CONCLUSION

The spatial distribution of magnetic susceptibility and the phase images mapped by gradient echo sequences is directly influenced by tissue microstructure and its molecular contents. Current advances have provided some new tools to assess these micro environment tissue. Further understanding of the relationship between susceptibility and microstructure will further improve the accuracy and utilities of these tools.

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