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Mean Magnetic Susceptibility Regularized Susceptibility Tensor Imaging (MMSR-STI) for Estimating Orientations of White Matter Fibers in Human Brain

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Abstract

Purpose—There is an increasing number of studies showing that magnetic susceptibility in white matter fibers is anisotropic and may be described by a tensor. However, the limited head rotation possible for *in vivo* human studies leads to an ill-conditioned inverse problem in susceptibility tensor imaging (STI). Here we suggest combined use of limiting the susceptibility anisotropy to white matter and imposing morphology constraints on the mean magnetic susceptibility (MMS) for regularizing the STI inverse problem.

Methods—The proposed MMS regularized STI (MMSR-STI) method was tested using computer simulations and *in vivo* human data collected at 3T. The fiber orientation estimated from both the STI and MMSR-STI method was compared to that from diffusion tensor imaging (DTI).

Results—Computer simulations show that MMSR-STI method provides a more accurate estimation of the susceptibility tensor than the conventional STI approach. Similarly, *in vivo* data show that use of MMSR-STI method leads to a smaller difference between the fiber orientation estimated from STI and DTI for most selected white matter fibers.

Conclusion—The proposed regularization strategy for STI can improve estimation of the susceptibility tensor in white matter.

Keywords

Susceptibility tensor imaging; magnetic susceptibility anisotropy; MSA; mean magnetic susceptibility; MMS; diffusion tensor imaging; white matter; fiber orientation

Introduction

High-resolution magnetic resonance (MR) phase or frequency images have shown unique tissue contrast due to tissue magnetic susceptibility effects (1). However, MR phase depends on the orientation of a tissue structure relative to the main magnetic field and holds a

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nonlocal relationship with the tissue susceptibility distribution (2–4). Quantitative susceptibility mapping (QSM) techniques developed in recent years aim at solving the ill-posed inverse problem to yield quantitative susceptibility images from the measured MR phase data and have made it possible to inversely map the intrinsic tissue susceptibility distribution with good image quality (5–14).

In addition to its dependence on different head orientations relative to the main magnetic field, it has been reported that MR phase is also sensitive to the orientation of brain tissue microstructures, such as white matter fibers, relative to the main magnetic field (15, 16). Such a microstructure-orientation dependent phase may be described by a generalized nonspherical Lorentzian model (17, 18) or by a magnetic susceptibility tensor model. The latter can be done either at a macroscopic level, i.e. at the order of magnitude of an imaging voxel (19–22) or at the molecular level, i.e. the lipid molecules in myelin sheath (23–25). For the apparent susceptibility tensor model at imaging voxel level, similar to diffusion tensor imaging (DTI), it is possible to estimate the susceptibility tensor at each voxel by combining MR phase measurements at more than six independent spatial orientations of the organ with respect to the field and solving the large-scaled susceptibility tensor imaging (STI) inverse problem. Previous STI studies on *ex vivo* mouse brain, which can be rotated by large angles in the MR scanner and scanned at many orientations, have demonstrated the potential of using STI to track certain white matter fibers similar as DTI (26), yet such kind of STI studies on human subjects are limited by the head rotation range achievable in the MR head coil, the long scan time and the discomfort associated with staying in the scanner with tilted head position. Despite all of these limitations, previous STI studies on human subjects at 3T have shown various agreements with DTI, especially in the estimated white matter fiber orientation that is important for potential fiber tracking (20, 22).

In the present study, we propose a regularization strategy for the STI inverse problem in which the anisotropy is limited to white matter only and morphology constraints are applied to the mean magnetic susceptibility (MMS), which is based on the tensor trace, i.e. the first tensor invariant of the susceptibility tensor. The imaging performance of conventional STI and the proposed MMS regularized STI (MMSR-STI) method are compared using computer simulations and *in vivo* human data collected at 3T.

Theory

Using the spherical Lorentz correction (27) the MR measurable relative magnetic field shift $(\delta B_z)_i$ (in units of ppm) at the i th head orientation ($i = 1 \dots N$) can be written in tensor notation as (19, 21)

$$(\delta B_z)_i = \text{FT}^{-1} \left\{ \frac{1}{3} (\hat{H}_0)_i \cdot \text{FT} \{ \bar{\chi} \} \cdot (\hat{H}_0)_i - (\hat{H}_0)_i \cdot \bar{k} \frac{\bar{k} \cdot \text{FT} \{ \bar{\chi} \} \cdot (\hat{H}_0)_i}{\|\bar{k}\|^2} \right\} \quad [1]$$

where $\bar{\chi}$ is the tissue magnetic susceptibility tensor, which is of second rank and is assumed to be real and symmetric; $\hat{H}_0$ is the unit vector of the applied main magnetic field strength; FT and FT^{-1} denote the Fourier transform and its inverse, respectively; $\bar{k}$ is the spatial

frequency vector. Note here that the Fourier transform of a tensor field is defined as a tensor with elements consisting of the Fourier transform of each tensor component, i.e.:

$$\text{FT} \{ \bar{\bar{\chi}}(\bar{r}) \} = \begin{bmatrix} \text{FT}(\chi_{11}(\bar{r})) & \text{FT}(\chi_{12}(\bar{r})) & \text{FT}(\chi_{13}(\bar{r})) \\ \text{FT}(\chi_{21}(\bar{r})) & \text{FT}(\chi_{22}(\bar{r})) & \text{FT}(\chi_{23}(\bar{r})) \\ \text{FT}(\chi_{31}(\bar{r})) & \text{FT}(\chi_{32}(\bar{r})) & \text{FT}(\chi_{33}(\bar{r})) \end{bmatrix} \text{ with } \bar{r} \text{ being the spatial position vector.}$$

The relative magnetic field shift $(\delta B_z)_i$ is proportional to the MR phase that can be derived from gradient echo experiments. It is important to realize that the subject frame of reference (21) is used in Eq. 1 and also in the following equations for the vectors and tensors unless stated otherwise. Since the defined susceptibility tensor has six independent components, theoretically, it is possible to solve the STI inverse problem and estimate the tensor $\bar{\bar{\chi}}$ by combining MR phase measurements collected at $N \geq 6$ independent head orientations. This is commonly done by solving the following minimization problem:

$$\min_{\bar{\bar{\chi}}} (\|O_1\|_2^2 + \|O_2\|_2^2 + \dots + \|O_N\|_2^2) \quad [2]$$

where $O_i = A_i \bar{\bar{\chi}} - (\delta B_z)_i$

Here A_i represents the mapping relationship from $\bar{\bar{\chi}}$ to $(\delta B_z)_i$ as described in Eq. 1.

The susceptibility tensor in the subject frame is a symmetric tensor, i.e.

$$\bar{\bar{\chi}} = \begin{bmatrix} \chi_{11} & \chi_{12} & \chi_{13} \\ \chi_{12} & \chi_{22} & \chi_{23} \\ \chi_{13} & \chi_{23} & \chi_{33} \end{bmatrix} \quad [3]$$

For brain tissue with isotropic magnetic susceptibility or with negligible susceptibility anisotropy, the susceptibility tensor is diagonal with the following relationships

$$\chi_{12} = \chi_{13} = \chi_{23} = 0 \quad [4]$$

$$\chi_{11} = \chi_{22} = \chi_{33} \quad [5]$$

In addition, even with full anisotropy, the first tensor invariant, i.e. the trace of the tensor is orientation independent, i.e. it does not change with rotation of the coordinate system:

$$\text{trace}(\bar{\bar{\chi}}) = \chi_{11} + \chi_{22} + \chi_{33} = \chi_1^{\text{diag}} + \chi_2^{\text{diag}} + \chi_3^{\text{diag}} \quad [6]$$

where χ_i^{diag} denotes the i th susceptibility tensor component in its diagonal frame of reference, i.e. the i th eigenvalue of the susceptibility tensor. According to the definition of the mean magnetic susceptibility (MMS) (21) and Eq. 6, we have

$$\text{MMS} = \chi_{avg} = \frac{1}{3}(\chi_1^{diag} + \chi_2^{diag} + \chi_3^{diag}) = \frac{1}{3}(\chi_{11} + \chi_{22} + \chi_{33}) \quad [7]$$

Based on the eigenvalues of the susceptibility tensor, we can also define a magnetic susceptibility anisotropy (MSA) as

$$\text{MSA} = \chi_{ani} = \chi_1^{diag} - \frac{1}{2}(\chi_2^{diag} + \chi_3^{diag}) \quad [8]$$

Here we assume χ_1^{diag} corresponds to the most paramagnetic tensor component and thus the MSA is always non-negative. MMS on the other hand can be positive or negative, depending on the reference magnetic susceptibility used. Relative to the magnetic susceptibility of CSF, white matter is generally diamagnetic (8, 28). Since MMS is a linear combination of three tensor components, we can easily add some regularization terms in the STI inverse problem based on MMS without changing its linearity. In this study we incorporated the morphology information (edge information about tissue structures) commonly used in QSM regularization (10, 29) and the final regularized STI minimization problem can be written as

$$\min_{\bar{\chi}} \left(\begin{aligned} &\|O_1\|_2^2 + \|O_2\|_2^2 + \dots + \|O_N\|_2^2 + \alpha^2 M(\|\chi_{12}\|_2^2 + \|\chi_{13}\|_2^2 + \|\chi_{23}\|_2^2) \\ &+ \alpha^2 M(\|\chi_{11} - \chi_{22}\|_2^2 + \|\chi_{22} - \chi_{33}\|_2^2 + \|\chi_{11} - \chi_{33}\|_2^2) \\ &+ \beta^2 \|W_g G \chi_{avg}\|_2^2 \end{aligned} \right) \quad [9]$$

where O_i has the same definition as in Eq. 2; M is a binary mask that is 1 in assumed isotropic regions, i.e. gray matter, CSF, and 0 in assumed anisotropic regions, i.e. white matter; α is a regularization parameter, which is generally chosen to make the off-diagonal tensor elements, i.e. χ_{12} , χ_{13} , χ_{23} , and the difference between the diagonal tensor elements in

the assumed isotropic regions to be close to zero; $G = \begin{bmatrix} G_x & G_y & G_z \end{bmatrix}^T$ with G_x , G_y , G_z being the matrix representation of the discrete gradient in the x, y and z directions,

respectively, $W_g = \begin{bmatrix} W_{gx} & W_{gy} & W_{gz} \end{bmatrix}$ is a weighting matrix containing the priori tissue structure information and β is also a regularization parameter. One way to obtain W_g is by thresholding the gradient of the QSM image, which is a good approximation of MMS, and setting voxels with a large spatial gradient to 0 and voxels with a small gradient to 1. The regularization parameter β needs to be optimized in order to get an optimum trade off between under- and over-regularization.

Methods

Numerical simulations

A 3D 128×128×128 numerical head phantom with structures having a cylindrically symmetric susceptibility tensor (MSA = 0.018 ppm) from a previous study (21) was used to validate the proposed method and to test the imaging performance under different conditions. In the subject frame of reference (x' , y' , z'), the central axial slices ($z' = 64$) of the

target MMS, MSA and principle eigenvector (PEV) maps of the phantom are shown in Fig. 1a–1c. Note here that the PEV map was masked with the MSA to show only the anisotropic regions.

Magnetic field shift data was simulated using Eq. 1 at N (6 to 10) head orientations, i.e. with N main magnetic field directions $(\hat{H}_0)_i$ in the subject frame of reference. Contrary to MRI magnitude data, noise in MR phase is better approximated by Gaussian distribution (30). As such, Gaussian noise was added to the magnetic field shift data with SNR of 30. The conventional STI method as in Eq. 2 and the MMSR-STI method as in Eq. 9 were both implemented using a conjugate gradient based LSQR solver, with the convergence tolerance set to 1×10^{-4} to ensure convergence. For the MMSR-STI method, an accurate isotropic region mask derived from the target MSA image was used for mask M as in Eq. 9 and a boundary image derived from the target MMS image was used for W_g . The regularization parameter α was set to 10 to force the off-diagonal tensor elements in the isotropic regions to be less than 1×10^{-4} ppm. The parameter β was determined to be 0.1 based on the L-curve method (31) by exploring different β values from 1×10^{-4} to 1×10^2 with a step size of a factor of 10. A L-curve with a corner was observed.

In order to compare the conventional STI method and the MMSR-STI method under different inverse conditions, we compared their imaging performances with different maximum head rotation angle $\theta_{\max}$, i.e. the maximum angle between $(\hat{H}_0)_i$ and z' among $i = 1 \dots N$, and with the use of different number of head orientations. We performed the test with the maximum head rotation angle $\theta_{\max}$ varying from 10° to 60° in a step size of 10° and the total number of head orientations varying from 6 to 10. In order to create a reasonable STI inverse condition under each circumstance, with certain $\theta_{\max}$, the zenith of vector $(\hat{H}_0)_i$ in the subject frame for the first 3 head orientations was set to $\theta_{\max}$ with uniformly distributed azimuth angles ($0, 120^\circ, 240^\circ$). The zenith of $(\hat{H}_0)_i$ in other head orientations was then set to $\frac{1}{2}\theta_{\max}, \frac{2}{3}\theta_{\max}, \frac{1}{3}\theta_{\max}$ or 0 depending on the total number of head orientations with appropriate azimuth setting to cover uniformly the part of spherical surface defined by $\theta < \theta_{\max}$.

For quantitative comparison of the imaging performances, relative error was used for evaluating the reconstructed MMS and MSA. Here the relative error was defined as

$$RE = \sqrt{\sum_{n=1}^P (\chi_{t,n} - \chi_{r,n})^2 / \sum_{n=1}^P (\chi_{t,n})^2}$$
 where $\chi_{t,n}$ and $\chi_{r,n}$ are respectively the target and reconstructed variables, e.g. MMS or MSA, at the n th voxel in the phantom; P is the total number of voxels inside the phantom. For evaluating the reconstructed PEV, the absolute angular error between the reconstructed PEV versus the target PEV was calculated. Here the angular error was defined by $AE(r) = \arccos(v_t(r) \cdot v_r(r))$, where $v_t(r)$ and $v_r(r)$ are the target and reconstructed PEV of the susceptibility tensor at location r , respectively. The angular error is in the range of 0° to 90° , taking the smaller angle between $v_t(r)$ and $v_r(r)$ or $-v_r(r)$.

Human brain in vivo data acquisition

For the *in vivo* study, MR phase data was acquired on three healthy volunteers (2 male subjects of 34 y/o and 29 y/o, 1 female subject 26 y/o) after IRB approval and written

informed consent. All subjects were scanned at 3T (Philips Medical Systems, Best, Netherlands) using a relatively large quadrature coil. For the first subject (34 y/o male) MR phase data was acquired at 12 different head orientations and for the other two subjects phase data was acquired at 6 head orientations. MR phase data was acquired using a 3D single-echo GRE sequence with flow compensation, 1.5 mm isotropic resolution, $216 \times 216 \times 135 \text{ mm}^3$ field of view (FOV) with axial slab orientation, matrix size of $144 \times 144 \times 90$, TR/TE = 40/25 ms, flip angle of 15° , bandwidth of 72.5 Hz/pixel, fat suppression was achieved using a water-selective ProSet 121 pulse and scan duration of 11:03 min per acquisition.

We also acquired DTI images at 3T using a single-shot EPI sequence, with 2.2 mm isotropic resolution, $212 \times 212 \times 143 \text{ mm}^3$ FOV, reconstruction matrix size after zerofilling of $256 \times 256 \times 65$, TR/TE = 6800/67 ms, b-value = 700 s/mm^2 , bandwidth of 35.7 Hz/pixel, 32 diffusion encoding gradients and scan duration of 4:25 min per acquisition. Two DTI acquisitions were performed and averaged to increase SNR and accuracy in the diffusion tensor calculation. For image coregistration and selection of different ROIs, T_1 -weighted MPRAGE images were also acquired at 3 T with 1.1 mm isotropic resolution.

Human brain data processing

For each dataset, the GRE magnitude images acquired at all head orientations were coregistered to the magnitude image acquired at normal supine head position by rigid body linear transformation using the FSL FLIRT tool (32). The transformation matrix was then applied on the real and imaginary images and to further generate the coregistered magnitude and phase images. After coregistration, all the data are in the subject frame of reference. The main magnetic field direction in the subject frame ($\hat{H}_0$)_i can then be calculated based on the scanner's angulation parameters and the coregistration transformation matrix. The T_1 -weighted MPRAGE image and DTI images were also coregistered to the GRE magnitude image and put in the same subject frame of reference. Trilinear interpolation was used in the coregistration.

MR phase data collected at each head orientation was unwrapped using a Laplacian-based phase unwrapping method (8). After that, the background gradient field, which is mainly generated by the big susceptibility changes at the air-tissue interfaces, was removed using the modified SHARP method (9, 33) to generate the frequency or magnetic field shift images. For this we used a SHARP deconvolution kernel size of 4.5 mm, the truncated singular value decomposition (tsvd) threshold of 0.05. Combining the frequency maps collected at different head orientations, a QSM image was calculated using the COSMOS method (35). For both STI and the MMSR-STI calculation, the convergence tolerance was relaxed to 1×10^{-3} for the in vivo study because large artifacts and high noise levels were observed in the STI calculation when the convergence tolerance was set to 1×10^{-4} . For the MMSR-STI method, the isotropic region mask M was derived by combining a white matter mask obtained from the coregistered T_1 image using the FSL FAST tool (36) and a mask obtained by thresholding the calculated QSM image to exclude iron rich deep nuclei. The binary image W_g containing the brain tissue boundary priori information was calculated by thresholding the gradient of the QSM image so that 60% of the image voxels in the brain

were considered tissue boundaries. This threshold was reported to be 30% in literature when using GRE magnitude images that have less tissue contrast (10, 11), yet with the QSM image, 60% was selected to better extract tissue boundaries according to visual inspection. In addition, for the MMSR-STI method, the regularization parameter α was set to 10, similar to the simulation study. When doing so, the off-diagonal tensor elements were found to be less than 1×10^{-4} ppm in most voxels in the defined isotropic region, with only a very small amount of voxels ($<0.2\%$ of the isotropic mask) exceeding this limit, but always less than 1×10^{-3} ppm; β was determined to be 0.1 similar to our computer simulation. Using the dataset collected from the first subject, we also calculated the susceptibility tensor maps using both STI and MMSR-STI method with MR phase data collected at different number of head orientations (6–12) with the same maximum head rotation angle. All the data processing were implemented using MATLAB R2011b (The Mathworks, Natick, MA).

The diffusion tensor calculation was conducted using DtiStudio (37). White matter fiber orientations estimated from diffusion tensor were used as a gold standard and compared with those estimated from STI and MMSR-STI. For quantitative comparison, regions of interest covering several big white matter fiber bundles such as corona radiata (CR, including superior and posterior sections) and corpus callosum (CC, including the genu, the body, and the splenium of corpus callosum) were selected based on a multi-contrast (DTI-QSM) human brain atlas (28, 38) using freely available software MRistudio (www.mristudio.org). The angular differences between the fiber orientations estimated from the susceptibility tensor and the diffusion tensor were calculated using the same angular error formula as in the simulation study with the DTI PEV as the target. Fiber tracking using the estimated susceptibility tensor was also briefly tested using the DtiStudio software on major fibers such as CC.

Results

Numerical phantom results

The central slices of the reconstructed MMS, MSA and PEV maps using conventional STI method are shown in Fig. 1d, 1e and 1f, respectively. These results are for magnetic field shift data simulated at 6 head orientations and with a maximum head rotation angle $\theta_{\max}$ of 40° . In comparison to the target susceptibility model (Fig. 1a–1c), the estimated MMS map has a relative error of 6.6%, the estimated MSA map has relative error of 364%. In addition, the angular error of the reconstructed PEV in the anisotropic regions is $24.5^\circ \pm 16.5^\circ$ (mean $\pm$ standard deviation). Using the same set of magnetic field shift data but the MMSR-STI method, the corresponding MMS, MSA and PEV (Fig. 1g–1i) show decreases in the relative error in the MMS and MSA maps to 0.42% and 19%, respectively. The angular error of the estimated PEV in the anisotropic regions decreases to $8.4^\circ \pm 4.8^\circ$.

A more comprehensive comparison of the imaging performance between the STI method and the MMSR-STI method under different inverse conditions is shown in Fig. 2. The red and blue curves represent the imaging performance in terms of relative errors for conventional STI and MMSR-STI, respectively. This is shown for MMS (Fig. 2a and 2b), MSA (Fig. 2c and 2d) and PEV (Fig. 2e). For MMS and MSA, the errors are much smaller

when using the MMSR-STI method and are therefore also shown on an enlarged scale in Figs. 2b and 2d, respectively.

In vivo results

Figure 3 shows example slices of the T_1 -weighted MPAGE image and QSM image of subject 1 that are used to derive the white matter (WM) mask (complement of M as in Eq. 9) and morphology a priori mask used in the MMSR-STI calculation. For subject 1 the 12 head rotation angles were 4.4° , 23.0° , 23.3° , 29.8° , 26.1° , 31.3° , 37.2° , 35.9° , 13.7° , 20.4° , 18.4° , 41.6° . For subject 2 the 6 head rotation angles were 4.1° , 10.2° , 5.4° , 16.7° , 18.9° , 11.6° . For subject 3 the 6 head rotation angles were 1.4° , 16.3° , 17.0° , 24.8° , 22.3° , 13.0° . The MMS, MSA and PEV maps estimated using the conventional STI method on phase data acquired at 10 head orientations on subject 1 are shown in Figures 4a–4c. The corresponding map of angular difference between the DTI PEV and the STI PEV is shown in Fig. 4d. Using the same MR phase dataset and the MMSR-STI method, the calculated MMS (Fig. 4e) and MSA (Fig. 4f) maps become more homogeneous. In addition, the white matter fiber orientations estimated from the susceptibility tensor PEV map (Fig. 4g) resembles more closely the DTI PEV map (Fig. 4k), which can also be seen from the corresponding map of angular difference (Fig. 4h) between the DTI PEV and the MMSR-STI PEV. A difference image generated by subtracting Fig. 4d by Fig. 4h is shown in Fig. 4l in order to highlight the improved estimation (white regions in Fig. 4l) of the fiber orientations. Fig. 5 specifies these angular differences for selected ROIs when using different numbers of head orientations (6–12). The angular differences obtained from all three subjects using only MR phase data at 6 head orientations are summarized in Table 1. The last row of Table 1 represents the decreased difference between the susceptibility tensor and diffusion tensor when using MMSR-STI versus STI.

Discussion and Conclusions

Mapping of the magnetic susceptibility properties of brain tissues has attracted a lot of interest in recent years because of its impressive contrast between different brain structures and its sensitivity to several biologically relevant compounds such as iron and myelin. Originally, most QSM studies assumed tissue susceptibilities to be isotropic, but recent studies (15, 19, 23, 24) indicate that the magnetic susceptibility in white matter fibers is anisotropic. Similar to the anisotropic diffusion in white matter, such anisotropic susceptibility as well as the consequential anisotropic R_2^* (39) may in principle be used for mapping the fiber orientations in white matter (26, 40, 41). Based on the apparent susceptibility tensor model, recent STI studies have shown encouraging potential to map the white matter fiber structures (20–22, 26), yet due to its requirement of acquiring MR phase data at multiple head orientations and the complexity of solving a large-scale inverse problem, it is currently still not suitable for clinical applications. Therefore this study explored a possible regularization strategy for STI that could help improve its performance, especially its estimation on the fiber orientations. Besides assuming that susceptibility anisotropy exists only in white matter area, i.e. Eqs. 4 and 5, the strategy utilizes the first tensor invariant to incorporate certain a priori information into the STI inverse problem. Of course one limitation of this approach is possible inaccuracy of the anisotropic mask. An

incorrect mask would give erroneous estimation of the susceptibility tensor elements and especially the PEV inside and closely around the mask. Several previous studies have shown that magnetic susceptibility anisotropy mainly originates from the myelin sheath around white matter fibers (20, 21, 23, 24), while anisotropy is expected to be small or negligible in gray matter. Restricting anisotropy to white matter therefore is not expected to give substantial artifacts in the MMSR-STI estimations.

Simulations

Our simulations show that by using the conventional STI method, the estimated susceptibility tensors in isotropic regions also exhibit large MSA values with large spatial variations (Fig. 1e), which is consistent with our *in vivo* results (Fig. 4b) and with previous STI studies on humans reported by other groups (20, 22). Besides the overestimation of anisotropy in isotropic regions, moderate spatial variations in the MMS images (Fig. 1g) were also observed. One possible reason for these artifacts that occur when using the STI method may come from the nonlocal nature of the relationship between susceptibility tensor and phase measurements, i.e. analogous to QSM. Any reconstruction error that comes from the ill conditioned inverse problem (because of the sampling ($\hat{H}_0$); not being well distributed over space) may get projected to surrounding or even distant locations. Suppression of these artifacts is the major motivation for using the anisotropy and morphology constraints in the proposed MMSR-STI method. In addition, since we are estimating the full tensor, the improved estimation of MMS and MSA would subsequently help improve the estimation of the PEV of the tensor.

In the present study, we tested two major factors that could affect the STI inverse conditions, i.e. the number of head orientations and the maximum head rotation angle. As shown in Fig. 2, using the current setup with at least 6 head orientations and 3 of them at maximum rotation angle, it seems that the angle range plays the more important role of these two factors in terms of improving the tensor estimation either using STI or MMSR-STI. Only when the head rotation angle is limited to 10°–20° can we see noticeable improvement by using more than 6 head orientations. In practice, a 10°–20° rotation is about the limit achievable in the relatively small 7T head coil. At 3T this rotation range can reach 30°–40° for our setup and even larger as reported by other groups (9, 20). It is clear from Fig. 2 that the proposed MMSR-STI method gives much better estimation of the susceptibility tensor than the conventional STI method. Yet it should also be noticed that, when the head rotation range is limited, e.g. at 20°, the MMSR-STI method still gives about 30% relative error in the reconstructed MSA, partly because of the small anisotropic effect in white matter (0.01–0.02 ppm) (15, 20–22) and about 20° in terms of the angular error in the reconstructed PEV. In addition, it should be noted that in the simulation study, we used perfect a priori information i.e. accurate isotropic region and morphology masks. In practice, however, such perfect a priori information is generally not easy to obtain and less improvement by the proposed MMSR-STI approach over STI is expected when the a priori masks contain errors.

In vivo human data

When using the conventional STI method, similar imaging artifacts in MMS and MSA were also observed in our *in vivo* human study, i.e. overestimation of anisotropy in CSF and gray

matter regions and large spatial variations in MSA image (Fig. 4b) and moderate spatial variations in MMS (Fig. 4a). The MMSR-STI method in comparison gives a much homogeneous MMS and MSA maps (Fig. 4e and 4f).

As shown in Fig. 5, when using the same maximum rotation angle, the estimated fiber orientation by either the STI method or the MMSR-STI method does not improve significantly by using MR phase measurements collected at more than 6 head orientations. This is consistent with our simulation study in Fig. 2. As shown in both Fig. 5 and Table 1, overall, by using the proposed regularization, the angular difference between the PEV of the susceptibility tensor and the diffusion tensor decreases in most selected white matter fiber bundles. However, the results also indicate that the improvements from the MMSR-STI approach are less in the human dataset than in the simulations. One reason may be less accurate a priori structural information for the human study. Another may be the presence of additional MR phase contributions that cannot be fully described by the bulk susceptibility tensor model, such as the effect of multiple cellular microstructures with different orientations (42).

Recent STI studies in *ex vivo* mouse brain have demonstrated the possibility of using susceptibility anisotropy information to study the white matter fiber orientations and tracking some major fibers (26) in the same manner as DTI. However, similar to the present study (Fig. 4), STI on *in vivo* human subjects also did not give very consistent estimation on the fiber orientations in comparison with DTI (20, 22). This can be partly explained by the different mechanisms underlying these two anisotropy measures, i.e. bulk susceptibility anisotropy in white matter originates from the lipid molecules in the myelin sheath (20, 23, 24, 43), while the diffusion anisotropy is mainly determined by water motion restricted by axonal symmetry plus a 20–30% myelin contribution (44). Another possible reason for this methodological difference is the magnitude of the errors consequential to the STI inverse reconstruction. The proposed MMS-regularization strategy is expected to partly correct for these errors. However as shown in the current study, even with the MMSR-STI method, the susceptibility tensor PEV was still not coherent enough for tracking major fibers in the human brain and further improvements in the data acquisition, preprocessing and STI inverse calculation are needed to make this technique of clinical value. Assessing the even smaller higher order susceptibility anisotropy effect that can be estimated from the p-space susceptibility multipole may be another valuable technique towards this goal (45). In addition, there are other tensor invariants that may be candidates for helping regularize the STI inverse problem (46). However most of them are in general nonlinear functions of the tensor components therefore it is more difficult to use these invariants because of the need to develop a nonlinear inverse solver for STI.

In conclusion, we propose the use of anisotropy and morphology constraints to regularize the ill-conditioned STI inverse problem. The results from computer simulations and *in vivo* human studies show that the proposed MMSR-STI method improves estimation of the susceptibility tensor principle eigenvector orientations in white matter.

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FIG. 1.

Numerical head phantom with one paramagnetic isotropic component (positive MMS) and three perpendicular diamagnetic structures (negative MMS), each with a cylindrically symmetric susceptibility tensor with $MSA = 0.018$ ppm. The first row shows maps of the target mean magnetic susceptibility (MMS) (a), magnetic susceptibility anisotropy (MSA) (b) and principle eigen vector (PEV) in anisotropic regions (c) of the susceptibility tensor model used for the simulation. The second row shows the reconstructed MMS (d), MSA (e) and PEV map in anisotropic regions (f) using the conventional STI method. The third row shows the corresponding MMS (g), MSA (h) and PEV map in anisotropic regions (i) using the MMSR-STI method.

FIG. 2.

Performance of the conventional STI (red curves) and MMSR-STI methods (blue curves) as a function of number of head orientations and maximum head rotation angle. Performance was evaluated in terms of the relative error in the reconstructed MMS (a), MSA (c) and absolute angular error in PEV maps (e). Panels (b) and (d) are enlarged plots of (a) and (c), respectively, to highlight the performance of the MMSR-STI method on an enlarged scale. Error bar in (e) indicates standard deviation. In the legend, the number indicates MR phase data from how many head orientations were used for the STI or MMSR-STI calculation, e.g. STI-O6 represents results using 6 head orientations and the STI method.

FIG. 3.

Example image slices of the white matter mask (complement of M as in Eq. 9) and morphology binary mask derived from the T1 MPRAGE and QSM images of subject 1. Note that the morphology binary mask shown here is a dot product of three binary weighting matrices derived from thresholding the spatial gradient of the QSM image in three orthogonal directions, i.e. $W_{gx} \cdot W_{gy} \cdot W_{gz}$

FIG. 4.

Comparison of STI, MMSR-STI and DTI imaging results for the human brain. The first row shows MMS (a), MSA (b) and PEV (c) maps based on phase data collected at 10 different head orientations from subject 1 and calculated using conventional STI. (d) shows a map of the angular difference between the PEV of the susceptibility (c) and diffusion (k) based tensors. The second row shows MMS (e), MSA (f) and PEV (g) maps calculated using the MMSR-STI method. The angular difference map (h) reflects the difference between (g) and (k). The corresponding DTI measurements are shown in (i) FA weighted colormap, (j) DTI FA map, (k) DTI PEV map. (l) shows a difference map by subtracting (h) from (d), showing that as compared to conventional STI, MMSR-STI gives smaller angular difference (white areas in (l)) between the estimated susceptibility tensor and diffusion tensor.

FIG. 5.

Comparison of the angular difference between the DTI PEV and STI PEV estimated by the conventional STI method (red curves) versus the MMSR-STI method (blue curves) for the human results at 3T. The comparison was done in different white matter fibers, i.e. SCR, PCR, GCC, BCC and SCC, with the use of phase data collected at different numbers of head orientations (6 to 12). SCR: superior corona radiata, PCR: posterior corona radiata, GCC: genu of corpus callosum, BCC: body of corpus callosum, SCC: splenium of corpus callosum. Error bar indicates standard deviation.

Table 1

Angular difference between the PEV of DTI and the susceptibility tensor estimated by conventional STI or the MMSR-STI

	$\theta_{\max}$	Method	Angular Difference (Mean $\pm$ Standard Deviation, in the unit of degree)					
			SCR	PCR	GCC	BCC	SCC	
S1	41.6°	STI	63.9±18.6	54.2±22.4	68.2±14.8	56.2±18.4	50.1±23.0	
		MMSR-STI	56.1±20.8	51.1±22.8	64.5±20.1	54.2±19.0	51.4±23.0	
S2	18.9°	STI	58.6±21.9	53.5±21.9	59.1±21.0	51.9±21.1	60.7±22.1	
		MMSR-STI	56.8±21.4	49.9±21.8	62.3±17.9	51.5±20.5	43.8±23.6	
S3	24.8°	STI	54.9±21.7	51.7±21.7	53.5±22.9	60.4±24.8	57.7±20.9	
		MMSR-STI	64.5±16.9	50.9±20.5	45.2±18.2	58.8±19.8	34.9±23.0	
		Angular difference decrease by using MMSR-STI (n=3)		-0.0±7.2	2.5±1.2	3.0±4.7	1.3±0.7	12.8±10.3

S1, S2 and S3 represent the three subjects; $\theta_{\max}$ is the maximum angle between $(\hat{H}_0)_j$ and $\hat{z}'$ in the subject frame among 6 head orientations for each dataset. SCR: superior corona radiata, PCR: posterior corona radiata, GCC: genu of corpus callosum, BCC: body of corpus callosum, SCC: splenium of corpus callosum.