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MEDI+0: Morphology Enabled Dipole Inversion with Automatic Uniform Cerebrospinal Fluid Zero Reference for Quantitative Susceptibility Mapping

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Abstract

Purpose—To develop a quantitative susceptibility mapping (QSM) method with a consistent zero reference using minimal variation in cerebrospinal fluid (CSF) susceptibility.

Theory and Methods—The ventricular CSF was automatically segmented on the R_2^* map. An L_2 -regularization was employed to enforce CSF susceptibility homogeneity within the segmented region, with the averaged CSF susceptibility as the zero reference. This regularization for CSF homogeneity was added to the model used in a prior QSM method (Morphology Enabled Dipole Inversion, MEDI). Therefore, the proposed method was referred to as MEDI+0 and compared with MEDI in a numerical simulation, in Multiple Sclerosis (MS) lesions and in a reproducibility study in healthy subjects.

Results—In both the numerical simulations and in vivo experiments, MEDI+0 not only decreased the susceptibility variation within the ventricular CSF, but also suppressed the artifact near the lateral ventricles. In the simulation, MEDI+0 also provided more accurate quantification compared to MEDI in the globus pallidus, substantia nigra, corpus callosum and internal capsule. MEDI+0 measurements of MS lesion susceptibility were in good agreement with those obtained by MEDI. Finally, both MEDI+0 and MEDI showed good and similar intra-subject reproducibility.

Conclusion—QSM with a minimal variation in ventricular CSF is viable to provide a consistent zero reference while improving image quality.

Keywords

QSM; zero reference; CSF homogeneity

INTRODUCTION

Quantitative susceptibility mapping (QSM) (1,2) advances MRI study of tissue magnetism from qualitative detection of blooming effects in magnitude and phase images to quantitative

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measurements of spatial distribution (3). Susceptibility measurements on QSM are meaningful only with respect to a chosen reference, given the fact that an arbitrary constant shift in QSM induces no change in the field perturbation due to singularity of dipole kernel at the k-space center. To resolve this issue, a common tissue is chosen whose susceptibility is subtracted from the susceptibility measurements of other tissues. This procedure is referred to as zero-referencing, which is necessary for longitudinal and cross-institutional studies. For brain parenchymal QSM, cerebrospinal fluid (CSF) is widely used as the zero reference because of its chemical resemblance to pure water (4). Unfortunately, ventricular CSF in current QSM is often non-uniform, which causes the uncertainty of the reference susceptibility (4,5). Literature suggests that CSF flow (6,7) and white matter anisotropy (8) might contribute to this variation in the estimated CSF susceptibility.

One of the central challenges in QSM is the presence of streaking artifacts that are caused by amplified noise during the ill-posed field-to-source inversion (9,10). These artifacts can be suppressed by regularizing the inversion, using a tissue structure prior as in current Bayesian QSM (morphology enabled dipole inversion, MEDI (11,12)). Similarly, we may use regularization in QSM recon to suppress ventricular CSF susceptibility inhomogeneity. The scalar field-to-source inversion of field contributions of anisotropic white matter may cause non-local artifacts in QSM, particularly in ventricles that are surrounded by white matter. We formulate a regularization that enforces the susceptibility homogeneity inside the ventricular CSF. In this paper, we present preliminary data demonstrating that minimal susceptibility variation in CSF can be achieved for a consistent and automated zero referencing of QSM, which is referred to as MEDI+0. Furthermore, MEDI+0 brings about additional image quality improvement.

THEORY

The optimization problem for QSM in literature has become converged to a MEDI type Bayesian formation (13–18):

$$\chi^* = \underset{\chi}{\operatorname{argmin}} \frac{1}{2} \|w \left(e^{-if} - e^{-i(d*\chi)} \right)\|_2^2 + \lambda_1 \|M_G \nabla \chi\|_1 \quad [1]$$

with χ the susceptibility map, $*$ the convolution operation, w the noise weighting, f the measured local field, ∇ the gradient operator and M_G the binary edge mask derived from the magnitude image (11). d is the dipole kernel which can be defined in both Fourier and spatial domains:

$$d = \text{FT} \left[\frac{1}{3} - \frac{k_z^2}{k^2} \right] = \frac{1}{4\pi} \frac{3\cos^2(\theta) - 1}{r^3} \quad [2]$$

where r is the magnitude of position vector $\mathbf{r}$ from the dipole source to the field observer, k is the magnitude of the corresponding Fourier vector $\mathbf{k}$ in k-space. k_z is the component of $\mathbf{k}$ along the B0 direction, and θ is the angle between $\mathbf{r}$ and the B0 direction.

In this work, we propose a method called MEDI+0 which solves:

$$\chi^* = \underset{\chi}{\operatorname{argmin}} \frac{1}{2} \|w \left(e^{-if} - e^{-i(d*\chi)} \right)\|_2^2 + \lambda_1 \|M_G \nabla \chi\|_1 + \lambda_2 \|M_{CSF} (\chi - \overline{\chi_{CSF}})\|_2^2, \quad [3]$$

which adds to MEDI (Eq. 1) an L_2 -regularization with M_{CSF} the ROI of ventricular CSF and $\overline{\chi_{CSF}}$ mean susceptibility within M_{CSF} . This additional term penalizes susceptibility variation within M_{CSF} in the search for a solution with homogeneous CSF susceptibility.

We propose an automated procedure to determine the ventricular CSF mask M_{CSF} from the brain ROI mask M and the R_2^* map by taking advantage of the low R_2^* values of CSF and by imposing connectivity. Implementation for automated generation of M_{CSF} consists of the following steps:

- a. Threshold $R_2^*: M_{R_2^*} \triangleq R_2^* < R$, for a given threshold R .
- b. Define brain centroid: $c = \frac{1}{N} \sum_{r \in M} r$, where N is the number of voxels in M .
- c. Define central brain region: $M_c \triangleq \{r \mid \|r - c\|_2 < 3\text{cm}\}$.
- d. Analyze connectivity in $M_c \cap M_{R_2^*}$: divide $M_c \cap M_{R_2^*}$ into connected components M_{ci} (6-neighbour) and merge the largest 3 components: $M_{cCSF} \triangleq \{M_{c1} \cup M_{c2} \cup M_{c3}\}$.
- e. Analyze connectivity in $M_{R_2^*}$: divide $M_{R_2^*}$ into connected components M_i (6-neighbour) and merge all components that overlap with M_{cCSF} : $M_{CSF} \triangleq \{\cup M_i \mid M_i \cap M_{cCSF} \neq \emptyset\}$.

The proposed algorithm introduces two new parameters: (λ_2, R) , which will be determined later using a numerical simulation. The problem in Eq. 3 is solved using Gauss Newton Conjugate Gradient (11). As a final step, $\overline{\chi_{CSF}}$ is subtracted from the entire map for zero referencing.

METHODS

Numerical simulation

We constructed a numerical brain phantom to simulate the CSF inhomogeneity related to anisotropic susceptibilities (Supporting Figure S1). The susceptibility tensor was originally reconstructed from the 12-orientation data (matrix size=256×256×126, voxel size=1×1×1.5 mm, TE=2.6 ms) in (19) using susceptibility tensor imaging (STI) (20). The ventricular CSF region was manually drawn (Y.Y., 4 years of experience). Under the assumption that ventricular CSF is homogeneous and hence not a source for susceptibility anisotropy, susceptibility was set to 0 for CSF in each susceptibility tensor element. The B0 direction was set to $\widehat{B_0} = [0, 0, 1]^T$, such that only three components ($\chi_{13}, \chi_{23}, \chi_{33}$) of the full susceptibility tensor were necessary for computing the forward field in simulating the effect of anisotropic susceptibility, while other tensor elements simply did not contribute to the

field in this orientation and were therefore not included. Then the synthetic local tissue field was generated in two ways: first, a tissue field f_{aniso} was generated with $\{\chi_{13}, \chi_{23}, \chi_{33}\}$ using the anisotropic forward tensor model (FT denotes Fourier Transform):

$$f_{\text{aniso}} = \text{FT}^{-1} \left[\left(\frac{1}{3} - \frac{k_z^2}{k^2} \right) \text{FT}[\chi_{33}] - \frac{k_x k_z}{k^2} \text{FT}[\chi_{13}] - \frac{k_y k_z}{k^2} \text{FT}[\chi_{23}] \right] \quad [4]$$

Second, a tissue field f_{iso} was generated solely with χ_{33} using the isotropic forward scalar model:

$$f_{\text{iso}} = \text{FT}^{-1} \left[\left(\frac{1}{3} - \frac{k_z^2}{k^2} \right) \text{FT}[\chi_{33}] \right] \quad [5]$$

Gaussian noise (SNR=100) was added to both fields. MEDI and MEDI+0 were applied to both fields. The root-mean-square-error (RMSE) between the reconstructed χ and the simulated true susceptibility map χ_{33} , $\|\chi - \chi_{33}\|_2 / \|\chi_{33}\|_2$, was calculated. λ_1 was determined by minimizing RMSE for MEDI (Eq. 1), and the same value was used for MEDI+0 (Eq. 3). λ_2 and R in MEDI+0 were jointly determined by minimizing RMSE. A region in 10mm proximity to the ventricular CSF was determined by convolving the binary CSF mask with a spherical kernel (radius 10mm) followed by thresholding: pixels with values over 0.001 were retained in the new mask. RMSE was also calculated within this region for both MEDI and MEDI+0. Susceptibility was measured within ROIs drawn in the globus pallidus (GP), substantia nigra (SN), posterior limb of internal capsule (IC), and splenium of corpus callosum (CC) for quantitative analysis.

In vivo experiment: Multiple Sclerosis

The brains of 8 patients with Multiple Sclerosis (MS) were imaged using multi-echo GRE at 3T (GE, Milwaukee, WI). All studies in this work were approved by our Institutional Review Board. Imaging sequences were: T2w fast spin echo (Flip angle=90, FOV=24 cm, TE=86 ms, TR=5250 ms, slice thickness=3 mm, acquisition matrix=416×256×68) and 3D T2* w spoiled multi-echo GRE (Flip angle=20, FOV=24 cm, TE1=4.3 ms, TR=57 ms, #TE=11, TE=4.8 ms, acquisition matrix=512×512×68, voxel size=0.47×0.47×2 mm³, BW=±62.5 kHz, A/P monopolar readout with flow compensation for all echoes, parallel imaging factor R=2 and a total scan time of ~10 min). Nonlinear field map estimation followed by graph-cut-based phase unwrapping (21) was applied to estimate the total field, then projection onto dipole fields (PDF) (22) was used for background field removal in order to obtain the local field. Next, MEDI+0 (using the parameters determined from the simulation) was compared with MEDI, which has been previously used for MS lesion assessment (23,24), using the same local field as input. To measure lesion susceptibility, one neuroradiologist (Y.Z., 4 years of experience) drew an ROI of each lesion on the T2w images, which were registered onto magnitude images of the T2* w scan. Reference regions for lesion susceptibility were determined by drawing an ROI in the normal appearing white matter (NAWM) on the contralateral side of the identified lesion (24). The difference of mean susceptibilities between the lesion and NAWM were measured and analyzed using linear correlation and Bland-Altman plots to quantify the agreement between MEDI and

MEDI+0. Mean susceptibility was also measured within ROIs in the gray matter (GP and SN) and white matter (IC and CC) for each subject for quantitative analysis. The segmented ventricular CSF region was used as zero reference for MEDI.

In vivo experiment: Reproducibility

The brains of 5 healthy subjects were imaged using multi-echo GRE at 3T (GE, Milwaukee, WI). All studies were approved by our Institutional Review Board. Imaging sequence was 3D T2* w spoiled multi-echo GRE (Flip angle=20, FOV=24 cm, TE1=4.3 ms, TR=52 ms, #TE=11, TE=4.4 ms, acquisition matrix=384×384×64, voxel size=0.63×0.63×2 mm³, BW=±62.5 kHz, A/P monopolar readout with flow compensation for all echoes, parallel imaging factor R=2 and a total scan time of ~8 min). Each subject was scanned twice, with the two scans separated by 10 minutes during which the subjects exited and reentered the scanner to be repositioned (25). These scans were referred to as Scan 1 and Scan 2. The local field was estimated as described for the MS data above. QSM was reconstructed using MEDI+0 and MEDI with the parameters as determined from the simulation. Reproducibility assessment was performed for each method separately, using Bland-Altman plots and linear regression analysis on measurements obtained for regions of interest (ROI) which cover major structures in gray matter, white matter and CSF (Supporting Figure S5). ROIs were manually drawn on QSM of Scan 1 for each subject, and after registering Scan 2 to Scan 1, the same ROIs were copied to corresponding registered QSM. Mean susceptibility within each ROI was recorded. For the MEDI+0 measurement, no further zero referencing was needed. For MEDI, the mean susceptibility within the CSF ROI manually drawn in the posterior lateral ventricles was subtracted from the measurement of all other ROIs for zero referencing (25).

RESULTS

Numerical simulation

Figure 1 shows the comparison of simulated true susceptibility χ_{33} , QSM reconstructed with MEDI and MEDI+0 given field input f_{aniso} and f_{iso} , respectively. Given f_{iso} as the input, both MEDI and MEDI+0 achieved relatively small RMSEs (22.4% and 29.1% respectively) compared to χ_{33} . The standard deviation of susceptibility within the segmented ventricular region was 5.1ppb for MEDI and 1.7ppb for MEDI+0. When susceptibility anisotropy was simulated (f_{aniso}), MEDI+0 produced a lower RMSE (73.7%) than MEDI (76.1%). The RMSE within a 10mm proximity of the ventricular CSF mask was 65.1% for MEDI+0 and 73.5% for MEDI, reflecting a reduced hypointense shadow artifact near the SN (red arrows in Figs. 1h and 1i). The standard deviation of susceptibility within the ventricular CSF were 28.1ppb for MEDI and 9ppb for MEDI+0. This reduced variation for MEDI+0 is also appreciated in the highlighted CSF QSM in Figs. 1j and 1k.

The optimized parameters values were $\lambda_1 = 0.001$ for MEDI and $\lambda_1 = 0.001$, $\lambda_2 = 0.1$, $R = 5 s^{-1}$ for MEDI+0. These values were used throughout this work. Keeping R fixed at $5 s^{-1}$, RMSE for MEDI+0 was minimized at 73.7% for $\lambda_2 = 0.1$ (Supporting Figure S2a). For $\lambda_2 \in [0.01, 1]$, RMSE was raised by less than 1%. Keeping λ_2 fixed at 0.1, RMSE was minimized at 73.7% for $R = 5 s^{-1}$ (Supporting Figure S2b). When R was too large ($R=12$),

structures outside the ventricles were included in the segmentation, while for R too small ($R=1$), the depiction of the ventricles was incomplete, especially the 4th ventricle anterior to the cerebellum (Supporting Figure S2c). As R increased from 5 to 8, the RMSE was below 75% with no significant change observed in QSM quality.

Supporting Figure S3 shows a comparison of ROI measurements for GP, SN, CC and IC. For f_{iso} , MEDI and MEDI+0 achieved almost identical accuracy in estimating each tissue (Supporting Figure S3a). When f_{aniso} was the input, MEDI+0 measurement of the mean susceptibility for each tissue was closer to χ_{33} compared to MEDI. The change of mean ROI susceptibility in MEDI+0 compared to MEDI was: GP: 7ppb, SN: 7ppb, CC: -11ppb, IC: 3ppb (Supporting Figure S3b).

In vivo experiment: Multiple Sclerosis

Figure 2 shows an example of reconstructed brain QSMs using MEDI and MEDI+0 for one MS patient. Hypointense shadow artifacts were suppressed in the region inferior to the horns of lateral ventricle and anterior to the substantia nigra, indicated by red arrows in Figure 2. The standard deviation of susceptibility within the segmented ventricular CSF mask M_{CSF} was 5-fold lower in MEDI+0 as compared to MEDI (Supporting Figure S4a). For each ROI (GP, SN, CC and IC), the susceptibility across the 8 subjects (all units in ppb) were 142.2 ± 42.5 (GP), 170.6 ± 56.7 (SN), -29.3 ± 9.9 (CC) and -60.9 ± 6.5 (IC) for MEDI. The corresponding values obtained with MEDI+0 were 149.6 ± 44.0 (GP), 180.1 ± 57.2 (SN), -37.9 ± 9.2 (CC) and -59.3 ± 6.5 (IC). The average changes in susceptibility from MEDI to MEDI+0 (GP: 7.3ppb, SN: 9.5ppb, CC: -8.6ppb, IC: 1.7ppb) were consistent with those found in the simulation, while the standard deviations were similar. Detailed ROI measurements per subject can be found in Supporting Figures S4b–S4e.

Figure 3 shows the T2w image, R_2^* map, segmented CSF mask, MEDI and MEDI+0 results in two axial cross sections for one MS patient. Heterogeneous structures within the ventricles were observed, particularly for the choroid plexus which had hypo-intense signal on T2w image and high value on R_2^* . The proposed segmentation procedure managed to detect mainly CSF and exclude the choroid plexus whose R_2^* was higher than $R = 5s^{-1}$. Consequently, MEDI+0 improves the homogeneity of ventricular CSF only, while preserving the paramagnetic vascular structure (red arrows) and the diamagnetic calcification (yellow arrows) in the choroid plexus.

In measurements of lesion susceptibility relative to NAWM, MEDI+0 showed a strong correlation with MEDI ($k = 1.15$, $R = 0.96$) for all 23 lesions from 8 patients (Figure 4). Bland-Altman analysis of MEDI+0 compared to MEDI revealed a small bias of 0.24ppb with narrow $[-8.0, 8.5]$ ppb 95% limits of agreement.

In vivo experiment: Reproducibility

Data analysis using ROI measurements from all subjects showed good reproducibility (Figure 5) for both MEDI and MEDI+0. For MEDI, measurement of Scan 1 vs. Scan 2 showed correlation coefficient $R = 0.98$ and slope $k = 0.95$, while MEDI+0 attained $R = 0.99$ and $k = 0.96$. Bland-Altman plots showed a bias of 0.59 ppb with 95% limits of agreement

of $[-17, 18]$ ppb for MEDI, and a bias of -1.5 ppb with 95% limits of agreement of $[-17, 14]$ ppb for MEDI+0.

DISCUSSION

In this work, the MEDI+0 method is proposed using automated ventricle segmentation combined with L_2 -regularization of ventricular CSF susceptibility variation for single orientation QSM. Our data demonstrate that MEDI+0 reduces artifacts, including ventricular CSF susceptibility inhomogeneity and hypointense shadows near the ventricles, which may be induced by susceptibility anisotropy of the adjacent white matter. Meanwhile, MEDI+0 does not affect the tissue contrast of MS lesions relative to NAWM. Good reproducibility was observed using MEDI+0, comparable with that of MEDI. Therefore, MEDI+0 enables a consistent CSF based zero referencing.

Zero referencing is needed in QSM for susceptibility quantification, because the measured tissue field is invariant with any uniform shift in the susceptibility distribution. Because CSF is chemically similar to pure water, it is a common choice for zero reference, using a manually drawn ROI in the posterior of the lateral ventricles (4). However, the size of the ventricles strongly varies across subjects (4), and CSF often appears non-uniform in QSM. Consequently, the measured CSF value is sensitive to the choice of ROI (5), bringing an inter-subject uncertainty in the zero referencing step. The MEDI+0 method described here revives the idea of utilizing a known uniform region as proposed in the original QSM paper (2), and now is fully developed to address the zero-reference challenge in two aspects. First, it eliminates the need for manually drawing the CSF ROI, since the ventricular CSF is automatically segmented and used as zero reference region. Second, it enforces CSF homogeneity during reconstruction, thereby decreasing the sensitivity of zero-referencing to the ROI, as is evidenced by the smaller standard deviations within the ventricular CSF in Supporting Figure S4a.

The insight for the described CSF-specific regularization comes from studying the origin of the CSF inhomogeneity in current QSM, which may be induced by anisotropy of the surrounding white matter tracts (8). The anisotropic influence of white matter on the frequency map has been extensively studied in literature: He and Yablonskiy (26) proposed a Generalized Lorentzian Approach (GLA) to analyze the local frequency shift induced by the longitudinal cellular microstructure in white matter, which was later experimentally validated in (27). Lee et al. (28) showed that the white matter tracts also had a non-local orientation-dependent influence on the field at the boundaries and outside the tissue, suggesting that scalar dipole inversion has limited capacity in fully resolving this anisotropic influence. Susceptibility tensor imaging (STI), which was first developed by Liu (29), can recover a full susceptibility tensor directly addressing the white matter anisotropic contribution using multiple orientation scans, and was further developed and applied on animal (29) and human (19,20,30,31). This non-local frequency perturbation was attributed to the lipid molecules within the myelin sheath, as first discussed by Lounila et al. (32) then later in (19,20,33). Utilizing the radial orientation of the lipid molecules, Wharton and Bowtell (33) designed a hollow cylinder fiber model to account for both white matter microstructure and anisotropy, which was then applied (34–36) to mapping orientation of

white matter fibers. Sukstanskii and Yablonskiy (37) provided a similar framework to model both local and non-local frequency perturbation by complementing GLA with lipoprotein structure within the myelin sheath. It is suggested that the non-local influence of white matter anisotropy cannot be fully resolved by only using scalar dipole inversion, while the unresolved component induces artifacts non-local to the white matter that is superposed onto nearby regions. In the current work, the white matter anisotropy was targeted as the major cause of the inhomogeneity of the estimated CSF susceptibility due to presence of white matter immediately adjacent to the ventricles. This was investigated using a numerical phantom, where the field contribution of anisotropic components (χ_{13} and χ_{23}), demonstrated as $f_{\text{aniso}} - f_{\text{iso}}$ (Supporting Figure S1), generated spatially smooth shadow artifacts in QSM in Figs. 1h and 1i. With the CSF homogeneity enforced in MEDI+0, shadow artifacts were suppressed markedly at the deep brain nuclei (Figure 1i). Similar observations were made in vivo (Figure 2). In the simulation, MEDI+0 achieved more accurate ROI measurements for GP, SN, CC and IC compared to MEDI in the presence of anisotropy contributions (Supporting Figure S3b). Accordingly, the L_2 -regularization in MEDI+0 reduced the shadow artifacts present at both the interior and neighborhood of CSF by penalizing the susceptibility variation within CSF, and quantitatively improved QSM near the ventricular CSF.

It should be noted that other sources might also be responsible to the CSF inhomogeneity or the shadowing artifact present near the ventricles for in vivo case, as seen in Figure 2. One possible source is the flow through lateral ventricles (6,7). It has been shown (7) that flow can degrade visualization of cortical veins in brain QSM. However, the peak systolic velocity of CSF flow is reported as 3~5 cm/s (38,39), which is much smaller than that of major veins in the brain such as superior sagittal sinus (10~20 cm/s) (40–42). It was found that for the superior sagittal sinus, quadratic fitting, which accounts for the phase induced by flow in the presence of field inhomogeneity, dramatically improves the fitting of phase signal across echoes, while, in the lateral ventricle no such improvement was observed (see Supporting Figure S6). This indicates that the effect of flow on CSF inhomogeneity might be small. Another possible source is the unresolved background field, which is prominent near the boundary of the brain. Using the same in vivo data of Figure 2, it can be shown that, when both PDF and MEDI were performed with a brain mask eroded by 3 voxels, most of the shadowing artifact remain unchanged (see Supporting Figure S7). This suggests that unresolved background field in the vicinity of air-tissue interface is not the only contributor for the shadowing artifact shown in Figure 2.

The L_2 -regularization of CSF susceptibility variation is conceptually similar to using weighted Total Variation (11,43) as a morphology prior which helps reduce streaking artifacts. Deconvolving the dipole kernel is an ill-posed inverse problem caused by the fact that the dipole kernel is zero on the cone surface defined by $k_z^2 = k^2/3$ in k-space. This allows streaking artifacts that can be seen as wave propagations associated with granular noise errors in the measured field (9,10). The Bayesian strategy for reducing streaking is to employ a prior term to penalize structures (edges) that are not consistent with tissue structures in anatomic (typically magnitude) images. Similarly, the CSF susceptibility inhomogeneity and shadow artifacts may be regarded as artifacts arising from spatially

smooth errors, such as $f_{\text{aniso}} - f_{\text{iso}}$ in Supporting Figure S1. A corresponding strategy to reduce these artifacts is to employ a prior term that penalizes CSF susceptibility variation, as described in this MEDI+0 work. It is noted that de Rochefort (2) proposed a similar framework penalizing the L_2 -norm of χ itself rather than $\chi - \bar{\chi}$ as used in the current work.

MEDI+0 may directly improve the delineation of deep gray nuclei, including the subthalamic nucleus, which is an important surgical target of deep brain stimulation (44). The zero reference in MEDI+0 will be very useful for longitudinal studies as in time-course investigation of multiple sclerosis lesions (23), for differentiation of diamagnetic materials from paramagnetic ones (45,46), for estimating the oxygenation level of venous blood (7,47,48) and tissue (6), for measuring biodistributions in magnetically labeled drug delivery (49,50), and for monitoring iron level during iron chelating therapy (51). As QSM has already been used in clinical applications, it is important to examine the extent to which MEDI+0 alters the relative contrast between tissues outside the CSF. For measuring relative susceptibility differences between MS lesions and NAWM (Figure 4), the strong agreement between MEDI and MEDI+0 suggests that MEDI+0 does not introduce significant changes in this relative tissue contrast. This work also demonstrated that MEDI+0 has a nearly identical reproducibility performance as MEDI (Figure 5), but eliminates the need for manual zero referencing to CSF. Therefore, MEDI+0 can be readily applied to the lesion contrast measurement as in literature (23,24,46).

Future work can be conducted in the following areas. First, our MEDI+0 is intrinsically limited by the scalar dipole model (Eq. 5). STI (19,20) would provide a more accurate model for white matter anisotropy, further suppressing the residual artifacts in Figure 1i. However, this would require multiple orientation measurements which are more challenging in clinical practice. Second, the proposed automated segmentation requires R_2^* which is typically only available in a multi-echo scan. If only single-echo data is available, other sophisticated segmentation methods such as FAST (52) may be used. Other image contrasts, such as proton density/T1/T2, may complement the proposed segmentation for the single-echo case. Third, the current work relies on the assumption that the susceptibility of ventricular CSF is homogeneous and approximately the same as water. In the future, the performance of MEDI+0 will be examined in case of abnormal CSF composition such as the leakage of blood from basal ganglia hemorrhage into the ventricles, where the CSF susceptibility might be inhomogeneous or different from pure water. Fourth, in this work we mainly focused on anisotropy contribution to CSF inhomogeneity and shadowing artifact. Future work might be conducted in assessing the extent to which flow or unresolved background field affects inhomogeneity besides anisotropy, using a fully flow compensated sequence (7) or more accurate background field estimation such as with Total Field Inversion (53). Finally, recent work showed that fat can be used as a zero reference tissue in liver QSM (54) and that the susceptibility of subcutaneous fat can be estimated in the head (53). A future study can be conducted that compares CSF based and fat based zero referencing for brain QSM.

CONCLUSION

In summary, the proposed MEDI+0 method uses automatic segmentation of CSF and enforcement of susceptibility homogeneity within the ventricular CSF to reduce QSM artifacts from susceptibility anisotropy and provides a consistent zero referencing for QSM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Simulation result: (a) χ_{33} . When f_{iso} is used as input field, QSM is shown for MEDI (b) and MEDI+0 (c). When f_{aniso} is used as input field, QSM is shown for MEDI (f) and MEDI+0 (g). (d, e, h, i) are the difference maps between (b, c, f, g) and χ_{33} (a), respectively. The CSF susceptibility in (f, g) is highlighted in (j, k) respectively.

Figure 2.

In vivo result: Examples of magnitude (left), QSM using MEDI (middle) and MEDI+0 (right). A hypo-intensity artifact close to anterior horn of the lateral ventricles is suppressed using MEDI+0 (indicated by red arrows).

Figure 3.

In vivo CSF segmentation: From left to right: T2w images, R2* map, segmented CSF ROI, QSM reconstructed by MEDI and MEDI+0. Choroid plexus is discernable with low signal on T2w image (indicated by arrows) and high values on R2*, as shown in two different slices. The proposed automatic segmentation excludes the choroid plexus by its high R2*. MEDI+0 improves the homogeneity of the CSF only, while preserving the paramagnetic vascular structure of choroid plexus (red arrows), which contains iron, and the diamagnetic calcification in the choroid plexus (yellow arrow).

Figure 4.

Scatter (left) and Bland-Altman (right) plots of QSM measurements of all 23 Multiple Sclerosis lesions relative to NAWM. This demonstrates strong correlation ($k=1.15$, $R=0.96$), a small bias of 0.24ppb and 95% limits of agreement of $[-8.0, 8.5]$ ppb.

Figure 5.

Scatter and Bland-Altman plots of ROI-based QSM measurements obtained from repeated scans in 5 subjects for MEDI and MEDI+0 respectively, demonstrate excellent correlation, small bias and 95% limits of agreement of ± 18 ppb or less.