QSMART: Quantitative Susceptibility Mapping Artifact

Reduction Technique

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Abstract

Purpose: Quantitative susceptibility mapping (QSM) is a novel MR technique that allows mapping of tissue susceptibility values from MR phase images. QSM is an ill-conditioned inverse problem, and although several methods have been proposed in the field, in the presence of a wide range of susceptibility sources, streaking artifacts appear around high susceptibility regions and contaminate the whole QSM map. QSMART is a post-processing pipeline that uses two-stage parallel inversion to reduce the streaking artifacts and remove banding artifact at the cortical surface and around the vasculature.

Method: Tissue and vein susceptibility values were separately estimated by generating a mask of vasculature driven from the magnitude data using a Frangi filter. Spatially dependent filtering was used for the background field removal step and the two susceptibility estimates were combined in the final QSM map. QSMART was compared to RESHARP/iLSQR and V-SHARP/iLSQR inversion in a numerical phantom, 7T in vivo single and multiple-orientation scans, 9.4T ex vivo mouse data, and 4.7T in vivo rat brain with induced focal ischemia.

Results: Spatially dependent filtering showed better suppression of phase artifacts near cortex compared to RESHARP and V-SHARP, while preserving voxels located within regions of interest without brain edge erosion. QSMART showed successful reduction of streaking artifacts as well as improved contrast between different brain tissues compared to the QSM maps obtained by RESHARP/iLSQR and V-SHARP/iLSQR.

Conclusion: QSMART can reduce QSM artifacts to enable more robust estimation of susceptibility values in vivo and ex vivo.

Keywords: Quantitative Susceptibility Mapping, streaking artifacts, artifact suppression, spatially dependent filtering, two-stage parallel inversion.

Highlights

- QSMART is a two-stage QSM inversion pipeline that suppresses artifacts induced by high-susceptibility veins and cortical air-tissue interface.
- Spatially dependent filtering is applied to a combined cortical surface and vasculature mask as part of the QSMART pipeline, eliminating the need for the cortical erosion step of SHARP-based methods.
- QSMART shows superior artifact suppression on 7T human, 9.4T mouse, and 4.7T rat data compared to the previous methods.
- The QSMART pipeline code is publicly available and the artifact-suppressed susceptibility maps generated by QSMART are well suited to studies of neurodegenerative diseases that require robust and non-eroded cortical susceptibility estimates.
1 Introduction

Quantitative susceptibility mapping (QSM) enables quantification of tissue magnetic susceptibility distributions from the phase of complex-valued MRI signals (1). The contrast in phase images arises from the susceptibility contributions of biometals and molecules, such as heme and nonheme iron, calcium, lipids and myelin (2). Tissue susceptibility is therefore an important biomarker of pathological processes including iron accumulation, calcification, cerebral micro-bleeds, white matter changes and demyelination (3, 4, 5). The phase of an MRI signal encodes susceptibility-induced shifts in the applied magnetic field. QSM reconstruction from phase images is challenging due to macroscopic background field effects from sources outside the brain and the ill-posed field-to-source inversion to estimate a local susceptibility source from non-localized field shifts (1, 6). Insufficient background field estimation and mathematical instabilities in the inversion process lead to noise amplification, surface and streaking artifacts in susceptibility maps, particularly in the vicinity of large susceptibility gradients at veins, and air- and bone-tissue interfaces (7).

Field-to-source inversion is a deconvolution of a point-dipole response kernel and the susceptibility source, which ideally would be performed over the entire imaged area. However, in practice the deconvolution is usually carried out within the brain due to unreliable signal from the outside regions. In brain tissue, the background field is a low spatial frequency field except at air-tissue interfaces where strong susceptibility differences induce high-frequency field contributions. Background field removal methods, such as high-pass filtering, projection onto dipole fields (PDF) (8), sophisticated harmonic artifact reduction on phase data (SHARP) (9) and regularization enabled SHARP (RESHARP) (10) filter out the external field contributions whilst preserving the local field shifts within the brain. In particular, PDF utilises approximate orthogonality of the local and background fields, while widely-used spherical harmonics based methods such as SHARP and RESHARP exploit the harmonic features of the background field in order to estimate the local field shift. An extended method, V-SHARP, uses spherical kernels with variable radii, in which the kernel becomes smaller near the brain boundary to reduce the artifacts and increase the usable region of interest (11, 12). However, the use of spherical mean kernels in harmonics-based methods necessitates erosion of the brain surface to constrain the estimation within brain tissue.

The deconvolution of susceptibility source distribution and the dipole kernel is typically performed in Fourier space for ease of implementation and computation. It is well known that the inversion is ill-posed in Fourier space due to zeros in the dipole kernel along the ‘magic angle’. The nature of this ill-posed deconvolution is the source of significant artifacts that are synonymous with QSM, thus necessitating methods that regularise the deconvolution (12, 13, 14, 15, 16, 17, 18, 19, 20). Such methods include the orthogonal and right triangular decomposition (LSQR) technique (21) that iteratively performs regularised field-to-source inversion until the relative residual norm becomes smaller than a certain threshold. The closely related iLSQR method estimates the streaking artifacts at susceptibility boundaries by constraining iterative estimation to the ill-conditioned
k-space regions (22), however recent studies used numerical phantom simulations and in vivo scans to demonstrate that severe streaking artifacts still remain in areas with high dynamic susceptibility range after applying iLSQR or other existing QSM algorithms (23, 24). Susceptibility estimation using multiple orientation sampling (COSMOS), referred to as the gold standard technique, recovers the “missing data” due to zeros in the dipole kernel by reorienting the subject and re-acquiring the MRI signal (25). However, taking multiple scans of a patient in the clinical setting is impractical and single orientation scanning is preferred (2). The inability of previous methods to reduce streaking artifacts near high susceptibility sources, and the inconvenience of acquiring multiple orientation scans, highlights the need to have a single orientation QSM pipeline that produces minimal artifacts. Furthermore, several recent studies have highlighted the importance of cortical susceptibility as a biomarker in neurodegenerative diseases like Alzheimer’s disease (26, 27, 28, 29), which further accentuates the necessity of QSM pipelines that yield artifact-suppressed and reliable susceptibility values without erosion of the cortex.

Here we propose a two-stage parallel inversion QSM Artifact Reduction Technique (QSMART) that suppresses artifacts induced by high-susceptibility veins and cortical air-tissue interface. QSMART achieves superior artifact suppression by 1) incorporating a 3D spatially dependent filter with automated venous masking using a Frangi filter to correct for vasculature-induced artifacts, 2) eliminating brain erosion requirement of SHARP-based background field removal algorithms, 3) reducing cortical artifacts caused by the air-tissue interface by adapting the filter size according to the shape of the cortical surface, and 4) using efficient two-stage parallel susceptibility reconstruction with and without high susceptibility sources to further suppress the streaking artifacts. We assess the performance of QSMART through numerical phantom simulations, single and multiple orientation in vivo human imaging experiments, ex vivo mouse brain, and in vivo rat brain with induced focal ischemia. Through constructing susceptibility maps from our data, we compare QSMART to combinations of two background field removal methods, RESHARP and V-SHARP, with two inversion techniques, iLSQR and COSMOS (RESHARP/iLSQR, V-SHARP/iLSQR, RESHARP/COSMOS and V-SHARP/COSMOS) and demonstrate consistently improved artifact reduction in QSMART susceptibility images.

2 Theory

2.1 Field-to-Source inversion in QSM

The susceptibility source distribution of an object in an applied field, $B_0$, induces spatially varying field shifts,

$$\Delta B(r) = \frac{|B_0|}{4\pi} \int \chi(r') \frac{3\cos^2\theta - 1}{|r' - r|^3} d^3r', \quad (1)$$
where \( \Delta B(r) \) is the field shift at location \( r \), \( \chi(r) \) is the susceptibility distribution, and \( \theta \) is the angle between \( B_0 \) and \( r - r' \). \( \Delta B(r) \) is related to the phase of a gradient echo signal,

\[
\phi(r) = \gamma \Delta B(r) TE,
\]

where \( TE \) is the echo time and \( \gamma \) is the gyromagnetic ratio. Eq. (1) becomes a point-wise multiplication in the Fourier domain,

\[
\Delta B(r) = \mathcal{F}^{-1} \left\{ \frac{1}{3} - \frac{k^2}{k^2_z} \right\} \mathcal{F}(\chi),
\]

where \( G(k) = \frac{1}{3} - \frac{k^2}{k^2_z} \) is the point-dipole kernel and \( k^2 = k^2_x + k^2_y + k^2_z \). Voxelwise field-to-source inversion is achieved by solving Eq. (3) as an inverse problem, which is ill-conditioned due to zeros at \( k^2 = 3k^2_z \).

3 Methods

3.1 QSMART

In QSMART, magnitude images are constructed from the complex multiecho gradient data. A brain mask, \( M_{\text{Brain}} \), from the magnitude images is constructed using FSL’s Brain Extraction Tool (FMRIB, Oxford University, UK) (30). A vasculature mask, \( M_{\text{Vein}} \), is estimated by applying a Frangi vessel enhancement filter on the echo-averaged magnitude data. The parameters in the Frangi filter are optimized to enhance venous tubular structures at multiple scales using eigenvalues of the Hessian of the magnitude image (31, 32, 33).

To reduce artifacts near indented cortical surfaces, such as the medial orbital gyrus, an indentation mask, \( M_{\text{Indent}} \), is generated by calculating the Gaussian curvature of the cortical surface (34, 35) and preserving the cortical areas with negative curvature. The indentation mask is subject specific, thus brain shape variability among subjects results in unique spatially dependent filter size maps for each subject in the background field removal step. Phase offset estimation from multi-echo (POEM) is used to combine the phase measured by the coils and produce phase images (36, 37, 38). The phase images are unwrapped using a Laplacian-based phase unwrapping technique (12) and the total field shift, \( \Delta B \), is estimated by fitting the echoes using Eq. (2), by a magnitude-weighted Least Squares method, and normalized by the main magnetic field.

3.1.1 Spatially Dependent Filtering

\( \Delta B(r) \) is a combination of a slowly varying background field and local field shifts. Spatially dependent filtering (SDF), first introduced in (39), removes the background field effects from \( \Delta B(r) \) by performing Gaussian filtering with spatially varying parameters to reduce cortical surface artifacts in 2D data. Here we generalize the SDF method to 3D data, and propose the use of a venous mask in order to account for the
artifacts caused by high susceptibility sources, along with the air-tissue interface. An indentation mask is also used to adjust the kernel size near concavities in the brain mask (Fig. 1). The cortical proximity map calculates voxel proximity to the brain surface,

\[ P_C = (F_{\sigma_C} \ast M_{\text{Brain}})M_{\text{Brain}}, \]  

where \( M_{\text{Brain}} \) is the brain mask, \( F \) is a 3D Gaussian filter with standard deviation, \( \sigma_C \), and kernel size \( \pm 2\sigma_C \) in voxels. \( P_C \) varies between \([0, 1]\), with lower values in voxels closer to the cortex.

High susceptibility sources, such as veins, produce shadow and streaking artifacts in \( \chi \) maps. \( P_C \) can be extended to include the venous proximity map,

\[ P_V = (F_{\sigma_V} \ast (1 - M_{\text{Vein}})) \ast (1 - M_{\text{Vein}}), \]  

where \( M_{\text{Vein}} \) is the vasculature mask. The surface curvature-based indentation mask is also used to derive a third proximity map,

\[ P_I = C_s F_{\sigma_I} \ast (1 - M_{\text{Indent}}), P_I \leq 0.5 = 0.5 \]  

where \( M_{\text{Indent}} \) is the indentation mask and \( C_s \) is a scaling constant. The indentation mask is lower-bounded at 0.5 to ensure appropriate kernel sizes. The combined proximity map, \( P \), is a voxelwise multiplication

\[ P = P_B P_V P_I. \]  

A map of spatially dependent standard deviations of \( P \) is given by

\[ \alpha = \sigma \times (P^n)_2M_{\text{Brain}}, \]  

where the element-wise exponentiation, \((P^n)_2\), is rounded to 2 decimal places to accelerate the adaptive filtering operation. \( n \) is chosen such that \( \alpha = 1 \) when \( P = 0.5 \), giving an ordered set, \( A = \{\alpha_1,...,\alpha_{101}\} \) consisting of all possible values of \( \alpha \) after rounding. A corresponding index map, \( X \), describes the spatial distribution of \( \alpha \) values. A set of Gaussian filtered images, \( \phi \), is constructed from \( A \), and the background field is estimated by indexing \( \phi \) using \( X \). The standard deviations \( \sigma_C, \sigma_V \) and \( \sigma \) are user defined parameters empirically chosen to remove the background field contributions whilst preserving the local structural details. The background field is subtracted from \( \Delta B(r) \) to produce estimates of the local field shifts. Refer to (39) for further details of Spatially Dependent Filtering.
3.1.2 Two-stage Parallel Inversion

The field-to-source inversion is implemented in two parallel stages. The first stage reconstructs a susceptibility map of the entire brain, $\chi_1$, using SDF and iLSQR method to solve the ill-posed problem in Eq. (3) (22). In a parallel stage, the vasculature is removed from the brain mask to suppress artifacts from high-susceptibility venous regions, followed by tissue-only SDF and iLSQR inversion to estimate a separate susceptibility map, $\chi_2$.

The two susceptibility maps, $\chi_1$ and $\chi_2$, are combined to construct a composite QSM image. To account for susceptibility offset difference between the two maps, an offset term, $\chi_o$, is determined according to (24, 40):

$$\chi_o = \frac{F^{-1}(G \cdot FM_{Vein}) \cdot \{\Delta B - F^{-1}[G \cdot F(\chi_2 + M_{Vein} \cdot \chi_1)]\} \cdot \{F^{-1}(G \cdot FM_{Vein})\}^{-1}}{\{F^{-1}(G \cdot FM_{Vein})\}}.$$  

(9)

where $A : B = \sum_{i,j,k} A_{i,j,k} B_{i,j,k}$ is the Frobenius product and $G$ is the point-dipole kernel in the Fourier domain.

The combined QSMART susceptibility map is

$$\chi_{QSMART} = M_{\text{tissue}} \cdot \chi_2 + M_{Vein}(\chi_1 + \chi_o).$$  

(10)
3.2 Numerical Phantom Simulation

A 3D modified Shepp-Logan phantom was generated in MATLAB to assess the performance of QSMART. The phantom size was $334 \times 386 \times 224$ voxels, with 0.6 mm isotropic resolution and consisted of multiple components resembling different susceptibility sources in the brain, including the air in the sinus and outside the brain, cortical bones, white matter (WM), grey matter (GM) and deep-brain GM structures. In particular, three cuboids mimicking veins were placed parallel to the axial, coronal and sagittal planes (Fig. 3A). The susceptibility values in SI units were adopted from literature and referenced to water (41, 3, 42). The phase maps were calculated using the forward formula in Eq. (1) and Eq. (2), and processed using QSMART, RESHARP followed by iLSQR (RESHARP/iLSQR) and V-SHARP followed by iLSQR (V-SHARP/iLSQR).

3.3 MRI Data Acquisition

All imaging experiments were approved by the University of Melbourne Human and animal Ethics Committees. Three healthy subjects (31, 34 and 39 years old) were scanned on a 7T Siemens MAGNETOM scanner (Erlangen, Germany) with a 1Tx/32Rx head coil (Nova Medical Inc.) using a 3D unipolar multi-echo Gradient-Recalled-Echo (GRE) sequence with parameters: echo time (TE) = 4.80, 8.35, 11.90, 15.45 ms, repetition time (TR) = 18 ms, bandwidth (BW) = 682 Hz/pix, flip angle (FA) = 9°, resolution = $0.6 \times 0.6 \times 0.6$ mm, matrix size = $334 \times 386 \times 224$, and GRAPPA acceleration factor of 2. Each subject was scanned once in 5 different head orientations (neutral, extension, flexion, left and right) for COSMOS reconstruction. The scanning duration for each acquisition was 8:50 minutes.

A 5 month old mouse was anesthetized with 100 mg/kg sodium pentobarbitone and intracardially perfused with cold 0.1M phosphate buffered saline (pH 7.3). The brain was post-fixed for 24 h in 4% paraformaldehyde (PFA) solution in 0.1M phosphate buffer at 4°C and then positioned in 2% agarose gel and stored at 4°C until scanning. The mouse brain was scanned in a 9.4T Bruker small animal scanner using a 3D multi-echo GRE sequence: initial echo time, $TE_0 = 4$ ms, 12 evenly spaced echoes with 4 ms inter-echo spacing, TR = 140 ms, NEX = 2, matrix size = $128 \times 128 \times 64$ with 125 μm isotropic resolution and total scan time of 38 minutes.

Focal ischemia was induced in a 22 week old male rat by an Endothelin-1 injection to the motor cortex. Endothelin-1 is a vasoconstrictor substance. Prior to the surgery the animal was anaesthetised with isoflurane (5% at 1L/min) and placed in a stereotaxic frame (Kopf, Germany) where the anaesthesia was maintained for the duration of the surgery. For MRI experiment, the rat was anesthetized with isoflurane and placed in a rat cradle with tooth and ear-bars to fix head position. During scanning, the animal was kept anesthetized with a mixture of 1-2% isoflurane and oxygen. A small air balloon attached to a pressure transducer was placed under the chest to monitor respiration. Body temperature was continuously observed using a rectal
probe and kept at 37°C via a hot water circulation system. MRI was performed using a 4.7T MRI with Avance III console and rat surface coil (Bruker, USA) using a 3D multi-echo GRE sequence: initial echo time, $T_E = 4$ ms, 20 evenly spaced echoes with 4 ms inter-echo spacing, $TR = 110$ ms, matrix size = $176 \times 128 \times 70$ with $150 \ \mu m$ isotropic resolution and total scan time of 16:25 minutes.

### 3.4 QSM Estimation

The QSMART pipeline was implemented in MATLAB R2019a (Mathworks, Natick, MA, USA). QSMART was applied to phase images with neutral head position to estimate single orientation $\chi$-maps. Besides the parameters used in the phase unwrapping, echo-fitting and iLSQR stages, that are common to all such methods, QSMART contains eight tuning parameters: $\{\alpha, \beta, c\}$ in the Frangi filter, and $\{\sigma_c, \sigma_v, \sigma_I, \sigma, C_s\}$ in SDF, as detailed below.

A vasculature mask was obtained using a Frangi filter with parameters: scale range = 0.5-6, $\sigma$ step-size = 0.5, and filter sensitivity thresholds, $\{\alpha, \beta, c\} = \{0.5, 0.5, 500\}$, which are the default values used for detecting the vasculature (31, 32). SDF parameters were chosen as $\{\sigma_C = 10, \sigma_V = 2, \sigma_I = 10, C_s = 500\}$, based on visual inspection of the local field maps and QSM images. The values for $\sigma_C$ were adopted from (39) for suppression of cortical artifacts, after validating the chosen value of 10 amongst a range of values 5-20. Correspondingly, $\sigma_V$ is applied on the vasculature mask to reduce filter sizes near veins. The value of $\sigma_V$ should be small so that the vasculature is not filtered out during this procedure. A value of 2 was chosen amongst a range of values 1-8, which preserved the vasculature and removed the dark artifacts near the veins; smaller kernels sizes did not suppress the artifacts, and larger kernel sizes were prone to deletion of the vasculature itself. After multiplication of the three proximity maps, all having values between 0 and 1, $\sigma$ scales the combined proximity map to $\alpha$, the spatially dependent filter size applied to the total field shift. The value of $\sigma$ was empirically chosen to be 10, after investigating a range of 5-15; smaller filter sizes failed to remove artifacts in the field shift, whereas larger values deleted tissue related information.

For comparison, single orientation $\chi$-maps using RESHARP background field removal (43) were estimated with regularization parameter $\lambda = 5 \times 10^{-4}$ determined by L-curve method, and kernel radius = 2 voxels followed by one-step iLSQR inversion (RESHARP/iLSQR). V-SHARP with a maximum kernel size of 12 mm followed by one-step iLSQR inversion was also applied (V-SHARP/iLSQR). In addition, the COSMOS pipeline using a uniform weighting matrix (25) was applied to the total field shifts estimated by V-SHARP (V-SHARP/COSMOS), RESHARP (RESHARP/COSMOS) or SDF (SDF/COSMOS).

For mouse and rat data, a brain mask excluding the olfactory bulb was generated by non-linearly registering the average magnitude image to the Waxholm space mouse and rat brain atlases (44). Manual corrections were applied where needed. A vasculature mask was obtained using a Frangi filter with parameters: scale range = 0.01-0.5, $\sigma$ step-size = 0.1, and filter sensitivity thresholds, $\alpha, \beta, c = 0.5, 0.5, 50$. QSMART was
applied on the phase data using two-stage parallel inversion with $\sigma_C = \sigma_V = 5$. Additional $\chi$-maps using RESHARP were estimated with $\lambda = 10^{-6}$, determined by the L-curve method and kernel radius = 2 voxels. The iLSQR algorithm was implemented using the code provided in STI-suite version 2.2 (number of iterations = 50).

3.5 Quantitative Analysis

In the numerical phantom, the tissue mask and the vasculature mask were generated by thresholding, and the mean and standard deviation of susceptibility estimates by QSMART, RESHARP/iLSQR, and V-SHARP/iLSQR are evaluated and compared to the ground truth.

In in vivo human data, four subcortical regions, Caudate Nucleus (CN), Globus Pallidus (GP), Putamen (PU), and Thalamus (TH), were segmented using FSL FIRST (45), as outlined in Fig. 2A. The Internal Capsule (IC) was also manually segmented on an axial slice by a neuroscientist. The susceptibility estimates in these regions are compared across QSMART, RESHARP/iLSQR, V-SHARP/iLSQR, SDF/COSMOS, RESHARP/COSMOS, and V-SHARP/COSMOS.

To compare artifact suppression near the vasculature and the cortical surface across different methods, susceptibility variance is plotted versus the distance from artifact sources. To compute the distance map for each voxel from the brain edge and the vasculature, the cortical surface mask excluding the vasculature was eroded incrementally using a spherical structuring element of increasing size, one voxel at a time. Variance of susceptibility values in equidistant voxels is plotted using the resultant distance map, an example of which is given in Fig. 2B.
4 Results

4.1 Numerical Phantom Simulation

The simulated phantom and the simulation results are shown in Fig. 3. In the results obtained by RESHARP/iLSQR (Fig. 3C), and V-SHARP/iLSQR (Fig. 3D), streaking artifacts and dark areas near veins are evident. In contrast, these artifacts are suppressed in the result obtained by QSMART (Fig. 3B). Difference maps (Fig. 3E-G) verify that QSMART has successfully reduced streaking artifacts caused by the simulated veins, without removing any structures. In Fig. 3H-K, the mean and standard deviation of susceptibility estimates measured using QSMART, RESHARP/iLSQR, and V-SHARP/iLSQR are compared to the ground truth. QSMART has reduced the variability of the susceptibility estimates in the tissue regions (Fig. 3I), as a result of suppression of streaking artifacts, with the cost of slightly suppressing the vein susceptibility values (Fig. 3K) compared to RESHARP/iLSQR and V-SHARP/iLSQR.
Figure 3: Numerical Phantom simulations of QSMART versus RESHARP/iLSQR and V-SHARP/iLSQR.

A. Sagittal slice of the simulated phantom with the susceptibilities marked on the figure. This phantom was used to produce the total field shift (TFS). B. Susceptibility map obtained by QSMART. C. The susceptibility map obtained by RESHARP/iLSQR. D. The susceptibility map obtained by V-SHARP/iLSQR. E, F and G. Difference maps between the ground truth susceptibility phantom and the values calculated by QSMART, RESHARP/iLSQR and V-SHARP/iLSQR. The streaking artifacts contained in the difference maps show successful suppression of these artifacts by QSMART. H. The tissue mask. I. Comparison of mean and standard deviation of susceptibility estimates measured in the tissue. J. The vasculature mask. K. Comparison of mean and standard deviation of susceptibility estimates measured in the vasculature. QSMART demonstrates considerably less deviation of susceptibility estimates in tissue, a strong indication of the suppression of streaking artifacts.
4.2 *In vivo* Human Experiment

4.2.1 Single Orientation QSM

The results of processing phase images for single orientation QSM of a 31 year old male (subject 1) are illustrated in Figure 4. For completeness, the QSM results for the two other subjects are provided in the supplementary material. The results shown in Fig. 4 demonstrate QSMART’s success in suppression of dark artifacts near the cortex (red arrows) without brain erosion. These surface artifacts are also observed in the difference map between the methods. Suppression of artifacts has resulted in better contrast between gray matter and white matter in QSMART compared to RESHARP/iLSQR. The difference maps show significant suppression of artifacts near veins (pointed by green arrows).

The susceptibility variance versus distance plots in QSMART, RESHARP/iLSQR and V-SHARP/iLSQR for all three subjects are shown in Fig. 5. Successful artifact suppression in QSMART has led to smaller variances in regions close to high susceptibility sources. As distance from high susceptibility sources increases, the variance curves converge, demonstrating that QSMART has reduced streaking artifacts near the vasculature and brain edge without altering the estimated susceptibility values in other regions.

Figure 4: Single Orientation QSM results from QSMART, RESHARP/iLSQR and V-SHARP/iLSQR, and the difference maps between the susceptibility values calculated by QSMART and the two other methods. Dark cortex surface artifacts (red arrows) and x-shaped artifacts caused by veins and high susceptibility sources (green arrows) are successfully suppressed by QSMART.
Figure 5: Variance in susceptibility values versus distance from high susceptibility sources in QSMART, RESHARP/iLSQR and V-SHARP/iLSQR. In regions closer to high susceptibility sources, QSMART has smaller variances, showing successful reduction of streaking artifacts. As distance from vasculature and brain edge increases, the variances converge, indicating equivalent performance of the methods in regions further from artifact sources.

4.2.2 Multiple Orientation QSM

Data acquired from five head orientations was used to construct QSM maps based on COSMOS. The results of SDF/COSMOS, RESHARP/COSMOS and V-SHARP/COSMOS are illustrated in Fig. 6. As with the single orientation results, the dark surface artifacts near cortex (red arrows) are successfully reduced in SDF/COSMOS. Better contrast between gray and white matter is also evident in SDF/COSMOS images compared to RESHARP/COSMOS.
Figure 6: Multiple Orientation QSM results of SDF/COSMOS, RESHARP/COSMOS and V-SHARP/COSMOS. Red arrows point to regions where cortical artifacts are significantly limited by SDF/COSMOS. Although COSMOS inversion reduces streaking artifacts by using multiple orientation data, the contribution of SDF in suppressing streaking artifacts near veins is shown in the difference images (pointed by green arrows).

4.2.3 Region of Interest Analysis

The mean and standard deviation of susceptibility values in CN, GP, PU, TH, and IC are shown in Fig. 7. QSMART and SDF/COSMOS show smaller variances compared to other single orientation and multiple orientation methods, respectively. The results of QSMART in deep grey matter regions are similar to V-SHARP/COSMOS (p-value > 0.05), demonstrating QSMART’s ability as a single orientation pipeline to achieve a susceptibility distribution similar to a multiple orientation pipeline in these four regions. In the Internal Capsule, SDF-based approaches attain negative susceptibility values comparable to V-SHARP approaches. In contrast, RESHARP-based methods show relative underestimation of negative susceptibilities in the white matter.
Figure 7: ROI analysis of susceptibility estimates for subject 1, where error bars represent standard deviation, for Caudate Nucleus (CN), Globus Pallidus (GP), Putamen (PU), Thalamus (TH), and the Internal Capsule (IC).

4.3 *Ex vivo* Mouse QSM

Visual examination of mouse brain QSM shows significant artifact reduction in QSMART maps compared to the RESHARP/iLSQR, and V-SHARP/iLSQR images (Fig. 8). The shadow artifact around an air bubble (blue arrow), segmented through Frangi filtering, is considerably reduced in the QSMART map. In the striatum (green arrow), the QSMART map has delineated the fine tissue micro-architecture of alternating white matter (WM) tracts and gray matter (GM), whereas the RESHARP/iLSQR method has produced a smoother map with diminished WM/GM striatal contrast. The GM/WM contrast in QSMART images is similar to V-SHARP/iLSQR, which is consistent with the *in vivo* human results.
Figure 8: Exemplar slices of $\chi$-maps in the \textit{ex vivo} mouse brain obtained using A. QSMART, B. RESHARP/iLSQR and C. V-SHARP/iLSQR. QSMART significantly reduces shadow artifact around an air bubble compared to RESHARP/iLSQR and V-SHARP/iLSQR (blue arrow). In the striatum, alternating white matter (WM) tracts and gray matter (GM) are better delineated in QSMART (green arrow).

4.4 \textit{In vivo} Rat Stroke QSM

Axial slices of the rat brain containing a stroke lesion (red arrow) are shown in Fig. 9. QSMART has significantly reduced the artifacts around the stroke lesion, compared to RESHARP/iLSQR. Note that the lesion was segmented automatically using Frangi filtering. Shadow artifacts near the cortex are also suppressed in QSMART (blue arrow).
Figure 9: Exemplar axial slices of $\chi$-maps in the *in vivo* rat brain with stroke lesion obtained using A. QSMART and B. RESHARP/iLSQR. QSMART significantly reduces artifacts around the stroke lesion (red arrow). Shadow artifacts around the cortex are reduced in QSMART (blue arrow).

5 Discussion

QSMART is a post-processing method to reconstruct susceptibility maps from phase images with optimised artifact reduction near high susceptibility differences. QSMART extends the spatial dependent filtering technique to three dimensional images and capitalises on vasculature proximity information to achieve superior artifact suppression near veins. Furthermore, the two-stage parallel inversion enables efficient and fast susceptibility estimation. In the cortex, QSMART suppresses typical shadow and streaking artifacts at air-tissue boundaries without employing SHARP-like brain-mask erosion. Artifact reduction in QSMART will enable more robust susceptibility quantification with applications to clinical data. Overall, QSMART substantially reduced streaking and dipole artifacts compared to the commonly employed RESHARP/iLSQR and V-SHARP/iLSQR method in the numerical phantom, *in vivo* human, and preclinical data.

The efficacy of QSMART in artifact reduction has been demonstrated in numerical phantom maps, where in comparison RESHARP and V-SHARP introduced significant artifacts in the structures with high dynamic range, spreading to adjacent regions. Using variable kernel sizes in extensions of SHARP method such as V-SHARP and R-SHARP, has shown superior artifact reduction in the literature (11, 12, 46). In R-SHARP, the application of a 3D region adaptive kernel with weights scaled to the energy function of the field map is used to limit phase artifacts near the air-tissue interface. The analysis of the numerical phantom using QSMART shows similar results to the results presented in (46), around the sinus and the brain boundary, confirming the ability of the SDF approach to suppress such artifacts in the field shift. We have taken advantage of SDF’s look-up table method to boost the computation speed and maintain a rapid QSM pipeline. In SDF,
using a Gaussian kernel with a variable $\sigma$ and size, the filter weights can also be adjusted in the same kernel
radius, which is not possible when using V-SHARP.

In addition to suppressing streaking artifacts, QSMART effectively suppressed cortical surface and venous
artifacts in in vivo human data. Difference maps (Fig. 4 and Fig. 6), show WM/GM contrast differences
between RESHARP/iLSQR and QSMART, whereas such difference is not evident when comparing QSMART
with V-SHARP/iLSQR. This may be the result of regularization applied in RESHARP which smooths out
the contrast. However, methods using variable sized kernels such as V-SHARP and SDF can better preserve
tissue contrast in the final susceptibility maps.

In fixed mouse brain tissue, QSMART demonstrated significant reduction of shadow artifact around air
bubbles, as well as suppression of cortical and venous artifacts. Superior artifact suppression near the stroke
lesion in rat brain was also observed in QSMART (Fig. 9). In the mouse and rat brain data, the parameters
used for the Frangi filter to segment the vessels, were also able to segment the air bubble and the stroke
lesion. According to (31), the Frangi filter parameters can be adjusted to segment a range of structures from
blob-like to tubular. The Frangi filter implemented in QSMART can be tuned to account for pathological
structures.

While iLSQR is designed to ameliorate streaking artifact in ill-determined regions, we found that artifact
from high susceptibility regions was not fully suppressed. Although increasing RESHARP’s kernel radius
is effective in suppressing cortical artifacts in RESHARP/iLSQR inversion, it results in erosion of voxels
located near the edge of the brain mask. Rather than adapt the grey-box iLSQR implementation, we chose
to use both SDF and Frangi filtering as pre-processing steps prior to iLSQR, and to implement a parallel
pathway of calls to iLSQR. The concept of segmenting veins and high susceptibility sources from other
tissues and processing them separately has a history in QSM and SWI for suppression of streaking artifacts
(23, 24, 47, 48). Serial two-stage inversion QSM methods (23, 24) identify high-susceptibility regions from
first-stage QSM maps, followed by a second stage to estimate low susceptibility sources. The superposed
dipole inversion method thresholds the first-stage QSM map to identify high-susceptibility regions, such as
a haematoma, and is sensitive to the choice of threshold in identifying small venous structures (24). STAR-
QSM identifies high-susceptibility regions in the first stage through regularized susceptibility estimation,
and retrospectively corrects the phase images and estimates tissue susceptibilities in the second step (23).
In both methods, the second susceptibility map is dependent on the first inversion. In contrast, QSMART
implements two independent inversions in parallel by identifying vasculature from magnitude images using a
Frangi filter and eliminates the need to use the first susceptibility map to determine high susceptibility veins.
The vasculature mask in QSMART can be adapted to incorporate pathological structures, such as ischaemic
haemorrhage, lesions or haematoma, by changing the parameters in the Frangi filter accordingly. However,
segmenting larger pathological structures may result in reduced coverage in the second QSM inversion, thus
introducing inaccuracies in the susceptibility estimation (49). Future studies are required to formulate a
technique that overcomes this issue in two-stage QSM pipelines.

Various spatial phase unwrapping methods have been utilised across the published QSM methods, with
Laplacian phase unwrapping (50, 51) and path-based methods (52, 53) being among the more popular ones.
In (54), a detailed evaluation of these methods demonstrates the superior robustness of Laplacian phase
unwrapping on simulated and \textit{in vivo} 7T data, at the cost of returning approximations of the exact phase.
In Laplacian phase unwrapping, the unwrapped phase is estimated using the Laplacian of the wrapped phase.
By incorporating boundary conditions into the underlying Poisson equation, the unwrapped phase can be
uniquely determined up to a global constant. However it has been shown that determining the unwrapped
phase up to the harmonic components is sufficient for QSM, as they will be removed in the subsequent
background field removal stage (55). It has further been shown that Laplacian based methods alter the
linearity of phase over time (56), but that a nonlinear formulation for QSM (57) can provide more accurate
estimation of susceptibility values especially around veins and high susceptibility sources.

Use of 3D spatial dependent filtering limits surface errors in the background field removal step. Conversely,
single-step techniques combine background field removal and inversion steps to reconstruct susceptibility
maps directly from unfiltered phase data to minimize error propagation (14, 13, 17, 16, 18, 19, 20). Pre-
conditioned total field inversion uses a precondition filter and a total variation term to achieve artifact
suppression (14). The whole-head total field inversion method uses total variation and Tikhonov regulariza-
tion to include susceptibility contributions from the skull and eye balls (13). The use of highly regularized
estimation algorithms typically results in spatial smoothing and limited ability to differentiate finer tissue
details. Moreover, single-step inversion eliminates the possibility of tracking and suppressing the sources of
error, resulting in less flexible artifact reduction.

QSMART underestimated the susceptibility values in the sagittal sinus, as observed in the difference maps
in Fig. 4 and Fig. 6, either due to smaller filter sizes near cortical regions or separate estimation of tissue
and venous susceptibilities. This issue can be addressed in further developments of QSMART, either in the
two-stage inversion or the spatially dependent filter. Advances in MR phase post processing have led to
an increasing use of deep learning methods in QSM, however, having more accurate QSM images is also
necessary in the training stage of these algorithms (58, 59, 60).

The combination of SDF and COSMOS demonstrated increased robustness in cortical regions compared to
RESHARP/COSMOS and V-SHARP/COSMOS, with the SDF-based method better suppressing the surface
and shadow artifacts. The direct comparison between SDF/COSMOS and single orientation QSMART is
arguable, as lack of ground truth makes it difficult to draw any robust conclusions. However, as shown
in the ROI analysis, both QSMART and SDF/COSMOS show smaller variances in the segmented brain
regions compared to other single orientation and multiple orientation methods, respectively. All COSMOS
based methods have smaller variances due to the nature of COSMOS inversion, as it uses information from five orientations. We have demonstrated, however, that single orientation QSMART better suppresses shadow artifacts compared to RESHARP/iLSQR and V-SHARP/iLSQR, and yields similar results to V-SHARP/COSMOS, while retaining tissue orientation information.

### 6 Conclusion

QSMART, a Quantitative Susceptibility Mapping Artifact Reduction Technique, has been introduced, comprising of a spatially dependent filter to remove background field contributions and a two-stage parallel inversion to correct for the artifacts caused by high susceptibility sources. The technique has been effectively applied to numerical phantom data, *in vivo* human data using both single and multiple orientations, *ex vivo* mouse brain, and *in vivo* ischemic stroke rat data. The suppression of streaking artifacts around veins and dark cortex artifacts that is inherent in QSMART is essential to generating QSM maps for diagnostic purposes. QSMART is a robust tool for studying magnetic susceptibility estimates in the brain. The QSMART pipeline code is publicly available, and will aid studying susceptibility estimates and their changes in neurodegenerative diseases.

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### Software

The QSMART pipeline code is accessible by the following link:

https://github.com/MBCIU/QSMART
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