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Comparing the Accuracy and Precision of Multi-echo Combination Methods for Quantitative Susceptibility Mapping Using Laplacian-Based Methods at 3 T

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Abstract

Purpose: To compare different multi-echo combination methods for MRI quantitative susceptibility mapping (QSM), aiming to elucidate, given the current lack of consensus, how to optimally combine multi-echo gradient-recalled echo (GRE) signal phase information, either before or after applying Laplacian-base methods (LBMs) for phase unwrapping or background field removal.

Methods: Multi-echo GRE data were simulated in a numerical head phantom, and multi-echo GRE images were acquired at 3 T in 10 healthy volunteers. To enable image-based estimation of GRE signal noise, 5 volunteers were scanned twice in the same session without repositioning. Five QSM processing pipelines were designed: one applied nonlinear phase fitting over echo times (TEs) before LBMs; two applied LBMs to the TE-dependent phase and then combined multiple TEs via either TE-weighted or signal-to-noise ratio (SNR)-weighted averaging; two calculated TE-dependent susceptibility maps via either multi-step or single-step QSM and then combined multiple TEs via magnitude-weighted averaging. Results from different pipelines were compared using visual inspection; summary statistics of susceptibility in deep gray matter, white matter and venous regions; phase noise propagation maps (error propagation theory); and, in the healthy volunteers, regional fixed bias analysis (Bland-Altman) and regional differences between the means (non-parametric tests).

Results: Nonlinearly fitting the multi-echo phase over TEs before applying LBMs provided the best compromise between regional accuracy/precision and mitigation of phase noise propagation compared to averaging the LBM-processed TE-dependent phase. This result was especially true in high-susceptibility venous regions.

Conclusion: For multi-echo QSM, combining the signal phase by nonlinear fitting before applying LBMs is recommended.

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Introduction

MRI quantitative susceptibility mapping (QSM) aims to determine the underlying spatial distribution of tissue magnetic susceptibility (χ) from the phase (ϕ) of a single-echo or a multi-echo gradient-recalled echo (GRE) sequence. For multi-echo QSM, there is still a lack of consensus on how to combine the information acquired at different echo times (TEs) and when to perform this combination in the processing pipeline.

Generally, ϕ measured using a multi-echo GRE acquisition evolves linearly over time:

$$\phi(\boldsymbol{r}, TE) = \gamma \Delta B_{Tot}(\boldsymbol{r}, TE) TE + \phi_0(\boldsymbol{r}) \quad (1)$$

where $\boldsymbol{r}$ is a vector of image space coordinates, γ the proton gyromagnetic ratio, ΔB_{Tot} the χ-induced total field perturbation along the scanner's z-axis, and ϕ_0 the TE-independent phase offset measured at a nominal TE=0 ms.

Based on Equation 1, previous studies using multi-echo GRE protocols and multi-step reconstruction pipelines for brain QSM at 3 T have combined the signal from multiple echoes by either averaging (1-4) or fitting (5-7) before or after the application of Laplacian-based methods (LBMs). For QSM, LBMs are commonly used to unwrap the phase, i.e., to remove 2π phase aliasing over TEs or in space (8,9). LBMs are also commonly used to remove background fields (ΔB_{Bg}), i.e., slowly varying field variation inside the region of interest (ROI) generated by sources outside the ROI (10). Based on the properties of the Laplacian of the wrapped phase or ΔB_{Bg}, LBMs perform nonlinear operations, thus they must be applied carefully to avoid introducing inaccuracies in the GRE phase (11).

For multi-echo combination in QSM, this study focuses on approaches based on weighted averaging (1-4) or complex nonlinear fitting (NLFit) (5,6), which outperform simpler approaches based on unweighted averaging (12) or linear fitting (7).

Multi-echo combination of the phase over time via weighted averaging has been performed using either TE-based weighting factors (1,2) or phase SNR-based weighting factors (3). Notably, TE-weighted averaging (TE-wAvg) only requires temporal unwrapping of the input multi-echo phase and results in a combined total field map (ΔB_{Tot}), which still contains ΔB_{Bg} contributions. Instead, SNR-weighted averaging (SNR-wAvg) requires both temporal and spatial unwrapping of the input multi-echo phase, thus resulting in a combined local field map (ΔB_{Loc}) free from ΔB_{Bg}. Alternatively, a distinct χ map has been calculated at each TE and then combined by weighted averaging with magnitude-based weighting factors (4). To determine the most accurate multi-echo combination method for QSM, this study aimed to compare the effect of these different approaches on the bias of the estimated tissue χ. Particularly, two different pipelines based on weighted averaging of TE-dependent χ images were implemented: in one, TE-dependent χ images were calculated using a multi-step

procedure similar to NLFit, TE-wAvg, and SNR-wAvg (Susc-wAvg); in the other, TE-dependent χ images were calculated in a single-step using total generalized variation (Susc-TGV-wAvg) (13). It was hypothesized that combining multiple TEs by fitting the temporally unwrapped multi-echo phase before applying LBMs for spatial phase unwrapping or ΔB_{Bg} removal (NLFit) gives more accurate χ estimates than averaging after applying LBMs (TE-wAvg, SNR-wAvg, Susc-wAvg, or Susc-TGV-wAvg), because LBMs alter the phase temporal evolution of the phase.

To determine the most precise multi-echo combination method for QSM, this study also aimed to compare the effect of fitting or averaging-based approaches on the propagation of noise from the multi-echo GRE phase into the ΔB_{Tot}, ΔB_{Loc} and χ maps. Previous studies using fitting (6) or SNR-wAvg (3) have calculated expressions for the noise in the total field map ($\sigma(\Delta B_{Tot})$). For TE-wAvg or SNR-wAvg, expressions for $\sigma(\Delta B_{Tot})$ have not been calculated and were therefore derived here. For each multi-echo combination method, expressions for noise propagation from ΔB_{Tot} to the corresponding ΔB_{Loc} and χ images were also calculated here.

Bias and noise propagation characteristics of different multi-echo combination methods were investigated using numerically simulated data and images acquired in vivo, incorporating LBMs for both phase unwrapping and ΔB_{Bg} removal into the QSM processing pipelines.

Theory

This section presents the expressions for multi-echo combination, noise propagation from the multi-echo signal phase to the ΔB_{Tot}, ΔB_{Loc} and χ maps.

Multi-echo combination

Multi-echo combination (with n echoes) of the phase over time via weighted averaging has been performed as:

$$\Delta B(\boldsymbol{r}) = \frac{1}{\gamma}\sum_{i=1}^{n} w(\boldsymbol{r}, TE_i)\frac{\phi(\boldsymbol{r}, TE_i)}{TE_i} \tag{2}$$

with TE-based weighting factors (TE-wAvg) equal to (1,2):

$$w(\boldsymbol{r}, TE_i) = \frac{TE_i}{\sum_{j=1}^{n} TE_j} \tag{3}$$

or phase SNR-based weighting factors (SNR-wAvg) equal to (3):

$$w(\boldsymbol{r}, TE_i) = \frac{TE_i \exp\left(-TE_i R_2^*(\boldsymbol{r})\right)}{\sum_{j=1}^{n} TE_j \exp\left(-TE_j R_2^*(\boldsymbol{r})\right)} \tag{4}$$

TE-wAvg requires temporally unwrapped phase images, because the weights in Equation 3 vary over TEs, whereas SNR-wAvg requires both temporally and spatially unwrapped phase images, because the weights in Equation 4 vary over both TEs and image space.

An alternative multi-echo combination approach has calculated a distinct χ map at each TE and then applied weighted averaging as (4):

$$\chi(\boldsymbol{r}) = \frac{1}{n}\sum_{i=1}^{n} w(\boldsymbol{r}, TE_i)\chi(\boldsymbol{r}, TE_i) \tag{5}$$

with weighting factors (Susc-wAvg and Susc-TGV-wAvg):

$$w(\boldsymbol{r}, TE_i) = \frac{M^2(\boldsymbol{r}, TE_i)TE_i^2}{\sum_{j=1}^{n}\left(M^2\left(\boldsymbol{r}, TE_j\right)TE_j^2\right)} \tag{6}$$

where M denotes the signal magnitude.

Multi-echo combination by fitting the signal phase over time according to Equation 1 enables estimation of both ΔB_{Tot} and ϕ_0 contributions from the coil-combined phase, whereas combining the phase by averaging according to Equations 2-6 does not enable ϕ_0 estimation. Moreover, multi-echo combination using NLFit does not require unwrapped phase images, thus avoiding the application of LBMs before multi-echo combination.

Noise in the total field map

Fitting

Regressing the phase on TE using a weighted linear least square fit enables calculation of a field map ($\omega^{Fit} = \gamma\Delta B_{Tot}^{Fit}$ in rad/s) and a phase offset (ϕ_0^{Fit}) by minimizing the following weighted residual sum of squares (WRSS):

$$WRSS(\boldsymbol{r}) = \sum_{i=1}^{n} w_i\left(\phi(\boldsymbol{r}, TE_i) - \left(\omega^{Fit}(\boldsymbol{r})TE_i + \phi_0^{Fit}(\boldsymbol{r})\right)\right)^2 \tag{7}$$

Where w_i is a weighting factor equal to the inverse variance of the phase, i.e. $w_i = 1/\sigma^2\left(\phi(TE_i)\right)$ and n is the total number of TEs (14).

The values of ω^{Fit} and ϕ_0^{Fit} that jointly minimize Equation 7 are calculated by solving a system, where the partial derivatives of WRSS relative to both ω^{Fit} and ϕ_0^{Fit} are jointly set to zero:

$$\begin{cases} \dfrac{\partial WRSS(\boldsymbol{r})}{\partial \omega^{Fit}} = 0 \\ \dfrac{\partial WRSS(\boldsymbol{r})}{\partial \phi_0^{Fit}} = 0 \end{cases} \tag{8}$$

Omitting the $\boldsymbol{r}$ dependency (because fitting is performed voxel by voxel) solving the system in Equation 8 yields (6):

$$\omega^{Fit} = \frac{\sum_{i=1}^{n} w_i \sum_{i=1}^{n} w_i TE_i \phi(TE_i) - \sum_{i=1}^{n} w_i \phi(TE_i) \sum_{i=1}^{n} w_i TE_i}{\sum_{i=1}^{n} w_i \sum_{i=1}^{n} w_i TE_i^2 - \left(\sum_{i=1}^{n} w_i TE_i\right)^2} \tag{9}$$

Based on error propagation, the noise in ΔB_{Tot} calculated using a linear least squares fitting approach (6) is equal to:

$$\sigma\left(\Delta B_{Tot}^{Fit}\right) = \frac{\sqrt{\sum_{i=1}^{n} \frac{1}{\sigma^2\left(\phi(TE_i)\right)}}}{\gamma\sqrt{\sum_{i=1}^{n} \frac{1}{\sigma^2\left(\phi(TE_i)\right)} \sum_{i=1}^{n} \frac{TE_i^2}{\sigma^2\left(\phi(TE_i)\right)} - \left(\sum_{i=1}^{n} \frac{TE_i}{\sigma^2\left(\phi(TE_i)\right)}\right)^2}} \tag{10}$$

Equation 10 also holds true for nonlinear least squares fitting (5), thus $\sigma\left(\Delta B_{Tot}^{NLFit}\right) = \sigma\left(\Delta B_{Tot}^{Fit}\right)$.

Weighted averaging

Based on Equations 2-4, ΔB_{Tot} calculated using TE-weighted averaging and SNR-weighted averaging respectively have variances equal to:

$$\sigma^2\left(\Delta B_{Tot}^{TE-wAvg}\right) = \sigma^2\left(\frac{\sum_{i=1}^{n} \phi(TE_i)}{\gamma \sum_{i=1}^{n} TE_i}\right) \tag{11}$$

$$\sigma^2\left(\Delta B_{Tot}^{SNR-wAvg}\right) = \sigma^2\left(\frac{1}{n\gamma}\sum_{i=1}^{n} \frac{TE_i \exp(-TE_i R_2^*)}{\sum_{j=1}^{n} TE_j \exp\left(-TE_j R_2^*\right)} \frac{\phi(TE_i)}{TE_i}\right) \tag{12}$$

Assuming that noise in the single-echo phase is temporally uncorrelated and based on error propagation, the noise in ΔB_{Tot} calculated using TE-weighted or SNR-weighted averaging is respectively equal to:

$$\sigma\left(\Delta B_{Tot}^{TE-wAvg}\right) = \frac{\sum_{i=1}^{n} \sigma\left(\phi(TE_i)\right)}{\gamma \sum_{i=1}^{n} TE_i} \tag{13}$$

$$\sigma\left(\Delta B_{Tot}^{SNR-wAvg}\right) = \frac{1}{\gamma}\sum_{i=1}^{n} \frac{\exp(-TE_i R_2^*)}{\sum_{j=1}^{n} TE_j \exp\left(-TE_j R_2^*\right)} \sigma\left(\phi(TE_i)\right) \tag{14}$$

Similar to Equation 10, Equations 13 and 14 omit the $\boldsymbol{r}$ dependency, because they combine multi-echo phase in a voxel-wise fashion.

Noise in the local field map

For all pipelines, based on error propagation and the orthogonality (15) of ΔB_{Loc} and the ΔB_{Bg} in the ROI, e.g., the brain:

$$\sigma(\Delta B_{Loc}) = \sqrt{\sigma^2(\Delta B_{Tot}) - \sigma^2\left(\Delta B_{Bg}\right)} \Leftrightarrow \sigma(\Delta B_{Loc}) \leq \sigma(\Delta B_{Tot}) \tag{15}$$

where the ⇔ symbol denotes an “if and only if” relationship. Therefore, in a worst-case scenario, the noise affecting ΔB_{Loc} equals the noise affecting the corresponding ΔB_{Tot}.

Noise in the susceptibility map

The noise in the susceptibility map $\sigma(\chi)$ is calculated based on (16):

$$\chi(\boldsymbol{r}) = d^{-1}(\boldsymbol{r}) \star \Delta B_{Loc}(\boldsymbol{r}) \tag{16}$$

where d is the magnetic dipole and $\star$ denotes a spatially-dependent convolution operation. Thus, based on spatial error propagation, $\sigma(\chi)$ is (see Supporting Information):

$$\sigma\big(\chi(\boldsymbol{r})\big) = \frac{1}{B_0}\sqrt{\tilde{d}^{-2}(\boldsymbol{r}) \star \sigma^2\big(\Delta B_{Loc}(\boldsymbol{r})\big)} \tag{17}$$

When the regularized inverse dipole function $\tilde{d}^{-1}$ can be derived analytically and independently of χ or ΔB_{Loc}, e.g., in thresholded k-space division (TKD) or Tikhonov-regularized minimal norm solution (6,16,17), Equation 17 can be solved as:

$$\sigma\big(\chi(\boldsymbol{r})\big) = \frac{1}{B_0}\sqrt{FT^{-1}\left(\widetilde{D}^{-2}(\boldsymbol{k})FT\left(\sigma^2\big(\Delta B_{Loc}(\boldsymbol{r})\big)\right)\right)} \tag{18}$$

where FT and FT^{-1} respectively denote the direct and inverse Fourier transforms, $\boldsymbol{k}$ denotes k-space coordinates, and $\widetilde{D}^{-1}$ the magnetic dipole in k-space.

Weighted averaging

For weighted averaging of TE-dependent χ (Equations 5 and 6), based on phase error propagation over time and Equation 15, $\sigma\big(\Delta B_{Loc}(TE_i)\big)$ equals:

$$\sigma\big(\Delta B_{Loc}(TE_i)\big) = \frac{\sigma\big(\phi(TE_i)\big)}{\gamma TE_i} \tag{19}$$

Based on Equations 5, 6, 18 and 19, $\sigma(\chi^{Susc-wAvg})$ is the square root of (see Supporting Information):

$$\begin{aligned}
\sigma^2(\chi^{Susc-wAvg}) = \\
&= \frac{1}{(B_0\gamma n)^2}\sum_{i=1}^{n}\chi^2(TE_i)\left(\frac{4M^2(TE_i)TE_i^4\sigma^2\big(M(TE_i)\big)}{\sum_{j=1}^{n}\big(M^2(TE_j)TE_j^2\big)^2}\right.\\
&+ \frac{M^4(TE_i)TE_i^4}{\sum_{j=1}^{n}\big(M^2(TE_j)TE_j^2\big)^4}\sum_{j=1}^{n}4M^2(TE_j)TE_j^4\sigma^2\left(M(TE_j)\right)\\
&\left.- \frac{2M^2(TE_i)TE_i^2}{\big(\sum_{j=1}^{n}M^2(TE_j)TE_j^2\big)^3}4M^2(TE_i)TE_i^4\sigma^2\big(M(TE_i)\big)\right)\\
&+ \left(\frac{M^2(TE_i)TE_i^2}{\sum_{j=1}^{n}M^2(TE_j)TE_j^2}\right)^2\sigma^2\big(\chi(TE_i)\big)
\end{aligned} \tag{20}$$

Notably, Equation 20 only applies to the Susc-wAvg pipeline, as it requires analytically describing $\sigma(\chi)$ (Equation 18). In the Susc-TGV-wAvg pipeline, such an equation could not be calculated, because the total generalized variation (TGV) method estimates χ iteratively (13).

Methods

When not otherwise stated, image analysis was performed using Matlab (R2017b, The MathWorks, Natick, MA) and statistical analysis using Stata (R15, StataCorp LP, College Station, TX). A preliminary version of this study was presented at the 2016 annual meeting of the International Society for Magnetic Resonance in Medicine (18).

In vivo data acquisition

Multi-echo 3D GRE imaging of ten healthy volunteers (average age/age range: 26/22-30 years, five females) was performed in two centers (University College London Hospital and Queen Square Multiple Sclerosis Centre, University College London) equipped with the same 3 T MRI system (Philips Achieva, Philips Healthcare, Best, NL; 32-channel head coil). Five subjects were acquired in each center. All the volunteers provided written informed consent and the local research ethics committees approved the experimental sessions. Images were acquired using a transverse orientation, field of view=240x240x144 mm^3, voxel size=1 mm^3 isotropic, flip angle=20 degrees, repetition time=29 ms, five evenly spaced echoes (TE_1/TE spacing=3/5.4 ms), bandwidth=270 Hz/pixel, SENSE (19) along the first/second phase encoding directions=2/1.5, flyback gradients along the frequency encoding (FE) direction, and without flow compensating gradients. To enable the image-based calculation of SNRs in the magnitude and phase images, five subjects were scanned twice within the same session without repositioning.

Data simulation from a numerical head phantom

To ensure the availability of ground-truth χ values against which to test the accuracy of QSM pipelines, a piece-wise constant Zubal numerical head phantom (20) was used to generate a simulated noisy multi-echo complex data set as previously described (11). The resulting phantom had matrix size=256x256x128 $voxels^3$, resolution=1.5 mm isotropic, and the following regions of interest (ROIs): the caudate nucleus (CN), globus pallidus (GP), putamen (PU), thalamus (TH), superior sagittal sinus (SSS), grey and white matter (GM and WM) and cerebrospinal fluid (CSF). Compared to our previous study (11), the numerical phantom was updated to also have realistic standard deviations (SDs) for χ, the proton density (M_0) and the transverse relaxation rate (T_2^*) in each ROI (see Supporting Information).

Data preprocessing

A brain mask was calculated for each subject by applying the FSL Brain Extraction Tool (BET) (21,22) with robust brain center estimation (threshold = 0.3) to the magnitude image at

the longest TE. The mask was based on the longest TE to account for the greater amount of signal dropout near regions of high-χ gradients compared to shorter TEs.
A whole-brain mask for the Zubal phantom was calculated by applying FSL BET with robust brain center estimation (threshold = 0.5) to the T_2^* map of the numerical phantom (11).

Processing pipelines for QSM

Five distinct processing pipelines (Figure 1) were applied to both the numerically simulated data and the healthy volunteer data. Three of these pipelines (NLFit, TE-wAvg, and SNR-wAvg) combined the phase across TEs at different stages before performing the ΔB_{Loc}-to-χ inversion. The two other pipelines (Susc-wAvg and Susc-TGV-wAvg) first calculated a distinct χ map at each TE and then combined the χ maps. The following paragraphs describe each processing pipeline in detail.
The NLFit processing pipeline (11) first combined the complex GRE signal by nonlinear fitting over TEs (5) using the Cornell QSM software package's Fit_ppm_complex function (http://weill.cornell.edu/mri/pages/qsm.html). It then applied simultaneous phase unwrapping and ΔB_{Bg} removal using Sophisticated Harmonic Artifact Reduction for Phase data (SHARP) (23), which is a direct solver of the discretized Poisson equation (23).
SHARP was chosen because it has been widely used in the literature on QSM and is both robust and numerically efficient (10). In addition, in our recent study comparing multi-echo and TE-dependent QSM, a multi-echo pipeline incorporating SHARP gave highly accurate multi-echo QSM values (11). As in this previous study (11), SHARP was implemented using the minimum-size 3-voxel isotropic 3D Laplacian kernel (23), and it was applied using a threshold for truncated singular value decomposition (tSVD) equal to 0.05 and a brain mask with a 2-voxel (numerical phantom) or 4-voxel erosion (healthy volunteers).
The TE-wAvg processing pipeline first applied Laplacian unwrapping to the phase at each TE using a threshold for tSVD equal to 10^{-10} (i.e., the default value in the Cornell QSM software package). Second, TE-wAvg calculated ΔB_{Tot} by averaging the unwrapped phase according to Equation 2 with the TE-based weights in Equation 3 (1,2). Then, it calculated ΔB_{Loc} by applying SHARP with the same parameters as in NLFit and removing residual phase offsets by applying SHARP with variable kernel size (V-SHARP) with an initial kernel radius of approximately 40 mm and a step size/final kernel radius of 1 voxel (24,25).
The SNR-wAvg processing pipeline first applied simultaneous phase unwrapping and ΔB_{Bg} removal to the phase at each TE using SHARP with the same parameters as in NLFit. It then calculated ΔB_{Loc} by averaging the unwrapped phase according to Equation 2 with the SNR-based weights in Equation 4 (3) and removing residual phase offsets by applying V-SHARP as in TE-wAvg.

In these three pipelines, ΔB_{Loc}-to-χ inversion was performed using Tikhonov regularization with correction for susceptibility underestimation and using the L-curve method to determine the optimal value for the regularization parameter (6,23,26). This inversion method was chosen because it is computationally efficient and substantially reduces streaking artifacts relative to the truncated k-space division method (27).

The Susc-wAvg processing pipeline calculated a distinct QSM image at each TE by applying simultaneous phase unwrapping and ΔB_{Bg} removal using SHARP as in NLFit, removing residual phase offsets by applying V-SHARP as in TE-wAvg and SNR-wAvg, and performing the ΔB_{Loc}-to-χ inversion using Tikhonov regularization as in NLFit, TE-wAvg and SNR-wAvg. This pipeline then calculated a combined QSM image by applying Equation 5 with the magnitude-based weights in Equation 6 (4).

The Susc-TGV-wAvg processing pipeline applied one-step TGV (13) to the phase at each TE, and then calculated a combined QSM image as in Susc-wAvg. The TGV method was chosen because it avoids stair-casing artifacts in the resulting QSM image while correctly preserving structural borders (13). Moreover, in our recent study comparing multi-echo and TE-dependent QSM, TGV provided highly accurate TE-dependent QSM images (11). TGV was implemented using Singularity (https://github.com/CAIsr/qsm; Sylabs, Albany, CA) and the default parameter values $(\alpha_1, \alpha_0) = (0.0015, 0.005)$, which are optimal for medical imaging applications (13).

ROI segmentation in the healthy volunteer images

Regional χ values were compared between the simulated and in vivo data similar to our previous study comparing multi-echo and TE-dependent QSM (11). To this aim, ROIs similar to the numerical phantom were segmented in vivo: the CN, GP, PU, TH, posterior corona radiata (PCR) as a WM ROI and the straight sinus (StrS) as a venous ROI. In brief, for each subject, the CN, GP, PU, TH and PCR were segmented based on the Eve χ atlas (28), whose GRE magnitude image was aligned to each subject's fifth-echo magnitude image using NiftyReg (29,30) (TE_{Eve}/TE_5 = 24/24.6 ms). The ITK-SNAP active contour segmentation tool (31) was used to segment the StrS in each subject based on the fifth-echo magnitude image, which presented the best contrast between the StrS and the surrounding brain tissue.

Quantitative evaluation of the measured χ

In the numerical phantom simulations, the performance of each QSM pipeline relative to the ground truth was visually assessed by calculating a difference image between the corresponding χ map and the χ^{True}. In the volunteers, owing to the lack of a ground truth,

similar difference images were calculated relative to χ^{NLFit}, because the NLFit pipeline provided the lowest regional susceptibility bias in the numerical phantom simulations (see the Results section).

In the numerical phantom simulations, the means and SDs of χ were calculated for each pipeline in each phantom ROI with $\chi^{True} \neq 0$, i.e., the CN, GP, PU, TH, SSS and WM. The root mean squared errors (RMSEs) of χ relative to χ^{True} were also calculated throughout the brain volume as previously described (11).

In the volunteers, the means and SDs of χ were calculated in each ROI and for each processing pipeline and compared against χ values in subjects of a similar age from the literature. In the volunteers, the RMSEs could not be calculated because of the lack of a ground truth.

For visualization purposes in the healthy volunteers, if it was possible to pool the regional means and SDs of χ across subjects (i.e., all intrasubject SDs of χ were larger than the intersubject SD of χ), the pooled averages and SDs were calculated as previously described (11).

Noise propagation maps

Only the healthy volunteers scanned twice were considered for this analysis. To enable image SNR calculation, in one healthy volunteer, five 20x20-voxel ROIs were drawn on a sagittal slice of the first-echo magnitude image (32), including both the GM and WM and taking care to exclude regions with artifacts induced by SENSE, motion or flow. All five ROIs were then rigidly aligned with the first-echo magnitude image of the four other volunteers using NiftyReg (30).

In each subject, ROI-based magnitude (M_{ROI}), magnitude noise ($\sigma_{ROI}(M)$) and phase noise values ($\sigma_{ROI}(\phi)$) were calculated based on the SNR difference method (33):

$$M_{ROI}(TE,\boldsymbol{r}) = \frac{1}{2} mean\big(M_1(TE,\boldsymbol{r}) + M(TE,\boldsymbol{r})\big), \qquad \boldsymbol{r} \in ROI \tag{21}$$

$$\sigma_{ROI}\big(M(TE,\boldsymbol{r})\big) = \sqrt{\frac{R}{2}} SD\big(M_1(TE,\boldsymbol{r}) - M_2(TE,\boldsymbol{r})\big), \qquad \boldsymbol{r} \in ROI \tag{22}$$

$$\sigma_{ROI}\big(\phi(TE,\boldsymbol{r})\big) = \sqrt{\frac{R}{2}} SD\big(\phi_1(TE,\boldsymbol{r}) - \phi_2(TE,\boldsymbol{r})\big), \qquad \boldsymbol{r} \in ROI \tag{23}$$

Here, M_1/ϕ_1 and M_2/ϕ_2 respectively denote the magnitude/phase images from the first and second scan, $R = 3$ is the 2D SENSE factor calculated by multiplying the SENSE factors applied along the two phase encoding directions (34). The values calculated based on

Equations 19-21 were averaged across the five ROIs, to calculate summary values of magnitude, magnitude noise and phase noise at each TE.

For both the numerical phantom simulations and the healthy volunteers, a $\sigma(\phi)$ map was calculated at each TE as (14,35):

$$\sigma\big(\phi(TE,\boldsymbol{r})\big) = c(TE)\frac{1}{SNR(TE,\boldsymbol{r})} = c(TE)\frac{\sigma_{ROI}\big(A(TE)\big)}{M(TE,\boldsymbol{r})} \tag{24}$$

where $c(TE)$ was a constant equal to 1 (by definition) in the numerical phantom simulations and equal to:

$$c(TE) = \frac{\sigma_{ROI}(TE)}{\frac{1}{SNR_{ROI}(M)}} = \frac{\sigma_{ROI}\big(\phi(TE)\big)\sigma_{ROI}\big(M(TE)\big)}{M(TE)} \tag{25}$$

in the healthy volunteers. Notably, calculating phase noise analytically as in Equation 24 enabled the direct comparison of noise propagation between numerical simulations and data acquired in vivo.

For each of the NLFit, TE-wAvg and SNR-wAvg processing pipelines, the $\sigma(\Delta B_{Tot})$ map was calculated based on the multi-echo $\sigma(\phi)$ maps according to Equations 10, 13 and 14, respectively. Then, the $\sigma(\chi)$ map was calculated based on the corresponding $\sigma(\Delta B_{Tot})$ map (Equation 18) with $B_0 = 3\ \mathrm{T}$ and the Tikhonov-regularized inverse magnetic dipole with regularization parameter α (6):

$$\widetilde{D}^{-2}(\boldsymbol{k};\alpha) = \frac{D(\boldsymbol{k})}{D(\boldsymbol{k})^2 + \alpha} \tag{26}$$

and correction for χ underestimation (23). For the Susc-wAvg pipeline, the $\sigma(\chi)$ map was calculated based on Equation 20. Notably, as explained in the Theory section, $\sigma(\chi)$ maps were not calculated for the Susc-TGV-wAvg pipeline, because an analytical expression for $\sigma(\chi)$ could not be derived using the TGV method.

To compare $\sigma(\chi)$ maps across pipelines, a line profile was traced in the same location of all $\sigma(\chi)$ images and the $\sigma(\chi)$ value of each voxel along this profile was plotted. To compare the noise intensity and its variability between processing pipelines, the mean and SD of this representative line profile were also calculated.

Statistical analysis

Statistical analyses were performed based on the healthy subject data. For each ROI and each pair of pipelines, potential symmetric biases between distinct processing pipelines were investigated using Bland-Altman analysis of the average χ. For each ROI, statistically significant differences between pipelines were tested by considering the corresponding distributions of average χ values across subjects. To assess whether to apply parametric paired t-tests or nonparametric sign tests, the normal distribution of the differences between

paired χ values was assessed using the Shapiro-Wilk test. All statistical tests were two-tailed and an uncorrected *P*-value of 0.05 or less was considered significant.

Results

Pooling of χ measurements

For each ROI and each processing pipeline, all intrasubject SDs of χ were larger than the intersubject SD. Thus, pooled means and SDs were calculated (11).

Performance of pipelines for multi-echo QSM

In the numerical phantom, Figure 2 shows the QSM images calculated by each processing pipeline for multi-echo QSM (A-L), their difference relative to the ground truth (M-V), and the RMSEs of χ throughout the brain volume (bottom row). Figure 3A shows the means and SDs of χ calculated using each processing pipeline in each ROI.

For the numerical phantom simulations, the error between the calculated and ground-truth χ appeared fairly similar for all processing pipelines, although slightly larger SDs were always observed for the NLFit pipeline (Figures 2M-V and Figure 2A). The SSS, which was the highest χ structure (χ^{True} = 0.30 ± 0.06 ppm), showed the largest susceptibility errors for all the processing pipelines (arrowheads in Figures 2G-L, R-V and Figure 3A).

For one representative volunteer, Figures 4A-J show the susceptibility images calculated using each processing pipeline for multi-echo QSM. Additionally, Figures 4K-L show the differences between each QSM image relative to the χ^{NLFit} image. For each ROI in the healthy volunteers, Figure 3B shows the pooled means and SDs of χ calculated using each processing pipeline. In the volunteers, susceptibility differences between processing pipelines were most prominent in the StrS (arrowheads in Figures 4F-J, O-R).

In general, the average χ measured in the deep-GM ROIs and in the PCR (Figure 3B) had values within the ranges reported by previous studies (28,36-40): 0.01–0.13 ppm for the CN, 0.06–0.29 ppm for the GP, 0.02–0.14 ppm for the PU, -0.02–0.08 ppm for the TH, and -0.06–0.03 ppm for the PCR. In the StrS, only χ^{NLFit} had an average value close to the previously reported range for venous blood, namely, 0.17–0.58 ppm (27,39,41,42) (Figure 3B).

Similar to the numerical phantom simulations, in the healthy volunteers, χ calculated using the NLFit pipeline (χ^{NLFit}) had slightly larger SDs in the GP, PU and StrS. In contrast with the numerical phantom simulations, in the healthy volunteers, χ calculated using the SNR-wAvg pipeline ($\chi^{SNR-wAvg}$) had slightly larger SDs in the CN, TH and PCR compared to χ^{NLFit}.

Finally, in the numerical phantom simulations, the QSM image calculated using the NLFit pipeline had the largest RMSE value (108.8%) followed, in decreasing order, by the QSM images calculated using the SNR-wAvg (94.7%), TE-wAvg (94.0%), Susc-wAvg (91.7%) and Susc-TGV-wAvg pipelines (79.6%) (Figure 2, bottom row).

Phase noise propagation into the QSM images

Figures 5 and 6 respectively show the estimated $\sigma(\chi)$ profiles in the numerical phantom simulations and a representative healthy subject. In both the phantom and the healthy volunteers, the NLFit and SNR-wAvg pipelines resulted in $\sigma(\chi)$ images with the lowest number of streaking artifacts (Figures 5A, E, C, G and 6A, E, C, G). Although a certain degree of streaking artifacts could be seen for all four pipelines, especially in the healthy volunteer the TE-wAvg and Susc-wAvg pipelines resulted in considerably worse streaking artifacts around high-χ venous structures.

Statistical analysis

In the healthy volunteers, for all processing pipelines and ROIs, the Shapiro-Wilk test always rejected the hypothesis of normally distributed paired differences of χ. Therefore, pairwise comparisons between pipelines were always evaluated using the nonparametric sign test. Significant differences between pipelines are highlighted in Figure 3B, whereas the between-pipeline biases are shown in Figure 7. Biases smaller than |0.01| ppm (|·| denotes the absolute value) were considered negligible.

A bias greater than |0.01| ppm was observed for the NLFit pipeline relative to all other pipelines in the CN, GP and StrS, for the Susc-TGV-wAvg pipeline relative to the TE-wAvg, SNR-wAvg and Susc-wAvg pipelines in the GP, and between the SNR-wAvg and Susc-wAvg pipelines in the GP (Figure 7).

In general, the bias was greater than |0.01| ppm for the same pairs of pipelines that differed according to the sign test (Figures 3B and 7).

Discussion

This study aimed to compare multi-echo combination methods for QSM, which were applied at different stages of the QSM processing pipeline before or after LBMs for phase unwrapping or background field removal. Methods for multi-echo combination were compared by applying each pipeline to numerically simulated data and images from healthy volunteers.

The relative accuracy of different processing pipelines in vivo was similar to the phantom simulations in the CN, GP and the venous ROIs, where the NLFit pipeline provided the highest and most accurate means of χ (Figure 3). Slightly different relative accuracies were

observed in the PU, TH and PCR. Here, however, no significant difference or systematic bias was detected between processing pipelines (Figures 3 and 7). Two exceptions were observed for the Susc-TGV-wAvg pipeline in the GP and the StrS, as this pipeline had the second highest mean of χ in the phantom simulations but the lowest mean of χ in the healthy volunteers (Figure 3). Both the TGV reconstruction pipeline and shortcomings of the numerically simulated data could explain these discrepancies in the performance of the Susc-TGV-wAvg pipeline. The numerically simulated data were generated based on a digital phantom containing regions of piece-wise constant χ distribution. As previously observed (43), piece-wise constant geometries allow good recovery of the underlying χ distribution using TGV-based algorithms, because the piece-wise constant constraints exactly match the underlying χ distribution. However, in regions with flow, anisotropic χ distributions or microstructure, these numerical models are likely to depart from a realistic representation of the head's bulk χ. Notably, the GP, contrary to the PU and CN, is traversed by multiple myelinated axons of the striato-pallido-nigral tract. In the GP in vivo, additional anisotropic χ contrast dependent on axonal orientation could explain the lower accuracy of the Susc-TGV-wAvg pipeline compared to the phantom simulations, in which the GP had isotropic χ (44). As for the StrS, the lower accuracy of the Susc-TGV-wAvg pipeline compared to the phantom simulations could be due to the presence of flow in vivo and the absence of flow compensation in the acquisition sequence, jointly violating the assumption of a piece-wise constant venous χ. To overcome this assumption, future studies could exploit a newly developed realistic head phantom for QSM, which also incorporates microstructural effects (45).

Generally, the higher accuracy of the NLFit pipeline suggests that, for QSM, combining the temporally unwrapped multi-echo phase before applying LBMs for spatial phase unwrapping or ΔB_{Bg} removal is preferable to combining the TE-dependent LBM-processed phase by averaging. This suggestion is in apparent contrast with the higher RMSE associated to the NLFit pipeline in the phantom simulations (Figure 2). However, the RMSE jointly reflects systematic and random errors, as it measures the bias between the estimated χ and χ^{True} but also reflects the variability of the estimated χ relative to its average value (43). Thus, the RMSE must always be interpreted in combination with complementary measurements of bias and precision.

There are several potential explanations as to why LBMs applied before multi-echo combination reduce the overall accuracy of QSM. Firstly, in contrast with path-based phase unwrapping, Laplacian phase unwrapping is likely to also remove some ΔB_{Bg} components from the input phase image (23). This effect might be explained by the periodicity constraint

imposed by evaluating the inverse Laplacian operator in Fourier domain (9,23) and by the practical effect of inverting the Laplacian kernel via tSVD with a minimal truncation threshold (i.e., 10^{-10}), which acts as a mild high-pass filter (10). Thus, the consistently lower accuracy of χ calculated using the TE-wAvg processing pipeline was probably driven by the incorrect assumption that the TE-dependent LBM-unwrapped phase corresponded to the true unwrapped phase. LBMs for ΔB_{Bg} removal also applied tSVD (with a larger truncation threshold) but here the high pass filtering effect was expected, as background fields are slowly varying. Finally, the similar accuracy of χ calculated using the TE-wAvg, SNR-wAvg and Susc-wAvg pipelines suggests a negligible difference between averaging the Laplacian unwrapped phase over TEs before (TE-wAvg pipeline) or after TE-dependent Laplacian ΔB_{Bg} removal (SNR-wAvg and Susc-wAvg pipelines).

In the numerical phantom simulations, all processing pipelines resulted in higher SDs of χ compared to the ground-truth, suggesting that they all intrinsically amplified the noise in the multi-echo signal phase. This result is in line with the known noise amplification of ill-posed inverse problems. However, the estimated SDs of χ varied across pipelines, with the Susc-TGV-wAvg pipeline generally having the lowest SDs in both the numerical simulations and healthy volunteers (Figure 3). This result was in agreement with a previous study showing that, for QSM, L_1-regularization (as in TGV) provides better noise suppression than L_2-regularization (e.g., Tikhonov regularization) (6).

In both numerical simulations and healthy volunteers, based on the line profiles traced on the noise maps and streaking artifact reduction, the NLFit pipeline had a better noise mitigation than the TE-wAvg, SNR-wAvg and Susc-wAvg pipelines (Figures 5 and 6). This result suggests that combining the temporally unwrapped multi-echo phase by nonlinear complex fitting, designed to account for noise in the complex signal (5), results in better noise management than combining the multi-echo phase by averaging. As previously shown (5), errors in the combined field map mainly result from both noise in the signal phase and phase unwrapping errors near high-χ regions (e.g., the veins). Both sources of error were successfully managed by nonlinear complex fitting, as shown by the dramatic reduction of streaking artifacts in Figure 6A. In line with previous observations (25), this result also suggests that the regularization strategy employed by the ΔB_{Loc}-to χ step can mitigate artifactual streaking errors only when major sources of error in the field map have been tightly constrained. In both the numerical simulations and healthy volunteers, the SNR-wAvg pipeline had the best noise mitigation of all averaging-based pipelines (Figures 5 and 6). Thus, if applying nonlinear complex fitting is not possible, averaging using the SNR-weighting method could offer the best alternative for noise reduction.

All these indications do not necessarily apply to χ estimation in WM tissue. Indeed, due to WM's ordered microstructure, QSM of WM requires acquiring GRE images at multiple head orientations and modelling χ as a tensor (46,47). Thus, further studies are needed to evaluate the translatability of these results to WM tissue.

In the present study, all experiments were limited to one field strength (i.e., 3 T). As tissue relaxation times (e.g., T_2^*) shorten with increasing field strength but the signal phase at a given TE increases, further work is needed to assess the translatability of these results to ultrahigh fields. Finally, it must be noted that in the numerical phantom simulations, all processing pipelines underestimated χ^{True} (Figure 3). However, in QSM, some degree of underestimation is always expected, because of the ill-posed nature of the ΔB_{Loc}-to-χ inverse problem (16).

Conclusions

For QSM using multi-echo acquisitions, combining the multi-echo phase by nonlinear complex fitting before applying LBMs for phase unwrapping or ΔB_{Bg} removal offers the best compromise between bias reduction and noise mitigation.

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Figures

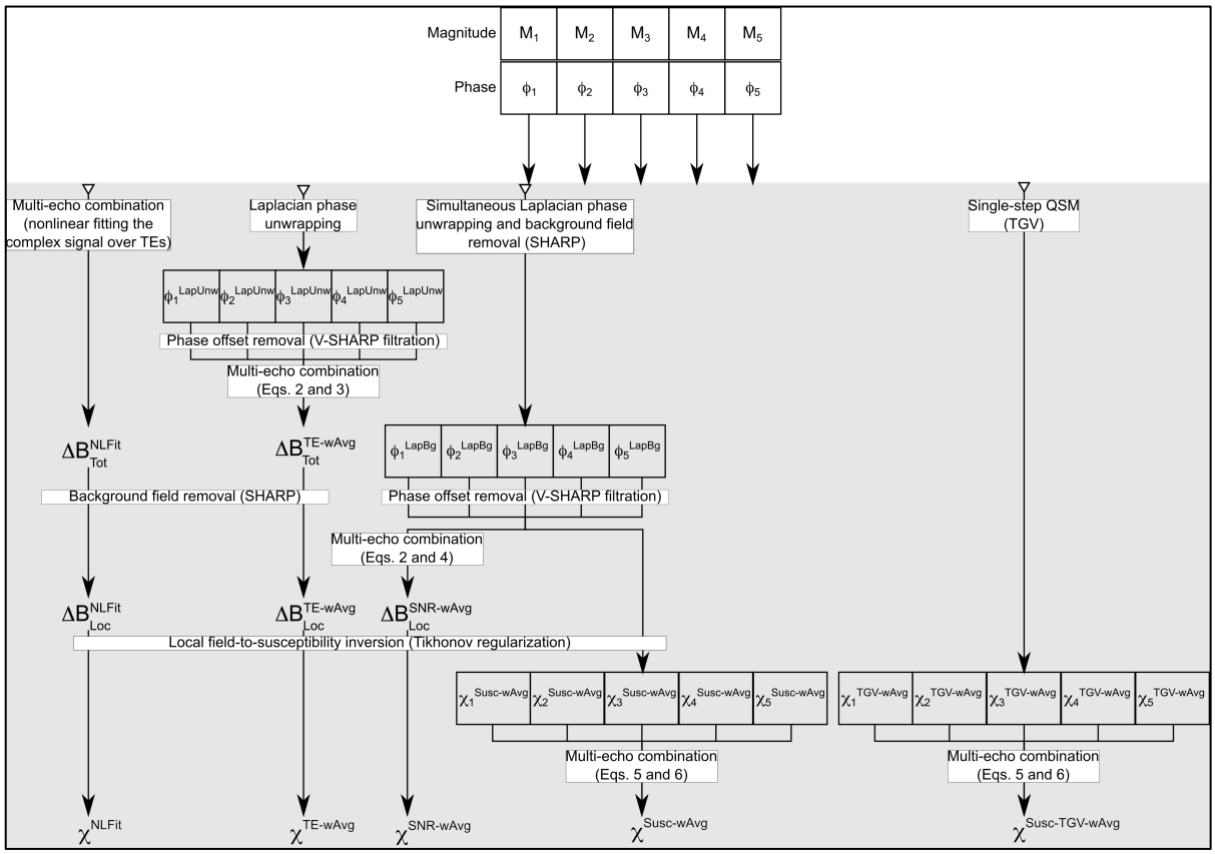

Figure 1. Processing pipelines for multi-echo QSM. For each multi-echo combination method (NLFit [nonlinear phase fitting], TE-wAvg [TE-weighted phase averaging], SNR-wAvg [SNR-weighted phase averaging], Susc-wAvg and Susc-TGV-wAvg [magnitude-weighted susceptibility averaging]) the processing steps are described as separate processing streams in the grey box.

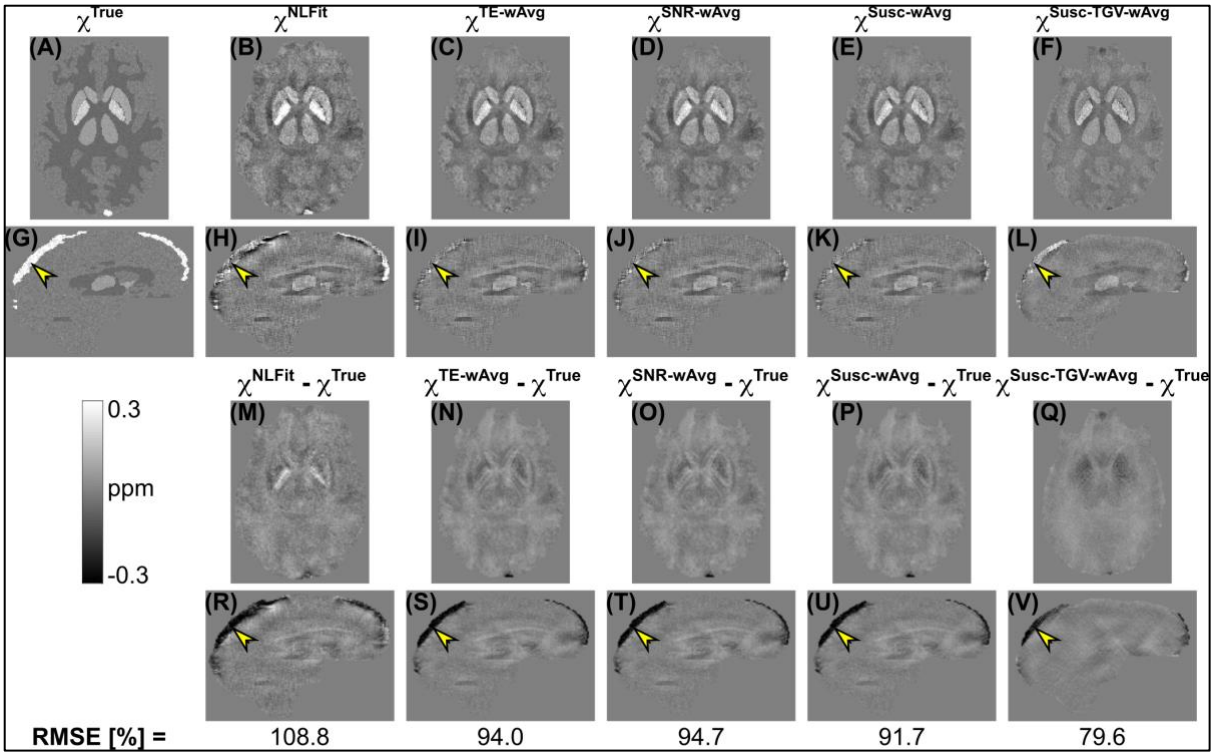

Figure 2. QSM images calculated using distinct multi-echo combination methods in the numerical phantom simulations. In the numerical phantom, the same transverse and sagittal slices are shown for the ground-truth susceptibility map (A, G), and for the susceptibility maps calculated using NLFit (B, H), TE-wAvg (C, I), SNR-wAvg (D, J), Susc-wAvg (E, K) and Susc-TGV-wAvg (F, L). The figure also shows the difference between each susceptibility map and the ground truth (M-V). The bottom row shows the root mean squared errors (RMSEs) of χ. In all the sagittal images (G-L, R-V), the yellow arrowheads point at the same location in the SSS.

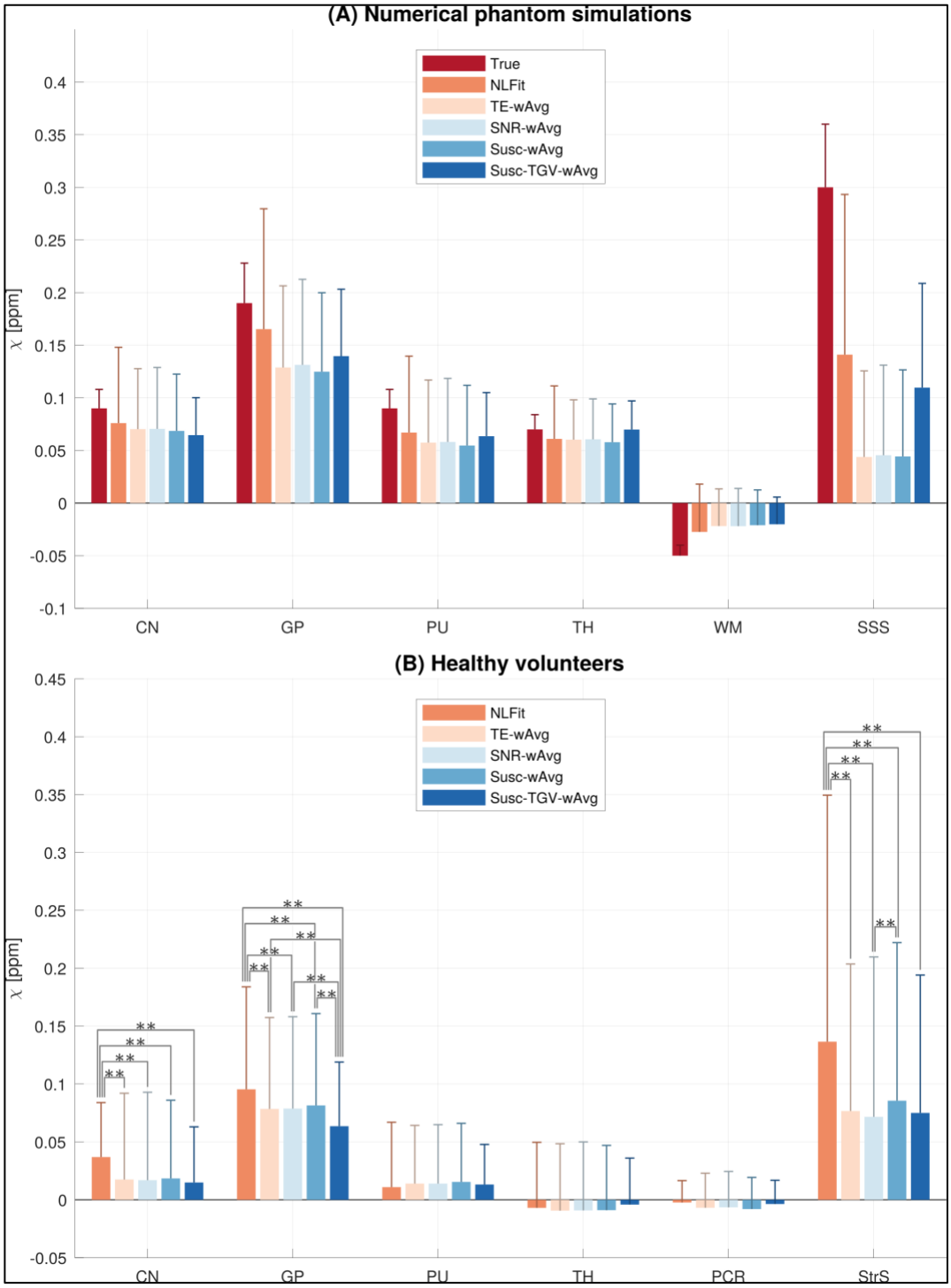

Figure 3. Means and SDs of χ in the phantom and healthy volunteer ROIs. The means and SDs (error bars) of χ are shown in each ROI of the numerically simulated (A) and pooled healthy volunteer data (B) for each processing pipeline. In the numerical phantom the ground-truth χ is also shown. In the healthy volunteers, significant differences between pairs of pipelines are denoted using the symbol ** (*P*-value < 0.05). Abbreviations: CN, caudate nucleus; GP, globus pallidus; PCR, posterior corona radiata; PU, putamen; StrS, straight sinus; TH, thalamus; WM, white matter.

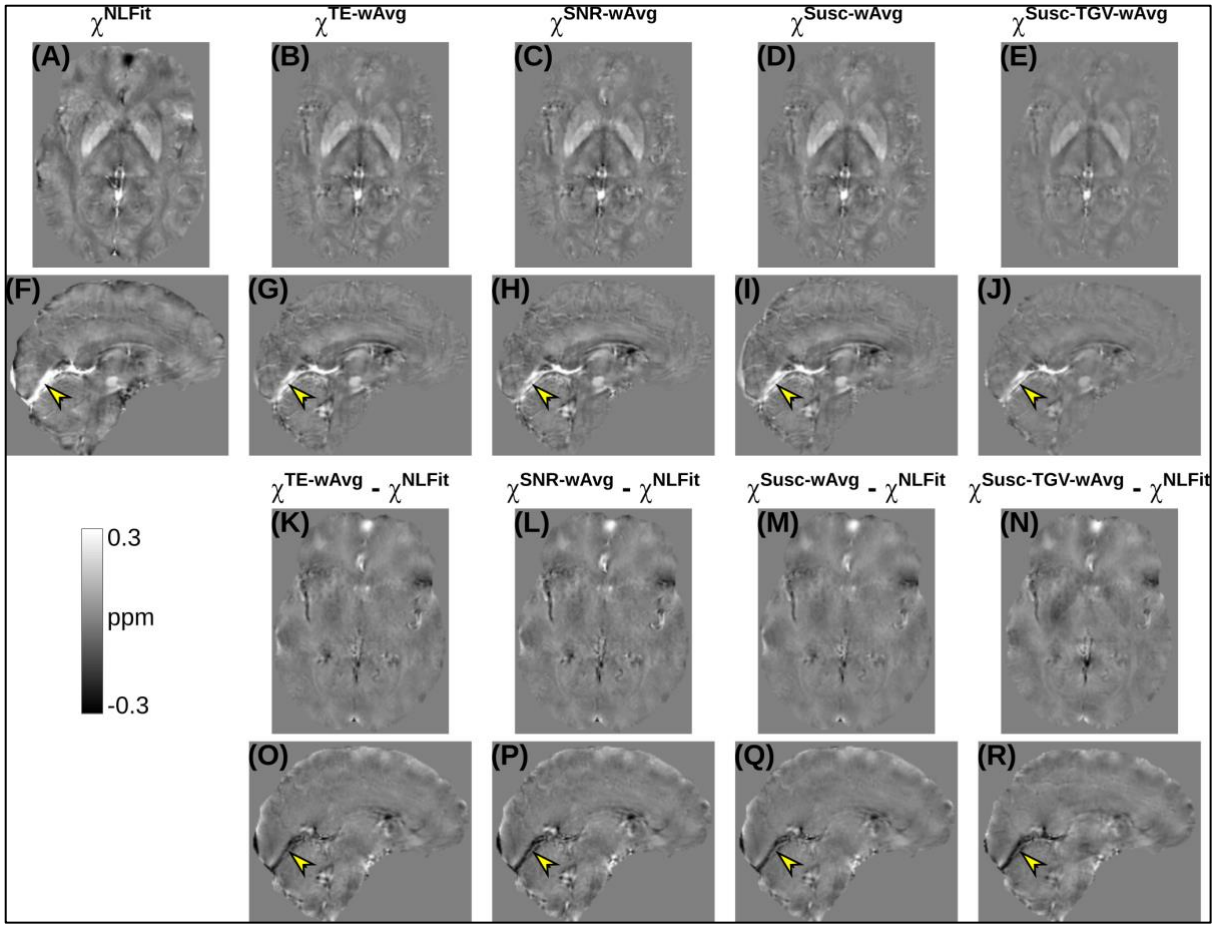

Figure 4. QSM images calculated using distinct multi-echo combination methods in a representative healthy volunteer. In a representative healthy volunteer, the same transverse and sagittal slices are shown for the susceptibility maps calculated using NLFit (A, F) [nonlinear phase fitting], TE-wAvg (B, G) [TE-weighted phase averaging], SNR-wAvg (C, H) [SNR-weighted phase averaging], Susc-wAvg (D, I) and Susc-TGV-wAvg (E, J) [magnitude-weighted susceptibility averaging]. The figure also shows the differences between the TE-wAvg, SNR-wAvg, Susc-wAvg and Susc-TGV-wAvg maps and the NLFit map (K-R). In all the sagittal images (F-J, O-R), the yellow arrowheads point at the same location in the StrS.

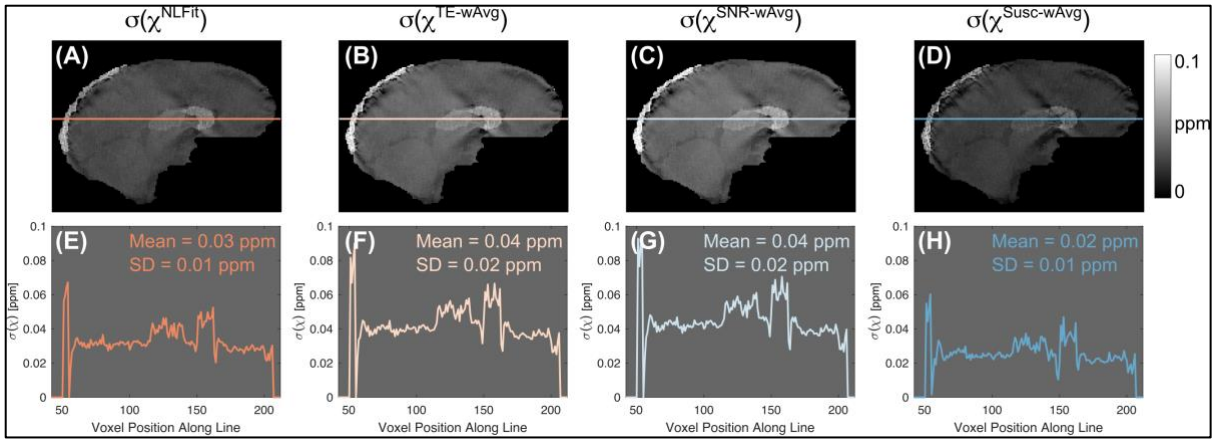

Figure 5. Susceptibility noise profiles in the numerical phantom simulations. In the numerical phantom, the same sagittal slice is shown for susceptibility noise ($\sigma(\chi)$) images calculated using the NLFit, TE-wAvg, SNR-wAvg and Susc-wAvg pipelines (A-D). The susceptibility noise is plotted for a line profile traced on the $\sigma(\chi)$ images (E-H) including the high-χ SSS.

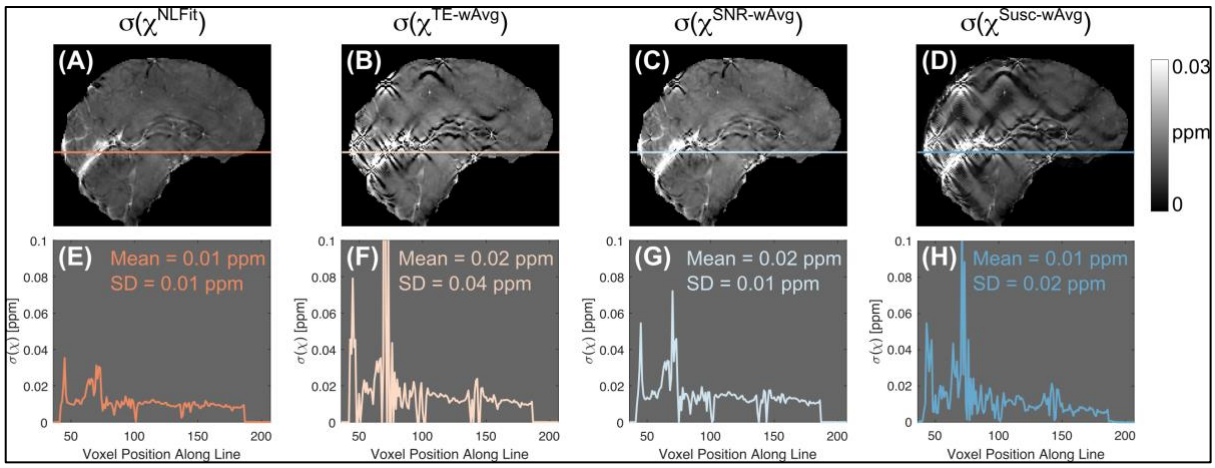

Figure 6. Susceptibility noise profiles in a representative healthy volunteer. For a representative healthy volunteer, the same sagittal slice is shown for susceptibility noise ($\sigma(\chi)$) images calculated using the NLFit, TE-wAvg, SNR-wAvg and Susc-wAvg pipelines (A-D). The susceptibility noise is plotted for a line profile traced on the $\sigma(\chi)$ images (E-H) including the high-χ StrS.

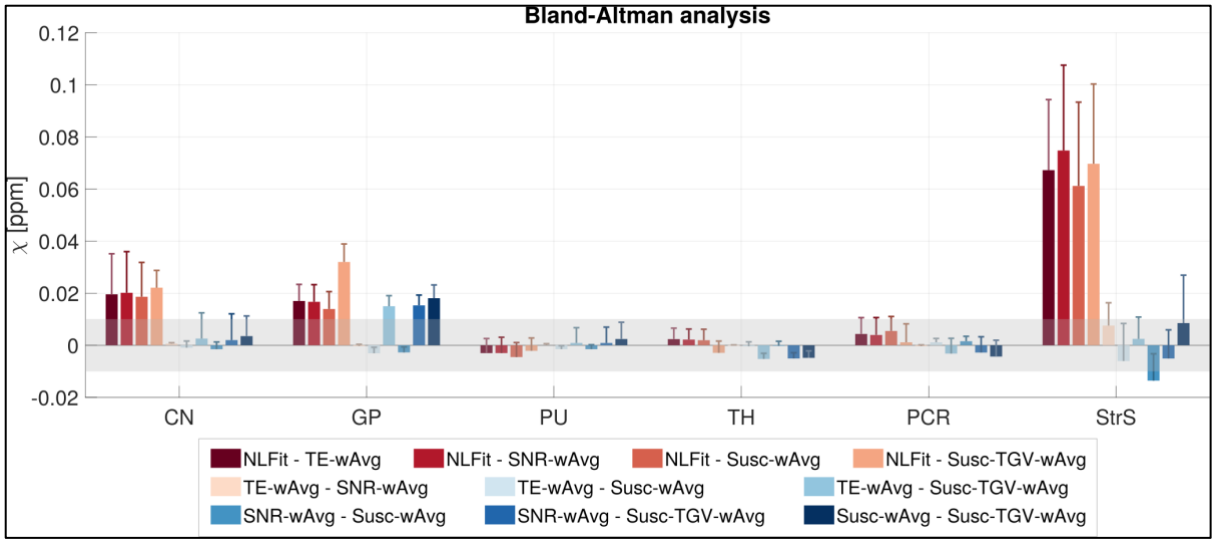

Figure 7. Bias between multi-echo pipelines for QSM in each ROI. The mean and SDs (error bars) of the bias are shown in each healthy volunteer ROI for all pairs of multi-echo processing pipelines. The grey band denotes the [-0.01 – 0.01] ppm interval. If the mean of the bias was within this interval, the difference between the corresponding pair of QSM pipelines was considered negligible.