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Quantitative Susceptibility Mapping (QSM) with an extended physical model for MRI frequency contrast in the brain: A proof-of-concept of QUAntitative Susceptibility And Residual (QUASAR) mapping

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Abstract

Quantitative susceptibility mapping (QSM) aims to calculate the tissue's magnetic susceptibility distribution from its perturbing effect on the MRI's static main magnetic field. The method is increasingly being applied to study iron and myelin in clinical and preclinical settings. However, recent experimental and theoretical findings challenged the fundamental theoretical assumptions that form the basis of current numerical implementations of QSM algorithms. The present work introduces a new class of susceptibility mapping algorithms, termed QUAntitative Susceptibility And Residual mapping (QUASAR), that takes into account frequency contributions not related to the spatial variation of bulk magnetic susceptibility in the Lorentz sphere model. We present a simple proof-of-concept QUASAR algorithm that, unlike most of the QSM algorithms currently used widely, results in an improved anatomical accuracy of the susceptibility distribution without any *a priori* assumptions about the susceptibility distribution during the field-to-source inversion. The algorithm was evaluated both *in silico* and *in vivo* in the preclinical setting. Our preliminary application of QUASAR in rodents provides the first *in vivo* evidence that the susceptibility-field model traditionally used in the QSM field cannot fully explain the frequency contrast in brain tissues. Only when an additional *local* frequency contribution is added to the physical model, the frequency contrast in the brain can be related properly to the underlying anatomy.

Graphical abstract

Quantitative susceptibility mapping (QSM) aims to calculate the tissue's magnetic susceptibility distribution from its perturbing effect on the MRI's main field. Recent experimental and theoretical findings challenged the theoretical assumptions that form the basis of current numerical implementations of QSM algorithms. The present work introduces a new class of susceptibility mapping algorithms, termed QUAntitative Susceptibility And Residual mapping (QUASAR), that takes into account frequency contributions not related to the spatial variation of bulk magnetic susceptibility in the Lorentz sphere model.

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Keywords

QSM; susceptibility mapping; rodents; phase contrast; exchange effects; GLTA

1. Introduction

Quantitative susceptibility mapping (QSM) ^{1–6} is a recent Magnetic Resonance Imaging (MRI) technique that aims to calculate the tissue's magnetic susceptibility distribution from its perturbing effect on the static main magnetic field. Susceptibility maps of the human brain present with a unique anatomical contrast ⁷ and QSM is currently regarded as the most sensitive technique to study the homeostasis of iron *in vivo* ^{8,9}. Over the past decade, numerous algorithms have been published that solve the mathematical ill-posed problem of QSM ⁶, namely the inversion of the Larmor frequency distribution in the tissue to its underlying distribution of magnetic susceptibility. All QSM algorithms that calculate the susceptibility distribution from a single frequency map (compared to using maps acquired in multiple head positions) rely on the following three fundamental assumptions: i) *bulk magnetic susceptibility* is the sole cause of Larmor frequency variations ¹⁰; ii) frequency perturbations related to the off-diagonal elements of the susceptibility *tensor* may be neglected ¹¹; and iii) the *Lorentz sphere correction* may be applied ¹⁰.

The first two assumptions stem from mathematical simplifications in the derivation of the physical model equation employed (Eq. 1 below). The third assumption, the Lorentz sphere correction, implies that the near-field contributions from magnetic dipoles in the vicinity of a probing (hydrogen) nucleus vanish when averaged over the *spherical* neighborhood around the probing nucleus ¹².

However, the validity of these three fundamental assumptions in brain tissue is increasingly being questioned. In particular, mounting evidence indicates that the local Larmor frequency is affected not only by static macroscopic field perturbations due to spatial variations in the tissue's bulk magnetic susceptibility, but also by biophysical mechanisms not directly related to susceptibility, such as fast exchange processes between water and macromolecules ^{13–17}

and chemical shift due to electron shielding¹⁸. Furthermore, in brain white matter (WM), the directional alignment of myelinated axons renders the voxel-average bulk magnetic susceptibility highly anisotropic, which implies that the total macroscopic frequency distribution depends not only on the susceptibility tensor component χ_{33} of the voxel but also on the tensor's off-diagonal terms χ_{13} and χ_{23} ^{11,19}. In addition, theoretical considerations²⁰ and Monte Carlo simulations²¹ predicted that, primarily in WM, the total near-field effect of magnetic moments on the probing nuclei depends on the distribution of magnetic moments at the cellular and subcellular levels (also referred to as the *tissue magnetic architecture*)²². Consequently, QSM algorithms that rely on the previously stated three assumptions will naturally result in artifacts on calculated susceptibility maps and misestimate tissue susceptibility, which has recently been demonstrated through numerical simulations²³.

In early, preliminary work, it has been proposed to disentangle the different frequency contributions *in vivo* by sampling the frequency distribution with the head in multiple orientations²⁴, similar to the well-established calculation of susceptibility through multiple orientation sampling (COSMOS)²⁵. However, although the computed maps of the different frequency sources showed a relatively high anatomical contrast in that study, the employed physical model did not take into account either susceptibility anisotropy or the orientation-dependency of the near-field effects due anisotropic sub-cellular magnetic architecture in WM.

In the present work, we propose a new single-orientation QSM method that explicitly accounts for frequency contrast mechanisms hitherto widely neglected in the QSM field. We coined the method QUAntitative Susceptibility And Residual (QUASAR) mapping because it retrieves composite information about the frequency contributions that cannot be explained by the traditional physical model. These deviations may be understood as the *residual* with respect to the widely employed physical model. We illustrate the discrepancy between the established QSM model and the measured frequency *in vivo*, optimise algorithmic parameters, validate the method in a numerical simulation, and demonstrate its application in the preclinical setting.

2 Materials and Methods

Currently, no gold standard technique exists for an independent validation of the proposed quantification technique. Hence, in the present work, our experimental approach heavily relied on numerical simulations with digital models, a comparison of simulations with *in vivo* results, and a critical assessment of the plausibility of the findings. After outlining the proposed extended frequency model (Sec. 2.1), the data acquisition (Sec. 2.2), and the reconstruction (Sec. 2.3), we will describe a simple experiment to illustrate the presence of non-susceptibility phase contrast *in vivo* (Sec. 2.4). Section 2.5 describes the mathematical QUASAR implementation and Sec. 2.6 a numerical model used for its *in silico* evaluation, which is outlined in Sec. 2.7. Section 2.8 describes the application of QUASAR *in vivo*.

2.1 Theory of the extended frequency model

Conventional QSM algorithms rely on the fundamental assumption that the observed MRI frequency f can be attributed *entirely* to field perturbations induced by the underlying bulk magnetic susceptibility distribution χ [see Ref. ¹⁰ for a detailed review of the derivation of this equation]:

$$f = f_{\chi} = d * \chi. \quad (1)$$

Here, the symbol $*$ denotes the convolution operation, d is the unit dipole response that includes the Lorentz-sphere correction, and f_{χ} is the frequency shift that reflects field perturbations caused by the variations of the underlying magnetic susceptibility distribution. All published QSM algorithms rely on Eq. (1).

Obviously, Eq. (1) does not model any frequency contributions other than those related to the voxel-average (bulk) magnetic susceptibility, χ . Hence, biophysical frequency contrast mechanisms not described by the model in Eq. (1) will inevitably cause artifacts when solving the equation.

We propose to lump all deviations from the model in Eq. (1) into a second frequency contribution f_{ρ} referred to as the *residual* of the traditional model in Eq. (1) or, less precisely, the *non-susceptibility contribution* f_{ρ} : $f = f_{\chi} + f_{\rho}$. In the extended frequency model proposed here, susceptibility mapping can be understood as solving the problem

$$f = d * \chi + f_{\rho} \quad (2)$$

with respect to both f_{ρ} and χ .

The approach in Eq. (2) is similar to that applied by de Rochefort et al. in a QSM algorithm referred to as Piece-Wise Constant Regularized Inversion of the Magnetic Field (PWCI) ²⁶ for one of the first published *in vivo* QSM applications. In their original publication, the authors aimed to use the f_{ρ} -component to model different chemical shift effects between fat and muscle, bone, and bone marrow for QSM in the human forearm.

2.2 Data acquisition

To study the contributions of f_{ρ} and χ to the total frequency contrast *in vivo* and demonstrate the proposed quantification technique in a homogeneous cohort, we acquired data from 23 Swiss Jim Lambert (SJL)/J mice (female, 6 weeks of age) in a prone position with a 200mm horizontal-bore 9.4 Tesla magnet (BioSpec 94/20 USR; Bruker Biospin) operated with ParaVision (version 5.1; Bruker Biospin). The system was equipped with a 440 mT/m imaging gradient coil (3440 T/m/s maximum linear slew rate; BGA-12S HP; Bruker Biospin) and a cryogenically cooled dual-element transceiver ¹H surface radio-frequency (RF) coil (CryoProbe, Bruker Biospin). We focused on the preclinical setting in this work because we originally discovered issues with the anatomical accuracy of calculated susceptibility maps in mice (see Results; Figure 3).

During MRI, the animals were physically stabilized using a custom-made bite bar and head fixation cushions. The protocol involved a coronal, non-gated 3D multi-echo gradient-echo pulse sequence (TR/TE₁/ TE=90ms/2.38ms/4.04ms, 9 monopolar/fly back echoes, 18° tip angle, 85kHz bandwidth, 75% Partial-Fourier in read direction [head-to-foot], 270×143×80 μm³ FOV, 252×180×100 acquisition matrix size [80μm isotropic resolution], 27min acquisition time) with fat suppression module (2ms Gaussian pulse, 1.4 kHz bandwidth, 2ms spoiler). We applied the sequence after field-map based higher-order shimming and iterative, water-line based linear shimming to a rectangular volume maximized within the brain. We calibrated the transmit pulse gain in a 2mm thick coronal slice located at a distance of approximately 1 mm from the top of the brain.

Induction and maintenance of anesthesia were achieved by inhalation of 3–5% and 1–1.5% Isoflurane in 1 liter per minute of 100% medical-grade oxygen, respectively. We monitored the respiration rate using an air-pillow (SA Instruments, Stony Brook, NY) and regulated the Isoflurane concentration to keep it around 50 breaths per minute. The body core temperature was stabilized between 36.5 to 37°C using a regulated water-based heating system (Thermo Fisher Scientific, Waltham, MA) and a rectal temperature probe (SA Instruments, Stony Brook, NY). The surface temperature of the RF coil was set to 37°C. We applied ophthalmic ointment to the animal's eyes to prevent corneal damage. We have published further detail of our experimental procedure elsewhere ²⁷.

Animals were housed in a temperature-controlled room maintained on a 12 hours light/dark cycle. Food and water were available ad libitum. The animal facility was fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International. All procedures involving animals were performed according to the guidelines of Institutional Animal Care and Use Committee (IACUC) [protocol NEU02123Y].

2.3 Image reconstruction

We calculated phase images from the raw multi-channel k-space data using scalar phase matching ^{28,29}. Frequency mapping and background field correction were achieved by best-path unwrapping ³⁰, signal-to-noise ratio optimal multi-echo combination ³¹, and sophisticated harmonic artifact reduction for phase with variable-radii (V-SHARP) ^{32,33} (10 radii from 40.8μm to 408μm on a twice up-sampled grid; threshold 0.05). We reconstructed magnitude images by Sum-of-Squares ³⁴. Maps of the effective transverse relaxation rate (R₂^{*}) were calculated on a voxel-by-voxel basis from truncated echo trains with the power-method ³⁵ and logarithmic calculus. Echo trains were truncated if the signal-to-noise ratio of the magnitude image intensity decreased below a value of two.

The pre-processing and all subsequent reconstruction and analysis steps (see below) were performed fully automatically and reproducibly with in-house developed software in MATLAB (2013b, The MathWorks, Natick, MA) on a Ubuntu 12.04 high-performance computation server with 48 cores (Intel Xenon E5–2697v2 at 2.7Ghz) and 396 GB RAM.

2.4 Demonstration of the limitations of the conventional physical model in Equation 1 via PWCI

We applied PWCI to the frequency maps of a randomly selected animal (Fig. 1a) to illustrate the discrepancy between the observed MRI frequency and the *traditional* QSM model in Eq. (1), i.e., the presence of frequency contrast that cannot be explained by bulk magnetic susceptibility. We applied the method twice, once with and once without allowing for a non-susceptibility contribution (the latter used $\sigma=0$ in Eq. 4 of Ref. ²⁶, essentially representing the conventional QSM model in Eq. 1 of the present work). The underlying hypothesis of this experiment was that the PWCI algorithm should not make use of its non-susceptibility component if in vivo frequency contrast can be described entirely by the anatomically defined susceptibility distribution.

PWCI fits to the measured frequency distribution a set of pre-computed field patterns that correspond to a priori defined anatomical regions with homogeneous tissue properties. In this experiment, for simplicity, we defined only two tissue types, cerebrospinal fluid (CSF) and brain parenchyma. This decision was motivated by the assumption that Eq. (1) should be valid within the ventricles because the Lorentz-sphere correction is valid within liquids and the macromolecule concentration is low in CSF compared to WM and gray matter (GM) ³⁶. We assumed that Eq. (2) would have to be applied in the surrounding parenchyma. In other words, this experiment assumed that the highest non-susceptibility related frequency contrast would be observed between CSF and parenchyma. Naturally, one may expect variations in both susceptibility and non-susceptibility contrast throughout the parenchyma but we neglected these variations in this experiment for simplicity and ease of interpretability of the results. Consequently, we expected that the frequency residual (discrepancy) after fitting the pre-computed field patterns would show no contrast between CSF and surrounding tissues, but unaltered frequency contrast elsewhere. While a model with only two tissue types cannot explain the subtle frequency contrast between different brain regions, it facilitated studying the frequency contrast originating from the two *major* brain tissue types in which Eqs. (1) and (2), respectively, apply.

We created the digital ventricle model for PWCI by thresholding the animal's R_2^* map (Fig. 1a, right) at an empirically determined value of 15/s. This value provided the best visual tradeoff for an extraction of the ventricles' geometry in the particular animal. The digital model was refined by applying 3D binary dilation and erosion operations, each with an extent of 1 voxel, to fill holes resulting from inhomogeneities on the R_2^* map potentially arising from signal instabilities (motion) and noise. We eliminated isolated voxels outside the ventricles with the help of a region-growing algorithm with a seed point placed in the ventricles (ITK Connected Threshold). Finally, to mitigate discretization effects, we smoothed the binary model using a 3D Gaussian kernel with a spatial-domain standard deviation of 0.3 voxels. Figure 1a (right) illustrates the resulting model.

We solved the linear problem of PWCI through the application of the pseudoinverse of the system matrix to the background-corrected frequency map. To construct the PWCI system matrix, which consists of the pre-computed field patterns for the pre-defined anatomical regions, we simulated the frequency response of the model at 9.4 Tesla for a susceptibility difference of $\chi=1$ between the two regions using Fast Forward Field computation with

Lorentz-sphere correction^{37–40}. Note that the chosen unit susceptibility difference ($\chi=1$) is an arbitrary algorithmic choice and does not imply any assumptions about the actual underlying in vivo susceptibility difference between the regions.

2.5 QUASAR algorithm

Equation 2 is mathematically highly under-determined because the number of unknowns, i.e., the voxel values of f_ρ and χ , exceeds the number of voxel values of frequency measurements f by a factor of two. Hence, a unique mathematical solution of Eq. (2) does not exist. The existence of a trivial solution with $\chi=0$ and $f_\rho = f$ illustrates this ambiguity. To obtain a unique and physically meaningful solution, constraints need to be added to Eq. (2). In their original PWCI publication, de Rochefort et al. overcame the under-determination in Eq. (2) by assuming that both the values of χ and the chemical shift did not vary throughout a few, large pre-defined tissue regions. If the number of tissue regions is sufficiently small, this constraint converts the under-determined problem into an over-determined problem that can be solved in a *least-squares* sense.

However, the restriction of PWCI to a few large regions is problematic for applications that require a detailed assessment of anatomical structures, such as imaging of the brain. Here, we propose a generalization of the original PWCI method in which the susceptibility distribution and most voxels of the non-susceptibility frequency contribution remain unconstrained. In earlier work, we have employed a similar approach to overcome the under-determination of Eq. (1) in the presence of magnitude signal-void lesions in the brain⁴¹, albeit without a non-susceptibility contribution at the time. Here, we generalized this concept to describe also the non-susceptibility frequency distribution, f_ρ .

It is reasonable to assume that the non-susceptibility frequency shifts are zero or constant throughout the ventricles because the CSF is a homogeneous liquid. Imposing this piece-wise constant constraint on f_ρ within the ventricles, leads to the following mathematical optimization problem:

$$\begin{aligned} \min_{\chi, f_\rho} & \|\chi\|^2 + \|f_\rho\|^2 \\ \text{subject to } & f = d * \chi + \lambda \cdot f_\rho \quad [3] \\ \text{and } & \nabla f_\rho = 0 \text{ within CSF.} \end{aligned}$$

where $\|\cdot\|$ denotes the Euclidean (L_2) norm, λ is a regularization parameter, and ∇ is the three-dimensional gradient operator. Eq. (3) obtains a unique *least-norm* solution of the underdetermined problem in Eq. (2). The particular solution obtained depends on the value of λ , which defines a trade-off between the attribution of observed frequency, f , to susceptibility-related frequency, f_χ (high λ), or non-susceptibility frequency, f_ρ (low λ), respectively. For $\lambda=0$, the conventional minimum-norm solution of Eq. (1) is obtained.

Equation (3) may be expressed as the *least-norm* solution of the following linear equation system:

$$\vec{f} = \begin{bmatrix} \mathbf{D} & \lambda \cdot \mathbf{I}_{\neq \text{CSF}} & \lambda \cdot \vec{u} \end{bmatrix} \cdot \begin{pmatrix} \vec{\chi} \\ \vec{f}_{\rho}^{\neq \text{CSF}} \\ \vec{f}_{\rho}^{\text{CSF}} \end{pmatrix}, \quad [4]$$

where vectors concatenate the individual voxel values of the respective spatial domain maps in Eq. (3), the matrix $\mathbf{D}$ performs the convolution with the unit dipole, $\mathbf{I}_{\neq \text{CSF}}$ is an identity matrix in which columns that correspond to constrained voxels in the non-susceptibility frequency pattern (CSF) are eliminated, $\vec{f}_{\rho}^{\neq \text{CSF}}$ concatenates the (unknown) voxel values of the non-susceptibility frequency pattern in unconstrained regions (outside of CSF), $\vec{f}_{\rho}^{\text{CSF}}$ contains the (unknown) f_{ρ} -value of the constrained CSF region, and, correspondingly, the elements of the vector, $\vec{u}$ are zero for voxels that are unconstrained and one for elements that are constrained. We solved Eq. (4) using the Least-Squares by QR-decomposition (LSQR) algorithm ⁴² (tolerance 10^{-5} ; maximum of 300 steps).

To reduce streaking artifacts in the susceptibility maps, which inevitably result from the ill-conditioning of the dipole inversion close to the magic angle, we incorporated the QUASAR algorithm into the previously published framework of Homogeneity Enabled Incremental Dipole Inversion (HEIDI) ⁴³. More specifically, we replaced the interim susceptibility solution, χ_{interim} , in Eq. (12) of the original HEIDI publication with the solution, χ , of Eq. (4) in the present work. As described in the original HEIDI work, the sole purpose of this post-processing step is the suppression of streaking artifacts that are related to the ill-conditioning of the inverse problem for Fourier coefficients located in a region close to the magic angle from the main field axis. HEIDI accomplishes this artifact suppression by replacing the Fourier coefficients of ill-conditioned spatial frequencies in the QUASAR solution by values calculated via a compressed sensing (CS) reconstruction strategy under *a priori* tissue homogeneity penalties. In the following, this hybrid approach will be referred to as QUASAR-HEIDI.

The HEIDI post-processing is justified because a recovery of the Fourier coefficients of the *susceptibility* distribution close to the magic angle is physically impossible based on frequency measurements at a single orientation.

2.6 Numerical model for the evaluation of QUASAR

We performed a systematic numerical simulation experiment to investigate the efficacy of QUASAR in disentangling susceptibility and non-susceptibility frequency contributions and to understand the effect of the regularization parameter values on the solution. To this end, we created a digital mouse brain model on the basis of the Brookhaven C57BL/6J Atlas ^{44,45}, which contains 20 labels for brain structures at an isotropic spatial resolution of $47\mu\text{m}$. We assigned a susceptibility value of $+0.1$ parts-per-million (ppm) relative to the surrounding tissue to the CSF segment of the atlas. This value was similar to the result of our PWCI experiment *in vivo* (see Fig. 1b,c and Results section). Considering the relatively

weak susceptibility contrast in mouse brain reported previously⁴⁶ and the lack of a reliable reference, we decided to assign arbitrary constant susceptibility values to all other labels in the range between -10 and 10 parts-per-billion (ppb); we considered the actual values for each label as irrelevant for the simulation. We filtered the susceptibility distribution with a three-dimensional (3D) Gaussian kernel (standard deviation of 0.3 voxels) to mitigate discretization artifacts due to sharp edges. Figure 2 (top, left) illustrates the final susceptibility model.

We simulated the frequency perturbation caused by the susceptibility model at 9.4 Tesla by Fast Forward Field computation with implicit Lorentz sphere correction^{37–40}. Figure 2 (top, left) shows the resulting susceptibility-related frequency distribution.

We created the non-susceptibility frequency model by assigning values to the CSF and brain tissue segments that were similar to those determined with the PWCI method *in vivo* (see Fig. 1c and Results section): CSF was set to zero and brain parenchyma was assigned a constant value of $+10$ Hz. Within the external capsule, we reduced the frequency contribution by an arbitrarily chosen value of 1.6 Hz to mimic the corpus callosum WM contrast observed in the frequency discrepancy image after applying PWCI (see Results section and Fig. 1c, left). Similar to the susceptibility distribution, we filtered the non-susceptibility pattern with a 3D Gaussian kernel (standard deviation of 0.3 voxels). We formed the total frequency model by adding the non-susceptibility frequency shift to the simulated susceptibility-related frequency model (Fig. 2, top right).

2.7 Investigation of the impact of the regularization parameter value

To investigate the effect of the choice of the regularization parameter value, λ , on the resulting susceptibility and non-susceptibility maps, we successively applied QUASAR to the numerical model with nine equally spaced values of λ between 0 and 0.4 . For every parameter value, we calculated the root-mean-squared error (RMSE) of the obtained maps relative to the known ground truth (Fig. 2, top middle). The parameter with the lowest RMSE (assessed in relation to the ground truth) was considered as optimal. For this optimization procedure, we applied QUASAR instead of QUASAR-HEIDI to avoid potentially confounding interactions with the nonlinear post-processing of HEIDI.

In addition to the digital model simulations, we studied the effect of regularization parameter values in a randomly selected mouse (female; age 8 weeks). Since a gold standard technique for solving Eq. (2) currently does not exist, we determined the optimal regularization parameter value via an L-curve criterion. To this end, we plotted the image power of the susceptibility map, $\|\chi\|^2$, over the image power of the non-susceptibility frequency, $\|f_p\|^2$. While the L-curve coordinate axes are often spanned by the power of the data fidelity term and the power of the penalty term, our choice of axes is justified by the role of the regularization parameter λ in defining the trade-off between susceptibility and non-susceptibility power in Eq. 3, rather than the trade-off between fidelity and penalty power.

Voxels dominated by CSF (for the constraint in Eq. 3) were automatically identified by thresholding the R_2^* map at an empirically determined value of $10/s$. No post-processing of the thresholding-based binary constraint was performed for simplicity. We used a more

conservative value here than for the digital model creation (15/s; see above) to minimize the number of false positives without the use of complicated filtering procedures. We used the R_2^* map for the identification of the CSF because CSF has a low R_2^* value compared to surrounding tissues enabling segmentation by simple thresholding of the voxel values. The simplicity and sequence-parameter independent nature of this approach facilitated the automation of the reconstruction. In principle, other image contrasts may be used to create the ventricle model, such as a magnitude image contrast, but in this case optimal segmentation parameters may depend on the particular pulse sequence parameters. To facilitate studying the performance of the algorithms in regions with *unconstrained* f_p , we constrained the corpus callosum WM in neither the *in silico* nor the *in vivo* experiment.

For comparison purposes, we calculated susceptibility maps both using the conventional HEIDI technique, which corresponds to setting $\lambda=0$ in Eq. (3), and the proposed QUASAR-HEIDI approach with the determined optimal parameters. We compared the QUASAR non-susceptibility distribution with the frequency residual of the *conventional* HEIDI solution obtained from a forward computation of the frequency based on the obtained HEIDI susceptibility map χ_{HEIDI} , followed by a subtraction of the background-corrected frequency distribution: $f - d^* \chi_{\text{HEIDI}}$.

2.8 Image analysis

To quantify the strength of non-susceptibility frequency effects in mouse brain, we analyzed the QUASAR-HEIDI results with a multi-atlas approach described in the Supplementary Material S.1. We calculated the mean values of the calculated magnetic susceptibility and non-susceptibility frequency within the basal ganglia, thalamus, corpus callosum (WM), and lateral ventricles. We used cortical GM as an internal reference for both susceptibility and non-susceptibility frequency. This region is relatively homogeneous and large enough in mice to limit the introduction of inter-subject variations into the referenced values. Mean values in different regions were compared using two-tailed paired t-test. A p-value below 0.01 was considered as statistically significant.

We performed a *post hoc* analysis of the cerebellar WM because we observed substantial non-susceptibility contrast in this region (see Results). We did not use the cerebellum label in the atlas that was employed for the other brain regions because the label did not distinguish between GM and WM. To assess voxel values in the cerebellar WM, an image analyst familiar with mouse brain anatomy manually defined a region of interest on each subject's non-susceptibility map located central to the deep WM using MRICron (v 12.12.2012; Chris Rorden).

3 Results

3.1 Demonstration of the limitations of the conventional QSM frequency model in Equation 1

Figure 1 summarizes the application of PWCI to the *in vivo* frequency map. When only bulk susceptibility was allowed as a source of contrast ($f_p=0$), we obtained a relatively high discrepancy in the ventricles between the measured frequency contrast and the frequency

contrast that could be explained by PWCI (Fig. 1b, bottom right). While the interpretation of the contrast discrepancy in the corpus callosum and the cerebellum is not possible because we did not model these anatomical regions with PWCI, the high discrepancy in the ventricles indicates that the conventional physical model in Eq. 1 (susceptibility-only) does not properly describe the observed frequency contrast between CSF and the surrounding tissue. The calculated susceptibility of the CSF segment was 0.059 ppm higher than that of the surrounding tissue segment.

When we applied PWCI *with* a non-susceptibility frequency shift (Fig. 1c), we obtained a similar susceptibility difference of 0.059 ppm and a non-susceptibility frequency shift of 6.0 Hz between CSF and surrounding tissue. In this case, the frequency discrepancy in the ventricles, i.e., the difference between the observed frequency contrast *in vivo* and the frequency contrast that was calculated by PWCI, was substantially reduced, as illustrated in Fig. 1c (bottom left). The remaining frequency contrast between CSF and surrounding tissues maybe attributed to inaccuracies in the tissue segmentations used for PWCI.

3.2 Impact of the regularization parameter values on the solution

Figure 3 shows the results of the systematic regularization parameter optimization experiment in the digital model (a,b) and *in vivo* (c). Susceptibility maps with the lowest RMSEs were obtained using λ between 0.1 and 0.15, with a minimum RMSE of 4.51 ppb for $\lambda=0.1$ (arrow in panel a). A similar relationship was found for the non-susceptibility reconstructions. The lowest RMSE of 0.2825 Hz was obtained for $\lambda=0.1$ (arrow in panel b). The L-curve criterion revealed an optimal *in vivo* value of $\lambda \sim 0.2$.

Figure 2 illustrates the application of HEIDI, QUASAR, and QUASAR-HEIDI to the frequency distribution of the digital model. The susceptibility map calculated with the conventional HEIDI algorithm, which relies on Eq. (1), suffered from typical streaking artifacts (“LSQR” in Fig. 2, middle right). The HEIDI post-processing, which affected only a small sub-region of the k-space, was not capable of compensating for all the streaking artifacts caused by the inaccuracy of the model used for the initial solution of Eq. (1) (with LSQR). The susceptibility map that resulted from QUASAR (Fig. 2, bottom right) showed a substantially reduced level of streaking artifacts compared to HEIDI, and the non-susceptibility pattern accurately depicted the modeled frequency difference between tissue and CSF. After the replacement of the ill-conditioned Fourier coefficients with HEIDI, streaking artifacts were further reduced.

Although susceptibility and non-susceptibility frequency distributions were disentangled to a substantial degree, the error patterns of both the QUASAR-HEIDI susceptibility map and the QUASAR non-susceptibility frequency map showed non-negligible deviations from the ground truth. In particular, the non-susceptibility frequency shift of the corpus callosum, which was not included in the QUASAR-constraint, appeared in both the magnetic susceptibility map and the residual map suggesting that unconstrained contributions cannot be disentangled completely with the proposed proof-of-concept algorithm. The application of QUASAR to the susceptibility-only frequency model (without non-susceptibility frequency contributions; Fig. 2, bottom left) revealed minor inaccuracies of the reconstructed susceptibility map, particularly in the CSF where the constraint was applied.

The calculated non-susceptibility frequency component erroneously showed a hyper-intense CSF, similar to the contrast seen on the susceptibility map. This observation indicates that in the hypothetical scenario of an absence of non-susceptibility frequency contributions, QUASAR may erroneously identify non-susceptibility contributions in the constrained region. Those erroneous non-susceptibility contributions will show a contrast similar to that on the magnetic susceptibility map in the same region (hyper-intense in this example). Hence, it may be concluded that non-susceptibility frequency contrast obtained with QUASAR is a physically correct solution and not a pure algorithmic artifact of QUASAR if it is opposite to the contrast seen on the susceptibility maps (i.e., lower non-susceptibility contrast in the ventricles compared to the surrounding tissue).

Figure 4 shows a side-by-side comparison of HEIDI and QUASAR-HEIDI with the *in vivo* background-corrected frequency map, and the R_2^* map. Conventional HEIDI was unable to correctly reconstruct the frontal horn of the lateral ventricles, whose spatial extent can be seen unambiguously on the corresponding slices of the R_2^* maps (Fig. 4, arrows). The QUASAR susceptibility map showed an anatomically correct susceptibility distribution with similar susceptibility values throughout the ventricles. A direct comparison of the frequency maps with the R_2^* maps illustrated the absence of frequency contrast in the frontal horn of the lateral ventricles (red arrows), most likely caused by compensating effects of susceptibility-related frequency and non-susceptibility frequency contributions. Similar results were obtained in all mice studied.

Figure 5 illustrates the effect of different λ -values *in vivo*. Using QUASAR-HEIDI, the susceptibility reconstruction of the ventricles was anatomically correct, even when λ was chosen relatively low. The non-susceptibility frequency pattern almost directly resembled the employed CSF constraint (shown on the right) when too low a value of λ was used. Too high a value yielded a reduced susceptibility contrast with dipole-like patterns around the ventricles, indicating an incomplete dipole inversion. The optimal λ -value ($\lambda=0.2$; see Fig. 3c) yielded an anatomically correct depiction of the ventricles in both the susceptibility and the non-susceptibility maps and an overall improved homogeneity in both the susceptibility and the non-susceptibility maps.

Table 1 lists the mean values of non-susceptibility frequency, and magnetic susceptibility in the different brain regions relative to cortical GM averaged over all 23 mice. Both susceptibility and non-susceptibility values were significantly different from those in the cortical GM ($p<0.001$) in all regions, except for the caudatal susceptibility ($p=0.025$). Between 23% (corpus callosum) and 73% (thalamus) of the average total frequency shift, f , was explained by non-susceptibility contrast, f_p .

4 Discussion

In the present work, we have introduced QUASAR, a novel quantification technique for MRI frequency contrast. QUASAR extends the physical model currently established in the QSM field by additional biophysical frequency effects (Eqs. 2–4). We demonstrated both *in silico* and *in vivo* that QUASAR yields maps of brain tissue magnetic susceptibility with improved anatomical accuracy compared to the traditional model (Eq. 1).

QUASAR successfully reduced the level of streaking artifacts on susceptibility maps without explicit regularization of the deconvolution part (Fig. 2) and yielded *in vivo* susceptibility maps with an anatomically more correct tissue contrast (Figs. 4 and 5). However, our numerical simulations showed that the performance of the employed simple proof-of-concept implementation of the QUASAR approach was limited concerning the disentanglement of susceptibility-related and non-susceptibility frequency shifts (Fig. 2). The present work represents a proof-of-concept study for the numerical solution of a physical frequency model that is more realistic than the one that is currently widely employed in the QSM field. We expect that future methodological developments toward more sophisticated regularization strategies for solving Eq. (2) will significantly improve the separation of susceptibility and non-susceptibility frequency contributions, just as algorithmic advancements have improved the reconstruction quality of QSM with the traditional physical model over the past decade^{47–50}. For example, instead of using a model with two tissue types for the non-susceptibility contribution, more tissue types may be defined covering major tissue types in the brain, such as the WM in our experiments. Nevertheless, our results indicate that the presented algorithm readily overcomes issues of anatomical misrepresentation on susceptibility maps as well as it provides valuable information on microscopic biophysical effects not related to bulk magnetic susceptibility. In particular, the latter exploits an entirely new MRI contrast mechanism that has been unavailable hitherto. Future studies will investigate the potential of QUASAR in humans to extract tissue microstructure information in diseases of the CNS, such as reduced myelin integrity in multiple sclerosis lesions²¹. Fig. 7 illustrates the feasibility of an application of QUASAR in humans (see Supplementary Materials S.2 for details). In the shown exemplary patient, QUASAR-HEIDI yielded a susceptibility map that, compared to the HEIDI map, showed better defined boundaries of the lateral ventricles with better correspondence in susceptibility values of the CSF between hemispheres (arrows VIII), mitigated hypointensities close to the cerebral aqueduct (arrows VI), and correctly depicted inter-hemispheric fissure (arrows VII). The non-susceptibility component visualized the internal capsule (arrows I), one of the regions with the highest myelin concentration and structural anisotropy, the optical tract (arrow II) as well as contrast between cortical GM and WM (arrows II).

Following numerous theoretical and experimental studies, our systematic application of QUASAR in mice provides the first *in vivo* evidence that the classical susceptibility model in Eq. (1) cannot fully explain the frequency contrast in the brain (Fig. 1), in line with numerous previous experimental and theoretical studies. Only when an additional *local* frequency contribution is added to the physical model, the frequency contrast in the brain can be related properly to the underlying anatomy.

Susceptibility map reconstruction issues similar to those observed in the present work with the traditional physical model (Figs. 4 and 6) may be found also in published rodent work by other authors. For example, susceptibility contrast was absent in the frontal horn of the lateral ventricles on all *in vivo* images presented by O'Callaghan et al.⁵¹ (Figs. 3 and 7 therein), Ziser et al.⁵² (Figs. 1 and 2 therein), Vaas et al.⁵³ (Fig. 5 therein), as well as studies we have contributed to^{54,55,46}.

The present study did not aim to and cannot elucidate the underlying biophysical mechanisms causing this additional frequency contribution, which may comprise contributions of different and contentious strength from macromolecular exchange effects^{14–17,56}, (sub-)cellular magnetic architecture^{20–22,57}, and temporal frequency variations due to tissue compartmentalization^{58,59}. In mathematical terms, the additional local component, here referred to as *residual* or *non-susceptibility frequency* contribution, may simply be understood as a lump sum of the discrepancy between the employed physical model and the physical reality.

Our application of QUASAR *in vivo* revealed a positive frequency shift in brain tissue compared to CSF. This finding is expected from fast exchange of bulk free water with the first water layer of the hydrophilic groups on the surface of proteins or lipids⁶⁰, in which water molecules are more densely packed resulting in a molecule size dependent^{56,61} net positive frequency shift due to electrostriction^{56,62}. The positive shift has also been shown experimentally in protein solutions^{13,14,17}, rat brain tissue⁵⁶, and human brain tissue¹⁵. Using Chemical Shift Imaging, Shmueli et al.¹⁵ reported an exchange-induced frequency shift of $+23.30 \pm 0.04$ ppb (mean $\pm$ standard error) in specimens of human GM and $+36.75 \pm 0.07$ ppb in WM. We found a non-susceptibility frequency shift in mouse GM of $+7.64 \pm 2.13$ ppb (mean $\pm$ standard deviation) relative to CSF with less than 1 ppb variation between brain regions. While the sign of our shifts was similar to the previous reports of exchange-related shifts, the magnitude of the observed shifts was significantly lower. However, while the exchange-related contrast may be difficult to compare directly between human and mouse brain due to large differences in the tissue myelination, the discrepancy may also be caused by the imperfect disentanglement of our simple prototype QUASAR approach. On the other hand, contrast on magnetization contrast ratio (MTR) images is considerably lower in mice than in humans⁶³, where a strong contrast is typically observed between GM and WM.

The relatively low calculated frequency shift could also be related to additional contributions from sub-cellular architecture. The convolution term in Eq. (2) models near-field effects on the hydrogen nuclei via the Lorentzian sphere correction^{12,37,39,40}, which assumes an *isotropic* microscopic magnetic environment. The theory of the Generalized Lorentzian Tensor Approach (GLTA)²² overcomes this simplification of brain tissue by modeling the near-field effects in environments with structural anisotropy and multiple compartments. In this context it has to be stressed that the relationships between measured frequency and the underlying susceptibility distribution in the Lorentzian sphere approach and the GLTA differ only regarding *local* contributions, i.e., the *local* microenvironment *within* an imaging voxel affects only the frequency measured in *that particular voxel*, but not the frequency measured elsewhere. The GLTA predicts a lower local frequency in WM than the Lorentzian sphere model²⁰. He and Yablonskiy estimated the frequency shift difference between the two models in human WM to be 22.4 ppb. Since the GLTA-related frequency shift acts in the opposite direction of the exchange-induced shift, both effects together could explain the comparatively low non-susceptibility frequency shift measured between CSF and brain tissue in our *in vivo* experiment. However, the GLTA predicts significant differences to the Lorentzian sphere correction only in regions with high structural anisotropy, but not, e.g., in GM²⁰. In our mouse experiments, WM regions showed a lower non-susceptibility frequency

shift than gray matter regions, with the cerebellar WM, which is the most highly myelinated region in the mouse brain, showing the lowest shift of all tissue regions (Tab. 1).

Duyn et al.⁶⁴ previously reported the visual absence of ventricular frequency contrast in humans at 7 Tesla. Consistent with their description, we observed a lack of frequency contrast in the frontal horn of the mouse lateral ventricles (arrows in Fig. 4) in the present work. However, as a cautious note, the direct interpretation of frequency contrast on individual frequency maps is problematic because field perturbations due to magnetic susceptibility depend on the three-dimensional spatial distribution of the magnetic susceptibility (shape and orientation of anatomical structures relative to the static main magnetic field). A lack of frequency contrast in a particular region at most *suggests* the existence or absence of non-susceptibility frequency contributions, but it cannot be considered as evidence. Only a mathematical solution of the physical inverse field-to-source problem can provide insights into the actual biophysical reality, and only if the employed physical model is a close enough representation of the physical reality. For example, while in the coronal views of our mouse data frequency contrast between the CSF and surrounding tissue seemed to be virtually absent in some parts of the frontal horn of the lateral ventricles (Fig. 4, left, arrow), the inspection of the sagittal views clearly revealed field perturbations at the interface between CSF and tissue (Fig. 4, top-right; arrow, bright signal). The non-local nature of this field perturbation, i.e., its extension beyond the anatomical region's boundaries, suggests that its cause is a difference in the *bulk* magnetic susceptibility between CSF and the brain parenchyma. However, the relative contributions of susceptibility and non-susceptibility contributions can only be determined with a physical model that takes into account the geometrical shape of the anatomical regions, such as PWCI or QUASAR.

Our work suggests that the incorporation of morphological priors^{48,65–71} into QSM algorithms that rely on the conventional physical model (Eq. 1) may not be the best strategy to address the significant level of streaking artifacts observed in susceptibility maps obtained with little regularization. Of course, the ill-conditioning of the inverse problem for coefficients close to the magic angle in the Fourier space is a source of noise amplification and streaking artifact⁷², which need to be addressed by appropriate numerical strategies, such as CS-based post-processing with HEIDI. However, if the source of streaking artifacts is a simplistic physical model that does not accurately describe the physical reality (cf. Fig. 2), regularization may be a relatively ineffective means to reduce the artifacts because it will result in too much of a weight on the employed penalty term, often associated with over-smoothing or other regularization artifacts. The simplicity of the widely employed physical model may be one of the reasons why many QSM algorithms have been criticized for yielding unnatural and over-smoothed susceptibility maps. To illustrate that the anatomically incorrect susceptibility reconstruction is not a phenomenon related to the employed HEIDI algorithm, but occurs also with different classes of algorithms, such as direct inverse filtering techniques and regularized inversion with spatial priors, we applied different, commonly used QSM algorithms in Fig. 6. We also tested if a piece-wise constant constraint on the susceptibility (instead of the residual) in the CSF would be sufficient to address the issue, as was recently proposed to facilitate referencing of susceptibility values⁷³, but this approach was ineffective (Fig. 6; top row, 4th from left). Only the introduction of the non-susceptibility phase contrast into the physical model resolved the reconstruction issue. In

that case, the ventricles were reconstructed properly with either constrained susceptibility or residual in the CSF (top row, first and second from right).

We want to emphasize that the presented QUASAR algorithm, unlike most of the widely used QSM algorithms, results in an improved anatomical accuracy of the susceptibility distribution without *any a priori* assumptions about the susceptibility distribution during the inversion. An introduction of additional piece-wise constant constraints on the susceptibility distribution, e.g., in the ventricles, as recently proposed,⁷³ is a straightforward generalization of the presented algorithm that may have certain benefits for referencing susceptibility values⁷³. However, our experiments demonstrate that susceptibility constraints are neither necessary nor effective for overcoming reconstruction artifacts related to non-susceptibility frequency contributions.

5 Conclusions

We have introduced a new class of susceptibility mapping algorithms, termed QUASAR, that takes into account frequency contributions not related to the spatial variation of bulk magnetic susceptibility in the Lorentz sphere model. The presented simple proof-of-concept QUASAR algorithm yielded anatomically correct susceptibility distributions in mice without spatial priors imposed on the susceptibility distribution itself, indicating that non-susceptibility frequency contributions due to microstructure and exchange effects play a critical role for in vivo frequency contrast in the brain and, hence, artifact generation in QSM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

3D	Three-dimensional
COSMOS	Calculation of susceptibility through multiple orientation sampling
CS	Compressed sensing
CSF	Cerebrospinal fluid
GM	Gray matter

HEIDI	Homogeneity enabled incremental dipole inversion
LSQR	Least-squares by QR-decomposition
MCPC-3D	Multi-channel phase combination using measured 3D phase offsets
MRI	Magnetic resonance imaging
ppb	Parts per billion
ppm	Parts per million
PWCI	Piece-wise constant regularized inversion of the magnetic field
R₂*	Effective transverse relaxation rate
RF	Radio frequency
RMSE	Root-mean-squared error
QSM	Quantitative susceptibility mapping
QUASAR	QUAntitative Susceptibility And Residual mapping
SJL	Swiss Jim Lambert
V-SHARP	Sophisticated harmonic artifact reduction for phase with variable-radii
WM	White matter

7 Literature

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Figure 1.

In vivo demonstration of the limitations of the widely used physical frequency model in Eq. 1. (a) From left to right: Total frequency map; background-corrected frequency map; unit frequency response corresponding to a unit susceptibility difference of $\chi=1$ between the ventricles and their surrounding; binary digital model of the ventricular spaces; the map of the brain's effective transverse relaxation rate (R_2^*) used to create the digital model. (b) Application of the PWCI algorithm *without* non-susceptibility frequency component ($f_p=0$), showing the susceptibility-related frequency distribution for the susceptibility difference calculated by PWCI and the discrepancy between this map and the measured in vivo frequency map. The discrepancy image illustrates that the Lorentzian sphere-based susceptibility model could not fully describe the local frequency shift between ventricles and surrounding tissues (bright regions marked by arrows). (c) Application of PWCI *with* non-susceptibility component, along with the resulting non-susceptibility frequency shift pattern and the susceptibility-related frequency perturbation calculated by PWCI, the total frequency, and the corresponding frequency discrepancy. The allowance of a non-

susceptibility component in PWCI greatly reduced the frequency contrast discrepancy between CSF and surround parenchyma (arrows).

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Figure 2. Numerical simulations. We created digital models of the mouse brain susceptibility and the non-susceptibility frequency contribution (top, middle) which served as a basis for the creation of a total frequency model (top, right). This total frequency model was used as the input to a conventional HEIDI QSM algorithm (“HEIDI”) relying on an LSQR-based interim susceptibility distribution with a significant level of streaking artifacts (“LSQR”). Replacing the LSQR algorithm by QUASAR (“QUASAR”) we obtained a susceptibility map with significantly reduced streaking artifacts and a non-susceptibility distribution showing a strong contrast between CSF and tissue. Streaking artifacts in the QUASAR *susceptibility map* could be further mitigated with HEIDI-based post processing (“QUASAR-HEIDI”). Note that HEIDI-based post processing was applied only to the QUASAR susceptibility distribution because only the field-to-susceptibility inversion requires post-processing of ill-conditioned Fourier coefficients; the non-susceptibility solution did not suffer from streaking artifacts. To study the efficacy of QUASAR-HEIDI in

the absence of a non-susceptibility contribution, we applied the algorithm to frequency data simulated from only the susceptibility distribution (top left). The resulting susceptibility map (“QUASAR-HEIDI”) had a similar appearance to the HEIDI-based susceptibility map (“HEIDI”) and both the QUASAR-HEIDI susceptibility and the non-susceptibility frequency had a relatively low deviation from the ground truth.

Figure 3.

QUASAR parameter optimization for the numerical model simulation (a,b) and in vivo (c). Panel (a) shows the RMSE of the calculated susceptibility distribution relative to the ground truth for different values of λ . Panel (b) illustrates the equivalent for the non-susceptibility contrast. The arrows indicate the parameter configurations with the best reconstruction. Panel (c) shows the L-curve for the in vivo data with the image power (squared Euclidean norm) of the susceptibility map plotted over the power of the residual (normalized values on both axes).

Figure 4.

A detailed comparison between HEIDI (traditional physical model) and QUASAR-HEIDI (new model), along with the background-corrected (input) frequency map, R_2^* , and the QUASAR non-susceptibility frequency map. The red arrows point to the regions in which the conventional QSM approach was unable to reconstruct correctly the susceptibility of the lateral ventricles and the tissue regions in which substantial non-susceptibility frequency contrast was observed, respectively. Contrast windows (black to white) were -7 to 7 Hz for the input frequency maps, -5 to 5 Hz for the non-susceptibility frequency maps, 0 to $100/s$ for R_2^* , and -40 to 40 ppb for the susceptibility maps.

Figure 5.

Comparison of QUASAR-HEIDI with different weighting parameters, λ , to conventional QSM using HEIDI. The right-most column shows the employed residual constraint (white; derived from R_2^*). Top and bottom rows show different coronal slices of the same animal. The red arrows in the susceptibility maps mark regions in which QUASAR overcame the reconstruction inaccuracy of HEIDI. The arrows on the non-susceptibility frequency maps highlight the dependence of contrast on the chosen value for λ (see text).

Figure 6.

Comparison of different QSM algorithms. Top row, from left to right: Least-squares solution of Eq. (1) with an LSQR algorithm (convergence tolerance 10^{-5}) showing a considerable level of streaking artifacts. LSQR solution using the R_2^* -derived homogeneity constraint in the CSF for the calculated susceptibility distribution, similar to ⁷³, showing a similar artifact level as without constraints; HEIDI with and without susceptibility constraints demonstrate with reduced artifact level but the susceptibility constraint did not resolve the incorrect estimation of the susceptibility in the CSF; QUASAR reconstructed the ventricular susceptibility accurately independent of the use and type of constraint. QUASAR-HEIDI with residual constraint produced the highest homogeneity in the CSF. Bottom row: SDI ⁷⁴ and non-linear MEDI ⁶⁹ [program code taken from the Cornell QSM toolbox ⁷⁵ with different degrees of regularization. Neither of the two algorithms was able to properly reconstruct the CSF susceptibility.

Figure 7.

Exemplary demonstration of the feasibility of applying QUASAR in the clinical setting. The three rows show different slices from the same patient. The QUASAR non-susceptibility map showed hypo-intense contrast in the corticospinal tract (arrows I), optic radiation (arrows II), and generally in WM compared to GM (arrows III). Deep gray matter nuclei were discernible on the non-susceptibility map (arrows IV). Compared to conventional HEIDI, QUASAR-HEIDI showed less signal variations in regions close to the ventricles (unlabeled arrows in column “susceptibility difference”), in particular in regions close to the cerebral aqueduct (arrows VI). Note the well-defined frequency reduction within the cerebral aqueduct on the frequency map (arrow VI, middle-row), which does not show the characteristic field perturbation that would be expected from a corresponding susceptibility distribution. Furthermore, QUASAR-HEIDI provided more consistent susceptibility values for the CSF in the lateral ventricles on both hemispheres compared to the conventional technique (arrows VIII), as well as a clear delineation of the interhemispheric fissure (arrows VII).

Table 1.

Group average total background-corrected frequency, f , magnetic susceptibility calculated with QUASAR-HEIDI, χ , and non-susceptibility frequency calculated with QUASAR-HEIDI, f_p , in caudate, CSF, WM, and thalamus. For caudate, CSF, corpus callosum WM, and thalamus, $N=23$ animals were averaged. In 5 animals, we could not analyze the cerebellar WM due to motion and respiration-related signal loss, resulting in $N=18$ animals for this region. The total and the non-susceptibility frequency have been converted into ppb to facilitate comparison with studies carried out at different field strengths (9.4T, 400 MHz). The bottom row showed the mean ratio of non-susceptibility frequency to total frequency shift, f_p/f . Note, the numerical value of the *mean* frequency ratio differs from the *ratio of the means* of the frequencies. Each map was referenced to cortical GM. Values represent mean $\pm$ standard deviation. Mean values of all measures were significantly different from cortical GM ($p<0.001$; one-sample t-test) except the magnetic susceptibility of the caudate ($p=0.025$).

	caudate	CSF	Corpus Callosum (WM)	thalamus	Cerebellar WM
Total frequency f [Hz]	0.62 ± 0.16	-5.42 ± 1.25	-0.95 ± 0.17	0.25 ± 0.16	-1.84 ± 0.30
Total frequency f [ppb]	1.54 ± 0.40	-13.54 ± 3.12	-2.38 ± 0.43	0.62 ± 0.41	-4.61 ± 0.76
Susceptibility χ [ppb]	-0.44 ± 0.87	39.77 ± 8.62	-4.33 ± 0.89	-1.29 ± 1.07	-2.56 ± 1.83
Non-susceptibility frequency f_p [Hz]	0.18 ± 0.04	-3.06 ± 0.85	-0.22 ± 0.06	0.15 ± 0.07	-0.55 ± 0.09
Non-susceptibility frequency f_p [ppb]	0.44 ± 0.11	-7.64 ± 2.13	-0.56 ± 0.15	0.37 ± 0.18	-1.39 ± 0.22
Frequency ratio	0.29 ± 0.03	0.57 ± 0.14	0.23 ± 0.04	0.73 ± 0.36	0.30 ± 0.03