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MRI estimates of brain iron concentration in normal aging using quantitative susceptibility mapping

Berkin Bilgic [a,*], Adolf Pfefferbaum [b,c], Torsten Rohlfing [b], Edith V. Sullivan [c], Elfar Adalsteinsson [a,d]

[a] Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, USA
[b] Neuroscience Program, SRI International, USA
[c] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, USA
[d] Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, USA

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ABSTRACT

Quantifying tissue iron concentration in vivo is instrumental for understanding the role of iron in physiology and in neurological diseases associated with abnormal iron distribution. Herein, we use recently-developed Quantitative Susceptibility Mapping (QSM) methodology to estimate the tissue magnetic susceptibility based on MRI signal phase. To investigate the effect of different regularization choices, we implement and compare ℓ_1 and ℓ_2 norm regularized QSM algorithms. These regularized approaches solve for the underlying magnetic susceptibility distribution, a sensitive measure of the tissue iron concentration, that gives rise to the observed signal phase. Regularized QSM methodology also involves a pre-processing step that removes, by dipole fitting, unwanted background phase effects due to bulk susceptibility variations between air and tissue and requires data acquisition only at a single field strength. For validation, performances of the two QSM methods were measured against published estimates of regional brain iron from *postmortem* and in vivo data. The in vivo comparison was based on data previously acquired using Field-Dependent Relaxation Rate Increase (FDRI), an estimate of MRI relaxivity enhancement due to increased main magnetic field strength, requiring data acquired at two different field strengths. The QSM analysis was based on susceptibility-weighted images acquired at 1.5 T, whereas FDRI analysis used Multi-Shot Echo-Planar Spin Echo images collected at 1.5 T and 3.0 T. Both datasets were collected in the same healthy young and elderly adults. The in vivo estimates of regional iron concentration comported well with published *postmortem* measurements; both QSM approaches yielded the same rank ordering of iron concentration by brain structure, with the lowest in white matter and the highest in globus pallidus. Further validation was provided by comparison of the in vivo measurements, ℓ_1-regularized QSM versus FDRI and ℓ_2-regularized QSM versus FDRI, which again yielded perfect rank ordering of iron by brain structure. The final means of validation was to assess how well each in vivo method detected known age-related differences in regional iron concentrations measured in the same young and elderly healthy adults. Both QSM methods and FDRI were consistent in identifying higher iron concentrations in striatal and brain stem ROIs (i.e., caudate nucleus, putamen, globus pallidus, red nucleus, and substantia nigra) in the older than in the young group. The two QSM methods appeared more sensitive in detecting age differences in brain stem structures as they revealed differences of much higher statistical significance between the young and elderly groups than did FDRI. However, QSM values are influenced by factors such as the myelin content, whereas FDRI is a more specific indicator of iron content. Hence, FDRI demonstrated higher specificity to iron yet yielded noisier data despite longer scan times and lower spatial resolution than QSM. The robustness, practicality, and demonstrated ability of predicting the change in iron deposition in adult aging suggest that regularized QSM algorithms using single-field-strength data are possible alternatives to tissue iron estimation requiring two field strengths.

Abbreviations: MRI, Magnetic Resonance Imaging; QSM, Quantitative Susceptibility Mapping; FDRI, Field-Dependent Relaxation Rate Increase; FSE, fast spin echo; ROI, region-of-interest; ppm, parts per million; SWI, Susceptibility-weighted imaging; CSF, cerebrospinal fluid.

* Corresponding author at: Massachusetts Institute of Technology, Room 36-776A, 77 Massachusetts Avenue, Cambridge, MA 02139, USA. Fax: +1 617 324 3644.
E-mail address: berkin@mit.edu (B. Bilgic).

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Introduction

Excessive iron deposition in subcortical and brain stem nuclei occurs in a variety of degenerative neurological and psychiatric disorders, including Alzheimer's disease, Huntington's chorea, multiple sclerosis, and Parkinson's disease (Hallgren and Sourander, 1960). Further, *postmortem* (Hallgren and Sourander, 1958) and in vivo (Bartzokis et al., 2007b; Haacke et al., 2007; Pfefferbaum et al., 2009; Pfefferbaum et al., 2010; Raz et al., 2007) studies have revealed that deep gray matter brain structures accumulate iron at different rates throughout adult aging. Structures that exhibit iron accrual support components of cognitive and motor functioning (Bartzokis et al., 2010; Raz et al., 2007; Sullivan et al., 2009). To the extent that excessive iron presence may attenuate neuronal function or disrupt connectivity, quantification and location of iron deposition may help explain age- and disease-related motor slowing and other selective cognitive decline.

Several MRI methods have been proposed for in vivo iron mapping and quantification. Bartzokis et al. (1993) capitalized on the enhanced transverse relaxivity (R2) due to iron with increasing main field strength for the Field-Dependent Relaxation Rate Increase (FDRI) method. FDRI relies on the use of R2-weighted imaging at two different field strengths and attributes the relaxation enhancement at higher field to iron, which may be a specific measure of tissue iron stores (Bartzokis et al., 1993).

Whereas FDRI relies on the modulation of signal intensity in MRI to infer iron concentration, MRI signal phase has also been proposed as a source signal for iron mapping, both by direct evaluation of phase images (Haacke et al., 2004, 2005a) and by reconstruction of magnetic susceptibility images that derive from the phase data (Haacke et al., 2005a, 2007). Local iron concentration is strongly correlated with the magnetic susceptibility values (Duyn et al., 2007; Liu et al., 2010c; Schweser et al., 2011b); therefore, quantification of this paramagnetic property presents a sensitive estimate of iron concentration, although possibly complicated by more uncommon factors, such as pathological manganese deposition (Hazell and Butterworth, 1999). Phase mapping yields high-resolution, high-SNR data that demonstrate correlation with iron (Haacke et al., 2007), but as an estimate of the underlying magnetic susceptibility, it suffers from non-local effects and spatial modulation artifacts due to the non-trivial mapping from susceptibility to phase (de Rochefort et al., 2010). To overcome these limitations, we made use of regularized Quantitative Susceptibility Mapping (QSM) algorithms that robustly estimate the magnetic susceptibility χ of tissues based on gradient-echo signal phase. The magnetic susceptibility χ maps to the observed phase shift in MRI via a well-understood transformation, but the inverse problem, i.e., estimation of χ from phase, is ill posed due to zeros on a conical surface in the Fourier space of the forward transform; hence, χ inversion benefits from additional regularization. Recently, elegant regularization methods were proposed for deriving susceptibility inversion. In the work by de Rochefort et al. (2010), smooth regions in the susceptibility map are promoted to match those of the MR magnitude image by introducing a weighted ℓ_2 norm penalty on the spatial gradients of χ. Likewise, Liu et al. (2010a) regularized the inversion by minimizing the ℓ_1 norm of gradients of χ, again weighted with a mask derived from the image magnitude. Kressler et al. (2010) experimented using ℓ_1 and ℓ_2 norm regularizations directly on the susceptibility values, rather than posing the minimization on the gradient coefficients. Another method to stabilize the susceptibility reconstruction problem is to acquire data at multiple orientations and invert them simultaneously w*ithout* regularization. This approach was introduced by Liu et al. (2009) and also investigated by others such as Wharton and Bowtell (2010) and Schweser et al. (2011b).

In this work, we investigate two different regularization schemes for susceptibility inversion; using ℓ_1-regularized QSM that parallels the approach of Liu et al. (2010a) and ℓ_2-regularized QSM which was introduced by de Rochefort et al. (2010). Given that magnetic susceptibility is a property of the underlying tissue, in ℓ_1-regularized QSM we make the assumption that it is approximately constant within regions of the same tissue type or within an anatomical structure. Based on this premise, the ℓ_1-norm-penalized QSM algorithm regularizes the inversion by requiring the estimated χ to be sparse in the image gradient domain. On the other hand, placing an ℓ_2 norm penalty on the spatial gradients of χ does not promote sparsity, but results in a large number of small gradient coefficients and thus incurs a smooth susceptibility reconstruction. In addition to regularized susceptibility inversion, our approach incorporates a robust background phase removal technique based on effective dipole fitting (Liu et al., 2010b), which addresses the challenging problem of removing phase variations in the data that arise primarily from bulk susceptibility variations between air and tissue rather than the more subtle changes of χ within the brain. Dipole fitting contains no parameters that need tuning and preserves the phase variations caused by internal susceptibility effects more faithfully than high-pass filtering, as employed in susceptibility-weighted imaging (SWI) (Haacke et al., 2004, 2005a). All susceptibility mapping methods require data acquired at only one field strength, thereby overcoming certain limitations of the FDRI approach, including long scan times and the need for spatial registration of image data acquired with different scanners at different field strengths.

Here, we describe the ℓ_1 and ℓ_2 norm regularized QSM methods and apply them to SWI data previously acquired in groups of younger and elderly, healthy adults (Pfefferbaum et al., 2009). To validate the iron measures, we compared the results of QSM methods with values published in a *postmortem* study (Hallgren and Sourander, 1958). As further validation, we compared QSM results with those based on FDRI collected in the same adults (Pfefferbaum et al., 2009) to test the hypothesis that the iron deposition in striatal and brain stem nuclei, but not white matter or thalamic tissue, would be greater in older than younger adults.

Methods

Susceptibility and MR signal phase

The normalized magnetic field shift $\boldsymbol{\delta}$ measured in a gradient-echo sequence is related to the MR image phase $\boldsymbol{\varphi}$ via $\boldsymbol{\delta} = -\boldsymbol{\varphi}/(B_0 \cdot \gamma \cdot TE)$, where B_0 is the main magnetic field strength, γ is the gyromagnetic ratio, and TE is the echo time. It follows from Maxwell's magnetostatic equations that the relationship between the underlying susceptibility distribution χ and the observed field shift $\boldsymbol{\delta}$ is given by (de Rochefort et al., 2010; Marques and Bowtell, 2005; Salomir et al., 2003)

$$\mathbf{F}\boldsymbol{\delta} = \left(\frac{1}{3} - \frac{k_z^2}{k_x^2 + k_y^2 + k_z^2}\right) \circ (\mathbf{F}\boldsymbol{\chi}) \tag{1}$$

where $\mathbf{F}$ is the discrete Fourier transform matrix, k_x and k_y are the in-plane frequency indices, k_z is the frequency index along B_0, and $\circ$ denotes Hadamard (element-wise) multiplication. Denoting with $\mathbf{D}$ the kernel that relates the field map to the susceptibility, the relation can also be expressed as

$$\boldsymbol{\delta} = \mathbf{F}^{-1}\mathbf{D}\mathbf{F}\boldsymbol{\chi} \tag{2}$$

The spatial frequencies at which the kernel is zero define a conical surface in k-space, which effectively undersamples the Fourier transform of χ and thereby gives rise to the ill-posed problem of susceptibility estimation from image phase. In addition, the susceptibility kernel is not defined at the center of k-space (the DC point), but one can choose a solution that vanishes at infinity, which is obtained by setting the Fourier transform of the field to 0 at $k = 0$ (de Rochefort et al., 2010). This assignment of signal for the k-space origin causes the resulting χ to have zero mean; but independent of the particular design choice for this DC signal, the susceptibility distribution is