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Exploring the origins of echo-time-dependent quantitative susceptibility mapping (QSM) measurements in healthy tissue and cerebral microbleeds

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ABSTRACT

Quantitative susceptibility mapping (QSM) is increasingly used to measure variation in tissue composition both in the brain and in other areas of the body in a range of disease pathologies. Although QSM measurements were originally believed to be independent of the echo time (TE) used in the gradient-recalled echo (GRE) acquisition from which they are derived; recent literature (Sood et al., 2016) has shown that these measurements can be highly TE-dependent in a number of brain regions.

In this work we systematically investigate possible causes of this effect through analysis of apparent frequency and QSM measurements derived from data acquired at multiple TEs *in vivo* in healthy brain regions and in cerebral microbleeds (CMBs); QSM data acquired in a gadolinium-doped phantom; and in QSM data derived from idealized simulated phase data. Apparent frequency measurements in the optic radiations (OR) and central corpus callosum (CC) were compared to those predicted by a 3-pool white matter model, however the model failed to fully explain contrasting frequency profiles measured in the OR and CC.

Our results show that TE-dependent QSM measurements can be caused by a failure of phase unwrapping algorithms in and around strong susceptibility sources such as CMBs; however, in healthy brain regions this behavior appears to result from intrinsic non-linear phase evolution in the MR signal. From these results we conclude that care must be taken when deriving frequency and QSM measurements in strong susceptibility sources due to the inherent limitations in phase unwrapping; and that while signal compartmentalization due to tissue microstructure and content is a plausible cause of TE-dependent frequency and QSM measurements in healthy brain regions, better sampling of the MR signal and more complex models of tissue are needed to fully exploit this relationship.

Introduction

Quantitative susceptibility mapping (QSM) provides image contrast by using measured B_0 field perturbations derived from gradient recalled echo (GRE) MRI phase data to calculate local variations of magnetic susceptibility in tissue (Liu et al., 2009; Shmueli et al., 2009; Wharton et al., 2010; Wharton and Bowtell, 2010; de Rochefort et al., 2010; Liu et al., 2011). This contrast can reveal features that are poorly depicted or entirely absent in conventional MRI images; and susceptibility heterogeneity within a region of interest (ROI) may be used to draw inferences about variations in tissue content including iron and myelin levels (Liu et al., 2011; Li et al., 2011; Schweser et al., 2011; Langkammer et al., 2012; Bilgic et al., 2012; Deistung et al., 2013; Sun et al., 2015; Klohs et al., 2011; Cronin et al., 2016; Al-Radaideh et al., 2012). These qualitative and quantitative observations are increasingly used as an adjunct to conventional MRI in the study of aging and a range of disease pathologies (Bilgic et al., 2012; Klohs et al., 2011; Cronin et al., 2016; Al-Radaideh et al., 2012; Liu et al., 2012; Langkammer et al., 2013; Chen et al., 2014; Blazejewska et al., 2014; Eskreis-Winkler et al., 2014; Rudko et al., 2014; Wisnieff et al., 2015;

Abbreviations: QSM, Quantitative Susceptibility Mapping; GRE, Gradient Recalled Echo; CMB(s), cerebral microbleed(s); CSF, Cerebrospinal fluid; CC, Corpus Callosum; CN, Caudate Nucleus; GCC, Genu of the Corpus Callosum; GP, Globus Pallidus; OR, Optic Radiations; IC, Internal Capsule; PU, Putamen; PUL, Pulvinar; RN, Red Nucleus; SCC, Splenium of the Corpus Callosum; SN, Substantia Nigra; TH, Thalamus

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Wang et al., 2013; van Bergen et al., 2016; Langkammer et al., 2016; Sharma et al., 2016; Hwang et al., 2016; Straub et al., 2016; Doring et al., 2016; Wang et al., 2016; Liu et al., 2015; Zivadinov et al., 2016; Gong et al., 2015; Betts et al., 2016; Liu et al., 2015; Poynton et al., 2015; Acosta-Cabronero et al., 2016).

It has recently been reported that frequency shift (Wharton and Bowtell, 2012; Sati et al., 2013) and QSM (Sood et al., 2016) values calculated in various brain regions vary with echo time when calculated from individual echoes from a multi-echo GRE acquisition. These observations are inconsistent with the assumption inherent in QSM that frequency shift is a time-independent function of the local magnetic field; and proper analysis and understanding of this effect is essential both for the interpretation of susceptibility measurements made using QSM and potential exploitation of new information that may be derived from multi-echo GRE data.

All QSM algorithms are fundamentally based on the inversion of the known relationship between an arbitrary magnetic susceptibility distribution and the perturbation of an applied magnetic field (Marques and Bowtell, 2005). These algorithms contain two assumptions: that each voxel may be approximated as a point-like source whose susceptibility is an isotropic (orientation-independent) scalar quantity; and that the measured phase in a voxel is a linear product of the local magnetic field perturbation and echo time. The assumed linearity of accumulated phase with time should make the calculated magnetic field perturbation, and therefore calculated magnetic susceptibility, TE-independent. These assumptions, however, are flawed. Some biological materials such as lipids have been shown to have an anisotropic magnetic susceptibility that must be characterized as a second order tensor, causing them to generate orientation-dependent field perturbations (Li et al., 2011; Wharton and Bowtell, 2012; Sati et al., 2013; Li et al., 2012; Yablonskiy et al., 2012; Wharton and Bowtell, 2015). Orientation-dependent susceptibility effects have been demonstrated *in vivo*, particularly in tissues with highly ordered microstructure (Li et al., 2012; Wharton and Bowtell, 2015; van Gelderen et al., 2015; Chen et al., 2013). Non-linear phase evolution has also been demonstrated *in vivo* in some white matter fiber tracts (Wharton and Bowtell, 2012; Sati et al., 2013) and, as expected, has been shown to cause TE-dependent QSM measurements in healthy brain tissue (Sood et al., 2016). These observations have been attributed to sub-voxel level compartmentalization of the MRI signal (Wharton and Bowtell, 2012; Sati et al., 2013; Sood et al., 2016). In the white matter, two and three compartment hollow cylinder models have been used to simulate microstructural compartmentalization (Wharton and Bowtell, 2012; Sati et al., 2013; van Gelderen et al., 2015; Chen et al., 2013; Wharton and Bowtell, 2013); and multi-component fitting has been used to test for compartmentalization of real data acquired *in vivo* (Sati et al., 2013; van Gelderen et al., 2012; Li et al., 2015; Sukstanskii and Yablonskiy, 2014; Nam et al., 2015; Menon et al., 1992; Beaulieu et al., 1998; Does and Gore, 2002; Does and Snyder, 1996; Xu and Cumming, 1999).

In this work we explore the phenomenon of TE-dependent frequency and QSM measurements through analysis of *in vivo* and simulated data; a gadolinium-doped phantom; and a simple three-compartment hollow cylinder model of white matter.

Materials and methods

MRI acquisition

Human data

Six patients (2 male and 4 female, 57–71 y.o.) with previously diagnosed cerebral microbleeds (CMBs) were scanned using a GE Signa HDxt 3.0 T scanner (GE Healthcare, Waukesha, WI) equipped with a 32-channel head coil. Magnitude and phase images with whole-brain coverage were acquired using a standard there-dimensional (3D) spoiled gradient-recalled echo (SPGR) sequence with the following parameters: TE1/ΔTE/TE16=3.0/3.1/49.5 ms; TR=54.4 ms; FA=12°; FOV=220×220×124 mm^3; matrix size=0.86×0.86×1 mm^3; readout bandwidth (BW)=62.5 kHz. The total acquisition time was about 15 min. Coil combination was achieved with SENSE reconstruction (ASSET on GE scanners). Prior to the gradient echo acquisition, coil sensitivity was calibrated with a low resolution scan. Given correct sensitivity maps, the SENSE algorithm results in accurate image reconstruction including both magnitude and phase.

In vivo brain image data from five adult (25–33 y.o.) healthy volunteers were acquired on a GE MR 750 3.0T (GE Healthcare, Waukesha, WI) scanner using an 8-channel head coil and a 3D SPGR sequence with the following parameters: TE1/ΔTE/TE16=4.0/2.3/38.5 ms; TR=50 ms; FA=12°; FOV=192×192×124 mm^3; matrix size=192×192×124; spatial resolution=1×1×1 mm^3; readout bandwidth (BW)=62.5 kHz. The total acquisition time was about 12 min. Coil combination was achieved by separately unwrapping and removing background fields from the phase data for each coil individually (see Section 2.2 for algorithm details) and combining the filtered data using a complex summation. The same experiments were repeated 5 times over 16 days. All the experiments were approved by the local institutional review boards.

Gadolinium phantom

To further evaluate TE-dependent QSM measurements in strong susceptibility sources, a cylindrical phantom with a known susceptibility distribution was constructed. Five straws, each in 5.5 mm in diameter and 50 mm in length, containing varying concentrations of gadolinium (0, 0.125, 0.25, 0.5, and 1 mM) were made with gadoteridol (ProHance®), and placed in a larger container filled with saline solution. A 5-ml volume of each solution was poured into separate straws. The cylindrical shape and low wall thickness of the straws (about 100 μm), as well as their orientation parallel to the field ensured that the susceptibility effects created by the straws were negligible. The five straws were separated by a plastic disk with five holes designed to keep the straws aligned in the container.

Imaging was conducted using a single-channel birdcage coil on a 20-cm bore 7 T scanner (Bruker BioSpec 70/20 USR, Billerica, MA) interfaced to an Avance III system. The phantom was positioned in the coil so that the long axes of the straws were parallel to the B_0 field. A multi-echo, 3D gradient echo (MGE) sequence was performed with the following parameters: flip angle (FA)=20°; TE1/ΔTE/TE20=2.3/2.2/44.1 ms; TR=200 ms; field of view (FOV)=128*128*128 mm^3, spatial resolution=400×400×400 μm^3 isotropic; readout bandwidth (BW)=62.5 kHz.

Quantitative susceptibility mapping and ROI analysis

For QSM processing, the phase data were unwrapped at each TE using Laplacian-based, path-based, and voxelwise temporal unwrapping algorithms in the CMB patients and Gd phantom (Li et al., 2011; Xu and Cumming, 1999; Schofield and Zhu, 2003), while phase data for the healthy volunteers were unwrapped using the Laplacian-based and voxelwise algorithms.

Voxelwise temporal unwrapping was carried out in MATLAB (Mathworks, Natick, MA, USA). The magnitude image was used to generate a binary mask of the brain tissue using the brain extraction tool (BET) in FSL (Smith, 2002) for the human data and a cylindrical ROI defined manually in MATLAB for the Gd phantom. For each voxel in the mask, the 1D phase evolution across the range of echo times was extracted and unwrapped using the 'unwrap' function in MATLAB, and the resulting unwrapped phase values assigned to the unwrapped phase volumes at each TE. The first echo was then subtracted from echoes 2:16 (human data) or 2:20 (Gd phantom data) to remove remaining wraps and B_1 phase.

The background phase was removed using V-SHARP (Li et al., 2011; Schweser et al., 2011).