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Functional quantitative susceptibility mapping (fQSM)

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ABSTRACT

Blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) is a powerful technique, typically based on the statistical analysis of the magnitude component of the complex time-series. Here, we additionally interrogated the phase data of the fMRI time-series and used quantitative susceptibility mapping (QSM) in order to investigate the potential of functional QSM (fQSM) relative to standard magnitude BOLD fMRI. High spatial resolution data (1 mm isotropic) were acquired every 3 seconds using zoomed multi-slice gradient-echo EPI collected at 7 T in single orientation (SO) and multiple orientation (MO) experiments, the latter involving 4 repetitions with the subject's head rotated relative to B_0. Statistical parametric maps (SPM) were reconstructed for magnitude, phase and QSM time-series and each was subjected to detailed analysis. Several fQSM pipelines were evaluated and compared based on the relative number of voxels that were co-incidentally found to be significant in QSM and magnitude SPMs (common voxels). We found that sensitivity and spatial reliability of fQSM relative to the magnitude data depended strongly on the arbitrary significance threshold defining "activated" voxels in SPMs, and on the efficiency of spatio-temporal filtering of the phase time-series. Sensitivity and spatial reliability depended slightly on whether MO or SO fQSM was performed and on the QSM calculation approach used for SO data. Our results present the potential of fQSM as a quantitative method of mapping BOLD changes. We also critically discuss the technical challenges and issues linked to this intriguing new technique.

Introduction

Functional MRI (fMRI) based on the BOLD-effect is widely used as a non-invasive tool for mapping brain activity (Kim and Ogawa, 2012). The increase in the BOLD contrast-to-noise ratio (CNR) with magnetic field strength has provided one of the main motivations for the technical development of MRI systems operating at ever higher magnetic field strength (Uğurbil, 2012). Nevertheless, the BOLD-effect is a secondary product of neural activation, relying on changes in blood flow which depend upon the coupling of the brain's vasculature to neuronal activation. Hence the neural specificity of the BOLD effect is physiologically limited by the brain's hemodynamics (Logothetis, 2008). Downstream spreading of the changes in blood oxygenation from the capillary bed at the activation site to distal veins draining blood from a larger brain volume areas exacerbates this intrinsic loss of specificity (Turner, 2002). Besides this loss of neural specificity, there is an additional loss of vascular specificity due to partial voluming effects arising from both the intrinsic spatial resolution (signal sampling) and the spatial extent of the field perturbations produced by vascular structures. Partial voluming effects due to limited spatial sampling can be reduced by investing the higher CNR of high magnetic field in improving the spatial resolution. Non-local magnetic field perturbation effects are caused by the microscopic local changes of the susceptibility of blood and the spatial extent of magnetic field perturbations due to veins is larger than that due to capillaries. Since the field perturbation is a function of susceptibility (depending directly on blood oxygenation) and field strength, BOLD magnetic field perturbations from the same source increase with field strength.

Conventionally, BOLD-contrast is measured from the magnitude image time-series, where the non-local intensity changes related to susceptibility changes are less pronounced than in phase time-series. Only a few studies have investigated BOLD contrast by also using the phase information in time-series (Arja et al., 2010; Bianciardi et al., 2014; Chen et al., 2013; Hagberg et al., 2008, 2012; Hahn et al., 2009;

Abbreviations: AP, anterior-posterior; COSMOS, calculation of susceptibility through multiple orientation sampling; DORK, dynamic off-resonance correction in k-space; FWHM, full-width at half maximum; HF, head-foot; HRF, hemodynamic response function; MC, motion correction; MO, multiple orientation; mrad, milliradian; NVR, nuisance variable regression; PPB, parts per billion; QSM, quantitative susceptibility mapping; PSF, point spread function; RELPOLY, relative polynomial filtering; RETROICOR, image-based retrospective correction of physiological motion effects; RL, right-left; RSO, regularized single orientation algorithm; SENSE, sensitivity encoding; SHARP, sophisticated harmonic artifact reduction for phase data; SI, superior-inferior; SO, single orientation dataset; TKD, thresholded k-space division algorithm.

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Menon, 2002; Petridou et al., 2009; Rowe, 2005; Rowe and Logan, 2004; Rowe et al., 2007; Tomasi and Caparelli, 2007). At the spatial resolution allowed by conventional magnetic fields (e.g. 1.5 T and 3 T), the BOLD phase effect, despite being stronger than the magnitude effect at microscopic level, is averaged out due to the orientation dependence of microscopic field perturbation effects, hence substantial phase contrast can only be found near a few large veins of diameter comparable to the voxel dimensions. At high spatial resolution, the phase of the fMRI time-series has been used to identify the dominant non-local BOLD effects due to large veins and to remove their contribution from the conventional magnitude BOLD statistical maps (Menon, 2002). Recently, a novel biophysical model for phase changes in BOLD fMRI based on the Lorentz-sphere approach was proposed (Zhao et al., 2007). This predicts that a non-zero average phase change occurs in the parenchyma due to BOLD effects in the vasculature (Feng et al., 2009). Experimental validation of the predicted maximum BOLD phase contrast of 17 mrad was performed by assuming a 3D Gaussian distribution for the BOLD susceptibility changes underlying the phase contrast. This assumption is arguably a good approximation for the sampling resolution of $3.75 \times 3.75 \times 4.5\ mm^3$ used in that study, but ignores the anatomical diversity of BOLD sources (e.g. large veins, parenchyma) and should be revised for higher spatial resolution. Furthermore, in a very recent study at 7 T, the observed phase and susceptibility changes in the cortex have been assigned to blood volume and oxygenation changes in pial and intracortical veins (Bianciardi et al., 2014).

The introduction of quantitative susceptibility mapping (QSM) (de Rochefort et al., 2008; Li and Leigh, 2004; Liu et al., 2009; Schweser et al., 2011; Shmueli et al., 2009; Wharton and Bowtell, 2010) has opened up new possibilities related to the use of phase images for fMRI studies. Quantitative susceptibility maps are calculated from phase data by deconvolution of field perturbations and hence, a voxel in the susceptibility map contains only the information about the respective voxel (i.e. without non-local effects). Provided that the phase effects from all susceptibility sources are detectable, susceptibility maps show the susceptibility changes that underlie magnitude signal changes in BOLD-based fMRI. Two recent reports (Bianciardi et al., 2014; Chen et al., 2013) propose the application of QSM for the quantification and better localization of functional BOLD contrast. Chen et al. (2013) proposed the use of susceptibility-based functional brain mapping by 3D-deconvolution of an MR-phase activation map, stating that the inversion of a phase t-score map is a reasonable solution for the purpose, as long as large phase angles can be ignored in the reconstruction. Such conditions are usually fulfilled for MRI acquisitions at short echo time, low field strength and low spatial resolution, and this approach has been applied to experimental data from a single subject to demonstrate the feasibility of the method. Bianciardi et al. (2014) generated QSM for each volume in the phase time-series of 2.5 mm isotropic fMRI data acquired at 7 T in order to compute activation related susceptibility change maps. They showed that functional, task related magnitude and phase changes can be detected with comparable sensitivity and that these changes have the same BOLD origins. The authors further demonstrated the feasibility of quantitative susceptibility mapping to estimate the functional change in blood fractional oxygen saturation in large veins (i.e. pial veins or sinuses) during task performance.

Here, we present a generalized approach for task-related BOLD susceptibility mapping, which we term functional quantitative susceptibility mapping (fQSM). We acquired high spatial resolution (1 mm isotropic) functional data at 7 T and combined these data across multiple orientations in order to provide a detailed comparison of the BOLD susceptibility contrast distribution with the magnitude BOLD contrast. We used different functional paradigms (motor, somatosensory and visual) in order to evaluate possible differences between BOLD responses in different brain areas. Several filter combinations for phase-specific artifact removal, QSM algorithms as well as alternative methods for the generation of statistical parametric maps were tested as integral parts of the multi-step fQSM pipeline. The final outputs of alternative fQSM pipelines were compared to results from standard magnitude based BOLD fMRI analysis performed on the same complex datasets, relying on the expectation that a BOLD susceptibility shift generates an intensity change in the magnitude with opposite sign. Preliminary results of fQSM were presented at conferences and workshops (Balla et al., 2012, 2013a, 2013b).

Materials and methods

Subjects and experiments

Four experienced volunteers participated in this study, which was conducted with approval from the University of Nottingham Medical School Ethics Committee and all subjects gave their informed consent. All four subjects participated in a scan session in which multiple fMRI runs were carried out during a motor task. Each fMRI run was performed with the head rotated to a different angle relative to B_0 (MO datasets or multiple-orientation experiments). The mean rotation angles ($\pm$std) across subjects for each of the four rotations were: $-8.9 \pm 5.8°$ and $15.4 \pm 6.8°$ achieved by nodding the head (single axis rotation around the right-left (RL) axis), and $-14.4 \pm 5.7°$ and $15.6 \pm 3.0°$ relative to B_0, achieved by performing two-step rotations, first around the RL-axis and subsequently tilting the head sideways, corresponding to rotations around both the superior-inferior (SI) and anterior-posterior (AP) axes, respectively. Even though rotations around the SI axis (B_0-direction) do not have an influence on the image phase, rotation around the other two axes yield field distribution data whose inversion is less susceptible to noise propagation, provided the movement is restricted to small angles of revolution (Wharton et al., 2010). Three of these subjects also participated in an additional multi-task scan session during which three fMRI datasets were acquired using different brain activation paradigms (motor, somatosensory and visual) with the head held at the same orientation to the field (SO dataset or multi-task experiment).

Stimuli and paradigms

The motor task comprised a block paradigm of a visually-cued finger tapping task of the left hand for a period of 12 s, followed by a rest period of 18 s duration, repeated for ten cycles. In the multi-task scan session, block-paradigms using motor, visual and somatosensory stimulation were used. Visual stimuli were projected onto a screen positioned in front of the scanner and subjects viewed the screen through prism goggles and were instructed to focus on a centrally-located fixation cross. The paradigm consisted of presentation of 12 s of a flickering checkerboard ring stimulus extending from 2° to 2.75° (eccentricity) on a gray background alternating with 12 s of a full gray screen. This resulted in a 24 s cycle that was repeated 8 times. The somatosensory stimulus consisted of 60 Hz vibrotactile stimulation applied to all five fingertips of the left hand using five independently-controlled, MR-compatible piezoelectric devices (Dancer Design, UK). Each stimulator delivered a supra-threshold (~100 μm peak-to-peak amplitude) vibrotactile stimulus to ~1 mm^2 of the glabrous skin of each site. Analogous to the motor paradigm, blocks of 12 s of somatosensory stimulation alternated with blocks of 18 s of rest, for ten cycles. In total, 2 fMRI runs were carried out for the visual and motor paradigms, while 4 fMRI runs were performed for the somatosensory paradigm in order to compensate for the reduced fMRI signal modulation in response to sensory stimuli relative to visual or motor stimuli (Sanchez-Panchuelo et al., 2010).

Data acquisition

Experiments were performed on a 7 T scanner (Achieva, Philips, Best, Netherlands) using a volume birdcage RF resonator for transmission and a 32-channel coil-array for reception (Nova Medical, Wilmington, MA). Magnetic field inhomogeneity was minimized by