Subcortical Grey Matter Susceptibility Mapping from Standard fMRI studies

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Purpose: BOLD fMRI is typically performed using a 2D gradient EPI time series, with moderate to low spatial resolution. Recently, 2D single-shot gradient EPI has also been demonstrated to be effective for structural quantitative susceptibility mapping (QSM) for iron measurement in subcortical grey matter (GM) [1], albeit at much higher spatial resolution than standard fMRI. Iron accumulation in subcortical GM is linked to neurodegeneration and occurs in healthy aging [2]. Here, we investigate the conditions under which subcortical GM structural QSM can be extracted from standard fMRI experiments enabling brain iron studies at no time cost. We examine the effects of spatial resolution and time series variation in both structural and functional QSM (fQSM) [3] in relation to standard BOLD magnitude fMRI at 1.5 and 4.7 T, and propose a structural QSM reconstruction pipeline for use in standard fMRI studies.

Methods: Healthy volunteers were studied with standard fMRI protocols using visual and single finger tapping paradigms at 1.5 and 4.7 T. Block-design paradigms used 24s blocks, starting and finishing with a rest block (presenting a fixation cross); the active blocks for motor task provided a visual clue for tapping of right-hand index finger (2Hz) which was recorded, while visual task presented a flickering checkerboard ring at a rate of 5Hz. The number of blocks varied by resolution: 4/6/9 active blocks for isotropic 4/3/2mm resolution on 1.5 T and 4/3 active blocks for 3mm/higher on 4.7 T. Experiments were performed with full coverage of the cortex using interleaved multi-slice gradient EPI at varying isotropic spatial resolution. MRI parameters at 1.5 T: TE 40ms; TR 2/3/4s corresponding to isotropic dimensions of 4,3 or 2mm with 36, 48 or 52 slices. Parameters at 4.7 T: TE 19ms; TR: 2s and isotropic dimensions of 1.5, 2 or 3 mm covering 35, 40 or 45 slices. In addition, susceptibility-weighted imaging (SWI) (0.72*0.72*2 mm^3) was performed to serve as a QSM standard. For all experiments, complex raw data was saved.

The reconstruction of standard SWI-QSM and EPI-QSM from a single shot have been previously described [1], including phase unwrapping, background field removal [4] and finally dipole inversion using total variation regularization [5]. For an fMRI time series, EPI-QSM was performed in the same manner on each individual volume. Motion correction was carried out using SPM8 to align magnitude images, and the same reslice matrix was saved then applied to QSM. Slice timing and normalization were performed prior to 1st-level model analysis on both the magnitude and susceptibility maps to examine activation regions. In addition to activated regions, mean susceptibility values of subcortical GM were measured along the time series. At 1.5 T, all QSM of different resolutions were registered to SWI-QSM, and at 4.7 T to 1.5mm EPI-QSM. The same 2D axial ROIs were drawn on subcortical GM nuclei from all measures.

Results: Structural QSM results extracted from fMRI visual paradigm time series at both 1.5 and 4.7 T are shown in Fig. 1 and 2. Subcortical GM iron susceptibility contrast is significantly reduced with lower resolution. As seen from the line profiles across putamen, globus pallidus, and internal capsule in the upper graph of Fig. 1, both isotropic 2 and 3 mm produce acceptable values at 1.5 T, but not 4 mm. Time series of basal ganglia and thalamus from susceptibility maps of various resolutions are also shown, with susceptibility variations (mean ± std) detailed in the graphs. The time series variations are greater at 4.7 T than at 1.5 T, due to more sensitivity to field variations particularly from breathing (air susceptibility effect).

Example visual paradigm BOLD activations and fQSM with 3 mm isotropic are displayed in Fig. 2. Strong BOLD effects were found in magnitude, while weaker but resolvable activations over a smaller region were found in fQSM.

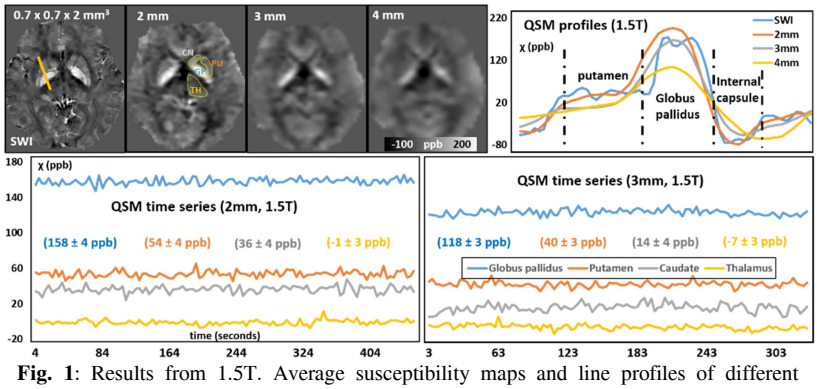

Fig. 1: Results from 1.5T. Average susceptibility maps and line profiles of different resolutions are shown. Mean susceptibility deep GM ROIs from 2mm and 3mm isotropic from along the time series are displayed with average and standard deviation written.

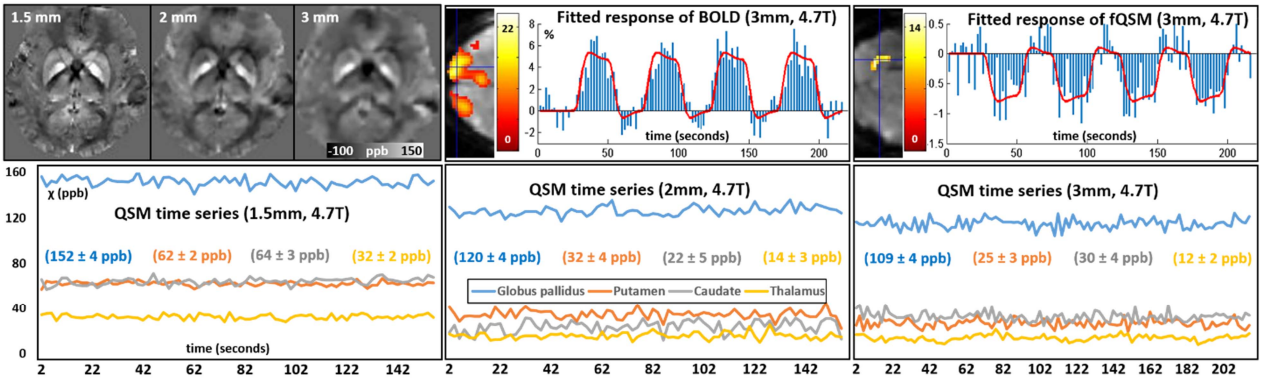

Fig. 2: Results from 4.7 T. EPI QSM acquired from 3 resolutions (top left). BOLD and fQSM from a visual task time series with 3 mm (top) and deep GM structural QSM time series from 3 resolutions (bottom).

Discussion: Phase images from standard fMRI time series can be used to generate susceptibility maps at no time cost, provided the raw data or unprocessed phase is saved. Although fQSM effects were seen in 1.5T or 4.7T, the strength of these effects was small for these robust paradigms that produce large magnitude BOLD effects, since QSM removes the valuable dephasing dipole effects that strengthen the magnitude BOLD effect. Our study suggests that even though fQSM may be challenging using typical fMRI protocols, structural QSM for subcortical GM can be obtained at no cost for the purpose of subcortical GM iron evaluation. However, susceptibility of iron-rich subcortical GM requires a spatial resolution of 3 mm isotropic or preferably higher at both 1.5T and 4.7T. As detailed in the graphs, different resolutions may give different susceptibility measurements; however, measurements are still quantitative and comparable between subjects using the same or similar spatial resolutions. For structural QSM, averaging the individual susceptibility maps over the time series gives a more accurate and stable susceptibility measurement than initially combining the complex raw images from the time series. Susceptibility induced fields are dependent on the direction of the brain to the main magnetic field, and therefore field maps across the time course cannot be simply added after magnitude motion correction. QSM solves this direction dependency problem. For example, in 1.5 T, susceptibility of GP varies ~5% maximum, while the dipole field around the GP region varies ~16% maximum over the time series.

Conclusion: Structural QSM offers a new avenue of research investigation within existing fMRI studies provided adequate spatial resolution with voxel dimensions of 3mm isotropic or preferably finer. In these cases, QSM can be performed on standard fMRI time series with acceptable susceptibility contrast of subcortical GM at both 1.5T and 4.7T. Structural susceptibility maps from the time series should be obtained by performing QSM on each volume independently, then realigning and averaging all the volumes to avoid background dipole field variations due to breathing and motion. Visual paradigm fQSM effects were also seen at 1.5 T and 4.7 T, but these effects are weak when using standard fMRI spatial resolution and analysis.

References: [1] H Sun and AH Wilman, MRM, 2014. [2] J Schenck and E. Zimmerman, NMR in Biomed, 2004;17(7):433-45. [3] D Balla et al., Neuroimage, 2014. [4] H Sun and AH Wilman, MRM, 2013;71(3):1151-7. [5] J Liu et al., Neuroimage, 2012;59(3):2560-8.