Simultaneous Spin Echo and Gradient Echo for fMRI using the USPIO Agent Ferumoxytol in Humans: Enhanced Sensitivity and Potentials for High Resolution Mapping

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Target Audience: MR physicists, Neuroradiologists, Neuroscientists

Introduction: Ultrasmall superparamagnetic iron oxide (USPIO) is a strong T2* contrast agent that stays intravascular with a prolonged halflife of about 19 hours when administered intravenously. Our previous work [1] in humans has shown that cerebral blood volume based functional imaging using USPIO is 2-3 times more sensitive than blood oxygenation level dependant (BOLD) method when using gradient echo technique. However, it is not clear whether the same advantage exists when using spin echo technique, which is believed to be more specific to region of neural activity and less sensitive to susceptibility related image artefacts. Therefore, in this study we study the relative sensitivity of ICE-BVI (Iron oxide Contrast Enhanced-Blood Volume Imaging) with respect to BOLD using a multi-echo EPI sequence that acquires both gradient and spin echo images [2] using the USPIO contrast agent ferumoxytol (AMAG Pharmaceuticals, Inc., Cambridge, MA), which is FDA-approved for treating iron deficiency anaemia.

Materials and Methods: MR imaging was performed at 3T with an 8-channel head coil (MR750, GE Healthcare, Waukesha, WI). Three subjects were scanned with the following protocol: a 3D T1-weighted inversion recovery spoiled gradient echo (IR-SPGR) sequence covering the entire brain was acquired. BOLD fMRI and ICE-BVI were performed using a 2D multi-echo gradient echo and spin echo EPI sequence before and after the injection of ferumoxytol (approx 7 mg Fe/kg) respectively (FOV=24cm, Matrix = 84x84, slice thickness = 4, number of slices = 17, TR=2s, GRAPPA acceleration factor =3, five echoes: two gradient echoes before the 180 degree refocusing pulse, three echoes after the refocusing pulse with spin echo formed at the last echo, with respective echo times 16, 32.6, 63.9, 80.4 and 97ms). The subjects were instructed via auditory cues to perform 4 epochs (48s of rest and 48s of finger tapping) with an additional 48s of rest at the end. The fMRI images were processed using SPM8 and custom MATLAB scripts. They were registered to correct for motion and minimally smoothed with a Gaussian kernel with a full-width half maximum of 1mm. Significant motion from one subject was observed during post-contrast functional task and therefore this subject was removed from further analysis. The General Linear Model was used to identify region of activation. Time courses from the activated region in the motor area were extracted and analysed using exponential response models to calculate the relative sensitivity gain of ICE-BVI with respect to BOLD. Following the design of F statistics, standard deviation of the fitted time curve was calculated to denote the contrast of the signal. Temporal noise of the activated region was also calculated from the images from the initial 48s of resting. The mean T value of the 20 most activated voxels was also measured.

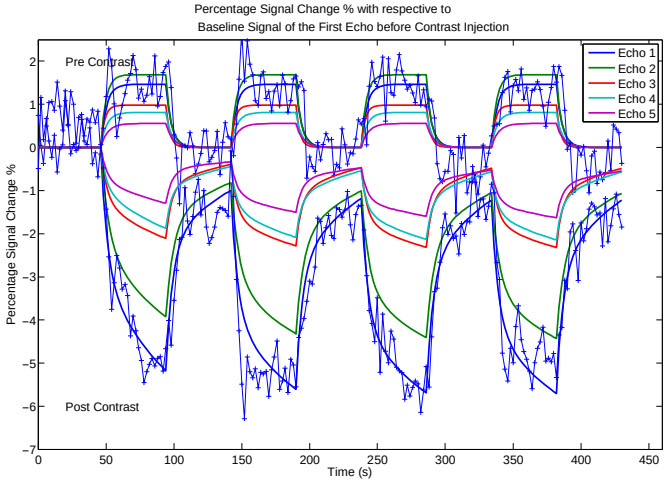

Fig 1: Exponential fit of time series of all five echoes before and after contrast injection during a task of finger tapping, one original signal curves of the first echo were also plot to demonstrate the quality of the fit (blue lines with marker +).

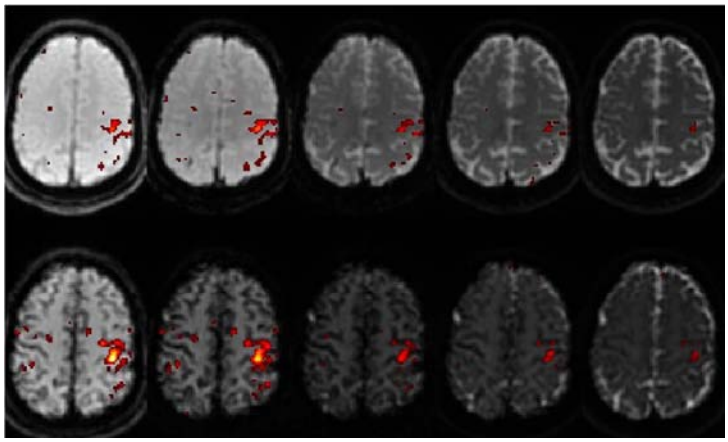

Fig 2:T statistic maps overlaid on EPI images before (top panel) and after (bottom panel) contrast injection for different echoes (from left to right: before 180 pulse, TE=16ms, 32.6ms, after 180 pulse 63.9ms, 80.4ms and 97ms). Full scale of the colorbar for T map is between [4.5, 24.5]

Results: Figure 1 shows signal dynamics as well their exponential fits during the finger tapping paradigm using both BOLD and ICE-BVI techniques. Positive signal response was observed with BOLD while negative signal response was observed for ICE-BVI due to increases in CBV and hence larger T2* effects because of the presence of USPIO contrast agent. For BOLD, the largest contrast due to task was found in the second echo with TE of 32.6ms, while for ICE-BVI the largest contrast was observed at the first echo. The largest signal contrast gain of ICE-BVI over BOLD occurred at the first echo for both subjects with a factor ranged from 2.7-3.8. When comparing the largest contrast of both methods (at the first echo for ICE-BVI, and second echo for BOLD), the contrast gain was 2.3-3.0. For the other echoes, the average gain was 2.0, 1.6, 1.9 and 2.0 for the second to fifth echo respectively. The average noise increases of ICE-BVI over BOLD ranged from 1.1 to 1.7. Figure 2 shows T statistics maps overlaid on average EPI images of different echoes. Among the five echoes, the largest T statistics were found in the first and the second echo for ICE-BVI and BOLD respectively. The mean T values of the 20 most activated voxels using BOLD were 14.8, 16.4, 13.6, 10.1 and 6.5 respectively for the five echoes, and for ICE-BVI the mean T values were 23.9, 21,4, 12.2, 10.7 and 8.0 respectively for the five echoes.

Discussion and Conclusion: Following our previous report of the first use USPIO as a contrast agent for enhanced fMRI using gradient echo technique in humans, we further study the advantage of USPIO for both spin echo and gradient echo based fMRI. For gradient echo, the contrast gain by ICE-BVI is about a factor of 2.3-3.0, while for spin echo the gain is about a factor of 2.0. As USPIO decreases T2 value of the tissue, we expect the contrast gain would be higher if a lower spin echo TE is used for ICE-BVI. The noise with ICE-BVI was also observed to increase, possibly due to enhanced sensitivity to respiratory and cardiac activities. Also, the larger intensity contrast between gray and white matter due to the presence of contrast agent would also increase signal fluctuation compared to BOLD even with the same amount of subject motion. In conclusion, ICE-BVI substantially improves the CNR for activation detection for both gradient echo and spin echo methods, and opens the possibilities of high-resolution fMRI at 3T, such as mapping of human ocular orientation columns [3].

References: [1] Qiu D. 2012. Neuroimage. 2012 Sep;62(3):1726-31. [2] Schmiedeskamp H. 2012. MRM. 68:30-40. [3] Yacoub E. 2008. PNAS. 105: 10607-10612.

Acknowledgements : National Institute of Health (2RO1NS047607, 1R01NS066506, 5P41RR09784), Lucas Foundation and Oak Foundation