Enhanced fMRI Sensitivity using CBV based Contrast with the Blood Pool USPIO Agent Ferumoxytol in Humans

Deqiang Qiu[1], Greg Zaharchuk[1], Thomas Christen[1], Wendy W Ni[1], and Michael E Moseley[1]
[1]*Radiology, Stanford University, Stanford, CA, United States*

Introduction: Functional MRI (fMRI) has commonly been performed using BOLD (Blood oxygenation level dependent) technique, which depends on complex interactions between multiple physiological processes and has inherent resolution limits due to sensitivity to large veins. Animal studies have shown that contrast agent based blood volume functional MRI (fBVI) technique using blood pool iron oxide contrast agent promises significantly improved contrast to noise ratio (CNR) [1]. fBVI therefore could allow mapping of brain function at high spatial resolution. This technique was however not possible until recently due to the lack of blood pool USPIO (ultrasmall superparamagnetic iron oxide) suitable for human use. Here we report the first study of the use of USPIO (ferumoxytol, AMAG Pharmaceuticals, Inc., Cambridge, MA) for fMRI in humans.

Materials and Methods: The study was approved by the local Institutional Review Board. MR imaging was performed at 3T with an 8-channel head coil (MR750, GE Healthcare, Waukesha, WI). Four 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 fBVI were performed using a 2D gradient echo EPI sequence before and after the injection of ferumoxytol (approx 7 mg Fe/kg) respectively (FOV=22cm, Matrix = 64x64, slice thickness = 4, number of slices = 36, TR=2s). The echo time (TE) was 35ms for pre-contrast BOLD, and both 20ms and 35ms were used for fBVI to explore the optimal TE for fBVI. The subjects performed 4 epochs of 48s of right hand finger tapping and 48s of rest. The fMRI images were processed using SPM8 and custom MATLAB scripts. They were registered to correct for motion and smoothed with a Gaussian kernel with a full-width half height of 7mm. The General Linear Model was used to identify region of activation. Time courses from the activated region in the motor area were extracted and analyzed using both mono- or bi-exponential response models to obtain a time constant (Tc) which characterizes the speed of BOLD fMRI and fBVI signal to stimulus (larger Tc indicates slower responses). The relative sensitivity of BOLD fMRI and fBVI were compared using CNR ratio and Student's T statistics. CNR ratio was calculated as the ratio between the standard deviation of fitted signal time course between fBVI and BOLD fMRI.

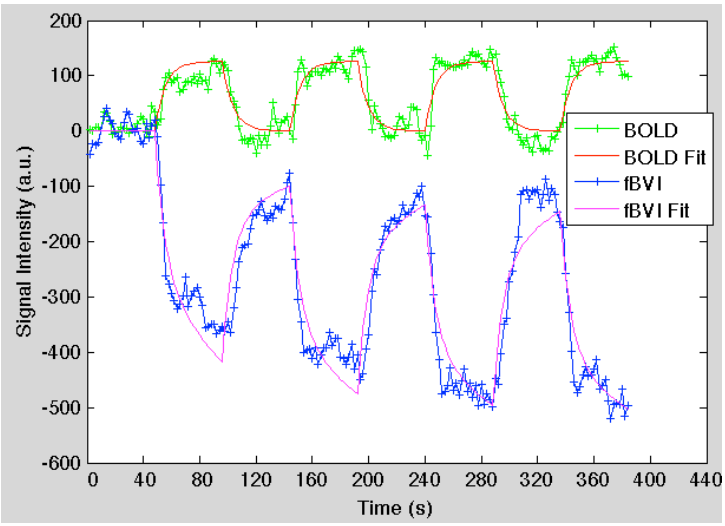

Fig 1: Time course of BOLD fMRI and fBVI as well as their exponential fits, CNR gain was calculated as 2.9

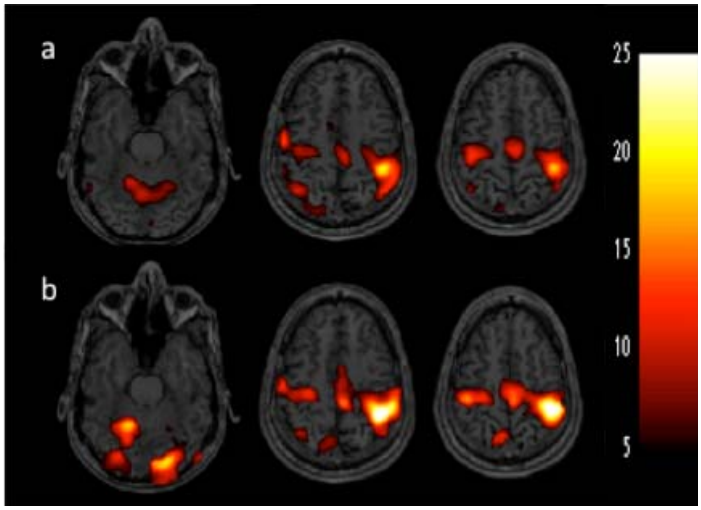

Fig 2: Activation maps with (a) BOLD fMRI and (b) fBVI overlaid on T1 weighted anatomic maps. Much higher T statistics were measured with fBVI over BOLD.

Results: A mono-exponential model provided a good fit for the BOLD fMRI time course with mean (std) Tc of 6.7(1.6s). For fBVI, both a slow and a fast component were found. The mean(std) Tc for the slow and fast components was 72.5(14.2)s, and 6.2(2.3)s, respectively. The normalized coefficient was defined as the ratio between the fitted coefficient and the sum of the coefficients of the two exponential components. And the mean (std) value of the normalized coefficient for the slower components was 0.09.7 (0.043). For fBVI with TE = 20ms, the mean CNR gain over BOLD was 2.5, ranging among subjects between 2 and 2.9 (Fig 1); while for TE=35ms, the average gain was 1.5. This CNR gain was reflected as higher student's T statistics in the activation map (Fig 2).

Discussion and Conclusion: To our knowledge, this is the first study on the use of USPIO as contrast agent for improved fMRI sensitivity in humans. The signal contrast of fBVI is primarily CBV based. This study shows that fBVI signal contains both a fast and a slow component, which may correspond to arteriolar and venular sources respectively [2]. fBVI fMRI has a CNR gain of a factor of 2 to 2.9 over BOLD fMRI. This CNR gain results in higher but non-proportional gain in T-statistics, as physiological noise is the primary source of noise at the current resolution. The CNR gain may be more effectively used to invest in high-resolution fMRI studies [3]. In conclusion, fBVI substantially improves the CNR for activation detection, and opens the possibilities of high-resolution fMRI at 3T, such as mapping of human ocular orientation columns [4].

References: [1] Leite FP. 2002. Neuroimage. 16:283-293. [2] Lu H. 2003. MRM. 50:263-274. [3] Triantafyllou C. 2005. Neuroimage. 26: 243-250. [4] Yacoub E. 2008. PNAS. 105: 10607-10612.

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