

Resting State Neural Network Demonstrated with Cerebral Blood Volume based fMRI using the USPIO Agent Ferumoxytol in Humans

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Target Audience: MR physicists, Neuroradiologists, Neuroscientists

Introduction: Analysis of the spontaneous physiological fluctuations [1] of the brain in the resting state has attracted significant interest, due to its potential for studying functional connectivity between different brain regions. This has been commonly achieved by techniques that are sensitive to blood oxygenation (BOLD) or to a lesser extent cerebral blood flow (CBF) using arterial spin labelling (ASL). Although it is anticipated that cerebral blood volume (CBV) may exhibit similar synchronous and spontaneous fluctuation, this has not been shown in humans, presumably due to limited MR methods that are sensitive to dynamic CBV. Ultrasmall superparamagnetic iron oxide (USPIO) is a strong T2* contrast agent that stays intravascular with a prolonged half-life of about 19 hours. The post contrast fMRI using gradient echo technique is primarily sensitive to changes in CBV and our previous work [2] in humans has shown that this method, termed ICE-BVI (Iron oxide Contrast Enhanced-Blood Volume Imaging) has 2-3 times higher contrast than BOLD in task-based fMRI. The purpose of current study is therefore two-fold: (1) to study whether CBV exhibits spontaneous fluctuation corresponding to neural networks and thus whether ICE-BVI can be used to study functional connectivity; (2) if so, whether it has higher sensitivity as in task-based fMRI.

Materials and Methods: MR imaging was performed at 3T with an 8-channel head coil (MR750, GE Healthcare, Waukesha, WI) under IRB approval. Five 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 EPI sequence before and after the injection of ferumoxytol (approx 7 mg Fe/kg) respectively (FOV=24cm, Matrix = 128x128, slice thickness = 4 mm, number of slices = 35, TR=3s, parallel imaging factor =2, 128 time frames). TE was 35ms except for one subject in whom TE=20ms was used for ICE-BVI. Both independent component analysis (ICA) and seed based analysis were performed using FSL, AFNI and home-written scripts. Image pre-processing included slice timing and motion corrections, spatial smoothing with 6mm FWHM, lowpass filtering at 0.1Hz, quadratic detrending and nuisance regression with 6 parameters of motion estimators and mean signal intensities from white matter and cerebrospinal fluid. For seed based analysis, a ROI with a radius of 3mm was placed in the posterior cingulate cortex (PCC) in the standard space to study the functional connectivity of the default mode network (DMN). The correlation map was calculated in the native space and the number of voxels with correlation coefficient larger than an arbitrarily selected threshold of 0.45 was also calculated. The correlation maps were then transformed to the standard space for further analysis. One ROI was placed to include bilateral PCC and another for the left angular gyrus (AG) and the mean correlation coefficients were calculated and compared before and after contrast injection. For spectral analysis, the time series of PCC after timing and motion correction and spatial smoothing was extracted and subjected to frequency spectrum analysis.

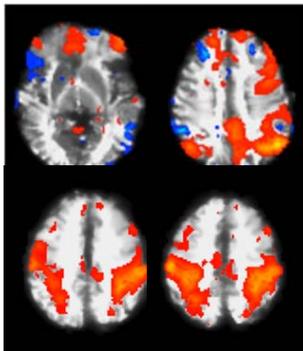


Fig 1: Default mode network (Top panel) and motor network (bottom panel) from ICA analysis

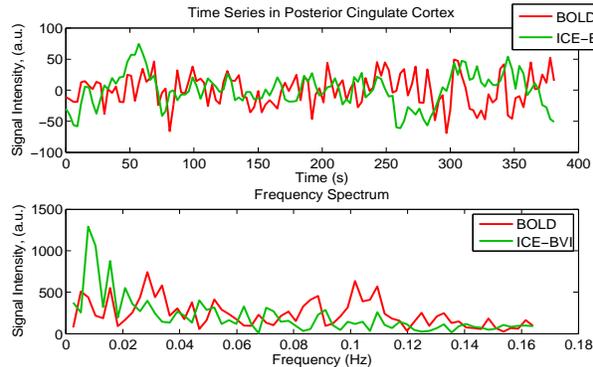


Fig 2: Signal time curve (Top panel) and its frequency spectrum (Bottom panel) from a region of interest in the posterior cingulate cortex before (BOLD) and after contrast injection (ICE-BVI). A shift of the peak spectrum to lower frequency of ICE-BVI was observed.

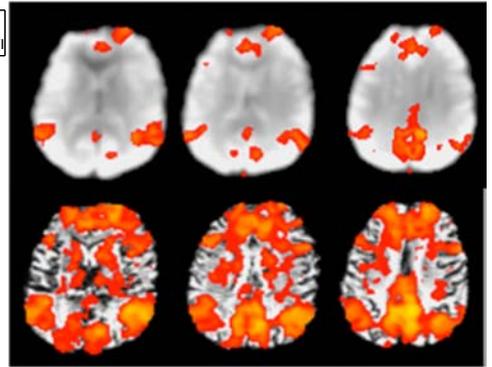


Fig 3. Correlation Maps with seed placed in posterior cingulate cortex (PCC) overlaid on mean BOLD (Top panel) and ICE-BVI (Bottom panel) images. The range of the colorscale is from [0.45, 1]. Higher correlation coefficient was observed with ICE-BVI, suggesting its higher sensitivity compared with BOLD

Results: ICA analysis identified major networks in all subjects using both BOLD and ICE-BVI techniques, including default mode, visual, motor and other networks (Figure 1). Interestingly, the regions with negative correlation with the default mode network were prominently identified using ICA-BVI (see blue colors in Fig.1). Two of the subjects had excessive head motion during the resting state scan, one during BOLD and the other during ICE-BVI, and they were removed from further quantitative analysis. Figure 2 shows signal dynamics and its frequency spectrum in the posterior cingulate cortex from an example subject for both BOLD and ICE-BVI. A shift of the frequency spectrum of the ICE-BVI to lower frequency was observed when compared with BOLD, possibly due to a slower component of CBV response [2]. Figure 3 shows correlation maps of an example subject overlaid on the mean EPI images before and after contrast injection. Larger areas were found to correlate with fluctuations in the posterior cingulate cortex, possibly due to increased sensitivity. Quantitative analysis (Table 1) showed higher correlation coefficients in posterior cingulate cortex and angular gyrus of ICE-BVI compared to BOLD in all subjects, and larger number of voxels with correlation coefficients greater than 0.45 in two of the three subjects.

Discussion and Conclusion: In this study, we demonstrated that CBV also exhibits synchronous fluctuations among putative neural networks. We further demonstrated that ICE-BVI offers higher sensitivity in studying functional connectivity between brain regions although the gain may vary from subject to subject. This apparent variability may be due to difficulties in controlling subject motion, respiration, cardiac pulsation, and state of resting neural activity. In conclusion, ICE-BVI offers a new means for studying functional neural connectivity with potential for increased sensitivity that may help increase clinical application of functional connectivity MRI.

References: [1]Biswal B. 2010. PNAS. 107:4734-9. [2]Qiu D. 2012. Neuroimage. 62(3):1726-31. **Acknowledgements :** National Institute of Health (2RO1NS047607, 1R01NS066506, P41EB015891), Lucas Foundation and Oak Foundation

Subject	#voxels with CC>0.45		CC in PCC		CC in AG	
	Pre	Post	Pre	Post	Pre	Post
1	23636	50488	0.69	0.80	0.60	0.71
2	10658	9864	0.59	0.63	0.23	0.33
3	9191	49051	0.63	0.78	0.52	0.79

Table 1. shows the number of voxels with correlation coefficient (CC) larger than 0.45, and the mean CC in posterior cingulate cortex (PCC) and angular gyrus (AG).