Spatial Variability in the Contribution of Cerebral Blood Flow Fluctuations to the Resting-State BOLD Signal

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Target Audience: This works is intended for researchers in neuronal activity, cerebrovascular physiology and resting-state functional connectivity.

Purpose: By assessing the coherence in the slow fluctuations of the blood-oxygenation level-dependent (BOLD) signal, many fMRI studies found particular brain regions to be inter-connected while at rest. To elucidate the neurovascular origins of this resting-state BOLD connectivity, a few studies have assessed functional connectivity based on cerebral blood flow (CBF)[1] using arterial-spin labeling (ASL). However, these studies did not delve into the dynamics of the CBF signal fluctuations underlying connectivity on a voxelwise basis, which has been difficult to assess due to the low signal-to-noise ratio (SNR) and to BOLD contamination of CBF measurements in conventional ASL. Thus, the interpretation of dynamic CBF contribution to resting-state BOLD fluctuations is still unclear. In this work, using simultaneously measured CBF and BOLD, we aim to clarify the spatial and temporal contribution of CBF fluctuations to the resting-state BOLD signal. We used the dual-echo pseudo-continuous arterial spin labeling (pCASL) technique to measure dynamic CBF changes, offering higher SNR than conventional pulsed ASL without the technical restrictions of continuous ASL[2]. We modeled the BOLD-CBF relationship using a multivariate general linear model, and employed a novel technique to estimate their temporal relationship. *Experimental results show that low-frequency resting-state fluctuations in CBF and BOLD are statistically significant but spatially variable. This correlation is particularly strong within dominant resting-state networks, including the default mode network and the anti-correlated network.*

Methods: We studied 9 healthy subjects (Age = 26.7±4.3 yrs, 3M/6F) using a Siemens Trio 3 T system. Resting-state CBF and BOLD data were simultaneously recorded with a dual-echo pCASL sequence. Detailed scanning protocols are as follows: TR = 3.5 s, echo-times TE1/TE2 = 10/25 ms, a 64x64 matrix, 16 slices (ascending interleaved), and voxel size = 3.4x3.4x5 mm^3. In addition, global cardiac pulsation was measured as the pulse oximetry waveform using an infrared pulse oximeter fixed onto the left index finger (50Hz sampling). The tag, control, and BOLD images in the pCASL data were preprocessed separately using SPM8 as follows: (1) retrospective motion correction; (2) slice-timing correction to compensate for acquisition delays; (3) transformation into a standard space; and (4) spatial smoothing with a 6-mm Gaussian kernel. Due to the different contribution of physiological noise, the tag and control images were subjected to physiological noise correction separately, by regressing out the significant principal components derived from noise regions-of-interest (ROI), which included white matter and cerebrospinal fluid areas[3]. To reduce BOLD contaminations, high-pass filtering at a cutoff frequency of 0.07 Hz was applied to the pCASL CBF data, and the filtered CBF signal was then demodulated to low frequency by multiplying by a cosine. To assess the local vascular effects (in terms of CBF) on the resting-state BOLD fluctuations, we applied the general linear model based on the presence of linearity between BOLD and CBF signals during resting-state[4]:

$$\mathbf{BOLD}_i = \mathbf{CBF}_i \beta_{f,i} + \mathbf{PO}\beta_{g,i} + \mathbf{C}_i\beta_{m,i} + \epsilon_i, \tag{1}$$

where $i=1,...,N$ represents the voxel, C = [m$_1$,...,m$_6$, 1] denotes nuisance parameters, including residual head motion. Here, CBF was orthogonalized from global cardiac pulsation, and the time difference between BOLD and CBF was estimated voxelwise using two basis functions, which were optimally chosen for a spectrum of time-shifted CBFs time course based on singular value decomposition[5]. To identify the physiological systemic confounds in the resting-state BOLD response, and enhance the sensitivity for detecting the local contribution of CBF, we included the down-sampled PO signals as a covariate. After estimating the individual-level effects, we performed a random effect group analysis using SPM8.
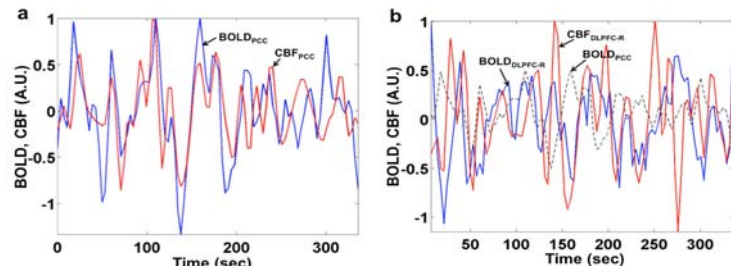

Fig. 1. ROI time-series of BOLD (blue) and CBF (red) within (a) PCC, and (b) right DLPFC, shown for one subject.

Results: The average BOLD and CBF time-series in the posterior cingulate cortex (PCC) and the right dorsolateral prefrontal cortex (DLPFC-R) are shown in Fig. 1. PCC, a node of the default mode network (DMN), selected as a 8 mm-radius sphere centered at coordinates x=-6, y=-58, z=28 in MNI 305 space. We also selected part of Brodmann area 46 as DLPFC-R, a main node of the anti-correlated network (negatively correlated with DMN, and positively related to cognitive and attentional tasks). The patterns of BOLD and CBF fluctuations in PCC were highly similar. BOLD signals in DLPFC-R were negatively correlated with BOLD signals in PCC. Interestingly, positively correlation between CBF and BOLD were again observed in DLPFC-R. Fig. 2 shows group-level *t*- maps for the BOLD-CBF relationship. Significantly positive links were found in the DMN (including PCC and medial prefrontal cortex), the anticorrelated network (including intraparietal regions and DLPFC), and the visual network (the primary visual area). Finally, we show the normalized power of BOLD and CBF in Fig. 2(c), which suggests that the spatial variability in the BOLD-CBF relationship is not determined by the variance in BOLD or CBF.

Discussion and Conclusion: In this study, using simultaneous CBF and BOLD measurements, we found that the dynamic characteristics of resting-state BOLD significantly corresponded to fluctuations in CBF. Importantly, this relationship is highly variable across the brain, with BOLD and CBF most tightly coupled within major resting-state networks (including anti-correlated), irrespective of the available variance in eit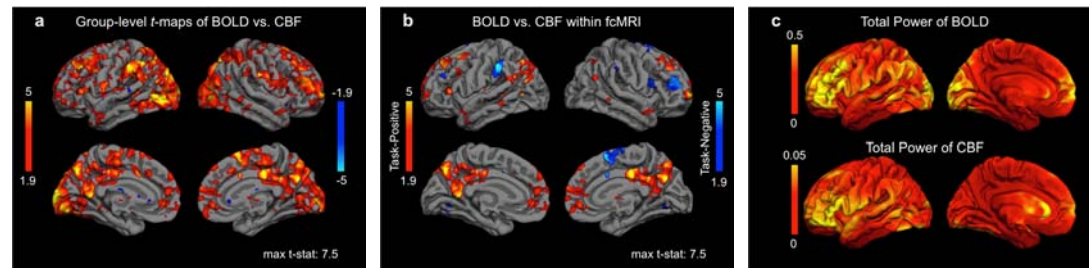her BOLD or CBF. This suggests that low-frequency CBF fluctuations to be one of the main physiological sources of resting-state BOLD response. This is in keeping with observations during functional activation and vascular challenges[1]. Note that our approach minimized BOLD contamination in the CBF signal. Furthermore, by regressing out physiological noises, we were able to target local vascular contributions to BOLD fluctuations. In future work, we will clarify the implications of this finding for resting-state connectivity. Also, the cerebral metabolic rate of oxygen

Fig. 2. Group-level maps of (a) *t*-statistics for voxelwise correlations between BOLD and CBF (*p*<0.05, uncorrected), (b) overlap between (a) and regions of the DMN (red) and anti-correlated network (blue), (c) normalized power of BOLD and CBF (only left hemisphere is shown due to space limitations). Note that (1) CBF and BOLD are highly correlated in both the positive and anti-correlated regions of resting-state connectivity; (2) this spatial variability is not entirely determined by signal power.

and cerebral blood volume are also contributors to the BOLD signal, and will be targets of future studies to examine physiological origins of resting-state BOLD.

Reference: [1] Chuang et al., NeuroImage 40: 1595-1605, 2008. [2] Dai et al., Magn. Reson. Med. 60: 1488-1497, 2008. [3] Behzadi et al., NeuroImage 37: 90-101, 2007, [4] Fukunaga et al., J. Cereb. Blood Flow Meta. 28: 1377-1387, 2008. [5] Liao et al., NeuroImage 16: 593-606, 2002.