Associations of Resting-State fMRI Functional Connectivity with Flow-BOLD Coupling and Regional Vasculature

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

Purpose: There has been great interest in applying resting-state functional connectivity using fMRI (fcMRI) to the study of brain function. However, as resting-state fcMRI is estimated using indirect measures of neuronal activity, functional connectivity is not a simple proxy for anatomic connectivity and is sensitive to confounding factors, including head motion and physiological artifacts[1]. Notably, it has been suggested that spurious correlations in fcMRI can originate from macrovascular draining routes across distal brain regions rather than from neuronal activity itself [2]. This limits our ability to interpret fcMRI findings and reinforces the importance of understanding the link between functional connectivity and neurovascular coupling factors. Cerebral blood flow (CBF) has been suggested to relate closely to neuronal activity[3], and in our previous work[4], we investigated the dynamic coupling between resting-state BOLD and CBF signals. In this work, we examine regional associations of resting-state fcMRI estimates with CBF-BOLD coupling, as well as the role of static large vessel volume.

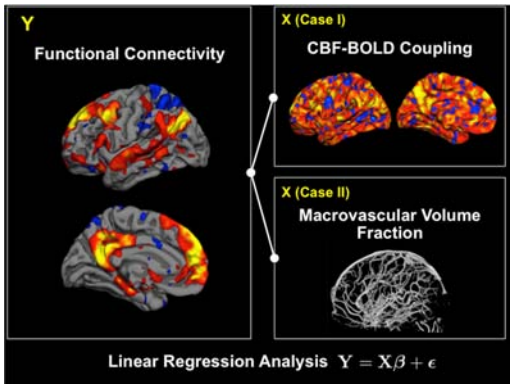

Fig. 1. Schematics of proposed methods: Linear regression analyses of the connectivity strengths within specific functional networks against the CBF-BOLD coupling (case I), and macrovascular volume fraction (case II).

Methods: We studied nine healthy participants (Age = 26.7±4.3 yrs, 3M/6F) using a Siemens TIM Trio 3 T system. Resting-state CBF and BOLD data were simultaneously recorded with a dual-echo pseudo-continuous ASL (pCASL) sequence. A 3D whole-brain time-of-flight (TOF) MR angiography (MRA) scan was acquired. Functional images, including the tag and control images in the pCASL data were separately preprocessed using SPM8. Physiological noise was then separately removed from the tag and control images by regressing out principal components derived from white matter and cerebrospinal fluid. To estimate the CBF signal with BOLD contamination removed, a series of tag and controls acquired at the first echo of pCASL data was high-pass filtered followed by demodulation. BOLD signal was estimated by surround addition of the tag and control time series acquired at the second echo. Dynamic CBF-BOLD coupling changes were then assessed by calculating the Pearson correlation coefficient between time series of BOLD and CBF for each voxel[4]. To estimate the macrovascular volume fraction, the vessel structures were segmented from TOF MRA data using a threshold-based approach, and then the ratio of large vessels to tissue volume in the fMRI measurements was calculated[5]. Regionally specific functional connectivity strength was assessed by calculating the sum of connectivity strengths among major nodes of established functional networks. Functional connectivity within well-known functional networks-including the default mode, dorsal attention, and primary motor-sensory networks-was calculated using conventional seed-based correlation approach. However, this *univariate* correlation approach does not account for potential interactions among nodes in the network and can be biased by the selection of seed voxel. Thus, to demonstrate that our findings are not biased by these potential drawbacks, we also estimated functional connectivity using *multivariate* partial least square (PLS) approach[6]. Finally, a linear regression analysis was performed to identify the relationship between the neurovascular coupling factors and functional connectivity strengths, as shown in Fig. 1.

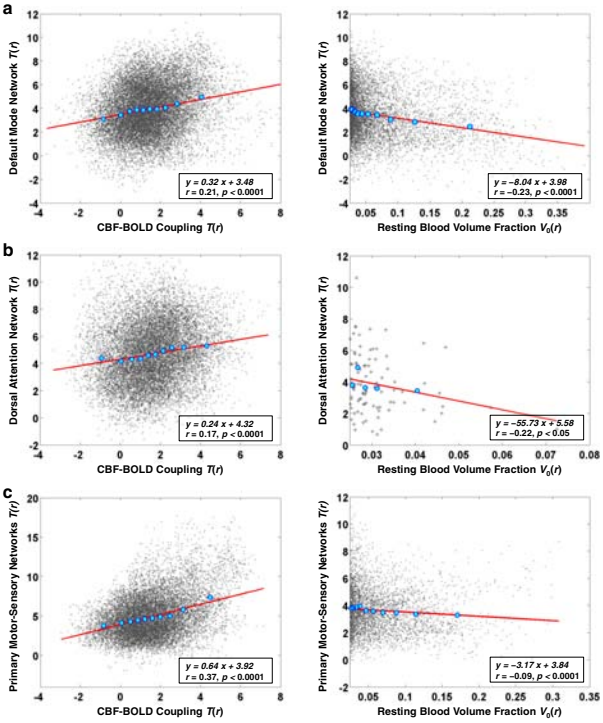

Fig. 2. Associations between functional connectivity strength, CBF-BOLD coupling and macrovascular volume fraction in multiple functional networks

Results: Regional relationships between correlation-based functional connectivity and CBF-BOLD coupling as well as macrovascular volume fraction are shown in Fig. 2. Scatter plots depict the above associations measured across all voxels in the (a) default mode network, (b) dorsal attention network, and (c) primary motor-sensory networks (including motor, auditory, and visual areas). Increasing CBF-BOLD coupling is associated with significantly increasing functional connectivity strength among all regions of the default mode network ($r = 0.21$, $p < 0.0001$), the dorsal attention network ($r = 0.17$, $p < 0.0001$), and the primary motor-sensory network ($r = 0.37$, $p < 0.0001$). Conversely, increasing the macrovascular volume fraction was significantly associated with decreasing functional connectivity strength among regions: default mode network ($r = -0.23$, $p < 0.0001$), dorsal attention network ($r = -0.22$, $p < 0.05$), and primary motor-sensory network ($r = -0.09$, $p < 0.0001$). Given the potential fallacies of conventional correlation estimates, we also computed functional connectivity using a multivariate PLS method as described earlier. Statistical significance of PLS-based connectivity estimates was consistently higher than the correlation-based estimates. Nevertheless, the resulting associations of the fcMRI estimates with CBF-BOLD coupling and macrovascular volume were consistent irrespective of the fcMRI estimation method (data not shown).

Discussion and Conclusion: In this study, we found that the functional connectivity strength was significantly proportional to the regional increase in CBF-BOLD coupling, and inversely proportional to the large vessel volume fraction. These relationships were consistently observed within all functional networks considered. These findings suggest that the synchronized BOLD time series giving rise to the common networks observed in resting-state fcMRI are not likely to be mediated by the macrovasculature or common vascular drainage linking distal cortical areas. Instead, BOLD-based functional connectivity is more likely to reflect tighter neurovascular connections, which might be associated with neuronal pathways. In addition, using both univariate and multivariate approaches, we confirmed that these physiological relationships between functional connectivity strength and CBF-BOLD coupling were consistent regardless of fcMRI computation approach, which may generalize our findings.

Reference: [1] Buckner et al., Nat. Neurosci. 16: 832-837, 2013. [2] Jo et al., Neuroimage 52: 571-582, 2010. [3] Hamel, J. Appl. Physiol. 100: 1059-1064, 2006. [4] Tak et al., Neuroimage 84: 672-680, 2014. [5] Hu et al., PLoS One 7: e31612, 2012. [6] McIntosh and Misic, Annu. Rev. Psychol. 64: 499-525, 2013.