Resting-State Functional Connectivity Mapping using Cerebral Blood Flow: Comparison with Simultaneously Acquired BOLD in High-Susceptibility Regions

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

Purpose: Since the discovery of synchronous low-frequency spontaneous oscillations in the blood-oxygenation level dependent (BOLD) response by Biswal et al.[1], resting-state functional connectivity has been most often measured using the BOLD fMRI technique. However, as the BOLD response reflects combined hemodynamic and metabolic responses, physiological origins of resting-state BOLD connectivity are unclear. In addition, conventional BOLD signals, acquired with gradient-echo EPI, suffer from signal loss in regions with high susceptibility gradients. As opposed to BOLD contrast, cerebral blood flow (CBF) measured with arterial spin labeling (ASL) technique is a simpler physiological parameter more directly linked to neuronal activity, and ASL contrast is not based on susceptibility. Recently, a few studies have reported CBF-based functional connectivity using pseudo-continuous ASL (pCASL)[2,3]. Although resting-state and motor networks were promisingly obtained with CBF responses, these studies did not compare simultaneously measured BOLD and CBF connectivity, and did not focused on regions of high susceptibility, eg. the orbitofrontal and medial temporal regions, important research targets for various diseases. In this work, using a dual-echo pCASL technique, we investigated CBF-based functional connectivity of default mode network, the hippocampus and adjacent medial temporal regions. As the pCASL sequence is much less sensitive to susceptibility effects than conventional BOLD[3,4], we hypothesized that functional connectivity in these regions can be better observed using CBF.

Methods: We studied 9 healthy subjects (Age = 26.7±4.3 years, 3M/6F) using a Siemens Trio 3 T system. Resting-state CBF and BOLD data were simultaneously recorded with a dual-echo pCASL sequence[4]. 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 = 3.4x3.4x5.0mm^3. The tag, control, and BOLD images in the pCASL data were preprocessed separately using SPM8 software 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, and BOLD images were corrected for physiological noise separately, by regressing out the significant principal components derived from the noise region-of-interest (ROI), including white matter and cerebrospinal fluid (CSF). To reduce the BOLD contaminations, high-pass filtering at a cutoff frequency of 0.07 Hz was applied to the pCASL CBF data, and CBF signal was then demodulated to low frequency by multiplying by a cosine. Band-pass filtering with a cutoff frequencies of 0.009 and 0.08 Hz was then applied to obtain the low-frequency fluctuations in CBF and BOLD signals. To assess the significance of functional connectivity, the general linear model analysis was applied to the BOLD and CBF signals by using average time course within the seed regions as a regressor. We selected the posterior cingulate cortex (PCC) (in a 8mm-radious sphere centered at coordinates x = -6, y = -58, z = 28 in MNI305 space) as the seed region of default mode network, and selected the parahippocampal cortex as the seed region for functional connectivity of the medial temporal lobe. After estimating individual-level effects, we performed a random effect group analysis using SPM8.

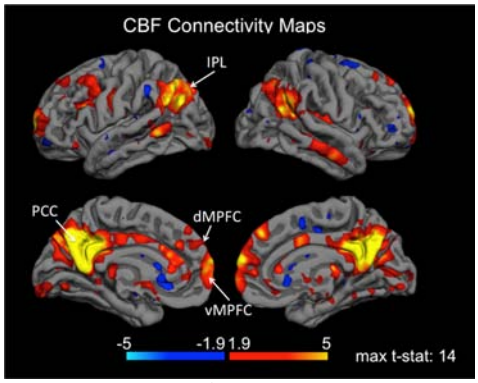

Fig. 1. Group-level functional connectivity maps measured from CBF signals (the colour bar indicates t-statistics). IPL: inferior parietal cortex, PCC: posterior frontal cortex, dMPFC, vMPFC: dorsal and ventral medial prefrontal cortex.

Results: The default-mode network mapped using functional connectivity analysis of CBF is displayed in Fig. 1, clearly showing the inferior parietal lobule (IPL), ventral medial prefrontal cortex (vMPFC) were significantly correlated with the PCC. The default-mode connectivity based on CBF agrees with the original estimate from positron emission tomography (PET) task-induced deactivation[5]. Compared to BOLD connectivity, CBF-based connectivity was associated with significantly less negative correlation. The resting-state connectivity of the medial temporal lobe estimated from CBF and BOLD responses are shown in Fig. 2. Strong connectivity between parahippocampal gyrus and entorhinal cortex was observed using both CBF and BOLD. Interestingly, part of functional connectivity to the entorhinal cortex was not detected from BOLD response, whereas the CBF-based connectivity map clearly extends to the whole entorhinal region (outlined in blue). Moreover, statistically significant connectivity between medial orbitofrontal cortex and parahippocampal cortex was only detected using CBF (outlined in yellow). Lastly, in the CBF connectivity map, connectivity within hemisphere was greater than across hemisphere.

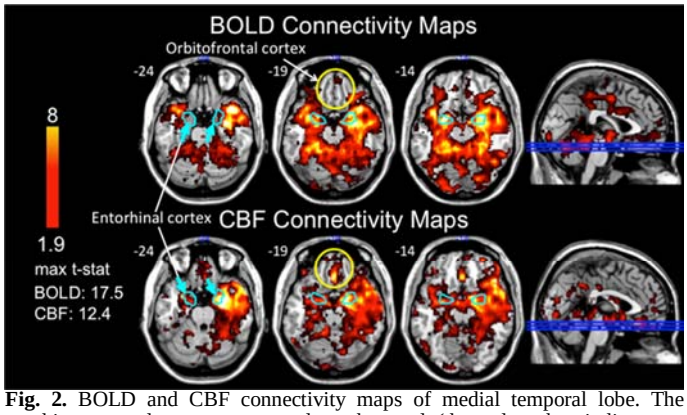

Fig. 2. BOLD and CBF connectivity maps of medial temporal lobe. The parahippocampal cortex was used as the seed (the colour bar indicates t-statistics). CBF connectivity was more sensitive in the entorhinal and orbito-prefrontal regions (outlined).

Discussion and Conclusion: This is the first study to compare simultaneously measured BOLD and CBF functional connectivity in humans. Although the signal-to-noise ratio of resting-state CBF fluctuations is lower than that of BOLD, and its sampling rate is usually lower, we reliably detected resting-state functional connectivity from low-frequency fluctuation in CBF by removing its BOLD contamination and physiological noise. In contrast to the previous comparison[2], we show that CBF connectivity does include a prefrontal node. Moreover, by exploiting its lower sensitivity to susceptibility gradients, we showed functional connectivity between the entorhinal cortex, medial orbitofrontal cortex and parahippocampal cortex, which is in agreement with anatomical connections but unobserved using BOLD[6]. This may be attributed to the large BOLD signal loss in these areas, which may have reduced the sensitivity of BOLD to detect the functional connectivity. This study showed that CBF provided robust functional contrast to detect the resting-state brain connectivity especially in regions of high susceptibility.

Reference: [1] Biswal et al., Magn. Reson. Med. 34: 537-541, 1995 [2] Viviani et al., PLoS One 6: e27050 [3] Liang et al., Int. J. Imag. Syst. Tech. 22: 37-43, 2012. [4] Dai et al., Magn. Reson. Med. 60: 1488-1497, 2008. [5] Shulman et al., J. Cog. Neurosci. 9: 648-663, 1997.[6] Lacy et al., Hippocampus DOI 10.1002/hippo.22047, 2012. **Acknowledgement:** This research was supported by fellowship funding from the Rotman Research Institute of Baycrest (S.Tak).