Estimating fluctuations in the rate of cerebral oxygen consumption associated with resting state networks

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Target Audience: Researchers interested in quantifying cerebral oxygen metabolism and resting state networks

Purpose: It is thought that the neurophysiological phenomenon of intrinsic cerebral activity is reflected in low frequency spontaneous variation in BOLD fMRI signal acquired at rest[1]. Examination of this signal has led to the definition of a number of basic networks composed of functionally connected voxels[2]. Since the BOLD signal depends on cerebral blood flow (CBF), cerebral blood volume (CBV), and cerebral metabolic rate of oxygen ($CMRO_2$), it would be desirable to assess the origin of resting state neurophysiologic fluctuations using signals more closely related to neuronal activity, thereby aiding interpretability of pharmacological and disease studies. Here we aim to demonstrate a method to measure relative CBF change associated with BOLD signal fluctuations and thereby to estimate the level of $CMRO_2$ variations in the visual resting state network. Our experimental approach uses the simultaneous measurement of BOLD and arterial spin labeling (ASL) CBF signals at rest and during the execution of a hypercapnic (breath-hold) calibration task.

Methods: 2 subjects participated in this pilot study and were scanned at 3T (Philips 3T Achieva, AE Eindhoven The Netherlands) using a SENSE 32-channel head coil. Dual echo pCASL was performed ($TR/TE_1/TE_2$=4694/9.4/37.6ms, label duration=1650ms, post-label delay=1525ms, 27 slices, voxel size=3x3x5 mm^3, SENSE acceleration factor=2). The resting state experiment consisted of 120 pairs of tag and control images. The calibration scan used 58 image pairs and was performed using a breath holding scheme[3] consisting of 10 cycles of 15 s end-expiration breath-hold alternated with 33 s of recovery. Data were motion corrected and smoothed (FWHM = 8 mm). Surround subtraction of the first echo tag and control images produced relative CBF timeseries, while surround averaging of the second echo tag and control images produced BOLD timeseries[4]. On the basis of the Davis model[5] the calibration parameter M was estimated voxelwise from the breath-hold experiment. (α=0.4, β=1.5). ICA[6] was run on the resting state BOLD data and the visual network was identified. The timeseries associated with this network was used as the waveform prior for a Bayesian nonlinear model fitting of the dual-echo ASL data using FABBER[7]. The model fitting returned maps of BOLD and CBF percentage changes associated with the input timeseries model and associated *Z* maps. The conjunction of BOLD and CBF *Z* maps, where for both *Z*>2.3, defined a region of interest within which the mean variation in $CMRO_2$ was estimated using the regional mean calibration parameter M, and the estimated regional mean BOLD and CBF variation[5].

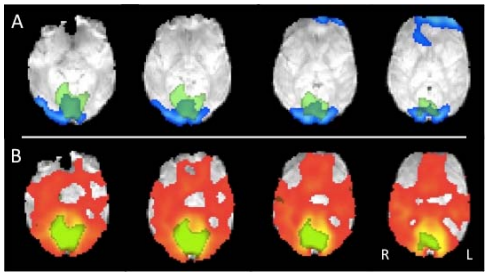

Fig1: *Z* statistic maps showing CBF (A. light blue to blue) and BOLD (B, red to yellow) thresholded to Z>2.3 resulting from model fitting to the dual echo ASL data. The visual network defined by BOLD ICA (light green) is superimposed on the CBF and BOLD maps.

Tab1. Mean values and standard deviations of Davis equation parameter estimates within the region of interest.

	$\Delta BOLD/(BOLD)_0$	$CBF/(CBF)_0$	M	$CMRO_2/(CMRO_2)_0$
Subj 1	0.0024±0.0009	1.13±0.01	0.05±0.02	1.06±0.04
Subj 2	0.0026±0.0005	1.07±0.01	0.06±0.03	1.02±0.05

Results: The table (Tab1) shows, for both individuals scanned, parameter estimates for the region in which there were significant variations of BOLD and CBF associated with the visual ICA-defined network and the calculated variation of $CMRO_2$.

Discussion: The principle challenge in estimating the fluctuations in oxygen metabolism associated with resting state networks using calibrated FMRI is the intrinsically low signal-to-noise ratio of ASL signal. The noise dominating the ASL data, risks also dominating the $CMRO_2$ timeseries estimated from it[7]. It has been shown[8] that it is possible to reduce the noise of a CBF timeseries using a constrained fitting of a specific model, on the basis of the BOLD timeseries. Here we offer a method with a similar end-goal but without invoking a specific biophysical model relating CBF and BOLD to inform such a fitting procedure, instead we use a non-linear model of pCASL data to identify BOLD and CBF fluctuations, having identified a resting state network timeseries of interest. This technique is promising in identifying the level of CBF fluctuations that can be used to obtain an estimation of $CMRO_2$ changes at the regional level, themselves appearing plausible. One weakness is that this method uses the BOLD timeseries as the "gold standard" of neurophysiological variations across time to define our resting state network.

Conclusions: We propose an approach for obtaining maps of relative changes in CBF associated with resting state network activity, which can then be used to evaluate the level of $CMRO_2$ changes within a region of interest in that network. Although the method is driven by the dynamics of the BOLD signal, it may offer a way of quantifying better the resting state network activity through estimating $CMRO_2$. Further improvements in the signal to noise ratio of the CBF signal are needed to estimate at the voxel level the fluctuations in metabolic oxygen consumption.

References: 1. Raichle ME, Mintun MA (2006). Annu Rev Neurosci 29: 449–476; 2. Damoiseaux JS, et al (2006). Proc Natl Acad Sci USA 103: 13848–13853; 3. Blockley NP et al (2012). NMR Biomed 26: 987; 4. Liu TT, Wong EC (2005). NeuroImage 24: 207–215; 5. Davis TL et al (1998). Proc Natl Acad Sci USA 95: 1834–1839; 6. http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC; 7. Chappell MA et al (2009). IEEE Trans Sig Proc 57(1): 223–236 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FABBER); 7. Liu TT (2013). NeuroImage 80: 339-348; 8. Simon AB et al (2013). PLoS ONE 8(1): e54816.