# Mapping Functional Connectivity Based on Synchronized CMRO2 Fluctuations during Resting State

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## INTRODUCTION

Synchronized low-frequency fluctuations in the resting-state functional MRI (fMRI) signal have been suggested to be associated with functional connectivity in brain networks (1). However, the underlying mechanism of this connectivity is still poorly understood. To better interpret the resting signal, we examined spontaneous fluctuations at the level of cerebral metabolic rate of oxygenation ($CMRO_2$), an index reflecting regional oxygen consumption and metabolism, and thus less sensitive to vascular dynamics. The $CMRO_2$ signal was determined based on a biophysical model (2) with simultaneously acquired blood oxygenation level dependent (BOLD) and perfusion signals.

## MATERIAL & METHODS

Twelve healthy subjects participated in the experiments on a 3T Allegra system with a head volume coil. A pulsed arterial spin labeling (PASL) sequence based on a flow-sensitive alternating inversion recovery (FAIR) echo-planar imaging (EPI) method was adopted for functional scans. Arterial blood was labeled with alternating slice-selective inversion (label) and non-slice-selective inversion (control) scans. Imaging parameters of the PASL sequence were: TI of 1400 ms, TR of 2000 ms, TE of 28 ms, and flip angle of 90º. Ten oblique imaging slices (220 × 220 $mm^2$ field of view, 64×64 in-plane matrix size, and 6 mm slice thickness) were aligned along the AC-PC line. Twelve minutes of continuous fMRI data were acquired for each subject, corresponding to 360 measurements. After the resting scan, a block-design visual stimulation experiment was performed (starting with a 32 s resting period and followed by five cycles of 32 s stimulation and 32 s resting periods), which lasted for 358 s, corresponding to 176 measurements.

Data were pre-processed with motion correction and detrending using MATLAB. Subsequently, each functional dataset was low-pass-filtered and high-pass-filtered, respectively, at the cutting frequency of 0.125 Hz using Chebyshev type II filters, for obtaining BOLD and perfusion signals without contamination (3). The data were then underwent spatial normalization (isotropic resolution 3×3×3 $mm^3$) and smoothing (Gausian kernel = 6 mm). BOLD signal was obtained from the sum of the label and control (odd and even) images of the low-passed dataset, and the perfusion signal was computed from the demodulation of the high-pass filtered dataset by multiplying $cos(\pi n)$, n = scan number (3). Using both BOLD and perfusion signals, the time series of $CMRO_2$ was determined through the following equation:

$$S_{CMRO_2} \cong \left(1 - \frac{S_{BOLD\%}}{M}\right)^{1/\beta} \left(S_{CBF}\right)^{1-\alpha/\beta}$$

where $\alpha$=0.38, $\beta$=1.5 and M is 0.22. To correct for potential influences of physiological noise, cardiac and respiratory estimations were calculated using a post-processing method with temporal independent component analysis (ICA) (4). Six motion parameters, respiratory/cardiac estimators and the averaged time-series retrieved from the segmented white matter mask were regressed out as nuisance covariates in the process. The CC maps of different TEs were converted to normal-distributed z-score maps, and then group-level analysis were performed to reveal significant connectivity maps ($p < 0.05$, corrected) for BOLD, perfusion and $CMRO_2$.

## RESULTS

Functional connectivity maps of the visual, default mode, and hippocampus networks from the entire group are shown in Fig. 1 (Fig. 1a for visual task and Fig. 1b for resting state) overlaid on the averaged anatomical images. Functional connections of relevant brain regions within these networks were observed in all three maps, indicating that the synchronized spontaneous oscillations exist at both hemodynamic and metabolic levels. Comparing to CBF- and $CMRO_2$-based connectivity maps, BOLD-based connectivity maps have larger spatial extents probably due to higher sensitivity of BOLD. In the visual cortex, the connection from the seed (V1) area to the ipsilateral lateral geniculate nucleus is strong during visual stimulation, but the connection is not detectable during the resting state. Instead, BOLD-based connectivity of the visual area has broad and symmetric spatial extent at rest, inclusive of bilateral insula/superior temporal gyrus (STG). The CBF- and $CMRO_2$-based connectivity maps in the visual network demonstrated laterally asymmetric spatial extent, while the BOLD-based maps are generally symmetric. Since the seed was chosen from right V1, the connection of the seeds can be traced to deep V1 areas on the ipsilateral side, while scattered connections to the contralateral insula/STG regions are also shown. In the default mode network, the connectivity strength between posterior and anterior cingulate is strong in the BOLD, perfusion and $CMRO_2$ maps at rest, but such connection is not observable during visual stimulation. Furthermore, insula and/or STG are also functionally connected to posterior cingulated cortex, especially at rest. Once again, the BOLD-based connectivity map is more laterally symmetric than the CBF- and $CMRO_2$-based maps. Compared to the other two networks, the connectivity in the hippocampal network has similar spatial patterns during both resting and task states, suggesting that functional connectivity in brain regions that are not generally involved in a task (visual stimulation in this case) may not be affected by that task.

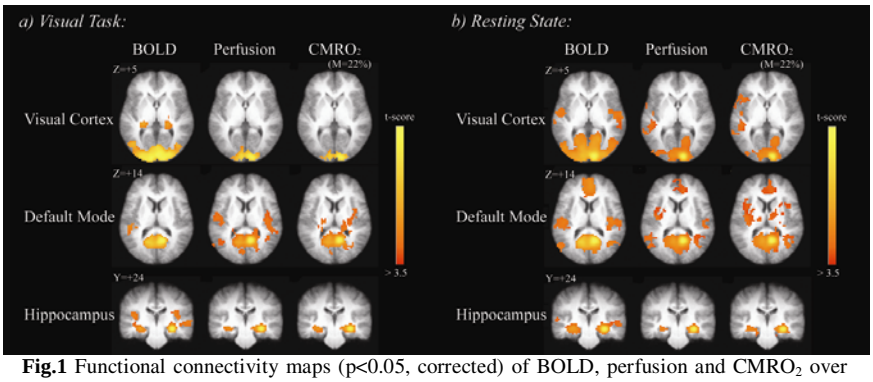


**Fig.1** Functional connectivity maps ($p<0.05$, corrected) of BOLD, perfusion and $CMRO_2$ over 12 subjects during (a) visual task and (b) resting state. The group-level statistics were spatially overlaid over the anatomical images.

## DISCUSSION & CONCLUSIONS

In this study, we investigated the synchrony of spontaneous fluctuations in BOLD, perfusion and $CMRO_2$ signals at rest, extending the functional connectivity analysis to a metabolic level. $CMRO_2$ was calculated from the simultaneously acquired BOLD and perfusion signals based on a biophysical model (2, 5), and the perfusion signal was processed with high-pass filtering to minimize BOLD contamination (3). Our results show that functional connectivity of the brain based on synchronized spontaneous fluctuations can be detected not only in BOLD and perfusion contrast, but also in $CMRO_2$. This observation provides direct evidence supporting the hypothesis that spontaneous fMRI signal fluctuations have a metabolic origin. Since regional metabolism is closely coupled with local neuronal activity, these fluctuations are likely associated with ongoing neuronal activity. These results are in line with recent electrophysiological and fMRI resting state investigations, which show that, like fMRI signals, electrophysiological signals between functionally-related brain regions are closely correlated.

## REFERENCES

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