Quantification of Resting State CMRO2 using Low-Frequency Hemodynamic Oscillations in Rat Brains

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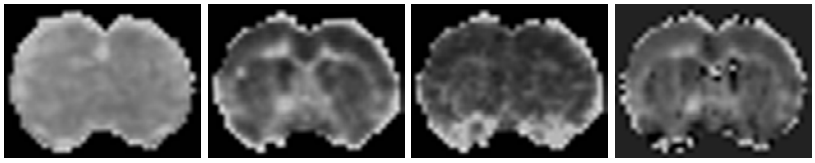
ABSTRACT Since the proposal of Davis et al.,[(1)] hypercapnic calibration of cerebral blood flow (CBF) and volume (CBV) contributions has been frequently used for the measurement of changes in cerebral metabolic rate of oxygen consumption ($CMRO_2$) during task-induced fMRI activations. In the current study, we expanded the initial proposal to quantify the resting state $CMRO_2$ based on the spontaneous low-frequency hemodynamic oscillation using the mean fluctuation magnitude (i.e., standard deviation) of BOLD, CBF, and CBV fMRI time courses.[(2)] We demonstrated that the low-frequency fluctuation is temporally synchronous in the cortex of anaesthetized rat brains. Such selective resting state activities were observed independent of fMRI hemodynamic parameters and were spatiotemporally similar between BOLD, CBF, and CBV time courses. As a result, the calculated mean resting state $CMRO_2$ pertaining to low-frequency fluctuations was approximately 20 % of the baseline $CMRO_2$ in the sensorimotor cortex, which was only slightly less than the measured $CMRO_2$ value (~ 30%) during the electrical stimulation of forelimbs.



(a) **(b)** **(c)** **(d)**

Figure 1. Percent fluctuation magnitude maps measured from BOLD **(a)**, CBF **(b)**, and CBV **(c)** time courses, base on which the $CMRO_2$ map **(d)** was calculated.

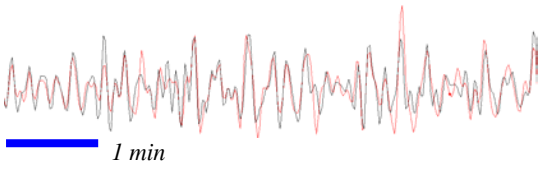
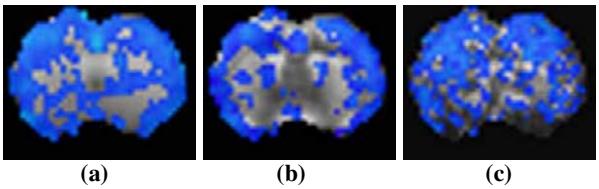


Figure 2. Simultaneously measured BOLD (red line) and CBF (black) time courses during resting state from a single voxel in the sensorimotor cortex.

MATERIALS AND METHODS Resting state and task-induced fMRI activities (electrical forelimb stimulations) were acquired using gradient echo planar imaging (GEEPI) pulse sequences equipped with alterial spin labeling (ADC) at 9.4 T using normal healthy Sprague-Dawley rats (n=3: 275~325g). Mechanically-ventilated rats were anaesthetized with the continuous infusion of alpha-chloralose (~30 mg/kg/h) and pencuronium (~1.25 mg/kg/h) during the fMRI session. Functional changes in BOLD and CBF signals were acquired for approximately 12 minutes of the resting state fMRI session using GEEPI sequence (3 slices: TR/TE = 3700/15 ms), which was followed by CBV-weighted fMRI study with the use of GEEPI (3 slices: TR/TE = 3700/11.3 ms) and a long-circulating intravascular susceptibility contrast agent (i.e., superparamagnetic iron oxide nanoparticles (SPION): 36 mg/kg). Prior to the functional analysis, each voxelwise time course was detrended to the second order and bandpass-filtered between 0.02 and 2 Hz, from which spatiotemporal correlation maps were generated by identifying voxels that are temporally synchronous with the neighboring voxels.



(a) **(b)** **(c)**

Figure 3. Clustered low-frequency activity maps using BOLD **(a)**, CBF **(b)**, and CBV **(c)** fluctuations: spatiotemporal correlation coefficient color maps were created by correlating each detrended and bandpass-filtered voxelwise time course with those of neighboring voxels.

RESULTS AND DISCUSSION In general, percent fluctuation maps acquired using standard deviations of CBF, BOLD, and CBV time courses (Figure 1) suggest evenly distributed vascular fluctuations in both cortical and subcortical regions. Moreover, these fluctuations were independent of measurement methods and highly correlated between differing hemodynamic parameters (e.g., between CBF and BOLD: Figure 2). However, despite the spatially homogeneous standard deviation in both cortical and subcortical areas (Figure 1), the spatiotemporal correlation analysis revealed that synchronous low-frequency activities were predominant in cortical regions in comparison to the caudate region (Figure 3), in which all the hemodynamic parameters (i.e., BOLD, CBF, and CBV) used in the study showed similar spatiotemporal correlation patterns (Figure 3a-3c). This discrepancy implies that resting state neurovascular activities in the subcortical areas (i.e., caudate) are not as spatially synchronous as shown in cortical regions and are possibly sporadic in nature. Therefore, it can be suggested that the resting state low-frequency activity is synchronously mediated by region-specific active neural pathways and is metabolically demanding. In this regard, Figure 4a shows that the resting state $CMRO_2$ for the synchronous low-frequency activity in the sensorimotor cortex is approximately 20 % of the baseline value, which is less but comparable to that measured during electrical forelimb stimulations (Figure 4b). However, other resting state parameters (i.e., BOLD, CBF, and CBV) were considerably less than those acquired during the forelimb stimulation. Gathered, the resting state hemodynamic activity appears to be based on a more metabolically efficient process than the task-induced activation.

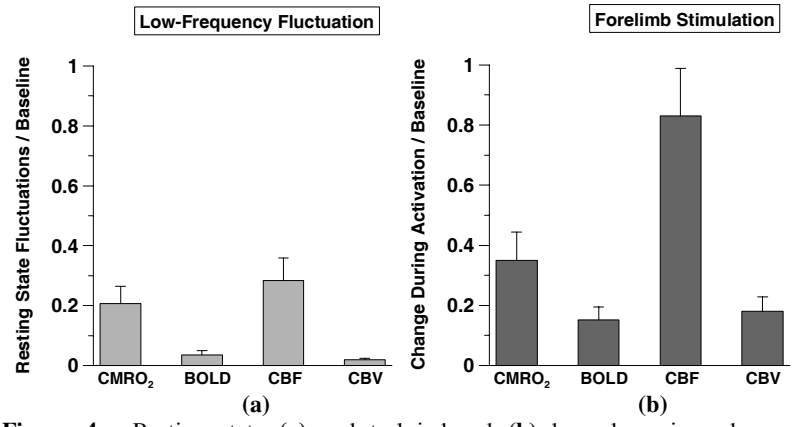


Figure 4. Resting state **(a)** and task-induced **(b)** hemodynamic and metabolic parameters measured in sensorimotor cortices (n=3).

REFERENCES

1. Davis, T. L., Kwong, K. K., Weisskoff, R. M. & Rosen, B. R. (1998) *Proc Natl Acad Sci U S A* **95,** 1834-9.
2. Biswal, B., Yetkin, F. Z., Haughton, V. M. & Hyde, J. S. (1995) *Magn Reson Med* **34,** 537-41.