Frequency-Dependent Cerebral Blood Flow-Volume Coupling in Activated Human Visual Cortex

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Introduction Neuronal activations elicit responses in cerebral blood flow (CBF) and volume (CBV). The coupling between relative changes in CBF (rCBF (%)) and CBV (rCBV (%)) has attracted intense interest in the fields of neuroscience and metabolic physiology due to its importance for understanding neurovascular coupling mechanisms, blood oxygenation level-dependent (BOLD) signals and oxygen metabolism determination (1, 2). Nonetheless, it remains unclear that whether the coupling persists unchanged, i.e., with a fixed power law constant $\alpha = 0.38$ (Eq. [1]), or varies with brain activities. Using functional magnetic resonance imaging (fMRI), the flow-volume coupling during differing levels of brain activations has been extensively studied in animal models (3,4), where it appears that the α is neuronal-activity dependent. In humans, however, the flow-volume coupling was predominately investigated and reported using positron emission tomography (PET) (1,5). The purpose of this study was, therefore, to verify the flow-volume coupling during graded visual stimulation with fMRI methods.

$$(1 + rCBV) = (1 + rCBF)^{\alpha} \qquad [1]$$

Material and Methods Five males (aged 20-34) participated the study. A black-white checkerboard was employed for visual stimulation. The experimental design consisted of 3-min 4Hz/3-min off/3-min 8Hz. fMRI studies were performed on a 3T Trio MRI scanner (Siemens, Erlangen, Germany). An intravenous line was inserted for Gd-DTPA contrast agent administration. An eight-channel phase array coil was used. Four slices (5 mm in thickness) encompassing the primary visual cortex were chosen for functional imaging. Images were acquired with a field-of-view (FOV) of 24 cm and in-plane matrix size of 64 x 64. rCBF(%) was determined using pulsed arterial spin labeling (PASL) techniques, with TR/TE/TI_1/TI_2 = 2000 ms/19 ms/700 ms/1000 ms (6). rCBV(%) was determined using 0.1 mmol/kg Gd-DTPA contrast agent (Omniscan, GE Healthcare, USA) per condition with the gradient echo EPI (echo planar imaging) sequence: TR/TE = 2000 ms/30 ms. *Data Analysis* The ASL image series were obtained by subtracting the adjacent slab-selective and nonselective images in the sequence. The voxels that passed through the threshold (Student t test, $P < 0.005$) were used to determine rCBF. Changes in brain signal intensity occurring during cerebral transit of the high magnetic susceptibility Gd-DTPA were converted to contrast agent concentration--time curves. The area under the concentration-time curve is proportional to the local rCBV. These calculations were performed on a voxel-by-voxel basis to generate images of rCBV (7). Those passed through the threshold ($P < 0.005$) and had common area with rCBF were used to calculate the α values.

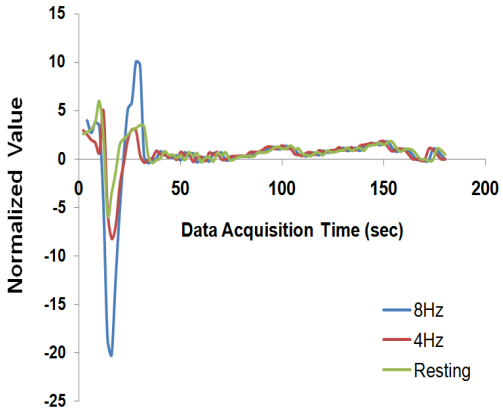

Figure 1 Time course of changes in signal intensity at each condition in a single voxel (ROI) during the first-pass trainsit of intravenously administrated GD-DTPA contrast agent.

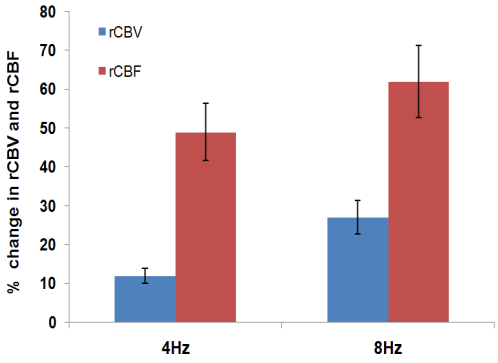

Figure 2 Changes in rCBF and rCBV at 4 and 8 Hz

Results and Discussion Figure 1 displays the Gd-DTPA intensity changes in a single voxel which passed through the threshold within the visual cortex in a single subject. The magnitudes of rCBF(%) and rCBV(%) averaged over the five subjects are shown in Figure 2 and Table 1. Both rCBF and rCBV were higher at 8 Hz than at 4 Hz. The α values were then calculated with Eq. [1]. As shown in Table 1, α varies with stimulus frequency with $\alpha = 0.28$ and 0.50 at 4 and 8 Hz, respectively. The result is in good agreement with a previous PET study with a similar visual stimulus design (α =0.37-0.64), though $\alpha = 0.3$ was demonstrated in the paper with the mixture of all three conditions, i.e., resting, 2 and 8 Hz with quantitative values (5). The results suggest that the flow-volume coupling is not constant, but varies with stimuli and brain activity, and the calculation of cerebral metabolic rate of oxygen ($CMRO_2$) cannot depend on the assumption of α=0.38 for all stimuli. The frequency-dependent flow-volume coupling would facilitate our future understanding of BOLD and $CMRO_2$ mechanisms.

Table 1

Stimulus Rate	Imaging Method	rCBV (%)	rCBF (%)	α
4Hz	fMRI	12 ± 3	49 ± 10	0.28
8Hz	fMRI	27 ± 5	62 ± 12	0.50
2Hz	PET(5)	10 ± 13	16 ± 16	0.64
8Hz	PET(5)	21 ± 5	68 ± 20	0.37

References: (1) Grubb, Stroke 1974, 5:630-639; (2) Davis, PNAS 1998, 95:1834-1839; (3) Kida, JCBFM 2007, 27:690-696; (4) Jin, Neuroimage 2008, in press; (5) Ito, JCBFM 2001, 21:608-612; (6) Wang, MRM 2003, 49:796-802; (7) Belliveau, Science 1991, 254:716-719.