Spatiotemporal characteristics of BOLD, CBV and CBF responses in the cat visual cortex

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Introduction In fMRI, the blood oxygenation level dependent (BOLD) contrast reflects activation-induced changes in the oxygen metabolism ($CMRO_2$) and the hemodynamic response which consists of the blood flow (CBF) and the cerebral blood volume (CBV). Currently, the fundamental relationship between oxygen metabolism and the hemodynamic responses has not been fully characterized. For example, there are controversies over whether the focal functional CBF increase is caused by the energy metabolism or the neurotransmitter release, and on the physiological source of the post-stimulus undershoot in the BOLD signal. Specifically for the BOLD undershoot, there are conflicting opinions on whether the venous CBV or $CMRO_2$ remains elevated for a prolonged period of time after the stimulus was turned off, assuming the CBF change quickly returns to the pre-stimulus basal level [1-4]. The discrepancies in the literature may partly be due to the difference in imaging techniques, stimulation type and duration, and spatial localization. Thus, multimodal studies with high spatial resolution would be helpful to clarify the debate. In this study, a cat visual stimulation model was used to investigate the spatial and temporal dynamics of BOLD, CBV, and CBF.

Materials and methods fMRI experiments were performed on a 9.4T/31cm MRI (Varian) system. Female adolescent cats (n=11) were anesthetized under ~1.1% isoflurane and kept under normal physiological condition. For all the experiments, coronal images were acquired with 2×2cm^2 FOV and 2mm slice thickness. A T_1 weighted image with 128×128 matrix size was obtained for anatomical reference. The binocular visual stimuli consisted of drifting square wave grating. CBV-weighted studies were performed following BOLD experiments on the same animal, but the CBF changes were measured separately on different animals because of time restriction.

BOLD and CBV studies (n=6): BOLD and CBV-weighted images were obtained using a 1.6cm diameter surface coil before and after the injection of 10 mg/kg MION, respectively. Imaging parameters were: 2-segmented GE-EPI, TR=0.5s/segment, 96×96 matrix size zero filled to 128×128. Two TEs of 10ms and 20ms were arrayed for BOLD; TE = 6ms, 10ms for the CBV-weighted studies. The temporal resolution was 2s, and the stimulation paradigm was 60s control, 60s stimulation, and 160s control. About 20 data sets were averaged.

CBF studies (n=5): FAIR images were obtained using an actively detuned two coil system and single shot GE-EPI technique with matrix size=64×64, TE=19ms, TR=1.5s, and TI=1.5s. The time resolution was 6s. The stimulation paradigm was 60s control, 60s stimulation, and 162s control. 40-50 data sets were averaged for each study.

Data analysis: The CBV-weighted signal change contained the contribution from the blood deoxyhemoglobin content change, which is more significant at the large vessel area and at higher fields. Therefore a BOLD correction was performed to calculate the CBV change [5]. Fractional signal change maps were calculated with a minimal cross correlation coefficient of 0.3 and minimal cluster size of 3 pixels. ROI-based data analysis was performed. For each experiment, two ROIs were drawn from the anatomic image: one at the surface of cortex and the other at the middle of cortex. The surface ROI contains large blood vessels such as arteries or veins, while the middle ROI contains mostly microvessels such as arterioles, capillaries, and venules.

Results Fig. 1 showed the normalized temporal dynamics of BOLD (at TE=20ms), CBV, and CBF for the two ROIs. Surprisingly, post-stimulus undershoots were found consistently for both CBV and CBF. Moreover, the spatial and temporal patterns of the normalized CBF and CBV response were very similar. At the surface of the cortex, there is no significant difference in the temporal dynamics of CBV, CBF, and BOLD. At the middle cortical ROI, the BOLD signal decays much faster than that of the CBV and CBF during the 60s stimulation period, and the peaks of the poststimulus undershoot are much more pronounced than those of the CBV and CBF. Compared to the middle ROI, the CBV (CBF) response at the surface ROI was faster: faster increasing to the positive peak, faster decaying during the 60s stimulation, faster decreasing to the peak of the post-stimulus undershoot, and faster recovering from the undershoot to the pre-stimulus baseline.

Discussions Our results show that the BOLD, CBV and CBF temporal dynamics are dependent on the spatial localization. Compared to the 40s-stimulation results of reference [4], their CBV-weighted signal showed no post-stimulus undershoot. The discrepancies may be due to the different stimulus durations, and the contamination of the BOLD signal change in their CBV-weighted signals. While CBF was usually assumed to quickly return to the basal level, a small poststimulus undershoot was observed for our 60s stimulation, in agreement with some previous reports [6, 7]. A relatively fast return of the *total* CBV to the basal level (and undershoot) was observed, in contrast to the expectation based on a delayed *venous* CBV compliance. The similarity in the CBF and CBV spatial-temporal characteristics and their faster response at the surface area not only indicated a tight coupling between the blood flow and volume, but also suggested that the functional total CBV changes is dominated at the arterial vessels rather than the venous vessels. Combining that with the CBV responses at the middle and surface ROIs, we can conclude that the BOLD undershoot is due to an elevated post-stimulus deoxyhemoglobin (dHb) concentration rather than an elevated venous CBV. This elevated dHb concentration may be caused by a mismatch between the blood flow and oxygenation metabolism (more specifically an elevated $CMRO_2$ to CBF ratio), and/or other mechanisms related to the dynamics of the oxygen transportation in the tissue.

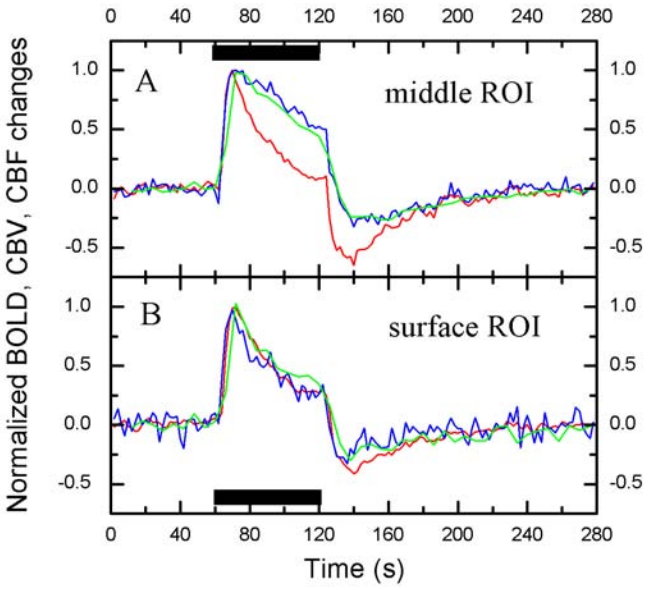

Fig. 1 *The averaged time courses of BOLD (red, n=6, TE=20ms), CBV (blue, n=6) and CBF (green, n=5) responses for two ROIs. The fractional changes were normalized to the peaks of the positive change. The black bar indicates the stimulation period.*

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