CBF, BOLD, CBV and $CMRO_2$ fMRI at 500-ms Temporal Resolution

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Introduction The intricate neural-vascular coupling associated with changes in neural activity forms the basis for many modern neuroimaging modalities. However, the temporal dynamics of the stimulus-evoked CBF and CBV responses and the resulting BOLD signals remain poorly understood and somewhat controversial. In this study, we further investigated the CBF, BOLD, CBV and $CMRO_2$ fMRI dynamics at high temporal resolution (500 ms) in a single setting. fMRI percent changes, onset times, time to peaks and post-stimulus undershoot were analyzed for the entire forepaw somatosensory cortices and for three operationally defined layers (Layer I-III, IV-V, and VI) within the forepaw somatosensory cortices. Although fMRI does not have sufficient spatial resolution to resolve different vascular compartments, the temporal latencies of the BOLD, CBF and CBV fMRI signals could shred lights on the fMRI signal sources and their spatial specificity.

Methods Eight male SD rats (300-375g) were anesthetized with 2% isoflurane during placement of a femoral vein catheter and needle electrodes under the forepaw skin. Isoflurane was switched to 1.1-1.2% during imaging. Rats breathed spontaneously without mechanical ventilation. Two forepaws were stimulated simultaneously in series using 6 mA, 0.3 ms pulse duration at 3 Hz, previously optimized for isoflurane anesthetic without inducing changes in MABP [1].

Multislice CBF, BOLD and CBV (MION, 14mg/kg) imaging at 4.7T was performed with a temporal resolution of 0.5s using single-shot, gradient-echo EPI acquisition. Changes in cerebral metabolic rate of oxygen ($CMRO_2$) were estimated using Davis' biophysical BOLD model [2]. Pseudo-continuous CBF measurements [3] were made using the two-coil system with an actively decoupled brain surface coil, data matrix = 64x64, FOV = 2.56 x 2.56cm^2, two 2.0-mm slices, and TE=16ms. Labeled and non-labeled (BOLD) image were acquired consecutively on two separate scans. MION CBV was measured following CBF and BOLD measurement using the same parameters as the control images of the CBF measurements. The forepaw stimulation consisted of 3 epochs of 60 seconds OFF, and 20 seconds ON.

CBF, BOLD, CBV and $CMRO_2$ percent changes, onset times and times to peak were analyzed for the entire forepaw somatosensory cortices and for three operationally defined layers (Layer I-III, IV-V, and VI) within the forepaw somatosensory cortices. CBF time courses were deconvolved [3] to remove the T_1 saturation effect due to pseudo-continuous labeling technique. Onset times (10% above baseline) and peak times (90% of maximum) were tabulated.

Results Representative single-animal activation maps and the group-average percent change time courses of the CBF, BOLD, CBV-weighted and CBV fMRI are shown in **Fig. 1**. Robust activations were observed. The average CBF, BOLD and CBV percent changes were 37±11%, 1.1±0.3%, and 6.4±2.0%, respectively. **Figure 2** shows normalized CBF, BOLD and CBV time courses, with the expanded time courses showing the detailed onset times and times to peak of the three fMRI signals. CBV increased first but grew slower over time. CBF started out slightly later than CBV but increased and peaked faster than CBV. BOLD showed the slowest onset and peaked last. The onset times for CBF, CBV and BOLD signals were 0.76±0.26, 0.69±0.13, and 1.15±0.21 s, respectively. The peak times of the CBF, CBV and BOLD signals were 4.5±1.1, 5.0±2.3 and 5.8±2.6 s, respectively. Percent changes from three operationally defined cortical segments, approximating the layers I-III, IV-V, and VI are shown in **Fig. 3**. The largest CBF, CBV and $CMRO_2$ changes were detected in Layer IV-V. In contrast, the largest BOLD changes were detected in Layer I-III. Only the BOLD time courses from Layer I-III showed a post-stimulus undershoot, as shown in **Fig. 4**.

Discussion 1) In the early phase, CBV increases first, likely due to arteriole dilation which actively drives CBF increase. In the later phase, the CBV fMRI increase is slower relative to the CBF signal, indicative of increased venule and venous contributions. 2) CBF increases second, but overtakes CBV and peaks first. The initial CBF increase is likely passive, driven by CBV changes. These results are consistent with the notion that the arterial spin-labeling CBF technique is predominantly sensitive to changes in the arteriole compartment and is less sensitive to changes in the venous compartment due to the loss of contrast associated with T1 recovery as spins traversed from the arteries to the draining veins. They also suggest that MION-CBV fMRI signals have significant draining vein contribution during the steady-state phase. 3) The onset time and time to peak of the BOLD signal significantly lag those of CBF and CBV signals, indicative of predominantly venule and venous contribution, where the stimulus-evoked deoxyhemoglobin saturation changes are most pronounced. 4) The magnitudes of the fMRI signals are cortical-depth dependent. The BOLD signal from the cortical surface (Layer I-III) showed the highest changes and only the BOLD signal from Layer I-III exhibits a post-stimulus undershoot. In contrast, CBF, CBV and $CMRO_2$ show the largest changes in Layer IV-V. No post-stimulus undershoot was detected for the CBF, CBV and $CMRO_2$ signals. Our results suggest that the post-stimulus BOLD signal does not appear to be the result of $CMRO_2$ change under this stimulus conditions.

Our data are in good agreement with those of Malonek et al., Vanzetta et al., and Jones et al.'s optical imaging data [4-6] and Silva's MRI data [7,8], but appeared to be inconsistent with Sheth et al.'s optical imaging data [9] and Mandeville's MRI data [10]. It should be noted that optical imaging and fMRI may not be measuring the same signal sources (arteriole, capillary, venule, or vein). It is important to note that fMRI measurements generally report changes deep in the cortex, in contrast to optical imaging which measures changes on the cortical surface. Our data indicated that hemodynamic changes vary with different cortical depth. Thus, caution must be exercised when comparing optical and fMRI data.

Conclusion This study reported the dynamic evolution of CBF, CBV, BOLD and estimated $CMRO_2$ fMRI responses with a 500-ms temporal resolution. These fMRI signal dynamics are cortical depth dependent. BOLD stimulus undershoot does not appear to be metabolic in origin but remained to be validated. Temporal latencies of different fMRI signals can thus provide valuable insights into their signal sources and their spatial specificity, have implications in columnar and laminar fMRI, and offer the potential to better understand the cerebral vasculature and its relationship to brain function in both healthy and diseased state.

Reference [1] Liu et al., MRM 2004, 52:277. [2] Davis et al., PNAS, 1998, 95: 1834. [3] Silva et al., MRM 2001, 42:425. [4] Malonek et al., PNAS, 1997, 94: 14826 [5] Vanzetta et al., J Neurosci 2005; 25: 2233 [6] Jones et al., Neuroimage 2001; 13: 1002. [7] Silva et al., JCBFM 2000, 20:201. [8] Silva et al., ISMRM 2004. [9] Sheth et al. JCBFM 2005, 25:830 [10] Mandeville MRM 1998, 39:615.

Fig. 1

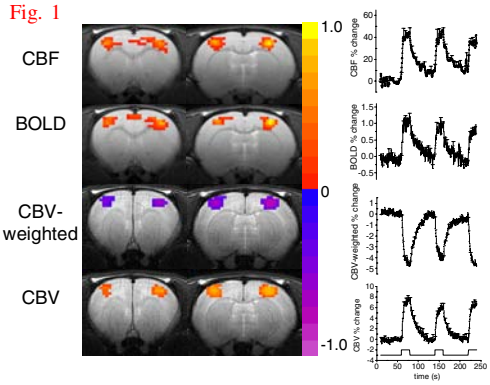

Fig. 2

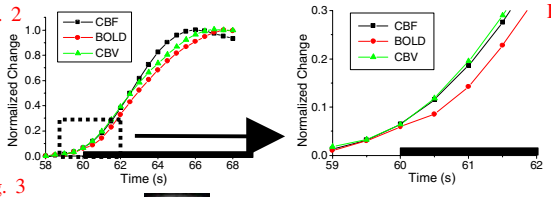

Fig. 3

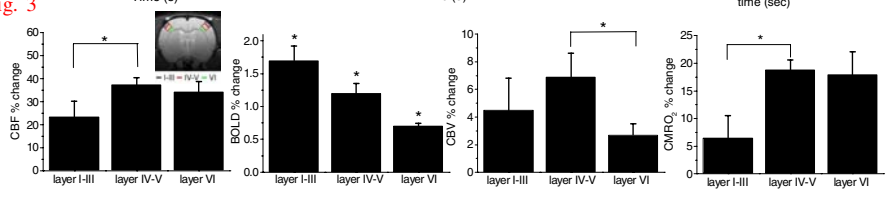

Fig. 4