Mapping the dynamic relationship between cerebral blood flow and BOLD fluctuations: Implications for quantitative fMRI

Aaron Benjamin Simon[1] and Richard Buxton[2]

[1]*Bioengineering, University of California San Diego, La Jolla, CA, United States,* [2]*Radiology, University of California San Diego, La Jolla, CA, United States*

Target Audience: Researchers interested in quantitative analysis of continuously fluctuating BOLD fMRI signals

Purpose: Interpreting BOLD MRI in terms of neural activity is challenging because BOLD contrast is not directly sensitive to neuronal signaling but rather to local hemodynamic and metabolic changes evoked by it. Through multimodal imaging and modeling techniques, progress has been made in quantitatively relating changes in BOLD contrast to local changes in cerebral oxygen metabolism ($CMRO_2$), a parameter that is closer to the underlying neural activity[1,2]. However, in general these techniques are only considered applicable to "steady-state" changes that occur slowly enough that the dynamics of blood flow (CBF), blood volume (CBV), and $CMRO_2$ may be ignored[3]. As interest has grown in studying the spatial and temporal patterns of continuously fluctuating BOLD signals, it has become increasingly important to understand the quantitative relationship between dynamically fluctuating BOLD signals and the underlying physiological processes that generate them. As a first step in probing this relationship, we simultaneously recorded the BOLD and CBF fluctuations in the human visual cortex evoked by a flickering checkerboard with a contrast that oscillated continuously at several different temporal frequencies. We asked whether the change in BOLD signal associated with a particular CBF change depended upon the phase or frequency of the visual stimulus and whether the relationship between CBF and BOLD during the stimulus was consistent with the period before the stimulus began. We hypothesized that differences in the dynamics of the CBF, CBV, and $CMRO_2$ responses to the stimulus would produce phase, frequency, or time dependent shifts in the relationship between the BOLD signal and underlying CBF fluctuations.

Methods: *Imaging:* Ten subjects were imaged. Simultaneous BOLD/CBF-weighted images were acquired using a PICORE QUIPPSII ASL imaging sequence[4] (TR=2s) with a dual-echo spiral readout (TE1=3.3ms, TE2 = 30ms). *Stimulus:* Each subject was presented with five stimuli. First stimulus was a functional localizer designed to activate a region of interest (ROI) in the visual cortex and consisted of an 8Hz, full-field, flickering checkerboard at 100% contrast alternated every 24s with an isoluminescent gray screen. The subsequent four stimulus paradigms each consisted of a 60 second period of gray screen followed by 308s of flickering checkerboards. The dark-light contrast oscillated sinusoidally throughout the 308s stimulus period from 0-100% with a period of 44s, 22s, 11s, or 6.3s. *Analysis:* To produce a BOLD-weighted image series, the 4-D second-echo data set was temporally low-pass filtered with a cut-off frequency of 0.125Hz. To produce a CBF-weighted image series, the first-echo data was first modulated at a frequency of 0.25Hz and then low-pass filtered. ROIs were selected based on supra-threshold responses in BOLD and CBF time series to the functional localizer. Before quantitative analysis, CBF and BOLD responses were averaged across the ROI. The BOLD and CBF responses to each stimulus were then normalized to their respective baselines, defined as the 60s period before the stimulus began.

Results: Figure 1a and figure 1b depict the mean BOLD and CBF responses to the contrast-oscillating stimuli, averaged over all stimulus cycles and subjects. Significant phase lags with respect to the stimulus appear in the BOLD and CBF responses at each frequency; however, no significant phase differences are observable between the BOLD and CBF responses. Figure 1c depicts the trajectories of the responses in the CBF-BOLD plane. The trajectories show little evidence of hysteresis within a stimulus cycle and appear to be independent of the stimulus frequency. However, the trajectories do not appear to include the origin, defined as the mean BOLD and CBF signals before the start of the stimulus, suggesting that the mapping from CBF to BOLD is not consistent between baseline and stimulus periods of the experiment. Figures 2a and 2b depict the 44s-running averages of the BOLD and CBF responses to the stimuli. The black lines show the average responses over all stimulus frequencies. Notable is an early overshoot and slow decay that is much larger in the BOLD than the CBF and observable regardless of the stimulus frequency. Figure 2c shows the running average CBF-BOLD trajectory (black line) as well as the intra-cycle trajectories for each frequency (scattered points). The slow decay in figure 2a produces a shift in the CBF-BOLD mapping function, and all intra-cycle trajectories oscillate similarly around this new steady state.

Discussion and Conclusions: That the mapping from CBF to BOLD signal changes appears to be consistent within a stimulus cycle and across stimulus frequencies but not from the baseline to stimulus periods suggests that the dynamics of $CMRO_2$, CBV, or both may have a significant component that is slow compared to even the lowest frequency stimulus and relatively insensitive to the frequency at which the stimulus is presented. Further work will be required to determine which of these physiological variables is responsible for the observed shift. However, This work does provide evidence that the three physiological variables that primarily influence the BOLD signal, CBF, $CMRO_2$, and CBV, may respond to stimuli on quite different time-scales, suggesting that some caution should be taken when interpreting dynamic BOLD signal fluctuations quantitatively in terms of the underlying physiological response.

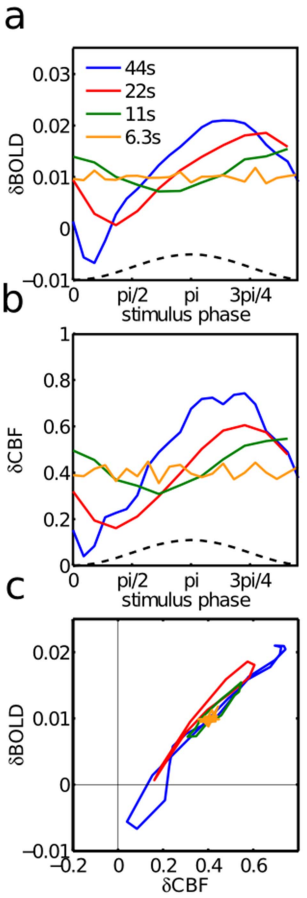

Figure 1: Mean intra-cycle BOLD and CBF responses to contrast-oscillating stimuli.

References:

(1) Davis, T. L., et al. (1998). PNAS. 95(4), 1834–1839.

(2) Griffeth, V. E. M., et al (2011). NeuroImage, 58(1), 198–212.

(3) Buxton, R. B. (2010). Frontiers in Neuroenergetics. doi:10.3389/fnene.2010.00008

(4) Wong, E. C., et al. (1998). MRM. 39(5), 702–708.

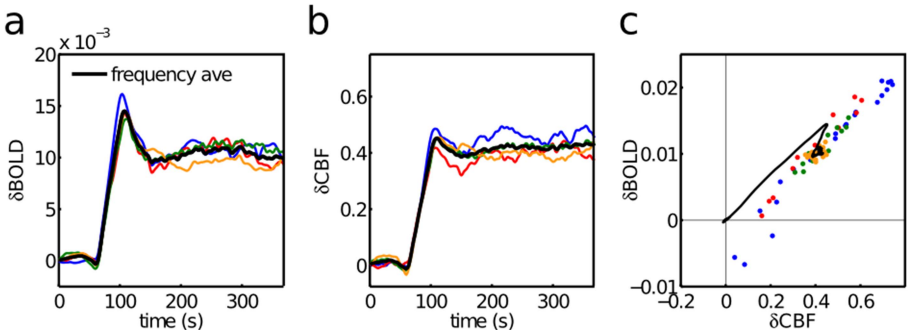

Figure 2: 44s running average of BOLD and CBF responses to contrast-oscillating stimuli.