New model and confirmatory measurement of the BOLD hemodynamic response function

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Introduction. In the brain, neural activity evoked by brief stimulation creates changes in local blood flow (CBF) and oxygen uptake ($CMRO_2$). Functional magnetic resonance imaging (fMRI) can measure this neurovascular coupling as a blood oxygen level dependent (BOLD) signal. The BOLD response to brief stimulation is often termed the hemodynamic response function (HRF). To understand brain physiology, it is critical to understand how CBF and $CMRO_2$ affect the BOLD signal to create the HRF. We measured BOLD responses in human cortical tissue, and developed a novel convection-diffusion model to quantitatively interpret the BOLD signal. Our model successfully fit the measured BOLD HRF response in human visual cortex, and provides estimates of the underlying CBF and $CMRO_2$ time courses. Results show how blood flow and oxygen demand compete with each other to shape the complete time course of the BOLD HRF.

Methods. We measured the BOLD HRF evoked by brief stimulation in 5 subjects. Stimulus was a 2-s presentation of 4-Hz flickering dots followed by a 26-s inter-stimulus interval to let the HRF evolve and subside. High-resolution (0.9-mm sampling) fMRI data was obtained using a 3T GE Signa Excite scanner. Acquisition used a 3-shot spiral trajectory, on 8 slices prescribed on a 90-mm FOV oriented normal to the calcarine sulcus; sampling was 1.5 sec/volume. Each session produced 72—85 HRF measurements that were averaged together through the gray matter in prescribed portions of V1—3 (Fig. 1).

A "vascular unit" for oxygen transport starts with a penetrating arteriole through its associated capillary bed (Fig. 2, dashed region). A one-dimensional cylindrical geometry with three concentric compartments (erythrocyte, plasma, and extravascular) was employed to represent this single stereotypical unit of the microvascular network in cerebral cortex (Fig. 2, right). We used a convection-diffusion transport model including accurate dynamics of hemoglobin oxygen dissociation. The model assumed physiologically reasonable forms for flow and $CMRO_2$ responses. Recent experiment suggested that microvascular vasodilation is initiated proximal to neural activity, and rapidly propagates upstream to the pial arteries creating a pressure fluctuation.[1] A lumped-linear flow model described the flow perturbation produced by this arterial pressure fluctuation. Motivated by experimental findings of fast increases and slow decays in oxygen uptake evoked by neural activation, we simulated $CMRO_2$ perturbations using a linear gamma function kernel.[2,3]

It is often assumed that the BOLD HRF is produced by both blood oxygen and volume changes, but recent experiments indicated that there is no significant change in venous volume for brief stimulation.[4] We therefore assumed a linear relationship between the BOLD signal and oxygen concentration: $\Delta S/S \cong T_E R'_{21} = T_E R'_{2L} (f_c \overline{Q_c} + f_v Q_v)/Q_L$, where R_{2L} = 5.2/s is the relaxation rate for deoxygenated blood, Q_L = 4.6 mmol/L at 4% blood volume fraction. Volumes fraction f_c = 0.65 is the fraction of total blood volume for capillaries (and small arterioles), and f_v = 0.24 for venules. Our model provides time-varying predictions for average capillary oxygen concentration, $\overline{Q_c}$, and venule concentration Q_v.

Results. Useful HRFs were obtained in each visual area independently. We found no significant difference between the three visual areas, so we averaged the responses across them for each subject. Our model provided excellent fits to the observed HRFs (Fig. 3, top) in all subjects. Fits indicated that the $CMRO_2$ response magnitude was ~15%, while the flow increase was 20~30%, in good agreement with previous measurements.[5,6] We observed two different types of HRF response. Subject 1 showed a typical HRF with noticeable initial delay and significant undershoot (Fig. 3, upper left), while subject 2 was a "fast responder" with no initial delay (Fig.3, upper right). The model explains these differences in terms of the relative shapes of the CBF and $CMRO_2$ responses (Fig. 3, lower panels).

Conclusions. We measured BOLD HRFs in human visual cortex using high-resolution fMRI and successfully applied our recent convection-diffusion model to explain and interpret them. The HRF was affected by both the $CMRO_2$ and flow responses, and our model can separate these effects to provide a detailed description of neurovascular and neurometabolic coupling in the brain.

References: [1]Itoh Y et al., JCBFM 2012; 32: 1167-76, [2]Kim JH et al., JCBFM 2013; 33: 1429-39, [3]Ress D et al., Front. Neuroenerg. 2009; 1(3): 1-13, [4]Drew PJ et al., PNAS USA 2011; 108: 8473-8, [5]Feng CM et al., Neuroimage 2004; 22:445-6, [6]Hua J et al., JCBFM 2005; 25:371-7

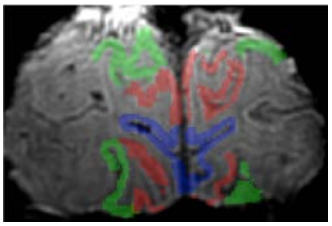

Fig. 1: T2* weighted image with ROIs, blue: V1, red: V2, and green: V3

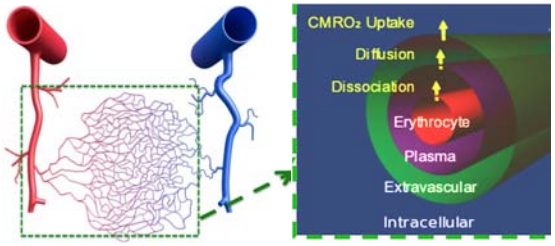

Fig. 2: Left: Schematic of a cortical vascular unit, Right: compartmental representation of O_2 transport in the whole of the microvasculature[1].

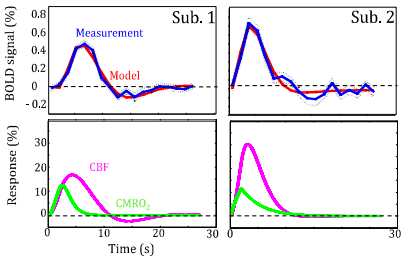

Fig. 3: Top: HRF measurements and model fits; bottom: predicted flow and $CMRO_2$ responses.