Evidence for a cerebral blood flow post-stimulus undershoot contributing to the BOLD undershoot

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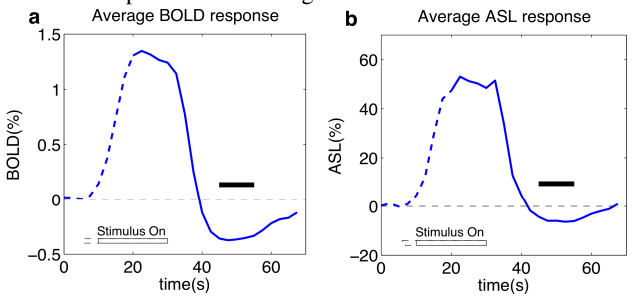
Target audience: Researchers interested in dynamic aspects of BOLD fMRI signals and the BOLD post-stimulus undershoot.

Purpose: In their seminal 1992 paper demonstrating functional MRI based on the BOLD response, Kwong and colleagues[1] noted a post-stimulus undershoot of the BOLD signal. Despite a number of experimental and theoretical studies exploring this phenomenon over the intervening years, there is still no consensus on its origin. Broadly speaking, the undershoot could have a neural, vascular, or metabolic origin, or some combination thereof. Except for one study[2], previous research has not found a significant cerebral blood flow (CBF) undershoot corresponding to the BOLD post-stimulus undershoot[3-6], so two alternative possibilities are usually considered: a slower return of either the cerebral metabolic rate of oxygen ($CMRO_2$)[4,5] or venous cerebral blood volume (CBV)[6,7]. These experiments have shown mixed results. The original motivation for the CBV explanation—the balloon model[6] and the windkessel model[7]—was the observation of a slow recovery of CBV in rats using an intravascular iron agent (MION) during the post-stimulus BOLD undershoot[8]. More recently however, studies with a different method for detecting CBV changes (VASO) concluded that CBV recovered quickly and used this as indirect evidence that $CMRO_2$ recovered more slowly[9]. This lack of a satisfying explanation brings into question the earlier assumption that there is not a CBF undershoot. CBF is a much noisier signal than BOLD so detecting a small undershoot sufficient to produce the BOLD undershoot is difficult. Here we used data from multiple studies to show there is a significant CBF undershoot that could explain the BOLD undershoot.

Methods: Data from four previously published experiments measuring the visual cortex response to variations in a flickering radial checkerboard stimulus were assembled and identified with the following names: caffeine[10], contrast[11], mixed stimulus[12], and blob[13]. All data were acquired using a 3T whole body system, an eight-channel receive head coil, and a single shot PICORE QUIPSS II (Wong et al., 1998) pulse sequence for quantitative arterial spin labeling (ASL) and BOLD-weighted images. Imaging parameters can be found in the noted publications with the exception of the mixed stimulus (TR=2.5s, TI_1=700ms, TI_2=1500ms, TE_1=9.1ms, TE_2=30ms). As in Perthen et al.[10], TE_1 tag-control signal differences were calculated for ASL (typically equivalent to CBF) and TE_2 signals were used to calculate the BOLD signal change. Stimuli were generally variations on an 8Hz flickering radial checkerboard: 100% contrast in the caffeine (20 scans total), 100% contrast from the contrast (9 scans total), 40% contrast from the mixed stimulus (28 scans total) and either black/white or red/green 100% contrast from the blob study (14 scans total). Since the blob data was acquired using TR=2s, it was resampled to 2.5s in Matlab to be consistent with the other 3 experiments. Single cycle averages 28 time points in length (corresponding to 67.5s) were calculated for subjects in each experiment such that the 13th time point of the time series corresponded to the stimulus turning off in all cases (see figure). Undershoot averages were calculated using five time points (solid black bar) corresponding to the maximum negative BOLD response average (from 15s to 25s after the stimulus turned off).

Alternative explanations for ASL undershoot: It is possible oxygen desaturation of the arteriolar vessels could play a role in any undershoot of the ASL signal by altering the signal of tagged blood. To test how big an effect this might be, we took two approaches: (1) calculated the ΔR_2^* necessary to produce the ASL undershoot measured with TE_1=9.3ms[13] using $\Delta S = e^{-TE^*\Delta R_2^*}$ and related this to an O_2 saturation change using empirical data[14] and (2) determined whether this O_2 saturation change is reasonable using as a limit the effect on saturation of the prolonged $\Delta CMRO_2$ necessary to produce the measured BOLD undershoot. To approximate the effect of $\Delta CMRO_2$ on BOLD, we used the optimized Davis model ($BOLD = M(1 - f^{\alpha-\beta} r^{\beta})$ where f and r are the normalized CBF and $CMRO_2$ changes respectively[15]. The scaling parameter (M) was approximated assuming a fixed response relationship of $\Delta CBF/\Delta CMRO_2$=2.5. BOLD and CBF stimulus responses were averaged over the last 10s of stimulus.

Results: The post-stimulus BOLD undershoot was -0.36±0.02% (p<0.005) and the ASL signal undershoot was -5.7±1.0% (p<0.005). To test the effect of a prolonged $CMRO_2$ response on desaturation of the arterioles, we first determined ΔR_2^*=6.3s^{-1} is necessary to produce a 5.7% decrease in the ASL signal. According to empirical data from Zhao et al.[14] a desaturation to 79% would be required for such a signal decrease (assuming starting O_2 sat of 90%). We then approximated the sustained $\Delta CMRO_2$ necessary for a BOLD undershoot of -0.4%. The BOLD stimulus response (1.30%) and CBF response (50.1%) were first used to approximate M (9.1%) was approximated assuming $\Delta CBF/\Delta CMRO_2$=2.5 with BOLD=1.3% and CBF=50%. From this, a sustained $\Delta CMRO_2$=5% (assuming CBF and CBV have returned to baseline) was found to produce a BOLD undershoot of -0.42%. This change in $CMRO_2$ will produce a 5% increase in the oxygen extraction fraction (OEF) and a 2% decrease in oxygen saturation in the venules assuming a baseline OEF of 0.4. Using the same signal equation, a 2% arteriolar saturation change (from 90% to 88%) would only produce a ΔR_2^*=0.75s^{-1}, which is large enough to explain only a -0.7% ASL signal decrease (12% of our finding). A similar approach using the Davis model can be employed to approximate the BOLD signal effect of a -5.7% CBF undershoot, which again using M=9.1% results in a BOLD undershoot of -0.43%.



Discussion and Conclusions: There is a significant (p<0.005) post-stimulus undershoot of the ASL signaling. Modeling potential artifacts in which the BOLD signal contaminates the ASL signal indicates that such an artifact is expected to be more than 5x weaker than the observed effect. Modeling also confirms that the observed CBF undershoot of -5.7% is able to produce a BOLD undershoot of -0.43%, consistent with the data. In summary, combining data across 4 visual stimulation studies (41 subjects, 392 stimulus cycles) shows that the BOLD post-stimulus undershoot can be fully explained by the CBF undershoot, without requiring a slow recovery of $CMRO_2$ or venous CBV. The physiological origins and implications of this CBF undershoot require further study.

[1]Kwong et al., PNAS 1992; [2]Chen and Pike, NIMG 2009; [3]Davis et al., SMR 1994; [4]Frahm et al., MRM 1996; [5]Kruger et al., MRM 1996; [6]Buxton et al., MRM 1998; [7]Mandeville et al., JCBFM 1999; [8]Mandeville et al., MRM 1998; [9]Lu et al., JCBFM 2004; [10]Perthen et al., NIMG 2008; [11]Liang et al., NIMG 2012; [12]Griffeth and Buxton, ISMRM 2011; [13]Leontiev et al., NIMG 2012; [14]Zhao et al., MRM 2007; [15]Griffeth and Buxton, NIMG 2011