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 (MRI) signals and the BOLD post-stimulus undershoot.

Purpose: In their seminal 1992 paper demonstrating functional MRI based on the BOLD response, Kwong and colleagues1 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 study2, previous research has not found a significant cerebral blood flow (CBF) undershoot corresponding to the BOLD post-stimulus undershoot3,4, so two alternative possibilities are usually considered: a slower recovery of either the cerebral metabolic rate of oxygen (CMRO2)5-7 or venous cerebral blood volume (CBV)5,7. These experiments have shown mixed results. The original motivation for the CBV explanation—the balloon model8 and the windkessel model9—was the observation of a slow recovery of CBV in rats using an intravascular iron agent (MIoN) during the post-stimulus BOLD undershoot10. 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 CMRO2 recovered more slowly3. 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: caffeine10, contrast11, mixed stimulus12, and blob13. All data were acquired using a 3T whole body system, an eight-channel receive head coil, and a single shot PICORE QUIPS 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=2s, TI1=700ms, TI2=1500ms, TE1=9.1ms, TE2=30ms). As in Perthen et al.10, TE1 tag-control signal differences were calculated for ASL (typically equivalent to CBF) and TE2 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 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 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). 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 mixed stimulus (28 scans total) and either black/white or red/green 100% contrast from the blob study (14 scans total).

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 CMRO2 response on desaturation of the arterioles, we first determined ΔR2* necessary to produce the ASL undershoot measured with TE1=9.3ms using ΔS=ΔTE1ΔR2* and related this to an O2 saturation change using empirical data of (from 13s 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 ΔR2* necessary to produce the ASL undershoot measured with TE1=9.3ms using ΔS=ΔTE1ΔR2* and related this to an O2 saturation change using empirical data14 and (2) determined whether this O2 saturation change is reasonable using as a limit the effect on saturation of the prolonged ΔCMRO2 necessary to produce the measured BOLD undershoot. To approximate the effect of ΔCMRO2 on BOLD, we used the optimized Davis model (BOLD=M(1-fα,β,M)) where f and r are the normalized CBF and CMRO2 changes respectively15. The scaling parameter (M) was approximated assuming a fixed response relationship of ΔCBF/ΔCMRO2=2.5. BOLD and CBF stimulus responses were averaged over the last 10s of stimulus.

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 CMRO2 or venous CBV. The physiological origins and implications of this CBF undershoot require further study.