

From Two-Photon Microscopy to BOLD-fMRI: Association of an Undershoot of Arteriolar Diameter with the BOLD Post-Stimulus Undershoot

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Purpose: The primary source of the BOLD response is the change in the oxygenation of blood due to mismatched changes in cerebral blood flow (CBF) and cerebral metabolic rate of O₂ (CMRO₂) following neuronal activation. However, a full interpretation of the dynamics of the BOLD response is complicated by the possibility of additional transient vascular changes, such as a slow recovery of cerebral blood volume (CBV) [1,2] that could alter the BOLD signal in a way that is not described by the dynamics of CBF and CMRO₂ alone. The primary area of controversy in this regard has been the BOLD post-stimulus undershoot, which could be: 1) a neural effect, with coupled CBF and CMRO₂ changes; 2) a metabolic effect, with a slow recovery of CMRO₂ relative to CBF [3,4]; or 3) a vascular effect, with a slow recovery of cerebral blood volume (CBV) relative to CBF. To test directly whether vascular dynamics are evident during the post-stimulus undershoot, we performed BOLD-fMRI and 2-photon microscopic dynamic vascular diameter measurements under the same conditions in rat primary somatosensory cortex (SI).

Methods: BOLD-fMRI experiments were done at 7T on a horizontal bore animal scanner (BioSpec, Bruker) using a GRE EPI technique with the following parameters: TE=10msec, FOV=2x4cm, flip angle=30°, in-plane resolution =250x500 μm, matrix=80x80, slice thickness=1 mm, TR=1 sec, 5 adjacent slices. The images were collected in coronal orientation with a 10-mm diameter transmit/receive surface RF coil. **Figure A/B** shows an example BOLD activation map and signal time-course from the forepaw region of SI in response to a weak electrical forepaw stimulus (20 sec at 3 Hz), exhibiting a pronounced post-stimulus undershoot. Two-photon measurements (**Figure C**) of single-vessel diameter and red blood cell (RBC) velocity changes were measured across vascular compartments (arteries, capillaries and veins) and the cortical depth (down to 500 μm) in a separate group of animals under the same stimulus conditions.

Results: Our results show no evidence for swelling of the venous vessels at any measured cortical depth (**Figure D**). Venous RBC velocity, on the other hand, increased by up to 50% from the baseline. On the arterial side, the temporal profile of the diameter change of surface and diving arterioles resembled that of the BOLD signal (**Figure D**). Specifically, we observed a decrease below baseline and slow return to baseline of the arteriolar diameter after the end of the stimulus.

Discussion and Conclusions: Although the origins of the BOLD post-stimulus undershoot have been debated since the early days of fMRI, there is still no consensus on whether it is a neural, metabolic or vascular effect, and experimental evidence has been presented for each interpretation. There is currently no clear way to reconcile these data with a single explanation, and conceivably each mechanism could contribute under different circumstances. Our current results for the rat forepaw stimulation model do not support a ballooning and slow recovery of venous CBV. However, they do show a reduction of arteriolar diameter and thus a vascular involvement during the BOLD post-stimulus undershoot, and so they also do not support the slow recovery of CMRO₂ with a fast recovery of CBF. Instead, these results suggest an extended vascular response, possibly with a CBF reduction during the BOLD undershoot, which could be due to a reduction in neural activity with a coupled CBF response or to a slowly recovering rebound of the vascular response. An important implication of the absence of CBF/CBV uncoupling is the potential to measure the dynamics of CMRO₂—which is currently not possible—from the measured dynamics of the CBF and BOLD responses analyzed in the context of an appropriate quantitative model of the BOLD response.

