The Spatial Dependence of the Post-Stimulus Undershoot as Revealed by High Resolution BOLD and CBV Weighted fMRI

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Introduction:

Increases in neural activity in the brain are followed by increases in cerebral blood flow (CBF), blood volume (CBV) and oxygen metabolism (CMRO2). These changes are detectable with the BOLD fMRI technique which is sensitive to any changes in the concentrations of paramagnetic deoxy-hemoglobin. The temporal dynamics of these vascular changes have been investigated experimentally and theoretically modeled. It has been suggested previously (1) that changes in CBV are slower both at the onset of the stimulus and the return to baseline once the stimulus is turned off. In addition, when the stimulus is off, there is an uncoupling between CBF and CBV, with the CBF returning to baseline more quickly. This mechanism, via the Balloon model (2), and *not* any sustained increases in CMRO2, which were not observed (3), was used to explain the post-stimulus undershoot in the BOLD signal. A more recent study (4) showed evidence for sustained increases in CMRO2 after the vascular response had fully recovered to baseline. These data suggest that the post-stimulus undershoot in the BOLD signal should be attributed to oxygen metabolism, and *not* delayed CBV changes, which were shown to return to baseline relatively quickly. This result suggests an uncoupling between energy metabolism and CBF. These seemingly contradictory findings serve as motivation for this work. In our study, we investigate the *spatial-temporal* dynamics of CBV and the BOLD response, using a high spatial resolution cat model at 9.4 T, in hopes of shedding light on the *apparent* discrepancies in the literature.

Methods:

Cats (n=4) were kept under isoflurane anesthesia throughout the experiment (1% in a N_2O:O_2 mixture of 70:30). Blood pressure, end-tidal CO_2 and body temperature were maintained at normal conditions. Visual stimuli consisted of binocular 40-s high-contrast square-wave moving gratings (0.15 cyc/deg, 2 cyc/s). All MR experiments were performed on a 9.4T/31cm (Oxford, UK) magnet. A 1.4-cm diameter transmit and receive surface coil was used. A coronal slice perpendicular to area 18 (crossing at Horsley-Clark AP2) was used for the functional study. Anatomic images were obtained using T1-weighted 2D TurboFLASH and a T1-weighted 3D GEMS sequence with a matrix size of 128 x 128 x 128 over a field of view of 5 x 5 x 5 cm^3. The GE BOLD response and GE CBV-weighted changes, following a bolus injection of MION (10mg Fe/kg), were both measured. Image parameters were: Data matrix = 128 x 128, 4 segment EPI, field of view= 1.92x1.92 cm^2. Slice thickness = 2 mm and TE/TR = 20ms (10ms with MION) /1 s. The scan time for 1 image was 4 s and the in plane resolution was 150 x 150 μm^2. Following the MR session, a 3mm cortical slab corresponding to the imaged plan was extracted and sectioned with a 15µm slice thickness with a cryostat and was stained with cresyl violet (Nissl) (5). The borders between layers were determined based on cytoarchitectonic criteria such as cell types, size and density. Functional time courses were generated by selecting ROIs in the tissue areas as well as in the surface vessel areas and averaged over all cats.

Results:

Figure 1 shows the temporal profiles (normalized) of BOLD and CBV-weighted signals changes as a function of spatial location. Tissue areas (layer 4 as determined by histology) contain mainly small vessels/capillaries; Vessel areas contain mainly large surface vessels. Focusing on the post-stimulus period, the BOLD response showed the commonly observed post-stimulus undershoot, similarly in both the tissue and large vessel areas, despite a larger positive BOLD signal observed in the vessel areas compared to the tissue areas. In contrast, CBV temporal profiles were more spatially dependent. In the tissue region, a sustained response is observed after the stimulus is turned off whereas the CBV response in the large vessel areas returns to baseline almost immediately after the stimulus is turned off.

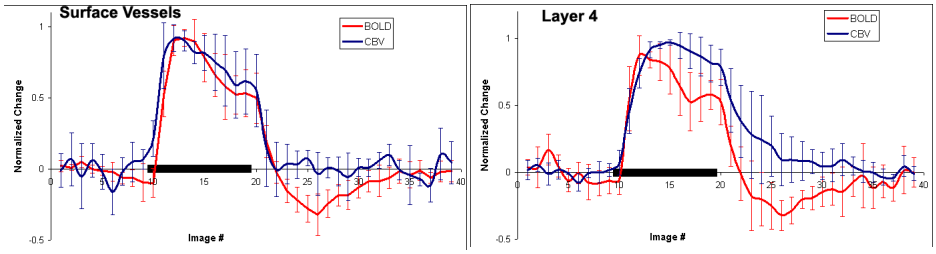

Fig.1 Average time courses of percent change from 4 cats in layer 4 and large vessel areas from both GE BOLD and GE CBV weighted MION data. The black box indicates the stimulus.

Conclusions: Our findings suggest that there is a spatial dependence of the post-stimulus undershoot. In the tissue, the post-stimulus undershoot must be in part explained by the sustained and elevated CBV response, however, there still may be contributions from elevated CMRO2 levels. In the vessel areas the data suggests that the undershoot must come from either sustained CMRO2 effects in the tissue which *drain* into the vessels, and/or decreases in CBF (without significant changes in CBV). If we assume that the vascular mechanisms controlling the *positive* BOLD response are the same for both the tissue and vessel areas, and that *different* mechanisms regulate the BOLD *undershoot* (i.e. tissue: CBF, CBV, CMRO2, and vessel: CBF, CMRO2 (draining effects)) than the ratio between the positive BOLD responses (1.96) and the magnitude of the undershoot BOLD responses (1.69) should be different, as they are. Changes in CBV, CBF, and CMRO2 are all possible mechanisms of the post-stimulus undershoot; however, the relative contribution of each to the BOLD signal is heavily spatial dependent.

References: **1**. *Mandeville et al 1998* **2.** *Buxton et al 1998* **3.** *Mandeville et al 1999* **4.** *Lu et al 2004* **5.** *Harel et al., 2004*

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