Spatiotemporal Dynamics of BOLD and CBV responses at submillimeter columnar resolution

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[Introduction] To understand the vascular source of functional signals which are specific to neuronal activity, it is critical to examine spatiotemporal characteristics. In previous intrinsic optical imaging studies in animal models(1,2), it was found that the early 2-3 sec hemodynamic response (CBV and deoxyhemoglobin) is more specific to neuronal active sites than the later response, indicating that hemodynamic response is initiated at neurally active sites and spread at a later time. However, high-resolution fMRI studies have typically used the averaged data acquired during a steady-state condition induced by long stimulation duration, due to its poor sensitivity and temporal resolution (3-5). Therefore it is important to characterize spatiotemporal responses of both specific and non-specific signals in commonly-used fMRI protocols at submillimeter-scale resolution. For this, we used a well-established cat orientation column model, in which orientation-selective columns (e.g., 0°) neuronally respond during preferred orientation stimulation (e.g., 0°), not for orthogonal orientation stimulation (e.g., 90°), and. an average inter-iso-orientation column distance is 1.2-1.4 mm.

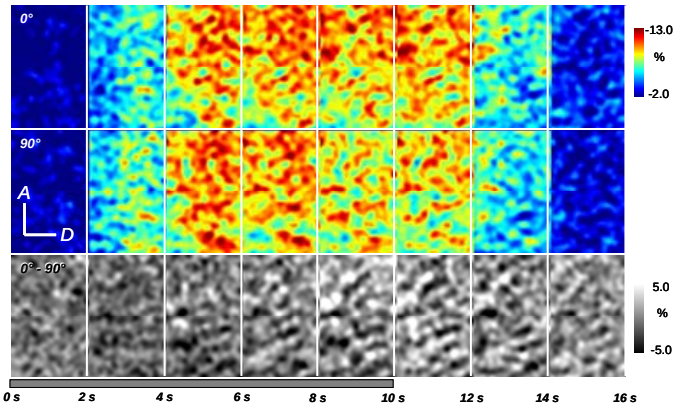

Fig. 1. Spatiotemporal responses of CBV-weighted fMRI signals. Time-dependent percent change maps responding to 0° and 90° stimulation were shown in top two panels. The bottom panel: subtraction maps (0° - 90° maps). The black pixels indicate higher signal changes during 0° stimulation. 10-s stimulation period is shown in bottom.

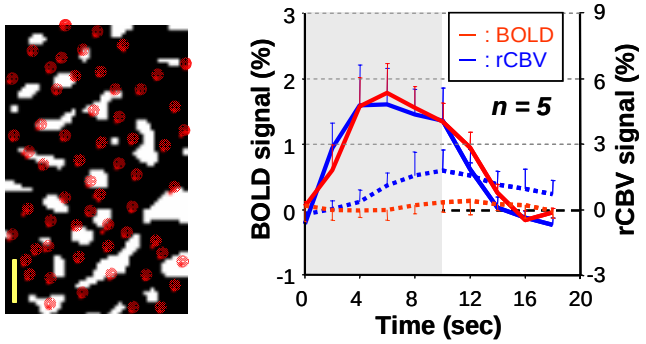

Fig 2. Time-courses of BOLD and CBV fMRI responses in 0° orientation-specific activation ROI (white patches in the left image). Red circles indicate intracortical veins. Solid timecourses indicate non-specific signal (e.g., 90° stimulation response in 0° columns), while dashed traces are orientation-selective signals. Relative CBV changes were calculated, instead of CBV-weighted changes Hatched area: stimulation duration; error bars: SD; scale bar: 2 mm.

[Methods] Five cats were used for both gradient-echo BOLD and CBV-weighted fMRI studies. All MR experiments were performed on a 9.4 T system (Varian) using a surface coil positioned over cat's primary visual cortex. All experimental protocols were described in details previously (4-5). In short, the position of the 1 mm-thick functional imaging slice was determined based on a 3-D venogram. High-resolution fMRI images were obtained using the four-shot EPI technique with data matrix = 128 × 128, FOV = 2 × 2 cm^2, and resolution = 156 × 156 × 1000 μm^3: *i*) GE BOLD fMRI with TR = 2.0 s and TE = 18 ms, and *ii*) CBV-weighted fMRI with TR = 2.0 s and TE = 10 ms following an intravascular bolus injection of a dextran-coated iron oxide contrast agent (MION dose of 10 - 20 mg Fe /kg body weight). EPI images were acquired before and after MION injection for the calculation of baseline R_2* change.

Block-design stimulation was used for obtaining spatiotemporal dynamics of BOLD and CBV responses; four orientations (0°, 45°, 90° and 135° each 10 s) alternated with 10-s homogeneous gray screen for 80 s, and this one cycle was repeated with 10 times over total of 800 s. Additionally, after MION injection, continuous stimulation was used for iso-orientation mapping as a reference for mapping orientation columns; eight consecutive orientations (0° to 157.5° with 22.5° step and 10 s each) were repeated as 10 times (or cycles) without gaps between different stimuli. Average repetitions of block-design BOLD and CBV studies were 5 and 5.2, respectively.

The single-condition map was obtained by subtracting an average of 4-s pre-stimulus baseline images from image *at every 2-s time point* from 0 to 18 s for each orientation stimulus (i.e., 0°, 45°, 90°, and 135°), and then by normalized with the corresponding baseline image. Differential spatiotemporal dynamic maps were determined by subtracting single-condition maps obtained from two orthogonal stimuli at every 2-s time point (0° - 90° or 45° - 135°). To obtain orientation-specific maps, Fourier analysis was used for continuous and block-design stimulation data.

[Results and Conclusion] BOLD signal responses are widespread in the visual cortical area, and the highest signal changes are located at intracortical veins, which appear as dark pixels in venographic images (data not shown). This observation is not surprising and consistent with our previous observation (5). The differential images between 0° and 90° single-condition BOLD maps are very noisy, and do not show any patchy patterns. On the contrary, the highest CBV-weighted fMRI responses did not match with visible intracortical vessels. Hot spots corresponding to 0° stimulation do not co-register with those responding to 90° stimulation (see red pixels in Fig. 1), indicating that CBV responses are relatively specific to neuronal activity. During 10-s stimulation, CBV-weighted fMRI signals peaked at 4-8 s after the onset of stimulation. Since both orientation-specific and non-specific components were included in single-condition maps, the orientation-specific signals were obtained from the differential map (see Fig. 1 bottom panel). Orientation-specific signals increase at a later time point in the 10-s stimulation period, and even sustain 2-4 s after the cessation of stimulation. In order to quantify these qualitative observations, the 0° column ROI (white pixels in Fig. 2) was obtained from the continuous stimulation data set. Then, orientation-specific (dashed traces) and non-specific responses (solid traces) of BOLD and CBV fMRI were obtained (Fig. 2). Clearly, in BOLD, the non-specific response is dominant. Unlike the expectation from optical imaging studies (1-2), dynamics of orientation-specific CBV responses is slower than non-specific CBV and BOLD signals. The slow specific CBV component may be originated from small pre-capillary arterioles, capillaries, and small post-capillary venules, while fast non-specific signal is likely occurring in intacortical and small branching arterioles.

To quantify the spatial specificity of CBV signals, the ratio of orientation-specific to non-specific CBV-weighted signals were calculated; 0.07 ± 0.18 and 0.60 ± 0.17 at 4 and 10 sec, respectively (n = 5). In accordance with these observations, orientation-specific CBV-weighted activation became much clearer at the end of stimulation (i.e. 8 – 12 s with 10-s stimulation duration, see Fig. 1). These results suggest that the late time part of CBV-weighted response suits for detecting spatially localized CBV response to the sites of increased neural activity.

[Reference] 1. Malonek & Grinvald, Science, 272, 551, 1996;. 2. Shetz et al., *J Neurosci*, 24, 634, 2004; 3. Zhao et al., *Neuroimage*, 27, 4126, 2005; 4. Fukuda et al. *J Neurosci*, 26, 11821, 2007; 5. Moon, C.H. et al., *J Neurosci* 27:6892, 2007.

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