Spatial specificity of post-stimulus BOLD undershoot signal

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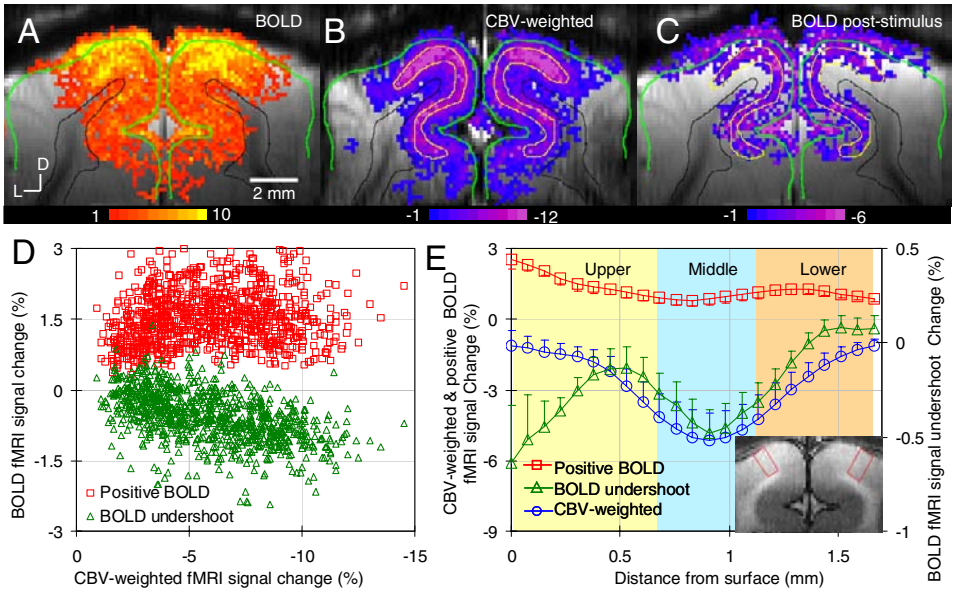
INTRODUCTION

The negative blood oxygenation level dependent (BOLD) signal following the cessation of stimulation (post-stimulus BOLD undershoot) has been commonly observed [1-6]. However, its spatial specificity is unknown and its physiological source remains controversial [5, 7]. To further understand the post-stimulus BOLD undershoot signal and its potential feasibility to be used as a mapping signal, high-resolution fMRI in response to visual stimulus was obtained in isoflurane-anesthetized cats at 9.4T using conventional gradient-echo (GE) techniques; BOLD and cerebral blood volume (CBV)-weighted data were acquired without and with injection of monocrystalline iron oxide nanoparticles (MION), respectively. CBV-weighted fMRI map was used as a criterion to decide the spatial specificity of the BOLD signals. TE-dependent study of post-stimulus BOLD undershoot was performed to understand its MR property.

METHOD

Cats (n = 10) were maintained under ~1.3% isoflurane. Blood pressure, arterial blood gases, end-tidal CO2 and rectal temperature were kept within normal ranges. NMR measurements were performed on a 9.4T/31cm system (Varian) with a 1.6-cm diameter surface coil. A single 2-mm thick imaging slice was selected perpendicular to the surface of the visual cortex in area 18. To measure the spatial specificity of the mapping signals, images with 128×128 matrix size and FOV of 2×2 cm^2 were obtained using the 4-segmented EPI technique. Data was obtained before (BOLD fMRI) and after (CBV-weighted fMRI) the injection of 10 mg/kg MION. Gradient echo times were optimized for each experiment; 20 ms for BOLD fMRI and 10 ms for CBV-weighted fMRI. Each run consisted of 10 – **10** – 10 image acquisitions (boldface represents stimulation on) with TR = 4 s. For TE-dependent study, images with matrix size of 64 × 64 and FOV of 2×2 cm^2 were obtained using the single shot GE EPI technique. BOLD fMRI data were acquired with interleaved TE of 10, 15, 20 and 25 ms. Each run consisted of 30 – **30** – 60 image acquisitions with TR = 2 s. At each study, 10 to 20 runs were repeated for signal averaging. Binocular visual stimuli consisted of drifting high-contrast square-wave gratings. Images acquired during the 8-40 sec after onset of visual stimulation were used for obtaining positive BOLD and CBV-weighted fMRI maps, while the images acquired during 8-36 sec after cessation of stimulation were used to calculate the post-stimulus BOLD undershoot maps. Quantitative analysis was performed on pixels with t-value ≥2 and active cluster size ≥ 4. For cortical depth-specific signal analysis, two quadrangular sections in area 18 within the visual cortex (red ROIs in inset of Fig E) were selected, and pixel values along lines perpendicular to the dorsal surface were determined without using any statistical threshold. Averaged signals across cortical layers were plotted as a function of distance from the surface of the cortex.

RESULTS AND DISCUSSION



Figs. show visual stimulation-induced positive BOLD (**A**), CBV-weighted (**B**) and post-stimulus BOLD undershoot (**C**) *t*-value maps of one representative animal. The highest CBV change areas in both hemispheres (**B**) were outlined by yellow contours, and then overlaid on the post-stimulus BOLD undershoot map (**C**). Peaks of post-stimulus BOLD undershoot within parenchyma and CBV responses are co-localized to the middle cortical area. The high post-stimulus BOLD signal change is also detected within the cortical surface where the large draining vein located (**C**), indicating an increase in deoxyhemoglobin content after the cessation of the stimulus. To determine the relationship between CBV and post-stimulus BOLD undershoot signals, common active pixels were chosen within the parenchyma (indicated by green contours). Then, pixel-wise percent signal changes were plotted in Fig. D. A strong positive correlation exists between post-stimulation BOLD undershoot and CBV-weighted fMRI signal changes (green triangle, r=0.50; 0.31 ± 0.11, n = 5). This indicates that the spatial specificity of post-stimulus BOLD undershoot and CBV-weighted fMRI signals are similar within the parenchyma. However, for the BOLD signal changes vs. CBV-weighted fMRI signal changes (red square in **D**), the correlation is weak (r=0.10; –0.02 ± 0.07, n = 5), indicating the spatial characteristics of BOLD and CBV-weighted fMRI signal are different. Fig. **E** shows average cortical depth dependent profiles of fMRI signals. One profile was generated for each animal from the quadrangular ROIs in area 18 (e.g., two red quadrangular ROIs in inset image), then data was averaged across all five animals. The surface of the cortex is at zero, with cortical depth represented by increasing distances. Approximate location of cortical layers was determined by relative distances of those layers in area 18 [8] and is differentiated by colored bands. Changes in both CBV-weighted fMRI (blue circles) and post-stimulus BOLD undershoot (green triangles) peak at middle cortical layer. From TE-dependent BOLD fMRI study, R_2* change and intercept were calculated by linear fitting of multi-TE data. The averaged R_2* value is 0.31 ± 0.06 s^{-1} (n=5) for positive BOLD signal and –0.26 ± 0.07 s^{-1} for post-stimulus BOLD undershoot, which are not significantly different (p=0.37). The averaged intercept is 0.32 ± 0.13 % (n=5) for positive BOLD signal, but –0.07 ± 0.04 % for post-stimulus BOLD undershoot. The intercept for post-stimulus BOLD undershoot is significantly smaller than that of positive BOLD (p<0.01). Since the intercept is likely due to intravascular signal contributions including inflow effect, the close to zero intercept indicates minimal inflow effects. The major finding in this study is that the post-stimulus BOLD undershoot can be detected in cat visual cortex by using the 40 sec and 60 sec stimulation. The location of the highest signal changes of both post-stimulus BOLD undershoot and CBV-weighted fMRI within parenchyma are in the middle cortex, indicating that the post-stimulus BOLD undershoot is as specific as the CBV-weighted fMRI to the site of neuronal activity. The post-stimulus BOLD undershoot is more likely caused by an increase in blood deoxyhemoglobin content which is most likely induced by the post-stimulus elevated CMRO2. Since the post-stimulus BOLD undershoot has been often observed in human fMRI studies, it is feasible to use the post-stimulus BOLD undershoot for high-resolution fMRI studies.

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