fMRI Impulse Response for BOLD and CBV Contrast in Rat Somatosensory Cortex

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Introduction: The contrast mechanism in BOLD fMRI is the result of several vascular processes with different timescales. These include vascular dilatation following a neuro-vascular stimulus, the ensuing blood flow response, and the transit of a bolus with reduced deoxyhemoglobin concentration across the local cerebral vasculature, from the arterial side to the venous side. Therefore, the temporal resolution of BOLD fMRI is limited by the combination of such processes, adding up to around 3-6 s full width at half maximum (FWHM) in humans. In BOLD fMRI experiments that suppress the macrovascular contribution, the resolution can be improved to 3-4 s FWHM [3]. Previously, it had been shown in rat primary somatosensory cortex that significant BOLD changes happen within 600 ms in the middle layers of the cortex [1] and that the perfusion response occurs significantly faster than the BOLD response [2]. The purpose of the present work is to investigate the impulse response for BOLD and cerebral blood volume (CBV) in rats and in particular to see if the reduced vascular transit times in rats result in further improved temporal resolution as compared to humans.

Materials and Methods: Adult male Sprague-Dawley rats (196 ± 34 g, n=8) were initially anesthetized with isoflurane and orally intubated. Arterial and venous femoral catheters were inserted for sampling of blood gases and injection of drugs. A pair of needle electrodes was inserted into each forelimb. The animals were placed on a stereotaxic, MR compatible head holder comprising ear pieces and a bite bar to prevent head movement. Continuous physiological monitoring was employed, including expired end-tidal CO2, rectal temperature, and blood pressure. Blood gases were measured at regular intervals and maintained at normal levels. Anesthesia was switched to a continuous α-chloralose infusion [1].

Functional MRI experiments were performed at an 11.7 T/31cm horizontal magnet (Magnex Scientific, Ltd., Abingdon, UK) interfaced to a Biospec-Avance console (Bruker-Biospin, Corp, Billerica, MA), and equipped with a 9 cm gradient set capable of providing 450 mT/m within 75 μs rise-time. BOLD (n=7) and CBV (n=5, subset) fMRI was performed using a gradient-recalled echo (GRE) echo-planar-imaging (EPI) sequence with the following parameters; FOV: 25.6 x 12.8 mm^2, matrix = 96 x 48, slice thickness = 1 mm, nominal resolution 300 x 300 x 1000 μm^3, acquisition bandwidth 333 KHz, TE = 16 or 20 ms for BOLD and TE = 9.1 or 20 ms for CBV, TR = 500 ms or 1000 ms. To allow estimation of the fMRI impulse response (IR) width, bilateral electrical stimulation of the forelimbs (333 μs pulses, 2 mA amplitude) was performed using a pseudo-random stimulus M-sequence [4], synchronized with the scanner, and controlled from a PC running *Presentation* stimulus software (Neurobehavioral Systems, Inc., Albany, CA). The M-sequence base-period was 500ms or 1000ms long, with active stimuli consisting of 2 or 3 electrical pulses respectively with 250 or 330ms separation respectively. The M-sequence (255 bins long) was repeated twice, and the total time for each run (including additional start and tail periods) was 300 or 600s. Two runs were performed each for BOLD and CBV fMRI. For CBV fMRI, 20 mg/kg of iron oxide were injected intravenously to the animal 5 minutes before commencing the CBV studies.

IR analysis was performed by correlation analysis [4]. Activated areas were determined by thresholding the first order kernel amplitude normalized to temporal noise level [4]. In activated pixels, FWHM and time-to-peak of the first order response were estimated after 5-10 fold temporal interpolation.

Results and Discussion: All BOLD and 3 of the CBV fMRI studies showed substantial activation (2 CBV studies were technical failures). An example of a combined BOLD-CBV study is shown in Fig. 1. Regions of activation were significantly larger in BOLD (Fig. 1, left column), than in CBV (right column), indicating the presence of large draining veins. A substantial spread in BOLD FWHM (Fig. 1, middle row) and TTP (Fig. 1, bottom row) over the activated area was observed, with the responses showing a longer delay in large pial veins. This effect was much reduced in the CBV data, which are presumed to have less contamination from larger draining veins [5].

Figure 2 shows typical BOLD and CBV fMRI impulse responses derived from the M-sequence. It is easy to notice from the plot that the CBV IR is narrower and peaks earlier than the BOLD IR. Interestingly, the CBV IR does not return to baseline for a long time, consistently with other CBV-based fMRI studies in rats [6]. Averaged over all studies, BOLD fMRI FWHM and TTP were 2.3 ± 0.6 s and 2.7 ± 0.6 s, n=8, respectively. These values are significantly reduced if compared to human values [3], suggesting a substantial contribution of blood flow response and oxyhemoglobin transit to the human IR. On the other hand, CBV FWHM and TTP were even shorter than their BOLD counterparts. CBV FWHM was 1.6 ± 0.2 s, and CBV TTP was 1.9 ± 0.3 s, n=3. This suggests that there is still a substantial oxyhemoglobin transit effect to the BOLD IR in rats. Furthermore, it implies that the temporal resolution of neurovascular control mechanisms is below 1.5s FWHM.

References: [1] Silva AC and Koretsky AP, PNAS 2002, 99: 15182-15187; [2] Silva AC et al, J. Cereb. Blood Flow Metab. 2000, 20: 201-206; [3] de Zwart J et al, submitted to this meeting; [4] Kellman P et al, Neuroimage 2003, 19:190-199; [5] Mandeville JB, Marota JJA., Magn Reson Med 1999; 42:591–598. [6] Mandeville JB et al, J Cereb Blood Flow Metab. 1999, 19:679-89.

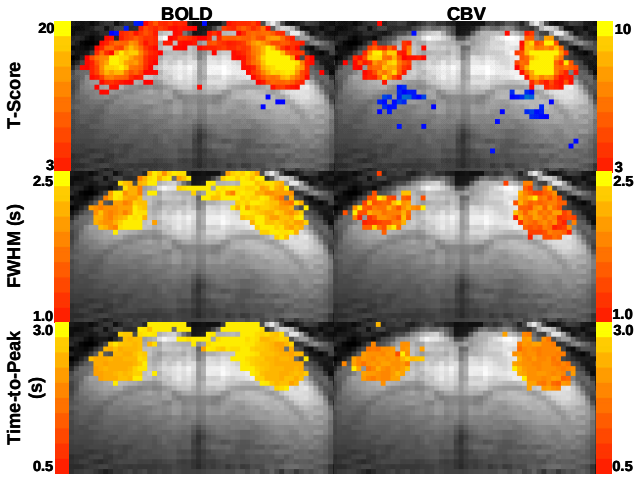

Figure 1: BOLD (left) and CBV (right) activation maps to bilateral stimulation of the rat forelimb. Top row: T-score maps; Middle row: Full-Width-at-Half-Maximum maps of the Impulse Response; Bottom row: Time-to-Peak maps.

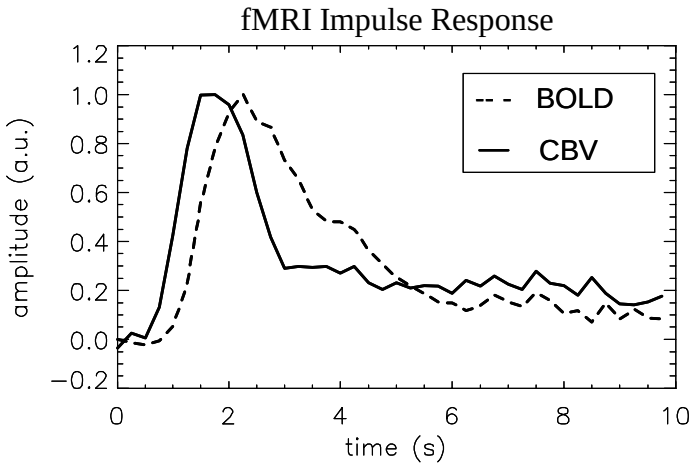

Figure 2: BOLD (red) and CBV (blue) impulse responses derived from the activation maps shown in Fig.1. The BOLD IR is significantly broader, and peaks significantly later than the CBV IR.