Spatial and Temporal Characteristics of the fMRI Response to Brief Somatosensory Stimulation in Rats

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Introduction: The specificity of the hemodynamic response (HDR) to functional brain stimulation is determined on the spatial domain by the vascular architecture and on the temporal domain by the evolution of hemodynamic changes. Previously, we showed significant heterogeneity of fMRI amplitudes and onset-times across the cortical layers, indicating that the fundamental spatial and temporal characteristics of the HDR are fine enough to resolve subcortical activity, and opening up the possibility of using fMRI to study laminar communication in the brain [1]. However, to date it is still not clear to what extent hemodynamic signals will be able to map elemental neuronal populations, and thus continued research on understanding the spatial and temporal evolution of the HDR will be essential to the increased applicability of neuroimaging to the study of functional brain organization. Here, we set out to measure the BOLD, cerebral blood flow (CBF) and volume (CBV) HDR to brief somatosensory stimulation as part of a continued effort to establish a set of stimulus parameters capable of isolating elemental vascular units.

Materials and Methods: Adult male Sprague-Dawley rats (n=7, 205 – 349 g), were initially anesthetized under isoflurane and orally intubated. Arterial and venous catheters were placed for monitoring of arterial blood gases and injection of drugs. Rectal temperature was monitored and maintained at 37.5 ± 0.5 ºC. Anesthesia was switched to α-chloralose (80 mg/kg initial bolus followed by 27 mg/kg/hr constant infusion) [1]. fMRI experiments were performed in a horizontal 7T/30 cm magnet (Bruker-Biospin, Billerica, MA) equipped with a 15 cm gradients capable of 450 mT/m amplitude within 100 µs rise-time (Resonance Research Inc, Billerica, MA). For CBF fMRI, a home-built small butterfly shaped labeling coil was positioned under the neck of the animal, approximately 3 cm away from isocenter. BOLD- and CBV-fMRI were obtained with a gradient-recalled echo (GRE) echo-planar-imaging (EPI) sequence and simultaneous BOLD and CBF-fMRI was performed using dynamic ASL (DASL) sequence [2] with the following parameters: FOV = 25.6 x 12.8 mm^2, matrix = 128 x 64, slice thickness = 2 mm, nominal resolution = 200 x 200 x 2000 μm^3, acquisition bandwidth = 200 kHz, TE = 25 ms, TR = 250 ms. To measure the HDR to somatosensory stimulation, a pair of needle electrodes was inserted into each forelimb and bilateral electrical stimulation (333 µs pulses, 2 mA amplitude, 3 Hz) was performed synchronized with the scanner and controlled from a PC running Presentation (Neurobehavioral Systems, Inc., Albany, CA). The stimuli consisted of individual epochs containing 1, 2, 3, 4, 6, 9, 15 or 30 electrical pulses (333 µs – 10 s stimulus lengths), respectively, repeated in randomized order 10 or 16 times. The total time for each run was 40 min (BOLD or CBV) or 80 min (CBF with BOLD). For CBV fMRI, 5 mg/kg of 30 nm iron oxide particles (Molday ION, BioPhysics Assay Laboratory, Inc., Worcester, MA) were injected intravenously to the animal before commencing the CBV studies. The forelimb region of the primary somatosensory cortex (S1FL) was divided into three similarly-sized regions according to the rat stereotaxic atlas [3]. The time series of the voxels in each region were averaged after image realignment and normalized to the mean of the prestimulus period.

Results and Discussion: Robust BOLD, CBF and CBV HDR were obtained at all stimuli conditions. However, only BOLD results are presented below. As shown in Fig. 1, the BOLD HDR to a single 333 µs pulse is easily detectable, indicating that even such a simple and brief stimulus is supra-threshold for fMRI and that CBF regulation occurs at the level of just a few neuronal events. Fig 2A shows that BOLD peak amplitude increases with stimulus duration up to 6 pulses, when it saturates. Accordingly, the area under the BOLD HDR grows fast with stimulus up to 6 pulses long, and then slowly with longer stimuli (Fig. 2B), in agreement with previous BOLD and CBF reports [4,5]. The BOLD time-to-peak (TTP) and full-width-at-half-maximum (FWHM) induced by a single pulse were short (Fig. 2C, D) and comparable to previous report using binary m-sequence probes [6,7]. Fig. 3 shows the BOLD t-score maps in a typical animal. The fMRI HDR to a single pulse is confined to the medially located regions in S1FL, and it grows to include periphery areas with increased stimuli durations. These results suggest that the HDR to extremely brief stimuli can be robustly determined. Detailed study of both spatial and temporal aspects of the HDR to brief stimuli will allow for a better understanding of the mechanisms of neurovascular coupling and allow establishment of the ultimately achievable spatial and temporal resolution of functional neuroimaging.

Fig. 1: BOLD HDR to stimuli of different durations

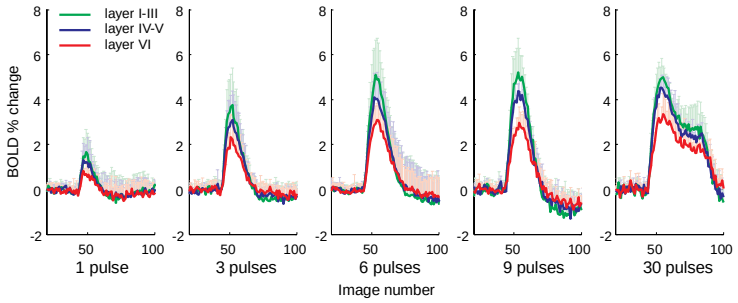


Fig. 2: BOLD amplitude and temporal parameters

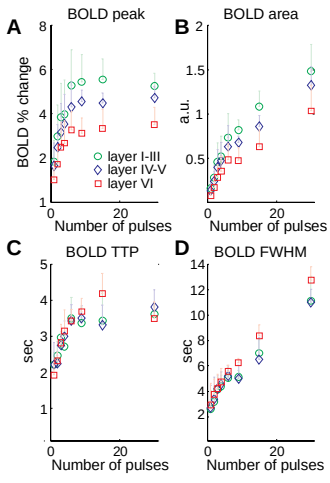
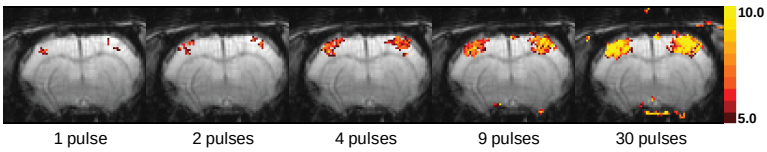


Fig. 3: BOLD t-score maps at different stimulus durations



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