

# Spatiotemporal Investigation of the fMRI Response to Brief Somatosensory Stimulation in Awake Marmosets

Y. Hirano<sup>1</sup>, J. V. Liu<sup>1</sup>, B. Stefanovic<sup>2</sup>, and A. C. Silva<sup>1</sup>

<sup>1</sup>Cerebral Microcirculation Unit, Laboratory of Functional and Molecular Imaging, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, United States, <sup>2</sup>Sunnybrook Health Sciences Centre, Toronto, ON, Canada

**Introduction:** Understanding the spatiotemporal features of the hemodynamic response (HDR) to functional brain stimulation is essential to the proper application of fMRI to study brain function. Previously, we showed that the BOLD-, CBF-, and CBV-HDR to a single electrical pulse can be robustly detected in  $\alpha$ -chloralose anesthetized rats [1], and that both spatial and temporal characteristics of such responses are fine enough to resolve the heterogeneity of fMRI amplitudes, onset times, and time-to-peak across the cortical layers. Here, we extend that work to investigate the spatial and temporal evolution of the BOLD-HDR in awake nonhuman primates.

**Materials and Methods:** Two adult male common marmosets (352 – 400 g), were acclimated to a body harness and habituated to being in the MRI scanner. Following acclimation, head posts were implanted in the skull and secured to a head holder. BOLD-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  $\mu$ s rise-time (Resonance Research Inc, Billerica, MA). A home-built two-element receive-only surface coil array (1.6 cm ID) was positioned near somatosensory cortex, and connected to home-built pre-amplifiers by short cables. BOLD-fMRI was obtained with a gradient-recalled echo (GRE) echo-planar-imaging (EPI) sequence with the following parameters: FOV = 32 x 32 mm<sup>2</sup>, matrix = 108 x 108, slice thickness = 2 mm, nominal resolution = 300 x 300 x 2000  $\mu$ m<sup>3</sup>, acquisition bandwidth = 333 kHz, TE = 20 ms, TR = 250 ms. To measure the HDR to somatosensory stimulation, a pair of contact electrodes was secured across each wrist and bilateral electrical stimulation (333  $\mu$ s pulses, 2 mA amplitude, 64 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, 4, 8, 16, 32, 64, 128 or 256 electrical pulses (333  $\mu$ s – 4 s stimulus lengths), respectively, repeated in randomized order 16 times. Two or three sessions were conducted in each animal, and their behavior during the fMRI experiments was continuously monitored by an MR-compatible camera (MRC Systems GmbH, Heidelberg, Germany). Active regions in the forelimb region of the primary and secondary somatosensory cortex (S1 and S2) and in the caudate were identified ( $p < 0.05$ ) after image realignment. The time series of activated voxels were averaged and normalized to the mean of the prestimulus period.

**Results and Discussion:** Robust BOLD-HDRs were obtained in S1 and S2 at all stimuli conditions, and in caudate for stimuli longer than 31 ms. Both the amplitude and number of activated voxels increased monotonically with stimulus durations up to 4 s (Figs. 1 – 3). Interestingly, the time-to-peak (TTP) in S1 induced by a single pulse ( $\approx 2.6$  s) in awake marmosets (Fig. 3C) was longer than that obtained in  $\alpha$ -chloralose anesthetized rats (1.48 s in layers IV-V) [1], suggesting a significant contribution from dispersive venous components of the marmoset cerebral vasculature. Indeed, the TTP measured in awake marmosets was comparable to that of human visual cortex (2.73 s) [3], indicating that the vascular length in marmosets may be more similar to humans than to rodents. In addition, the onset time of the BOLD-HDR in S1 was shorter than those of S2 (Fig. 3D). The shorter onset in S1 is consistent with previous MEG studies in humans [4, 5], and suggest that the HDR starts in S1 before progressing to higher-order brain regions.

In summary, the BOLD-HDR to extremely brief stimuli can be robustly determined in awake marmosets. The spatiotemporal features of the HDR in are more similar to that of humans, and contrast those of anesthetized rodents, indicating that the refinement of awake non-human primate models is crucial to maximize applicability of animal fMRI studies to the investigation of human brain function and to increase our understanding of the mechanisms of neurovascular coupling.

Fig. 1: BOLD HDR to stimuli of different durations

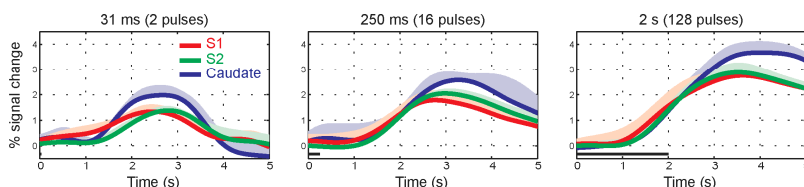


Fig. 2: BOLD activation maps at different stimulus durations

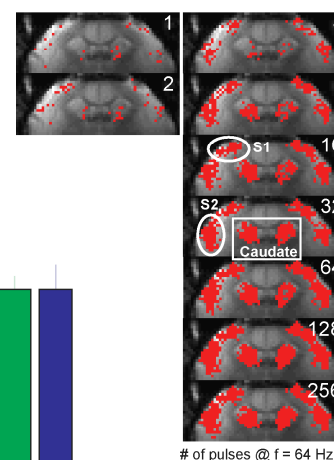
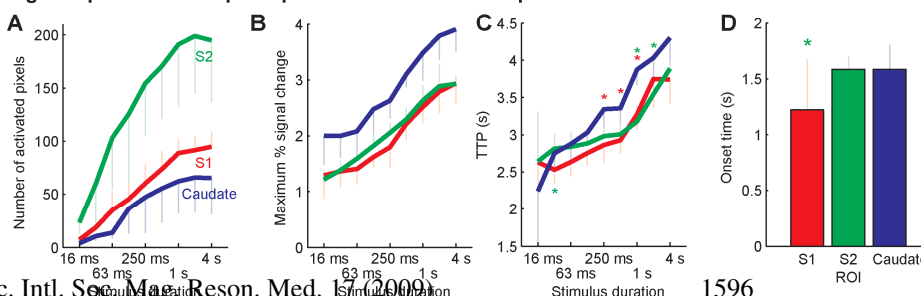


Fig. 3: Spatial and temporal parameters of BOLD response



**References:** [1] Hirano Y *et al.*, ISMRM 2008. [2] Liu JV *et al.*, GRC Brain Energy Metabolism and Blood Flow 2008. [3] de Zwart JA *et al.*, Neuroimage 2005; 24: 667-77. [4] Del Gratta C *et al.*, Neuroimage 2002; 17: 1373-83. [5] Lin YY *et al.*, Behav Brain Res 2002; 135: 141-5