

Facilitation of the BOLD response to bilateral somatosensory stimulation in awake marmosets

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Introduction: The development of awake behaving animal models to study brain function presents the advantages of eliminating confounds introduced by anesthesia and of enhancing applicability of findings to human research [1]. The common marmoset (*Callithrix jacchus*) is a small non-human primate that is gaining significant status and relevance in biomedical research [2]. Recently, there has been much interest in using fMRI to understand the cortical representation of tactile information of the hands in non-human primates [3]. In the present work, we used BOLD fMRI to measure the hemodynamic response to unilateral and bilateral somatosensory stimulus paradigms aimed at probing neurovascular integration in the primary somatosensory cortex (S1).

Materials and Methods: Five adult common marmosets were acclimated to a body harness and to being in the MRI scanner. The animals' heads were secured rigidly yet comfortably by custom-made helmets shaped to each individual's head anatomy. While in the magnet, the animals were continuously monitored by an MR-compatible camera. Experiments were performed in a horizontal 7T/30cm MRI (Bruker AVIII, Ettlingen, Germany) equipped with a 15 cm gradient coil (Resonance Research Inc, Billerica, USA). Images were acquired using a home-built transmit volume coil and a two-element (1.2 cm ID) receive surface coil array. BOLD fMRI was obtained using a gradient-recalled echo-planar-imaging sequence (TE = 15 ms, TR = 250 ms, flip angle = 30°, matrix size = 64 × 64, in plane resolution = 400 × 400 mm², slice thickness = 2 mm, acquisition bandwidth = 170 kHz). Somatosensory stimulation was performed by applying 1.5 mA, 333 µs pulses to the wrists of the animals via contact electrodes, at two different stimulus frequencies, 4 or 40 Hz, unilaterally, bilaterally or in combination (Fig. 1A). BOLD responses were analyzed from regions-of-interest placed in ipsilateral and contralateral primary somatosensory cortex (S1).

Results and Discussion: Unilateral stimulation produced positive BOLD responses in contralateral S1 both at 4 and 40Hz (Fig. 2, left). On the other hand, in the ipsilateral cortex, stimulation at 4 Hz produced weak and delayed negative BOLD responses, while 40 Hz stimuli produced robust positive BOLD responses. Moreover, the BOLD responses to bilateral stimulation were positive at both 4 and 40 Hz stimuli, with amplitudes larger than the summation of responses to unilateral stimulation ("Estimation" in Fig. 2) and the actual response to bilateral stimulation showed that facilitation occurred mainly in the offset phase of the response after ceasing the stimulation. These findings suggest that unilateral stimulation produces ipsilateral BOLD responses that range from being negative due to transcallosal inhibition at low frequencies to positive due to transcallosal excitation at high frequencies, while bilateral stimulation always facilitates (i.e., augments) the hemodynamic response in contralateral S1 through transcallosal interactions.

References: [1] Silva AC et al., Longitudinal Functional Magnetic Resonance Imaging in Animal Models. In Magnetic Resonance Neuroimaging, Humana Press, 2010 [2] Newman JD et al., Brain Res Rev, 2009. [3] Lipton ME et al., J Neurosci, 2006.

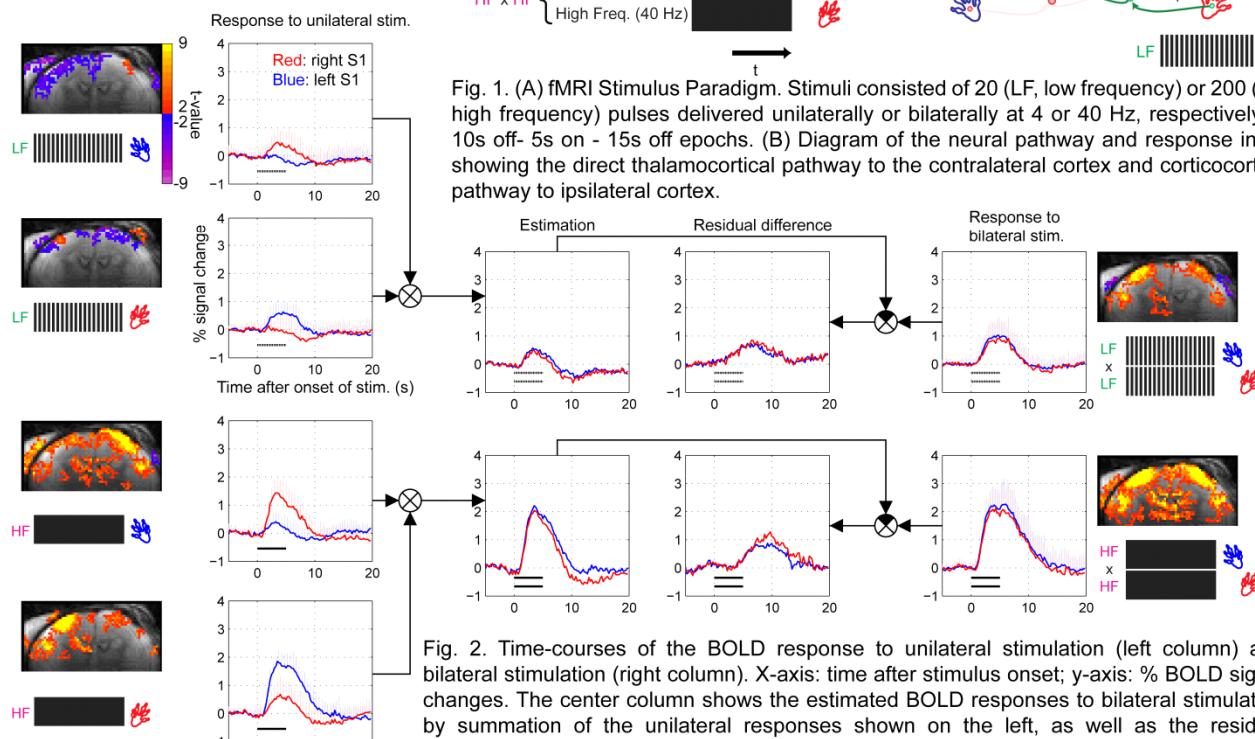


Fig. 1. (A) fMRI Stimulus Paradigm. Stimuli consisted of 20 (LF, low frequency) or 200 (HF, high frequency) pulses delivered unilaterally or bilaterally at 4 or 40 Hz, respectively, in 10s off- 5s on - 15s off epochs. (B) Diagram of the neural pathway and response in S1 showing the direct thalamocortical pathway to the contralateral cortex and corticocortical pathway to ipsilateral cortex.

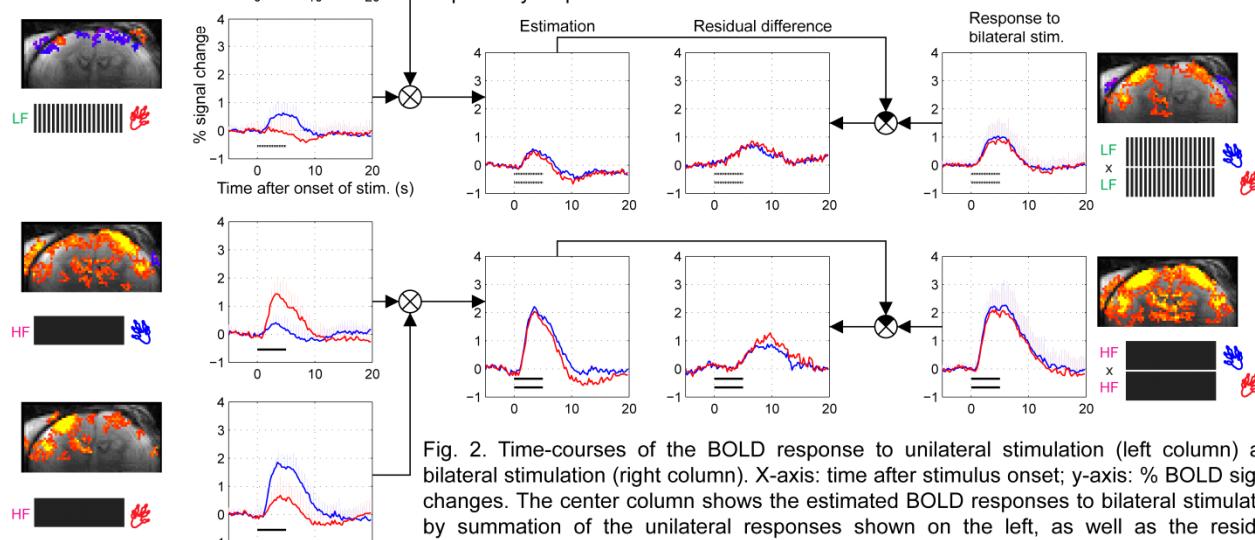


Fig. 2. Time-courses of the BOLD response to unilateral stimulation (left column) and bilateral stimulation (right column). X-axis: time after stimulus onset; y-axis: % BOLD signal changes. The center column shows the estimated BOLD responses to bilateral stimulation by summation of the unilateral responses shown on the left, as well as the residual differences calculated by subtracting the estimated response from the actual responses to bilateral stimulation. The actual responses were always larger than the estimated responses.