Neurophysiological verification that unilateral tactile stimulation evokes contralateral cortical but bilateral thalamic activations

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INTRODUCTION:

fMRI with BOLD contrast is widely used to study sensory responses in the brain of anesthetized rats. Electrical forepaw stimulation is one of the most frequently chosen activation models in anesthetized rats producing well defined BOLD signal increase in the primary somatosensory cortex. BOLD activations of subcortical regions, in contrast, are harder to detect because of low sensitivity and/or difficult access with conventional RF coils. Because different peripheral sensory pathways converge onto these subcortical regions, these are important sites for studying the interplay across different sensory modalities [1-8]. The main tactile somatosensory pathway, the medial lemniscal system of the thalamus has well defined pathway but it has been mainly studied by cross sectional studies and evoked electrical potentials [9]. The aim is to describe thalamic and cortical responses to forepaw stimuli in rat brain by high field fMRI and neural recordings [10]. Changes in BOLD contrast and CBV were compared with MUA measurements in the same regions. The results demonstrate the potential of fMRI at 11.7T to study system wide (cortical and subcortical) integration of sensory inputs [11].

MATERIALS and METHODS:

Animal preparation: Sprague-Dawley male rats were tracheotomized and artificially ventilated (70% N_2O, 30% O_2). During the animal preparation 2% isoflurane was used for induction. Intraperitoneal line was inserted for administration of α-chloralose (46±4 mg/kg/hr) and D-tubocurarine chloride (1 mg/kg/hr). An arterial line was used for monitoring physiology (blood pH, pO_2, pCO_2) throughout the experiment. ***Forepaw stimuli*** (2mA, 0.3 ms, 3Hz): Stimulation was achieved by insertion of thin needle copper electrodes under the skin of the forepaw. ***fMRI (n=10):*** All fMRI data were obtained on a modified 11.7T Varian horizontal-bore spectrometer using a ^{1}H surface coil (Ø = 1.4 cm). The images were acquired with gradient echo EPI sequence (TR/TE = 1000/15). CBV measurements were performed in presence of contrast agent ferumoxtran (12mg/kg). ***Neural activity (n=5):*** The rat was placed in a stereotaxic holder on a vibration-free table inside a Faraday cage. Tiny burr holes above the contralateral somatosensory regions [4.4 mm lateral and 1.0 mm anterior to bregma] and bilateral ventral posterior lateral (VPL) thalamic nuclei [3.0 mm lateral and 3.0 mm posterior to bregma] were drilled and tungsten microelectrodes (FHC Inc, Bowdoinham, ME) were inserted up to layer 4 for $S1_{FL}$ and 5 mm ventral for both contra and ipsilateral thalamic nuclei (VPL) with stereotaxic manipulators (Kopf). Neural data were acquired with both low and high impedance electrodes. The signals from these regions were normalized to the initial peak response during forepaw stimulation. All signals were then digitized (>20 kHz) with a μ-1401 interface using Spike2 software (CED, Cambridge, UK). Multi unit activity was processed using RMS (root mean square) approach [10].

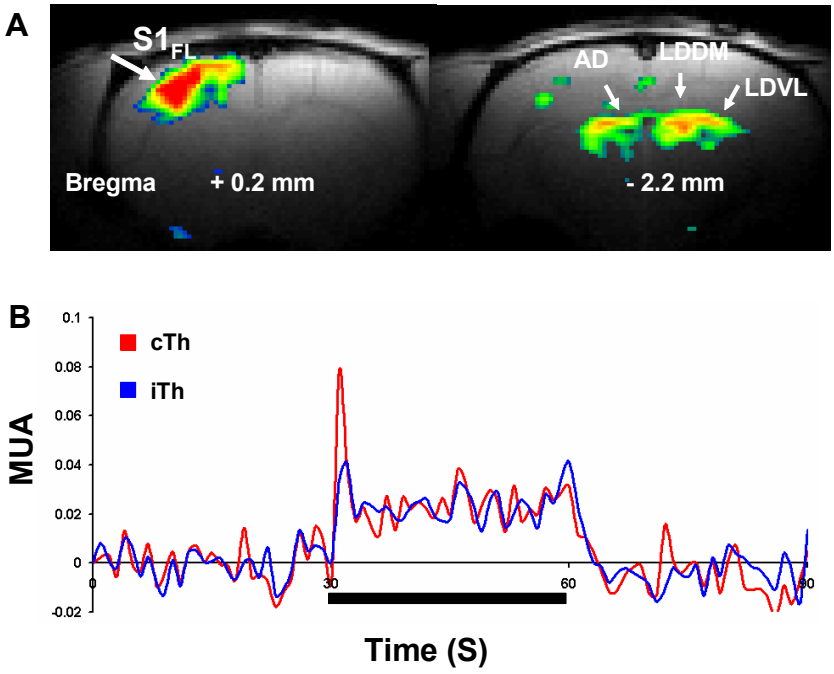

Fig 1. (A) Unilateral forepaw stimulation (30 s) induced contralateral cortical and bilateral thalamic BOLD responses. All data from single trial runs. Low and high thresholds were $p<0.01$ and 0.001, respectively. ***Abbreviations***: **AD**: anterodorsal thalamic nuclei; **LDDM**: laterodorso-dorsomedial thalamic nuclei; **LDVL**: laterodorso- ventrolateral thalamic nuclei; **$S1_{FL}$**: somatosensory forelimb area. **(B)** Averaged MUA responses revealing contralateral (cTh) and ipsilateral (iTh) thalamic nuclei during unilateral forepaw stimulation (30 s).

RESULTS and DISCUSSION:

Unilateral forepaw stimulation evoked strong contralateral cortical activation but also bilateral thalamic responses. Our results demonstrated reproducible BOLD (Fig. 1) and CBV (data not shown) and neural (MUA) responses at the cortex and thalamus during forepaw stimulation. Thalamic activations were more pronounced in the medial and lateral portions of the thalamic nucleus (Fig. 1A). We found no significant differences in the amplitude of fMRI and neural responses in contralateral and ipsilateral thalamus during forepaw stimulation (Figs. 1A and 1B). Earlier studies using electrophysiological recordings have also reported bilateral thalamic activations during unilateral tactile stimulation in rats [9].Thus we applied high field fMRI (high S/N ratio) to study thalamo-cortical interactions during sensory stimulation. The medial lemniscal system is known to carry the sensory information in the spinal cord, intersect in the medulla, and then switch in the VPL thalamus. Our results show that there is a strong ipsilateral thalamic activation which is not a part of the medial lemniscal pathway. Future ablation studies will be important in revealing the mechanistic basis of the bilateral thalamic responses. These results have significance in understanding the role of both cortical and subcortical areas during sensory processing [11].

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