Cortical and thalamic sensory responses in rat brain by fMRI and neurophysiology

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INTRODUCTION

In rodents, perception of frequency variation of tactile stimuli (e.g., forepaw or whisker) is considered to be important in correct identification of environmental settings. Earlier studies show that several frequency-specific mechanisms impact information transmission in the rodent sensory system and suggest that these properties play a crucial role in perception [1]. Along the sensory pathway, the thalamus relays the sensory information which originates from sensory organs and ends in primary sensory cortex. , Does the thalamus only relay the information or play an important role in processing tactile sensory information? Thalamic cells in waking and anesthetized monkey show differential capacity for frequency-following tactile stimuli [2]. However it is not clarified which connection of the sensory pathway tunes the frequency dependent response in rodents. We hypothesized that the first modification of frequency response can happen in the ventral posterior lateral (VPL) nucleus of thalamus. Furthermore it is known that anesthesia profoundly affects both neural activity and the vascular system, thus impacting neurovascular coupling in the brain [3-5]. Our recent studies using two different anesthetics (α-chloralose and Domitor) revealed that peripheral electrical stimulation of the forepaw in certain frequency range induce specific neural response in the somatosensory cortex [6-7]. In the present study we investigated the neural and BOLD responses of somatosensory cortex and VPL thalamus to electrical stimulation of the rat forepaw with different stimulation frequencies under different anesthetics (Isoflurane, Domitor and α-chloralose).

METHODS:

Animal preparation: Sprague-Dawley rats were tracheotomized and artificially ventilated (70% N_2O, 30% O_2). During the animal preparation isoflorane (3 - 4%) used for induction and 1 - 2 % for maintenance. Intraperitoneal lines were inserted for administration of α-chloralose (46±4 mg/kg/hr) or domitor (0.1mg/kg/hr) and D-tubocurarine chloride (1 mg/kg/hr). An arterial line was used for monitoring vital signs such as blood pressure, pH, blood gases throughout the experiment. ***Forepaw stimulation:*** Stimulation was achieved by insertion of thin needle copper electrodes under the skin of the forepaw. Electrical stimulation (2mA) consists of 0.3ms square wave pulses provided with an isolator stimulator (World Precession Instruments, Saratoga, FL). Variation of functional response is achieved by varying the frequency (1–48 Hz) of the stimulus. The stimulus was controlled with a computer by custom written script with 30s off 30s on block design. ***fMRI (n=15):*** All fMRI data were obtained on a modified 11.74T horizontal-bore spectrometer (Varian) using a ^{1}H surface coil (Ø = 1.4 cm). The images were acquired with gradient echo EPI sequence (TR/TE = 1000/15) [6]. ***Extracellular neural measurements (n=18):*** The rat was placed in a stereotaxic holder on a vibration-free table inside a Faraday cage. Tiny burr holes above the contralateral fore limb somatosensory cortex ($S1_{FL}$) [4.4 mm lateral and 1.0 mm anterior to bregma] and ventral posterior lateral (VPL) of thalamus [3 mm lateral and 3 mm posterior to bregma] were drilled and tungsten microelectrodes (FHC inc, Bowdoinham, ME) were inserted up to layer 4 for $S1_{FL}$ and VPL for thalamus with stereotaxic manipulators (Kopf). All signals were then digitized (>20 kHz) with a μ-1401 interface using Spike-2 software

RESULTS:

Electrical stimulation (2 mA) of the forepaw with 0.3 ms duration pulses for 30 s evoked a strong positive BOLD signal change in the contralateral primary somatosensory area of the forelimb ($S1_{FL}$) and thalamus (data not shown) under different anesthetics (Isoflurane, Domitor and α-chloralose) **(Fig.1A)**. Each stimulation frequency (1-24 Hz) evoked BOLD responses under all the anesthetics. However, the largest volume of activated pixels and the maximum amplitude of BOLD signals were found at 12 Hz, 9 Hz and 1.5 Hz for Isoflurane, Domitor and α-chloralose respectively. In separate experiments we simultaneously recorded neural activity (MUA) from $S1_{FL}$ and thalamus (VPL) using the same experimental conditions. MUA responses at $S1_{FL}$ were similar to BOLD responses showing peak neural activity at 12, 9, and 1.5 Hz for Isoflurane, Domitor and α-chloralose, respectively **(Fig.1B)**. The thalamic MUA responses increased linearly with increase in the stimulation frequency (1–48 Hz) under all the anesthetics used **(Fig.1C)**.

DISCUSSION:

Using simultaneous neural recordings in rat $S1_{FL}$ and VPL of thalamus we showed that frequency dependent sensory responses are different in the subcortex and the cortex **(Fig.1B-C)**, the high frequency dependent responses are smaller in the $S1_{FL}$, while there is a linear increase with frequency in the VPL. The same response characteristics are found with BOLD-fMRI **(Fig.1A)**. Furthermore peak response in the $S1_{FL}$ is anesthesia dependent, while in VPL it does not show anesthesia dependency. These results suggest that subcortical structure (i.e. VPL of thalamus) is not influenced by anesthesia, while in the cortex the deeper anesthesia augments the process of faster stimuli.

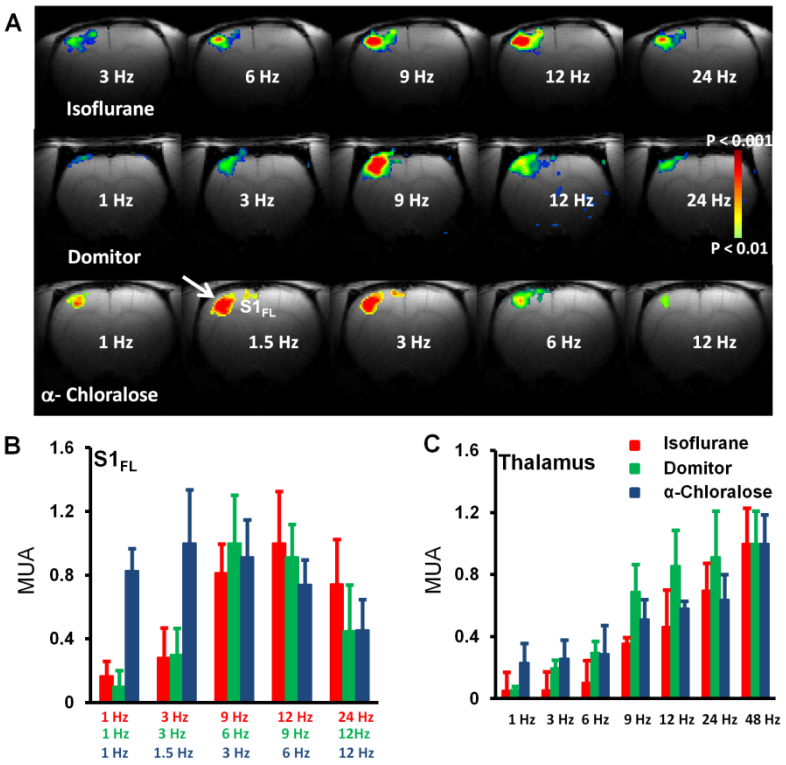

Fig.1 BOLD (A) activations during contralateral forepaw (2 mA, 0.3 ms) stimulation under varying frequencies (1 - 24 Hz). Strong cortical $S1_{FL}$ responses were observed under each anesthetics. All data from single trial runs where the stimulation period was 30 s in duration. Lowest and highest thresholds were $p < 0.01$ and 0.001, respectively. Fig.1 (B-C) shows multi unit activity (MUA) responses at cortex ($S1_{FL}$) and thalamus (VPL) for different stimulation frequencies (1 – 48 Hz) under different anesthetics. The MUA data were normalized to maximum response under each anesthetics both at $S1_{FL}$ and thalamus

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