

Deep brain stimulation fMRI of the rat ventral posterior medial thalamus

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INTRODUCTION Deep brain stimulation (DBS) is clinically used to treat a variety of neurological symptoms, but the underlying mechanisms remain largely unexplored [1]. Combining DBS and fMRI has a potential to unambiguously study a specific neuroanatomical pathway/connectivity, determine optimal treatment parameters for a disease, and monitor the treatment outcome. In this study, we aimed to demonstrate thalamocortical connectivity in rats using DBS. Ventral posterior medial (VPM) thalamus was selected for DBS due to larger innervated area in the cortex [2]. Our hypothesis was that the barrel cortex is reliably activated by DBS and the responses exhibit frequency and amplitude-dependent properties.

METHODS Adult male Sprague Dawley rats ($n = 12$, 250–300 g) were anesthetized with 1-1.2% isoflurane, ventilated, and paralyzed. The respiratory rate was set between 57–60 stroke/min. End-tidal CO_2 was continuously monitored and kept within normal range (3–3.5%) by adjusting the tidal volume. A regulated heated pad was used to maintain body temperature at 37° C. A MRI-compatible, two-channel microelectrode (PlasticsOne, Roanoke, VA) was implanted 3 mm posterior to the bregma, 3 mm lateral to the midline, 6 mm below the cortical surface [3], and fixed with dental cement. MRI was performed on Bruker 11.7 T Biospec with a surface coil (ID~2 cm). BOLD fMRI was acquired with 4-shot gradient-echo EPI sequence using spectral width = 200 kHz, TR/TE = 1250/12 ms, FOV = 2.56x2.56 cm, slice thickness = 1 mm, matrix = 128x128, and temporal resolution = 5 s. Bipolar square wave was used for stimulation. In the first experiment, stimulus frequency of 1, 3, 7, 11, 15, 20, 25, 30, and 40 Hz (fixed at 1 mA) were studied, with corresponding pulse width of 1, 1/3, 1/7, 1/11, 1/15, 1/20, 1/25, 1/30, and 1/40 ms. In the second experiment, stimulation amplitude of 0.2, 0.6, 1, 1.2, 1.4, 1.8, and 3.6 mA fixed at 7 Hz and 1/7 ms pulse width were studied. The order of various stimuli was randomized. Repeated scans were performed to study cortical spreading depolarization (CSD) occurred or to increase SNR if needed. Stimulation paradigm was OFF-ON-OFF-ON-OFF, where OFF = 100 s and ON = 50 s. Statistical analysis employed ANOVA followed by Fisher's post-hoc test. Significant level was set at $P < 0.05$. Error bars were SEM.

RESULT & DISCUSSION This study demonstrated cortical BOLD fMRI response to DBS at the rat VPM thalamus. The major findings were: (i) BOLD response in the sensory cortex exhibited a tuning curve shape that peaked at 25 Hz (Fig. 1), (ii) BOLD response in the sensory cortex increased with stimulus amplitude and reached a plateau at 1 mA (Fig. 2), and (iii) CSD was occasionally found when the stimulation frequency was 7–20 Hz (Fig. 3). DBS-induced BOLD responses were highly reproducible and had high contrast-to-noise ratio (up to 8% BOLD at 11.7 T). The 25 Hz peak response differed from the peak response of 8–12 Hz induced by forepaw stimulation under isoflurane anesthesia [4,5]. This may be because the VPM encodes different frequency bands compared with VPL (a major thalamic relay for S1 forepaw/hindpaw), or the stimulus pulse widths were adjusted accordingly to ensure the same amount of current was delivered. Stimulation at 1 mA produced reliable and repeatable cortical activation. No obvious lesion was observed in the T_2^* -weighted images up to 3.6 mA (7 Hz, 1/7 ms pulse width). Trials after 3.6 mA stimuli were also not affected, indicating the neurons in VPM were not lesioned and still responsive. However, a single pulse of 0.1 mA with 5 s pulse width produced observable lesion in the T_2^* -weighted images (image not shown). This cautions the use of DBS with long pulse width and highlights the importance of calibrating DBS parameters.

Interestingly, CSD was observed 12 out of 151 trials in 12 animals and the occurrence rate peaked at 11 Hz (23%). CSD evoked 10% BOLD response, initiated 1 min after the stimulus onset, propagated toward the midline, anterior, and posterior part of the cortex with an estimated speed at 4 mm/min. The depolarization waves never crossed the hemisphere and only stayed in the cortex. CSD has been shown to occur in many neurological disorders and it has negative effects on disease outcome [6]. DBS at VPM provides a unique opportunity to repeatedly evoke CSD. In contrast to optical imaging [7], fMRI offers depth-resolved whole-brain monitoring of CSD spatio-temporal dynamics.

CONCLUSION The present study demonstrated thalamocortical connectivity by stimulating VPM thalamus in rats. This connectivity was evident only when certain patterns of the electric signals were delivered to the VPM. We also demonstrated DBS can artificially induce CSD in the MRI environment for the first time. This DBS-fMRI technique has the potential to (i) explore unknown functional connectivity in the brain, (ii) validate resting state fMRI data, (iii) assist in finding optimal DBS treatment parameters for various neurological disorders, and (iv) investigate the spatiotemporal characteristics of the CSD.

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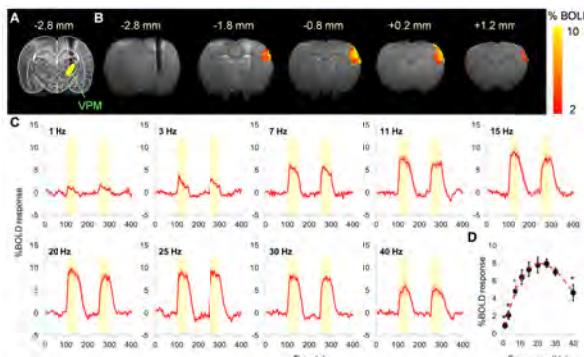


Fig 1. DBS fMRI of varying stimulus frequency ($n = 12$). **(A)** Rat brain atlas overlaid on an anatomy (Bregma -2.8 mm), showing the position of the microelectrode. **(B)** BOLD activation maps of a typical animal. Responses were mainly located in the S1 barrel field/upper lip. ROI was placed at -0.8 mm. **(C)** Grand-averaged BOLD responses to 9 stimulus frequencies. Yellow-shaded area indicates stimulus epoch. **(D)** Primary somatosensory cortex exhibited a frequency-dependent activation, where the response peaked at 25 Hz. $*P < 0.05$, different from peak value.

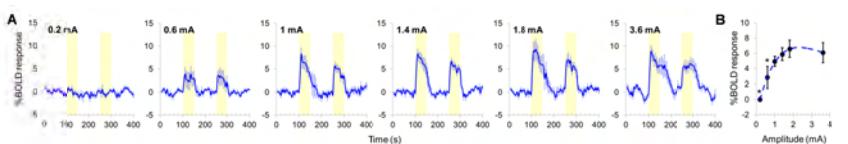


Fig 2. DBS fMRI of varying stimulus amplitude ($n = 7$). **(A)** Grand-averaged BOLD responses to 6 stimulus frequencies. **(B)** Primary somatosensory cortex exhibited a amplitude-dependent activation, where the response reached a plateau at 1 mA. $*P < 0.05$, different from peak value.

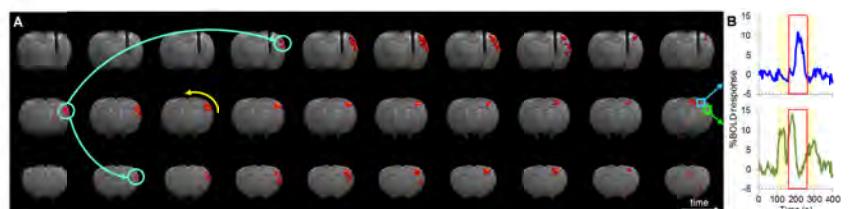


Fig 3. DBS induced spreading depolarization. **(A)** The CSD initiated in the barrel cortex, propagated toward the midline and spread in both anterior and posterior directions. **(B)** fMRI time-course data from two ROIs from (A). The red window between two stimulus epochs indicates the temporal span of (A).