Deep brain stimulation at the internal globus pallidus produces fMRI response in the motor cortex

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Introduction: Deep brain stimulation (DBS) is a neurosurgical technique which is currently used to treat a variety of neurological and psychiatric disorders, including Parkinson's disease (PD). The mechanism by which DBS alleviates PD symptoms is still incompletely understood [1,2], limiting the generalizability of this procedure to new targets. The combination of DBS and fMRI enables the study of regional responses to stimulation, with the potential to optimize treatment parameters and monitor therapeutic response. In this study, we aimed to characterize BOLD response to DBS of the internal globus pallidus (GPi). GPi was targeted due to its common use in clinical DBS treatment for PD [3] and the potential for mechanistic differences with DBS at the subthalamic nucleus (STN). GPi is known to send inhibitory efferents to the ventral lateral thalamus which further sends excitatory efferents to the motor cortex [4,5]. Therefore, we hypothesized that DBS at the GPi would reliably produce fMRI-visible responses in the motor cortex in a frequency-dependent manner.

Methods: MRI-compatible two-channel microelectrodes (PlasticsOne, Roanoke, VA) were stereotactically implanted into the GPi (2.4 mm posterior to bregma, 3.0 mm right of midline, and 7.4 mm ventral to the cortical surface)[6] in 5 adult male Sprague Dawley rats (300-450 g) under deep anesthesia with 2-2.5% isoflurane **(Fig. 1)**. The electrode was fixed with dental cement and the rats were allowed to recover for at least 48 hours before imaging studies. For fMRI, rats were anesthetized with 1.25-1.75% isoflurane (based on stability of physiological parameters), intubated, paralyzed, and ventilated with medical air. The ventilation volume and rate were adjusted to maintain $EtCO_2$ of 2.6-3.2% and SpO_2 above 96%, and a water-circulated heating pad was used to maintain rectal temperature at 37 ± 0.5 ^{o}C. fMRI was performed on a Bruker 9.4T system using a home-made surface coil (ID = 1.6 cm) and a double-sampled 4-shot gradient-echo EPI sequence (BW=160 kHz, TR = 750 ms, TE = 13 ms, 128x128 matrix, FOV = 2.56x2.56 cm^2, slice thickness = 1, temporal resolution = 3 s). DBS frequencies of 10, 40, 70, 100, 130, 160, 190, 220, 250, 310 and 400 Hz were studied with a bipolar square-wave current of 1 mA and a pulse width of 7.8/f ms where f = frequency in Hz. The frequencies were performed in a pseudo-random manner. 2 to 5 repeated scans were performed for each parameter to improve accuracy and SNR. The stimulation paradigm was 60 s initial rest, 30 s stimulation, followed by 120 sec rest and an additional 2 min minimum resting interval between scans. CC maps were generated according to the stimulus paradigm after inter-subject coregistration with a temporal delay of 15 s, significant level of p<0.05 (Bonferroni corrected) and 3x3 low pass smoothing. Statistical analysis employed ANOVA followed by Fisher's LSD test, with p<0.05 indicating statistical significance. Error bars used were SEM.

Results and Discussion: This study demonstrated fMRI response to DBS at the GPi **(Fig 2)**. In addition to motor cortex, BOLD response was seen bilaterally in somatosensory and cingulate cortex, as well as diffusely throughout subcortical areas in the contralateral hemisphere. BOLD fMRI response ipsilateral to stimulation was positive, peaking at 100 Hz, and frequencies between 40 and 220 Hz were shown to exhibit a significant positive response to DBS **(Fig 3A)**. Contralateral BOLD fMRI response was negative, peaking at 40 Hz, with significant negative responses at frequencies up to 160 Hz **(Fig 3B)**. Response to DBS was durable at the amplitude and pulse width used, which are known not to produce a lesion [7]. BOLD responses to DBS were reproducible in this study with up to a 3% response observed. Variability in degree and area of response was observed to a much greater degree in the contralateral cortex than in the ipsilateral cortex. Although the nearby internal capsule (IC) sends projections to and from many cortical regions and could hypothetically be responsible for a cortical BOLD response, our pilot trial of DBS at the IC under these physiological and stimulation parameters has not evoked a similar BOLD response in M1. The ipsilateral positive response peaked near the high frequencies (100 Hz) that are therapeutic for DBS, while the contralateral negative response peaked in the frequency range (40 Hz) known to either exacerbate or be ineffective in treating parkinsonian symptoms [8], suggesting that the observed responses may be related to the mechanism of action of DBS in alleviation of parkinsonism. However, significant positive response was still observed ipsilaterally at low frequencies (40 Hz) and significant but declining negative response was observed at therapeutic high frequencies (100 Hz and above), while no response was noted at very low frequencies (10 Hz) where exacerbation of symptoms is common. Activation of ipsilateral cortex may be produced by several hypothetical mechanisms, including (a) inhibition of GPi cell bodies or efferent axons leading to relief of tonic inhibition of motor cortex [9], (b) direct orthodromic conduction of stimulation through thalamic synapses to motor cortex [10], and (c) antidromic conduction of stimulation through thalamic, STN or striatal synapses to motor cortex [11]. The etiology of the negative contralateral response is unclear, although DBS may cause inhibition via corticocortical projection neurons [12].

Conclusion: This study demonstrates significant changes in activity at the ipsilateral and contralateral motor cortex, with somatosensory and subcortical involvement, as a result of DBS at the GPi. These changes in activity were frequency-dependent in a manner which suggests a possible relationship to the therapeutic mechanism of DBS for parkinsonian symptoms both in animal models and clinically in humans. DBS fMRI at the GPi reveals response patterns not previously observed and is capable of probing and quantifying large-scale circuit functionality in vivo. Future use of this technique in hemiparkinsonian animals may permit correlation of fMRI with symptomatology, which will be crucial in understanding the significance of these results.

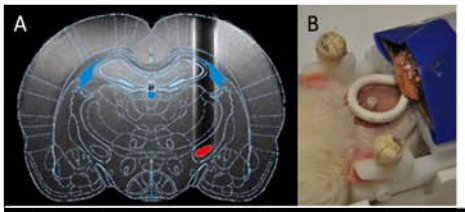

Fig. 1: Electrode placement and acquisition setup. **(A)** Rat brain atlas (Bregma -2.4 mm)[6] overlaid on anatomical image demonstrating electrode position at GPi (marked in red). **(B)** Image acquisition setup with surface coil positioned around electrode.

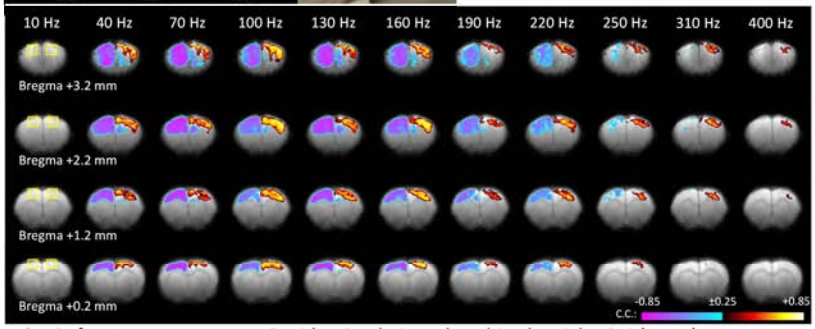

Fig. 2: fMRI responses to DBS with stimulation placed in the right GPi (n = 5). Maps are averaged CC responses in the study population correlated to the stimulation with a temporal delay of 15 s. This delay was chosen as an intermediate between the peak delay seen in negative and positive BOLD. The response was primarily concentrated over motor cortex with bilateral diffuse cortical involvement and subcortical involvement in the contralateral hemisphere. Yellow boxes indicate approximate ROIs (8x8 voxels).

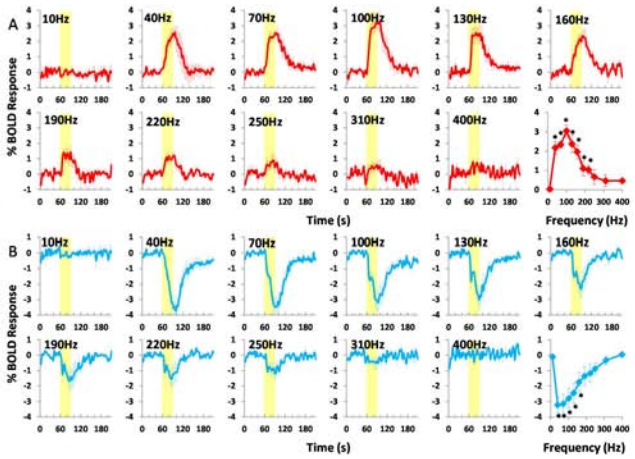

Fig. 3: Grand averaged BOLD responses to DBS at the GPi in **(A)** ipsilateral and **(B)** contralateral motor cortex. Yellow areas represent stimulation epoch. Positive responses were observed ipsilaterally, significant from 40 to 220 Hz, and negative contralaterally, significant from 40 to 160 Hz. BOLD frequency tuning curve (lower right in each section) peaked at 100 Hz in ipsilateral and 40 Hz in contralateral cortex. Asterisks indicate significant difference from 10 Hz at p<0.05.

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