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Network Effects of Deep Brain Stimulation in Parkinson's Disease using fMRI

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Objectives

This study examines the neuromodulatory effects of deep brain stimulation (DBS) on large-scale brain networks using functional magnetic resonance imaging (fMRI). Recent advances in MRI-compatible DBS systems enable simultaneous stimulation and fMRI, providing real-time insights into the effects of DBS on brain activity and network connectivity[1]. While high frequency stimulation (130 Hz) is the clinical standard for motor symptom management in Parkinson's Disease (PD) and has been shown to modulate neural activity within motor circuits[1], lower frequencies in the theta range (4-8 Hz) may influence cognitive and affective circuits[2,3]. We investigate these frequency-dependent whole-brain effects of subthalamic nucleus (STN) stimulation in PD patients.

Methods

- Four patients with 3T MRI-compatible STN-DBS systems underwent cycling-state fMRI with alternating 30-second ON/OFF stimulation cycles. See Table 1 for details on the stimulation conditions.
- Functional connectivity analysis was performed using a connectivity matrix derived from 89 regions-of-interest (ROIs) across 11 functional networks. Between-network connectivity was calculated by averaging Fisher-transformed correlation coefficients across ROI pairs connecting distinct networks.
- Functional activation analysis in a subset of 49 ROIs assessed regional blood oxygen level-dependent (BOLD) signal changes associated with different stimulation frequencies.
- Given the limited sample size (n=4) and variability in precise electrode placement within STN subregions; our primary analytical approach focused on stimulation frequency effects (high vs. low frequency) rather than anatomical subregion differences.
- For both functional connectivity and activation analyses, data were averaged across stimulation locations (VM and DL) within each frequency condition.
- Statistical significance was assessed using one-sample and two-sample t-tests (p<0.05, uncorrected) for within- and between-group analysis.

Table 1: DBSFMRI stimulation conditions

High and low frequency of the dorsolateral (motor) and ventromedial (associative-limbic) subthalamic nucleus.

Condition	Frequency	STN target area
HF_DL	135 Hz	Dorsolateral
HF_VM	135 Hz	Ventromedial
LF_DL	6 Hz	Dorsolateral
LF_VM	6 Hz	Ventromedial

Preliminary Results

Network Connectivity Analysis

Analysis of functional connectivity revealed distinct patterns of network modulation dependent on stimulation frequency.

- High frequency stimulation significantly increased connectivity between the language network and the dorsal attention (t=7.18, p=0.006) and sensorimotor networks (t=5.10, p=0.015), as well as between the default mode network and the dorsal attention (t=4.70, p=0.018) and sensorimotor networks (t=4.90, p=0.016). The only significant decrease in connectivity was between the basal ganglia and salience networks (t=3.97, p=0.029).
- Low frequency stimulation most notably produced a significant increase in connectivity between the cerebellar and dorsal attention networks (t=10.57, p=0.0018), while decreasing connectivity between the dorsal attention and visual networks (t=-7.65, p=0.0046) and the default mode and language networks (t=-11.71, p=0.0013).

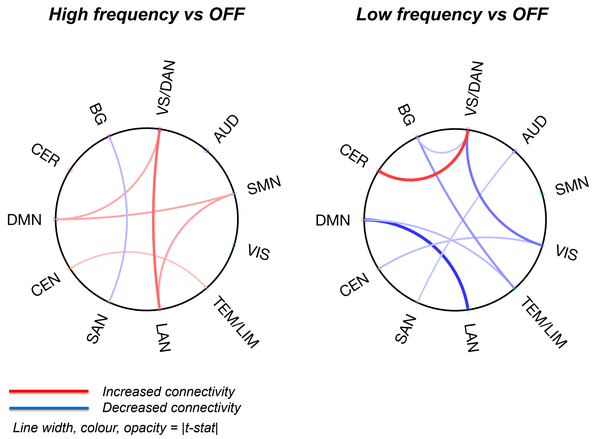

Figure 1: Between-network average functional connectivity

Networks: CER = Cerebellar Network; BG = Basal Ganglia; VS/DAN = Dorsal Attention Network; AUD = Auditory Network; SMN = Sensorimotor Network; VIS = Visual Network; TEM/LIM = Temporal/Limbic Network; LAN = Language Network; SAN = Salience Network; CEN = Central Executive Network; DMN = Default Mode Network.

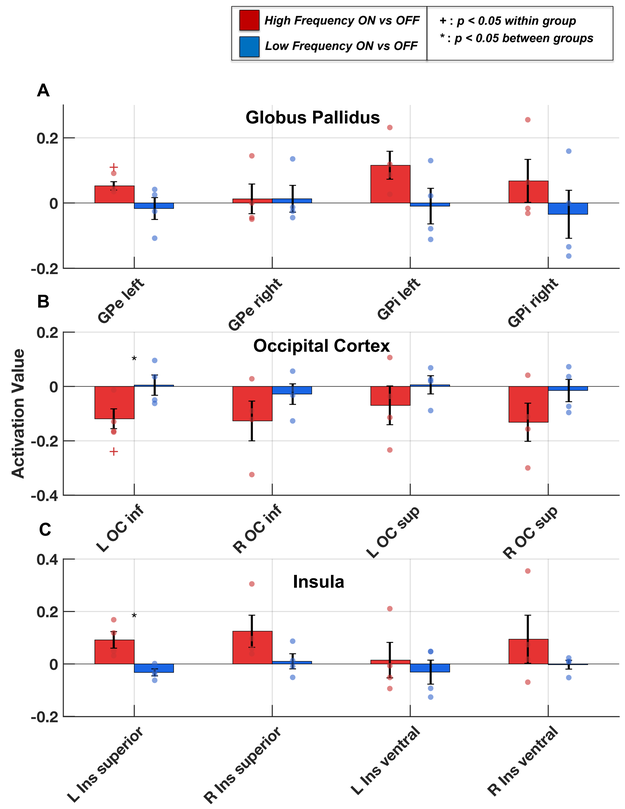

Figure 2: Frequency-dependent modulatory effects on ROIs

Bar graphs illustrating mean magnitude of activation intensity produced by high frequency (135 Hz; red bars) and low frequency (6 Hz; blue bars) deep brain stimulation.
(A) Globus Pallidus regions: Globus pallidus external (GPe) left and right.
(B) Occipital Cortex regions: Inferior occipital cortex (OC inf) and superior occipital cortex (OC sup) left and right.
(C) Insular Cortex regions: Insula superior (Ins superior) and ventral (Ins ventral) left and right.

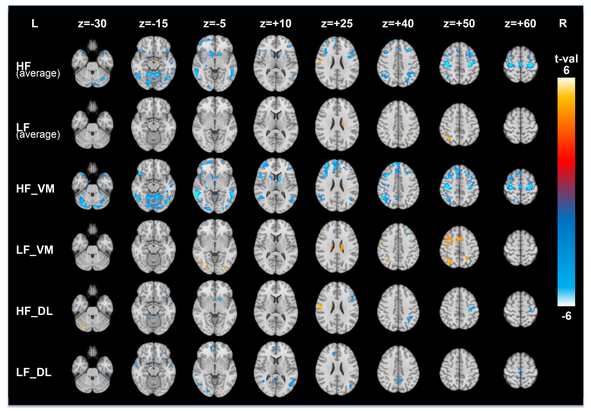

Figure 3: DBSFMRI_05 activation across stimulation conditions

Individual response to STN-DBS conditions. Clusters displayed pass an exploratory threshold of p<0.001 (uncorrected), cluster size > 10 voxels.

Regional Activation Analysis

- High frequency stimulation was associated with activation in the external globus pallidus (GPe left: t=4.09, p=0.026), internal globus pallidus (GPi left: t=2.69, p=0.074) and superior insula (L Ins superior: t=2.89, p=0.063), and deactivation in the primary motor cortex (R PreC: t=-2.39, p=0.097). Low frequency stimulation activated the cuneus (t=3.06, p=0.055), temporal thalamus (t=11.96, p=0.001), left cerebellum (L Cerebellum: t=2.52, p=0.086), and primary motor cortex (L PreC: t=1.95, p=0.147).
- Comparing high to low frequency conditions resulted in significant deactivation of the occipital cortex (L OC inf: t=-8.80, p=0.003), cerebellum (t=-6.90, p=0.0062), primary motor cortex (R PreC; t=-2.58, p=0.097), while producing activation of the insula (L Ins superior; t=3.34, p=0.045) and globus pallidus (GPe left; t=4.09, p=0.026; GPi left; t=2.69, p=0.074).

Discussion & Future Directions

- Our pilot data suggest that STN-DBS induces frequency-dependent modulation of brain networks, affecting both connectivity and regional activation patterns.
- High frequency stimulation (135 Hz), enhanced connectivity between the language, sensorimotor, and attention networks while modulating key basal ganglia and motor cortex structures (GP, PreC, Cerebellum), consistent with its clinical efficacy for motor symptoms.
- Low frequency stimulation (6 Hz), distinctly modulated cerebellar-attention and default mode-language functional connectivity, potentially relating to cognitive processing pathways.
- However, insights are substantially limited by the sample size and inter-subject variability of responses.
- These results demonstrate the feasibility of simultaneous DBS-fMRI to analyze stimulation effects across distributed brain networks, but further participant recruitment and analysis are required to establish robust conclusions.

References

1. Loh A, Gwun D, et al. (2022). Probing responses to deep brain stimulation with functional magnetic resonance imaging. Brain Stimul. 15(3):683-694. doi:10.1016/j.brs.2022.03.009
2. Lam, J., Lee, J., et al. (2021). Cognitive effects of theta frequency bilateral subthalamic nucleus stimulation in Parkinson's disease: A pilot study. Brain Stimul. 14(2), 230-240. doi.org/10.1016/j.brs.2020.12.014
3. Salehi, N., Nahrgang, S., et al. (2024). Theta frequency deep brain stimulation in the subthalamic nucleus improves working memory in Parkinson's disease. Brain, 147(4), 1190-1196. doi.org/10.1093/brain/awad433