2025 47th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) | 979-8-3315-8618-8/25/$31.00 ©2025 IEEE | DOI: 10.1109/EMBC58623.2025.11253515

Electrophysiological Changes of Multi-site Local Field Potentials after Deep Brain Stimulation in the Medial Prefrontal Cortex

Chang Wang, Chaonan Yu, Weihuang Chen and Kedi Xu*

***Abstract*—Depression is a major global cause of disability, with a portion of cases being treatment-resistant, which has led to the exploration of deep brain stimulation (DBS) as an alternative treatment. Currently, research on DBS in depression has largely focused on the effects of one or two brain regions, but the connections among multiple targets, especially deep brain regions associated with depression, remain poorly understood. Multi-site local field potential (LFP) analysis provides a means to study these connections. In this study, electrodes were implanted into twelve depression - related brain regions. The effects of acute DBS on the brain network on the medial prefrontal cortex (mPFC) were investigated, especially the functional connectivity changes between these targets. Spectral analysis revealed altered power spectral density (PSD) in the mPFC after acute DBS. Additionally, functional connectivity analysis using the imaginary part of coherence (iCOH) showed significant changes between the mPFC and other potential DBS targets, including the lateral habenula (LHb), subthalamic nucleus (STN), medial forebrain bundle (MFB), nucleus accumbens (NAc), and the CA1 region of the hippocampus. These connectivity changes were restricted to the stimulated hemisphere. Based on these results, we further analyzed information flow between sites using the phase slope index (PSI), a directional connectivity measure. This analysis revealed significant changes in information flow between the left mPFC and contralateral depression-related regions following left-sided mPFC DBS. In conclusion, this study provides electrophysiological insights into the acute effects of mPFC DBS on the brain network of depression, which may contribute to the optimization of DBS treatments in depression.**

I. Introduction

Depression is a major global health concern and a leading cause of disability, with approximately thirty percent of patients remaining resistant to standard antidepressant treatments[1]. This high prevalence of treatment-resistant depression (TRD) has prompted the exploration of alternative therapeutic approaches, including deep brain stimulation (DBS). DBS, which involves implanting electrodes to stimulate specific areas of the brain, , presents a promising therapeutic approach for patients with TRD[2].

Among the various targets for DBS in depression, the medial prefrontal cortex (mPFC) has emerged as a prominent focus. Recent studies have demonstrated that mPFC DBS can improve depressive-like behaviors, restore stress-induced alterations in brain-derived neurotrophic factor levels in the hippocampus and key signaling pathways[3]. Additionally, mPFC DBS increases hippocampal volume, blood vessel size, and synaptic density, modulates brain circuits linked to the dorsal raphe nucleus, and significantly reduces the firing rate of DRN neurons. These findings indicate that mPFC DBS holds substantial potential for inducing antidepressant-like effects and improving brain function in depression.

Currently, research on DBS for depression has primarily focused on studying the effects of one or two specific brain regions. However, the intricate connections between multiple targets, particularly deep brain regions implicated in depression, are still not well understood. To address this, multi-site local field potential (LFP) analysis offers a powerful approach to explore the interactions and network dynamics across multiple regions. This study aimed to study the electrophysiological changes of the stimulation target following mPFC DBS. Furthermore, we explored the direct interactions between the mPFC and other targets that are known to be closely associated with depression, enabling a comprehensive investigation of their functional connectivity. To assess these interactions, we employed the imaginary part of coherence (iCOH) and the phase slope index (PSI), both of which analyze electrophysiological interactions from a phase perspective. The iCOH measures functional connectivity strength based on the phase angle and is unaffected by volume conduction effects. In contrast, PSI is a method to measure directional effective connectivity, allowing the investigation of information flow between different brain regions. This study analyzed multi-site electrophysiological signals during mPFC DBS, investigating acute electrophysiological and functional connectivity changes. The findings offer valuable electrophysiological insights that could inform the development of future DBS treatments for depression.

II. Methods

A. Depression model and Surgery

Chronic restraint stress (CRS) model is a widely recognized model of depression, known to induce behaviors characteristic of anxiety and depression, and decrease glucocorticoid receptor expression[4]. Male Sprague Dawley rats (230-250g) were subjected to two hours of restraint in acrylic cylinders for two weeks. Eight rats exhibiting depressive behaviors were selected for DBS analysis.

*Research supported by STI 2030 - Major Projects (2021ZD0200405), Pioneer R&D Program of Zhejiang (2024C03001), Outstanding Youth Program of Zhejiang Natural Science Foundation (LR23H180002) and the Fundamental Research Funds for the Central Universities (2024ZFJH01-01).

Chang Wang and Kedi Xu* (corresponding author, xukd@zju.edu.cn) are with the Department of Biomedical Engineering, Zhejiang University, and the Nanhu Brain-computer interface institute, Hangzhou, China.
Chaonan Yu is with the Nanhu Brain-computer Interface Institute, Hangzhou, China.

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The surgical procedures were discribed in our previous study[5]. Twelve 65 μm diameter nichrome electrodes (A-M Systems™) were bilaterally implanted into twelve brain regions implicated in depression. The specific implantation targets were the lateral habenula (LHb: -3.50 mm AP, ±0.90 mm ML, -4.40 mm DV), subthalamic nucleus (STN: -3.90 mm AP, ±2.40 mm ML, -7.50 mm DV), medial prefrontal cortex (mPFC: +3.0 mm AP, ±0.8 mm ML, -2.50 mm DV), hippocampal CA1 (CA1: -4.20 mm AP, ±3.00 mm ML, -2.20 mm DV), nucleus accumbens (NAc: +1.80 mm AP, ±1.00 mm ML, -7.20 mm DV), and medial forebrain bundle (MFB: -3.60 mm AP, ±1.80 mm ML, -8.70 mm DV), and the implantation sites are shown in Figure 1. LFPs were recorded to assess the acute electrophysiological effects of mPFC DBS and its interactions with other depression-associated regions. All procedures were approved by the Animal Care and Use Committee of Zhejiang University.

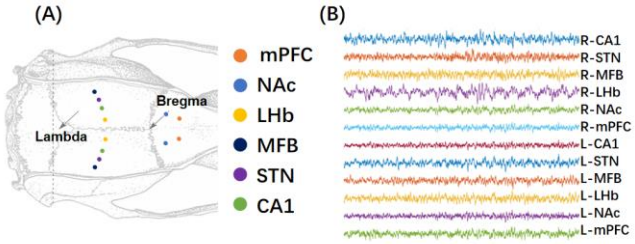

Figure 1. (A) Schematic diagram of the top view showing the implanted targets. (B) Multi-site LFP signals.

B. DBS procedure, Behavioral tests and Signal recording

The parameters for mPFC DBS were based on previous study[2], with a stimulation frequency of 130 Hz and a duration of two hours for two weeks. Behavioral tests, including the open field test (OFT) and sucrose preference test (SPT), were conducted before and after CRS, as well as before and after DBS. LFPs were recorded at a sampling rate of 1 kHz using RHD2132 system (Intan Technologies). For each rat, a 10-minute resting baseline phase was first recorded prior to DBS as the baseline. After two hours of DBS, a 10-minute resting phase was immediately recorded and classified as the acute DBS signal.

C. Data Analysis

Power spectral density (PSD) is a commonly used method in LFP analysis[6]. In this study, LFP signals were processed using the Chronux toolbox to analyze spectral power alterations (http://chronux.org). Signals were notch-filtered at 50 Hz. The following frequency bands were analyzed[7]: delta (0.3–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), low gamma (30–48 Hz), and high gamma (52–98 Hz). The spectral power within each frequency band was normalized.

Coherence is used to describe brain interactions by quantifying the phase between two signals. However, one limitation of magnitude coherence is its potential to be influenced by volume conduction effects. To improve this, the iCOH was considered[8]:

$$C_{xy}(f) = \frac{S_{xy}(f)}{\sqrt{S_{xx}(f)S_{yy}(f)}}$$

$$iCOH = \mathrm{Im}ag(C_{xy}(f))$$

$S_{xy}(f)$ represents cross-spectrum at frequency f. In contrast to magnitude coherence, iCOH is unaffected by volume conduction and reflects genuine source interactions. For the iCOH analysis, data were divided into non-overlapping 1-second intervals, with all analyses performed using the Chronux toolbox. The iCOH values between the stimulation site and all other potential depression-related targets were calculated across six distinct frequency bands.

The phase slope index (PSI) quantifies the direction of the phase slope in the cross-spectrum between two time series[9], derived from the iCOH:

$$\Psi_{i,j} = \prod(\sum coh_{ij}^{*}(f)coh_{ij}(f+sf))$$

The sign of the slope indicates the direction of causal flow: a positive slope suggests upward information flow (from one site to another), while a negative slope indicates the reverse direction. It is important to note that PSI does not differentiate between direct and indirect causal effects. Further details on the calculation of PSI can be found in the study[9]. The PSI between the target site and other regions was calculated within the range of each frequency band.

D. Statistical analysis

Statistical analyses were performed using MATLAB, Jamovi, and GraphPad Prism. Paired t-tests were employed to assess the effects of acute DBS. Results are presented as mean ± SEM, with significance levels defined as *p < 0.05, **p < 0.01.

III. RESULTS

A. Behavioral analysis

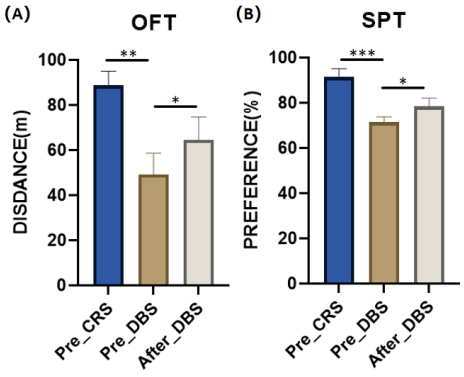

Figure 2. Depression-like behaviors induced by CRS and DBS. (A) Total distance in the OFT test; (B) Sucrose preference in the SPT test.

Due to electrode displacement, subsequent analysis was conducted on the LFP signals from 8 rats. Following CRS, eight SD rats exhibited depression-like behaviors, showing significant differences compared to their pre-modeling state (OFT: p=0.0059, SPT: p=0.0003, paired samples t-test)[5]. After two weeks of chronic DBS, both SPT and OFT outcomes improved significantly (OFT: p=0.0452, SPT: p=0.0251, paired samples t-test), and depressive-like behavioral symptoms decreased.

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B. *Spectral analysis of L-mPFC after acute DBS*

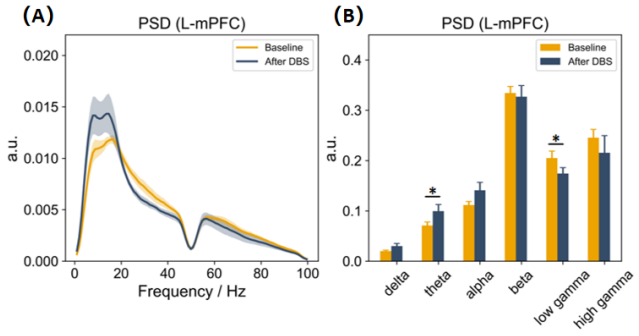

Figure 3. Spectral analysis of L-mPFC after acute DBS. (A) Normalized power spectral density curve at Baseline (yellow) and after acute DBS (blue), and the shaded region indicates SEM; (B) L-mPFC PSD values of each frequency band. L-mPFC, left medial prefrontal cortex.

To study the electrophysiological effect of the L-mPFC after acute DBS, we compared the PSD features before and after DBS. The PSD curve is shown in Figure.2. Decreased PSD in the low gamma band ($p = 0.036$, paired samples t-test) and elevated PSD of theta band $p = 0.049$, paired samples t-test) were observed.

C. *iCOH changes after acute DBS*

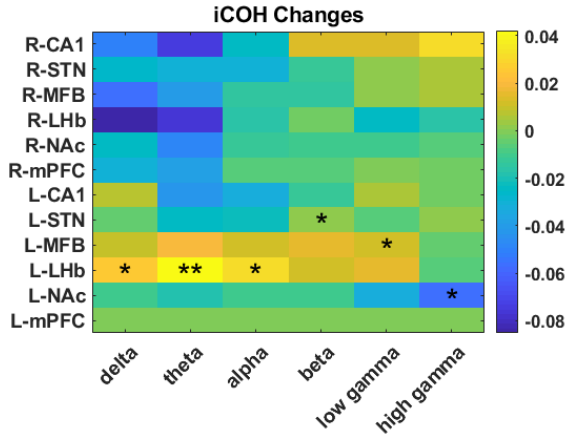

Figure 4. Rate of Change in iCOH Matrix. Each rectangle represents the rate of change in iCOH values between the stimulation site and other regions across different frequency bands. L-mPFC, left medial prefrontal cortex; R-mPFC, right medial prefrontal cortex; and similarly for other regions.

We plotted the changes in iCOH between the stimulation site (L-mPFC) and other regions following DBS, as shown in Figure 4. All the iCOH values that showed significant statistical differences post-DBS are depicted. The most significant changes were observed between the L-mPFC and the ipsilateral LHb, with notable increases in the delta ($p=0.0100$, paired samples t-test), theta ($p=0.0034$, paired samples t-test), and alpha ($p=0.0123$, paired samples t-test) frequency bands. These results suggestted that acute DBS activates the mPFC-LHb circuit, and according to previous studies, this activation might be linked to changes in extracellular ATP and P2X2 receptors in GABAergic interneurons[10]. Additionally, significant changes in functional connectivity were also observed between the L-mPFC and the ipsilateral STN ($p=0.0469$, paired samples t-test), MFB ($p=0.0443$, paired samples t-test) and NAc ($p=0.0136$, paired samples t-test). The iCOH changes with significant changes are shown in Figure 5.

Notably, when assessing functional connectivity using iCOH, all significant changes were observed on the same side as the stimulation site, with no significant differences in connectivity between the stimulation site and contralateral regions. This lateralized effect suggestted that DBS primarily influences ipsilateral brain circuits, likely due to the limited spread across hemisphere[10]. An additional possible explanation is that iCOH, as a measure that does not indicate the direction of information flow, might fail to capture changes in the directionality of communication between regions. While information flow may have altered between the sites, no significant changes were detected in the iCOH, which does not represent the directionality of interactions.

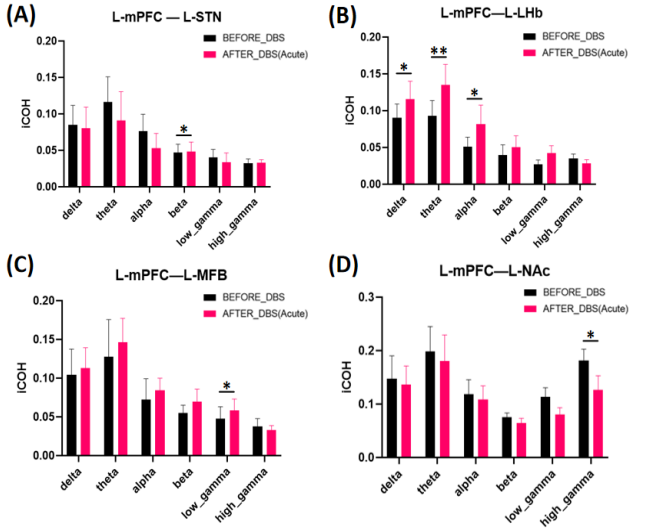

Figure 5. iCOH between the L-mPFC and L-LHb (A), L-STN(B), L-MFB (C), and L-NAc (D) in six frequency bands.

D. *PSI changes*

Figure 6 shows the PSI changes after DBS. Significant changes in information flow using PSI were observed between L-mPFC and R-CA1 ($p=0.0407$, paired samples t-test), R-MFB ($p=0.0349$, paired samples t-test), and R-LHb ($p=0.0278$, paired samples t-test), as well as between R-NAc and R-LHb ($p=0.0222$, paired samples t-test). These findings reveal distinct patterns in information flow alterations. Notably, no significant PSI-based functional connectivity changes were detected within the left hemisphere following L-mPFC DBS, indicating possible disorder in its functional connectivity. In contrast, significant changes in information flow were observed between the left mPFC and several right - hemisphere depression-related targets such as R-CA1, R-MFB, and R-LHb. It suggests that acute DBS can effectively modulate information flow across hemispheres, influencing the communication between the stimulated region and contralateral depression-related areas, which may play a pivotal role in the antidepressant mechanism of DBS. These findings suggest that acute DBS induces substantial modifications in the information flow associated with the stimulation site, highlighting the complex impact of DBS on brain network communication across hemispheres.

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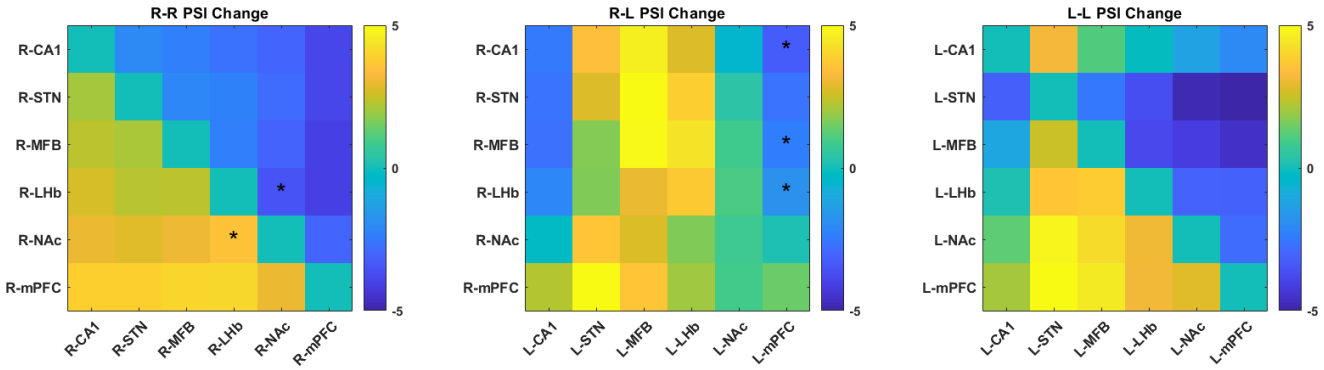

Figure 6. PSI changes after acute DBS. Each PSI (i, j) square represents the PSI change from site i to site j. Positive values indicate upward information flow (from site i to site j), while negative values indicate downward information flow.

IV. DISCUSSION

This study aimed to investigate the acute effects of DBS in a depression model using multi-site LFPs. By analyzing changes in PSD, functional connectivity and information flow, we identified significant alterations in brain activity following acute mPFC DBS. These results contribute to the understanding of how DBS influences brain circuits related to depression.

Acute mPFC DBS led to distinct alterations in the PSD. Specifically, an increase in theta band power and a decrease in low gamma band power were observed. These changes in PSD might reflect the modulation of neural activities within the mPFC, potentially influencing its downstream functions related to mood regulation. Regarding functional connectivity, the iCOH analysis showed that mPFC DBS induced significant changes in connectivity, but these were confined to the stimulated hemisphere. The most prominent changes occurred between the left mPFC and the ipsilateral LHb, along with other ipsilateral regions. This lateralized effect implies that DBS has a more immediate impact on the ipsilateral brain circuits, possibly due to the limited spread of stimulation across the hemisphere. However, when exploring information flow using the PSI, a different pattern emerged. Despite no significant PSI-based functional connectivity changes within the left hemisphere after L-mPFC DBS, significant alterations in information flow were detected between the L-mPFC and several contralateral depression-related regions. This indicates that although iCOH failed to capture cross-hemisphere changes, PSI revealed that DBS can effectively modulate information flow across hemispheres.

While our study provides insights into the acute effects of mPFC DBS, there are several limitations to consider. First, the sample size of rats used in this study was relatively small, and future studies with larger sample sizes will be necessary to confirm the generalizability. Moreover, it would be beneficial to investigate the chronic effects in future studies. An innovation of this study lies in the use of multi-site LFPs. LFPs allow for direct recordings from deep brain structures, providing a more comprehensive view of the neural dynamics involved in depression.

V. CONCLUSION

In conclusion, we studied the acute electrophysiological changes of multi-site LFPs after DBS in mPFC. We found that different electrophysiological measures, such as PSD, iCOH, and PSI, provide complementary information about the effects of DBS on neural activities, connectivity, and information flow. These findings not only enhance our understanding of the electrophysiological mechanisms underlying mPFC DBS in depression, but also hold promise for optimizing DBS treatment strategies in the future.

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