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Prefrontal delta oscillations during deep brain stimulation predict treatment success in patients with obsessive-compulsive disorder

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Deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS) is a promising neurotherapeutic approach for severe and refractory cases of obsessive-compulsive disorder (OCD). Successful VC/VS-DBS treatment alters function in frontostriatal pathways important for the etiopathogenesis of OCD [1–3]. Monitoring changes in frontostriatal functioning resulting from active DBS can reveal signatures of DBS engagement with disease-relevant pathways [1,4]. In particular, modulation of the dorsal-medial prefrontal cortex (dmPFC) seems to be crucial for therapeutic success: symptomatic OCD patients demonstrate hyperconnectivity between the VC/VS and dmPFC, which is normalized following successful VC/VS-DBS [1,5,6]. VC/VS-DBS also alters delta oscillations (1–4 Hz) across frontostriatal regions in rodents and humans, including the dmPFC [1–5]. However, the relationship between dmPFC delta during VC/VS-DBS stimulation and clinical outcome has not been directly tested. We expected that changes in dmPFC delta resulting from active VC/VS-DBS would predict better therapeutic outcomes.

This study included data from ten patients (5 females) with refractory and severe (Yale-Brown Obsessive Compulsive Scale [YBOCS] $\geq$ 25) OCD that were being treated with DBS implants in the VC/VS (for details on study design and recruitment see Ref. [7]). Patients underwent bilateral stereotactic implantation of quadripolar leads (Model 3387 or 3389 DBS Lead; Medtronic; Minneapolis, MN, USA) with the two most ventral/distal contacts targeting the VS and two most dorsal/proximal contacts located in the VC (Fig. 1A). Stimulated contacts and stimulation parameters were chosen based on the best clinical outcome (Stimulation parameters are reported in Supplementary Table 1). Participants were hospital inpatients for one week during post-surgical follow-ups (6 month and 12 month), and completed electroencephalographic (EEG) recordings and clinical assessments at that time. EEG and clinical data from 6 month follow up were the focus of this report. Total score on the YBOCS at 6 months was the primary measure of treatment success. At 6 months, three participants showed a partial response (25–35% YBOCS reduction) and two participants showed a full response ($\geq$35% YBOCS reduction). Clinical assessments were completed with DBS-ON.

EEG (58 electrodes with 10–20 placement sampled at 5000 Hz) was recorded for 10 min consisting of six eyes-closed segments lasting one-minute each, intermitted by 5 eyes-open segments lasting 26 seconds each. Stimulator artifacts were removed using a combination of spectral outlier rejection, zero phase-shift FIR filters (1–45 Hz), semi-automatic ICA-based component subtraction, and spherical-spline interpolation using EEGLAB and custom MATLAB code. Delta amplitude in the dmPFC was calculated using the eLORETA software for inverse modeling (http://www.uzh.ch/keyinst/loreta). In four participants, EEG measurement was first carried out in the DBS-ON, in the other six participants in the DBS-OFF.

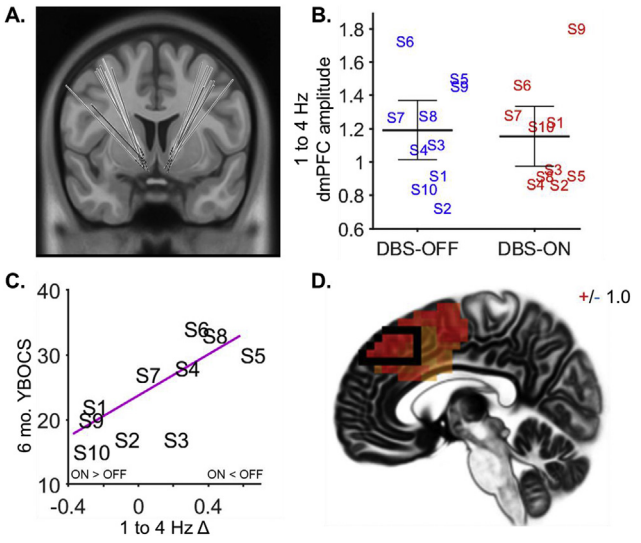

Fig. 1. Enhancement of resting delta amplitude within the dmPFC during VC/VS-DBS predicts fewer OCD symptoms at 6 months postsurgery. **A.** DBS electrode locations lie within the VC/VS on postoperative imaging. A postoperative scan was missing for one patient. **B.** There was no significant DBS-OFF vs. DBS-ON condition difference for dmPFC delta amplitude, but there was substantial variability in delta responsivity to DBS across patients. **C.** Patients characterized by more dmPFC delta amplitude for DBS-ON than DBS-OFF had lower YBOCS scores at 6 months postsurgery. **D.** Significant ($p < .05$) positive correlations between delta responsivity and 6 month YBOCS scores, indicating that more delta for DBS-ON than DBS-OFF in the dmPFC predicted fewer OCD symptoms at follow up. Black outline indicates dmPFC region-of-interest used for main analysis (e.g., Fig. 1B and C).

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The DBS device was shut down for at least 12 hours prior to DBS-OFF EEG recordings. Eight of ten participant's EEG recordings were collected during 6 month follow up. One participant's EEG was from 12 month follow-up. Another participant had data from both 6 month and 12 month follow up, and eLORETA delta amplitudes from both recordings were averaged together for this participant.

Hypothesis-driven Spearman correlations were calculated between dmPFC delta responsivity (DBS-OFF minus DBS-ON change scores) and OCD symptoms (YBOCS) at 6 months. An exploratory analysis examined correlations between amplitude change and OCD symptoms across canonical frequency bands (1–4 Hz, 4–8 Hz, 8–13 Hz, and 15–25 Hz) and 84 Brodmann areas (42 parcels in each hemisphere from eLORETA software). Exploratory correlations were corrected for multiple comparisons using the False-Discovery Rate (FDR) method.

Fig. 1B shows that resting dmPFC delta activity was unchanged at the group-level for DBS-OFF compared to DBS-ON. Notably, there is significant variation in delta band amplitude within individual subjects across the two conditions. Fig. 1C shows that individual variability in responsivity of dmPFC delta correlated significantly with 6 month YBOCS scores ($r = 0.809$, $p = .005$): patients with greater dmPFC delta during DBS-ON compared to DBS-OFF had the fewest OCD symptoms. Greater delta responsivity within the dmPFC also predicted relative improvement (i.e., YBOCS change scores) in OCD symptoms from presurgical baseline ($r = 0.87$, $p = .001$). Fig. 1D shows the dmPFC ROI used for our primary analysis overlaid on correlations between YBOCS scores and delta responsivity at each voxel. Greater delta oscillations for DBS-ON than DBS-OFF within the right dmPFC (i.e., BA 8) strongly predicted fewer OCD symptoms at 6 months ($r = 0.921$, FDR-$p = .013$) in an exploratory/data-driven analysis. There were no other frequency bands or brain regions associated with treatment outcome.

In general, delta oscillations are hypothesized to facilitate coordinated activity across frontostriatal regions important for goal-directed activity [2,3,8], and delta activity within the dmPFC may have a more specific role in anxiety and compulsive behavior [1,8,9]. Mean delta amplitude across the 10 participants was unchanged by DBS (Fig. 1B), but four of five treatment responders had increased dmPFC delta amplitude during DBS-ON. More frontal delta at rest is consistently related to more OCD symptoms in nonsurgical cohorts [reviewed in 8]. In contrast, EEG studies with VC/VS-DBS cohorts have found stronger [1] and weaker [2,3] frontostriatal delta oscillations during DBS-ON recordings. Some small neurometabolic studies with VC/VS-DBS patients also implicate the dmPFC, with results showing more dmPFC [10] and less dmPFC [4] activity during DBS-ON in treatment responders. In this regard, direction of modification of dmPFC function probably varies with stimulator placement and patient anatomy, insofar as treatment-relevant pathways are highly specific [4,6]. Altogether, these results suggest that monitoring of dmPFC delta may facilitate placement of DBS electrodes into treatment-relevant circuitry and be a promising target for less invasive neuromodulatory treatment of refractory OCD and related diseases.

Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.09.008.

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