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Toward Closed-Loop Intracranial Neurostimulation in Obsessive-Compulsive Disorder

To the Editor:

Studies in Parkinson's disease have demonstrated suppression of symptoms using beta-band power intensity in the subthalamic nucleus as an adaptive control signal for deep brain stimulation (DBS) (1–3). While improvement in motor symptoms is readily evaluated, clinicians rely on subjective self-reporting to optimize DBS parameters and guide therapy in psychiatric diseases. Stimulation ideally would be tailored to electrophysiological biomarkers of the patient's symptomatic state (4). Several signals in the ventral capsule/ventral striatum (VC/VS) related to obsessive-compulsive disorder (OCD) symptom severity have been studied (5–7), but no clear biomarker has emerged. Recently, a biomarker-driven closed-loop stimulation therapy was implemented in a patient with depression, stimulating VC/VS in response to amygdala gamma signals (8), illustrating the complexity and promise of these therapies for psychiatric disease.

A proof-of-concept strategy to identify neural biomarkers of behavioral states in patients with OCD was recently reported, using intracranial VC/VS local field potentials (LFPs) recorded with a research device (Medtronic Summit RC+S) (9). Wireless recording in 1 individual during at-home activity demonstrated the feasibility of capturing chronic intracranial electrophysiology during daily symptom fluctuations, in which negative correlations of delta power with symptom severity were observed. Using a commercially available sensing-enabled DBS device (Percept; Medtronic), we found a different correlation in a 46-year-old female patient with OCD who underwent VC/VS DBS (Figure 1A, B). The patient reported mixed obsessive (fear of self-harm and passing out, obsessions with body movement) and compulsive (mental rituals, persistent pursuit of verbal reassurance) symptoms, refractory to cognitive behavioral therapy, pharmacotherapy, and electroconvulsive therapy. The patient was implanted with bilateral leads (model #3387) and the Percept device, which is approved by the Food and Drug Administration for clinical use and allows recording of selected 5-Hz-wide-band LFP amplitudes.

Following electrode implantation, LFP signals were measured using the clinician programmer, which displays the amplitude of the differential signal between each contact pair. The bipolar pair with largest peak was chosen for chronic tracking (left: E0–E2, 12.7 ± 2.5 Hz; right: E8–E10, 7.8 ± 2.5 Hz) (Figure 1B). The device records at 250 Hz, calculates the fast Fourier transform, and logs out the mean amplitude in the tracked frequency band every 10 minutes. Recordings over 19 months (9366 hours) spanned programming epochs of varying stimulation amplitudes (0–6 mA). Bilateral chronic recordings were estimated to account for ∼10% of the battery life in a typical patient, but battery longevity is expected to be 15% greater than in the previous-generation device (10). Impedance measurements at each session (clinic visit where data were downloaded and the Yale-Brown Obsessive Compulsive Scale

and Montgomery–Åsberg Depression Rating Scale were collected) confirmed the stability of neural recordings. In reviewing these chronic data, we filtered out spike-shaped artifacts using a 1-hour moving-median window (Figure 1C). Data analysis occurred under an institutional review board–approved protocol.

We found a consistent suppression of LFP alpha amplitude (left: ∼27%; right: ∼71%) (Figure 1E) compared with the initial amplitude recorded, with concomitant improvement (>34.3%) of OCD symptoms and general improvement in quality of life. During a period of worsening postoperative self-reported OCD symptoms and an anxiety surge secondary to a decrease in clomipramine dosing (25% tapering, from 200 mg to 150 mg), we observed an increase in left alpha amplitude (∼1724 [arbitrary units (AU)] vs. ∼1405 [AU], mean value in a 2-week window after vs. before clomipramine tapering). We interpret the LFP amplitude peaks during session 3 (S3) as indicating unstable therapeutic suppression, unmasked by medication reduction, which subsequently resulted in sustained higher amplitudes. When clomipramine dosing was increased, symptoms improved and left LFP alpha amplitude again decreased (∼716 [AU] vs. ∼1357 [AU], mean value in a 2-week window after vs. before clomipramine baseline levels). We note that LFP amplitude started to decline prior to increasing clomipramine, in conjunction with a 0.5-mA increase in stimulation, but remained stably lower following the medication dose increase. The average left hemisphere amplitude dropped between S7 (∼1158 [AU]) and S8/S9 (∼918/∼492 [AU]), in conjunction with the Yale-Brown Obsessive Compulsive Scale decrease, despite lowering stimulation amplitude to 3 mA. These observations suggest that clomipramine and stimulation may each exert therapeutic benefit through a mechanism reflected in alpha amplitude (Spearman's ρ = 0.89, p = .033). Sustained clinical benefit in the setting of a lower stimulation dose may reflect a shift to an improved clinical state that does not require the same stimulation strength to maintain.

We collected event-locked power spectral density (PSD) in a 30-second window after self-reported excessive thought events tracked by the patient using the BrainSense Events modality (Medtronic). The patient was instructed to mark her excessive thoughts when deemed most debilitating. The patient marked events only during the first 6 months following initiation of stimulation, suggesting a reduction of the likelihood of a surge in excessive thoughts as therapy proceeded. When comparing the event-locked PSD with the BrainSense Survey PSD, we found a broadband increase of power in 5 to 30 Hz for both sides (Figure 1F, left). Both change from baseline of the event-locked power at 7.8 Hz and LFP alpha amplitude in the right hemisphere were suppressed over time during therapeutic stimulation. Differences in sensing contact location and the frequency tracked by the device precluded direct left versus right hemisphere comparison and may explain the differential temporal dynamics of LFP activity between hemispheres.

Capturing robust electrophysiological biomarkers in OCD DBS is challenging because of the individuality and complexity
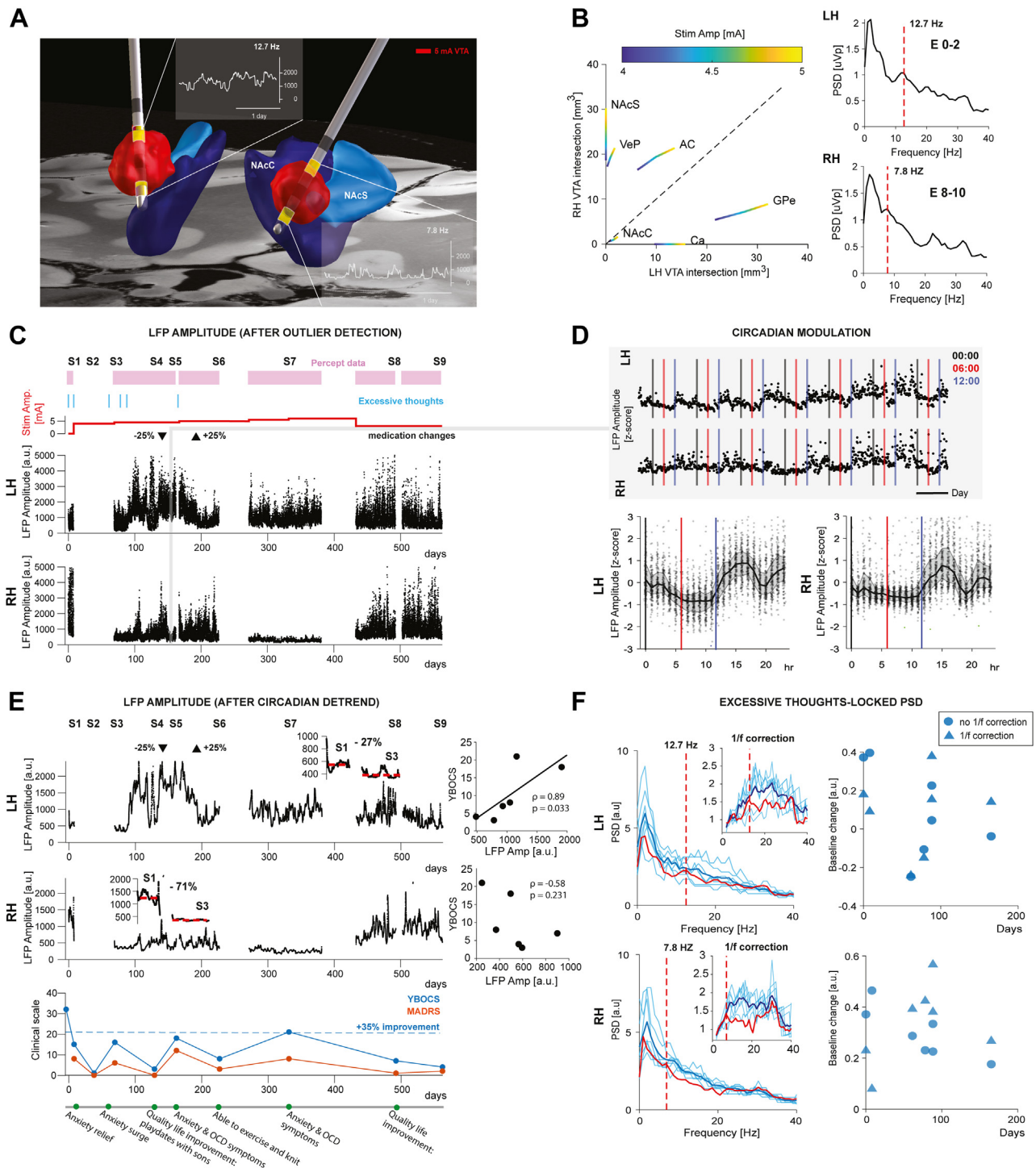
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Figure 1. Chronic ventral capsule/ventral striatum recordings from a patient with obsessive-compulsive disorder (OCD) with a Food and Drug Administration–approved sensing-enabled deep brain stimulation device. **(A)** Chronic bipolar local field potential (LFP) amplitude changes were recorded from adjacent contacts (yellow) to the active contact used for therapeutic stimulation. Electrodes are visualized in standard (Montreal Neurological Institute) space with respect to the nucleus accumbens ([15],[16]), and the volume of tissue activated (VTA) is featured in red. **(B)** (Left) The VTA overlaps with anatomical regions, across the different stimulation settings used during the 8-month period. (Right) The power spectral densities (PSDs) logged out by the device in the BrainSense Survey modality are depicted, which demonstrated 12.7-Hz and 7.8-Hz power peaks in the left hemisphere (LH) and right hemisphere (RH), respectively. These frequencies (vertical dashed red line) were used to build the narrow-band filter to chronically record the LFP signal. **(C)** Chronic bipolar recordings acquired over 8 months by the Percept device in the BrainSense Timeline modality. Spike-shaped artifacts more than three local scaled mean

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of symptoms, day-to-day physiological fluctuations, and latency between therapeutic interventions and symptom evolution. Continuous chronic recordings spanning multiple days during naturalistic states is crucial for understanding the complex interaction between electrophysiology and behavior. Indeed, we observed location and frequency-independent circadian LFP alpha amplitude changes (Figure 1D). Accounting for circadian changes may be critical to optimize the therapeutic potential of adaptive DBS algorithms that rely on an amplitude threshold–based control policy (4,11).

Our report constitutes a first step in characterizing a potential LFP biomarker of OCD symptom severity, in line with previous data correlating alpha oscillations with OCD symptoms (6,7,12). Generalization of these results is limited by single-subject data, scattered postoperative assessments, and symptom cofluctuations. Determining the optimal computational time scale of alpha amplitude and defining its variability within and between patients may help to establish whether adaptive DBS strategies (13) could be used to optimize treatment in individuals with OCD. Exploration of cortical LFPs, which have advantages over lead-recorded electrophysiological triggers in closed-loop DBS (14), may also be valuable.

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absolute deviations away from the local median within a sliding window (window size: 6 samples; 1 hour) were considered as outliers and removed (on average, 3% of data points were removed per recording). Outliers were replaced by linearly interpolating neighboring points. Note that these LFP signals should be interpreted as signal amplitude in a specific narrow frequency window instead of as time domain fluctuations. Self-marked excessive thoughts events are depicted as vertical cyan lines. Stimulation amplitude (Stim Amp) is displayed with a red line. Triangles indicate clomipramine dose changes. The time points session 1 (S1), S2, etc., constitute different data download sessions (S1 = immediate postoperative). Pink rectangles indicate Percept data availability. No data were available for S2 because the data recording had been turned off accidently during this period. **(D)** LFP amplitudes exhibited a circadian pattern in both hemispheres, as seen in an example week (top) and the average of the 24-hour LFP amplitude values across all days (bottom), in which a positive peak was visible around 15:00. **(E)** The time course of the 1-day rolling median LFP amplitude (i.e., after circadian modulation removal), Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (blue line), Montgomery–Åsberg Depression Rating Scale (MADRS) (orange line), and self-reported OCD symptoms (green dots). Y-BOCS improvement was consistently >35% (blue dashed line). Horizontal red dashed lines indicate median LFP amplitude values around each session. Spearman's ρ and p values were computed to assess the correlation between LFP amplitude and Y-BOCS. **(F)** Normalized PSD locked to excessive thought markings (light cyan lines for single events and bold cyan for the mean across events) were computed in a 30-second postevent window by the Percept device in the BrainSense Events modality. PSD during the BrainSense Survey is depicted for comparison (red line). The inset plot shows the PSD after the 1/f correction. LFP power change is shown before (cyan circles) and after (cyan triangles) aperiodic-fitting removal. This information was extracted from the PSD at the same frequency identified in the BrainSense Survey modality (horizontal red line). In all panels, days are expressed as days after surgery. a.u., arbitrary units; AC, anterior commissure; Ca, caudate; GPe, globus pallidus external; NAcC, nucleus accumbens core; NAcS, nucleus accumbens shell; VeP, ventral pallidum.

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