High beta power in the ventrolateral prefrontal cortex indexes human approach behavior: a case study

Abbreviated Title: Neural correlates of approach behavior in vlPFC

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Abstract

Deep brain stimulation (DBS) of the ventral capsule and ventral striatum (VC/VS) is an effective therapy for treatment resistant obsessive-compulsive disorder (trOCD). DBS initiation often produces acute improvements in mood and energy. These acute behavioral changes, which we refer to as "approach behaviors", include increased social engagement and talkativeness. We investigated the relationship between stimulation amplitude, spectral power in the ventrolateral prefrontal cortex (vlPFC), and speech rate in one male patient with trOCD implanted with bilateral VC/VS DBS leads and subdural electrodes adjacent to orbitofrontal cortex (OFC) and vlPFC. Several times over the first 17 weeks of therapy, we conducted experiments where we recorded data during epochs of high amplitude or zero/low amplitude stimulation. We found that both speech rate and vlPFC power in a high beta frequency band (31±1.5Hz, 1/f activity removed) increased during high amplitude as compared to low amplitude periods. Speech rate correlated with vlPFC high beta power. These effects were more consistent across time points in the left hemisphere than the right. At week 17, we performed an experiment where stimulation was held constant while the patient was asked to speak or remain silent. We showed that the presence or absence of speech was not sufficient to increase the vlPFC high beta power, suggesting stimulation is a key driver of the observed neurobehavioral phenomenon. Our results suggest vlPFC high beta power is a biomarker for approach behaviors associated with VC/VS DBS.

Significance Statement

In one patient receiving DBS of the ventral capsule and ventral striatum (VC/VS) for OCD, we leveraged a unique clinical opportunity to study the neurophysiological basis of approach behaviors using chronic intracranial recordings from prefrontal cortical regions. VC/VS DBS initiation often produces acute improvements in mood and energy associated with increased social engagement and talkativeness (approach behaviors). Our results suggest that vlPFC high beta activity (particularly in the left hemisphere) may index approach behaviors (quantified here by speech features). This neural signal is consistent with our previous non-invasive studies identifying predictors of mania in patients with bipolar disorder, and we hope to gather further evidence that it indexes a continuum from adaptive approach behavior to maladaptive manic symptoms.

Introduction

Obsessive-compulsive disorder (OCD) is common and debilitating, with a prevalence of 2-3% in the general population (Goodman et al., 2021). Pharmacological and cognitive behavioral therapy are first-line treatments but fail to provide substantial benefit in 20-40% of patients (Romanelli et al., 2014; Öst et al., 2015). For treatment resistant individuals, deep brain stimulation (DBS) targeting the ventral portion of the anterior limb of the internal capsule and subjacent ventral striatum (ventral capsule/ventral striatum, VC/VS) is approved by the U.S. FDA in the form of a humanitarian device exemption and produces clinical response in approximately 66% of patients (Gadot et al., 2022). However, the neural and behavioral mechanisms by which DBS achieves therapeutic benefit in OCD are not well understood.

Whereas improvement in OCD symptoms after DBS activation generally requires months, stimulation initiation and subsequent adjustments can have immediate effects on mood and energy. These acute effects were first described as “mirth” or “positive affect” responses, referring to smiling (often a hemi-smile contralateral to the side of stimulation) along with variable degrees of laughter, or feelings of increased energy (Goodman et al., 2010; Provenza et al., 2021; Shofty et al., 2022; Sheth and Mayberg, 2023). These behaviors are not synonymous with OCD improvement, but their early appearance has been considered a possible predictor of eventual clinical response (Haq et al., 2010; Tsai et al., 2014; Shofty et al., 2022). We often observe a constellation of more subtle behaviors even in the absence of mirth response, including increased talkativeness, a desire to socialize and engage in pleasurable activities, and extroversion consisting of asking questions rather than simply responding.

We refer to this set of behaviors as "approach" behaviors, as they encompass approach-related elements of mood, energy, and socialization. Characterizing them like so helps explain certain side effects precipitated by over-stimulation. Whereas some degree of increase in these approach behaviors can be adaptive, their over-exuberant expression can produce an overly approachful, disinhibited "hypomanic" phenotype involving impulsivity, reward seeking, overabundant energy, increased libido, and decreased need for sleep (Okun et al., 2004; Haq et al., 2010; Tsai et al., 2014; Widge et al., 2016; Denys et al., 2020).

Approach behavior has been widely studied in the context of hypomania and mania onset in bipolar disorder. In previous human fMRI studies, we found that during reward anticipation increased activity in the ventrolateral prefrontal cortex (vlPFC) predicted risk of future hypomania/mania (Bermpohl et al., 2010; Nusslock et al., 2012; Caseras et al., 2013; Chase et al., 2017; Edmiston et al., 2020). Our scalp electrophysiology (EEG) studies further revealed that high frequency activity in the beta and gamma bands in ventral/orbital regions may be driving this vlPFC-mania relationship (Coffman et al., 2021). Importantly, circuits involving fibers that connect the prefrontal cortex (including orbitofrontal and vlPFC) with the thalamus and other deep nuclei via the ventral capsule are known to be involved in reward processing, cognition, and mood—processes that are both dysregulated in OCD and modulated by VC/VS DBS (Sheth et al., 2012; Haber and Heilbronner, 2013; McGovern and Sheth, 2017; Calzà, 2019). Therefore, we hypothesized that we might find a similar neural signature underlying the acute increases in approach behavior we observe after VC/VS DBS.

The aforementioned imaging and scalp EEG studies are limited in spectral and spatial resolution, respectively. Intracranial neural recordings provide simultaneously high spatial and spectral resolution. We took advantage of a unique opportunity to chronically record intracranial

neural data from the vlPFC in a patient with severe OCD implanted with a recording capable DBS device targeting VC/VS. Whereas recordings enabled by these implants are usually limited to the stimulation site, this individual also had chronically implanted electrocorticography (ECoG) electrodes over the orbitofrontal cortex (OFC) and vlPFC as part of a clinical trial (NCT04806516). By synchronizing these recordings with DBS parameter adjustments and audio/video data of the participant, we identified a relationship between stimulation-induced increases in approach behavior and changes in vlPFC activity.

Materials and Methods

Study design

One adult male (age 33, Caucasian) with a principal diagnosis of severe, treatment-resistant OCD underwent DBS of the VC/VS following informed consent (NCT04806516). The protocol was approved by the local institutional review board at Baylor College of Medicine (Protocol number H-44941). His primary OCD symptoms include contamination OCD characterized by excessive and ritualized hygiene and avoidance measures, and a need for exactness (related to contamination). Initial Yale Brown Obsessive-Compulsive (Y-BOCS) (Goodman et al., 1989) score was 38, and initial Y-BOCSII (Storch et al., 2010) score was 46. The participant previously failed adequate trials of selective serotonin reuptake inhibitors (SSRIs), clomipramine, and antipsychotic augmentation, as well as a course of expert exposure and response prevention (ERP) therapy. Due to the single subject design, we did not conduct age/sex/gender-based analyses.

We bilaterally implanted DBS leads (model 3387) with 1.5 mm spacing in the ventral striatum/ventral striatum (VC/VS) region. Additionally, we placed electrocorticography electrodes (Medtronic Resume II, model 3587A25) over the orbitofrontal cortex (OFC) and vlPFC. In each hemisphere, we connected the DBS lead and ECoG lead to an ipsilateral pulse generator. We used an investigational DBS device, the Summit RC+S (Medtronic, Minneapolis, MN, USA), capable of both stimulating and recording local field potential (LFP) activity.

DBS electrode localization

MRI scans were acquired preoperatively using a Siemens Prisma 3T apparatus, equipped with a 64-channel head-neck coil. We acquired both contrast-enhanced and non-contrast-enhanced preoperative stereotactic MRI scans, in addition to a stereotactic CT scan without contrast, followed by a non-contrast CT scan post-surgery. Subsequently, the postoperative CT imagery was precisely mapped to the T1-weighted MRI framework, facilitating the delineation of electrode contact points in correlation with the pertinent neural structures.

Reconstruction and visualization of final electrode placements utilized preoperative stereotactic T1-weighted MRI without contrast and postoperative stereotactic CT scans. Cortical (pial) surfaces were reconstructed using FreeSurfer version 7.1.1 (https://surfer.nmr.mgh.harvard.edu/) (Fischl, 2012) and the T2-weighted MRI was used to enhance the reconstruction quality. The postoperative CT data were aligned to the preoperative T1w MRI using the Functional Magnetic Resonance Imaging for the Brain Software Library's Linear Image Registration Tool (v6.0) (Jenkinson and Smith, 2001; Jenkinson et al., 2002). Electrode coordinates, derived manually from the merged CT data within BioImage Suite version 3.5b1 (Joshi et al., 2011), were integrated into the native MRI framework. Visualization

of the reconstructed cortical surface, the delineated subcortical structures, and the electrode coordinates for depth and cortical strip electrodes was performed using a Multi-Modal Visualization Tool (Felsenstein et al., 2019; Peled, n.d.). The ventral striatum was delineated on the T1-weighted images based on subcortical segmentation, and the anterior commissure was manually traced on these images to depict the white fiber tracts.

Stimulation Amplitude Modulation Experiment

We designed the amplitude modulation experiment to evaluate the effects of DBS amplitude adjustments on spontaneous talkativeness. We performed iterations of this experiment at approximately 1 week (10 days), 3 weeks (25 days), 10 weeks (67 days), and 5 months (171 days) after DBS activation. At each timepoint, our psychiatrist selected safe low and high DBS amplitudes for subsequent testing based on acute behavioral evaluations during clinical programming adjustments. These parameters evolved over time throughout the course of therapy and are included in Table 1. DBS pulse width and frequency did not vary from the clinically determined, therapeutic settings.

Before beginning the experiment, we informed the participant that we would record video and audio to evaluate behavioral responses after changes in DBS amplitude over several minutes. The participant was blinded to stimulation changes and allowed to speak freely throughout the experiment. To begin, we reduced DBS amplitude in both hemispheres to the low threshold. After four minutes, we bilaterally and instantaneously increased amplitude to the safe high threshold (without ramping) and held DBS constant for three minutes. We repeated this entire sequence twice, and then recorded for four more minutes after restoring DBS parameters to usual

therapeutic levels. Throughout the entire experiment, we recorded intracranial neural data synchronized to video and audio (details included in the following sections).

Initial analyses of neural activity and speech collected during the first four timepoints revealed an association between high vlPFC beta power and speech rate, however it was unclear if DBS mediated this relationship. To help determine causality, we conducted a control experiment to test whether beta power was responsive to speech alone, in the absence of changes in stimulation amplitude. Instead of allowing the participant to speak freely throughout the participant as we had done previously, we held stimulation amplitude constant and cued the participant to start and stop talking according to the same block pattern as in the original experiments, with the total duration reduced by one third (1 minute 20 seconds no talking, 1 minute talking, repeated twice).

After the control experiment, we ran a second iteration of our legacy amplitude modulation experiment (denoted as 'Control Experiment 2' in Tables 1, 3, 4, and 5) to confirm that the elevated vlPFC beta power and speech effects were still present. During this experiment, the safe low and high amplitude thresholds were determined as 0 mA and 6 mA, respectively. Again, to maximize time, experiment duration was again reduced by one third (1 minute 20 seconds low DBS amplitude, 1 minute high DBS amplitude, repeated twice).

Throughout the experiment, we acquired time domain LFP recordings sampled at a rate of 500 Hz in the clinic by streaming data from the Medtronic Summit RC+S devices to a computer running a custom software application (https://github.com/openmind-consortium/App-aDBS-ResearchFacingApp). Communication between the pulse generators and the recording computer was established via Bluetooth through two Clinician Telemetry Module (CTM) devices. Telemetry parameters "mode" and "ratio" were set to 4 and 11, respectively. LFPs were

recorded in a bipolar configuration from both the DBS contacts, where the recording contacts flanked the stimulation contact (e.g., 0-2), and ECoG electrodes, where the recording contacts in each pair were adjacent to each other (8-9, 10-11). Both the stage 1 and 2 low pass filter cut-off frequencies were set to 100 Hz to further attenuate stimulation artifact, while the high pass filter cut off frequency was set to 0.85 Hz. Stimulation contacts for each experiment are recorded in Table 1. All stimulation was delivered using active recharge to minimize stimulation-related artifacts.

Simultaneously with LFP recordings, we recorded three lead electrocardiography (ECG) at 5kHz using the BrainVision Recorder software and amplifier (BrainAmp ExG). ECG leads were placed on the left collarbone and below the left pectoral muscle and grounded to the right collarbone.

We additionally recorded simultaneous video and audio using the GoPro Hero 6 (GoPro, San Mateo, CA, USA) at 25 fps, and an external microphone (Zoom H4n Pro 4-Track Portable Recorder, Zoom Corporation, Tokyo, Japan) at 44.1 kHz.

Time Synchronization of Multimodal Data

Electrophysiology: We synchronized electrophysiology, audio, and video using methods that we have described previously (Provenza et al., 2021, 2022). The start and stop times of the amplitude modulation experiment were sent via USB by a task application (Provenza et al., 2022) running on the research-facing computer to the BrainVision Trigger Box (Brain Products GmbH). At the same time the event marker was sent, a photodiode attached to the computer monitor captured a flickering UI element, and a corresponding UTC network timestamp was

recorded in a JSON file on the research-facing computer. LFP data packets were organized into a time-domain stream where each sample is associated with UTC network time (packetGenTime) using the Analysis-rcs-data toolbox (Sellers et al., 2021). We then used packetGenTime information to time synchronize LFP data to the UTC times recorded at the start and stop of the experiment.

In order to achieve more precise synchronization than what can be achieved by using network timestamps alone, we followed a procedure to generate DBS artifacts that would be detectable on both LFP and ECG recordings. By generating these artifacts just prior to the start and after the conclusion of each experiment, we then were able to use these artifacts to enable high resolution synchronization between LFP recordings onboard the DBS device and external recordings (ECG, video, and audio). To generate the artifacts for synchronization purposes, we changed stimulation bilaterally from the clinically determined frequency (150.6 Hz) to a slightly lower frequency (146.2 Hz), and back again. We repeated this process a total of 8 times in rapid succession to reduce the likelihood that a packet loss would occur at the exact timepoint of the frequency change. These changes in stimulation frequency led to changes in both the recorded LFP and ECG signals. We bandpass filtered the LFP and ECG signals around the clinical stimulation frequency (148.4 Hz to 152.8 Hz) and took the envelope of the bandpass filtered LFP to estimate power at the high stimulation frequency. We repeated the procedure a second time for the lower stimulation frequency used for synchronization (144 to 148.4 Hz), creating a second array corresponding to an estimation of power at the low stimulation frequency. We then generated a Boolean vector where true corresponded to when the lower frequency power was greater than the high frequency power. We identified a synchronization point for each data stream by using the timepoint with maximum correlation between the ECG and LFP Boolean

vectors. Finally, we adjusted timestamps of each data stream such that the identified synchronization points occurred at the same time. We applied these adjustments in full to all datasets analyzed in this case report except for the experiment performed approximately 1 week after DBS, due to corruption of the ECG signal. The mean shift time was 711 ms with a standard deviation of 1004 ms.

Audio/Video: At the same time the event marker was sent and the UI element on the computer flickered, an audible tone was generated by the computer speakers that was captured on the microphone and GoPro audio streams. We synchronized the audiovisual data to the start event marker by aligning the time of tone onset to the time of the corresponding event marker and photodiode signal in the data recorded by the BrainVision system. We used the photodiode stream as ground truth timing for each tone.

Neural Data Preprocessing and Analyses

Data Preprocessing: To analyze spectral power changes across the low and high amplitude conditions, we first normalized the time domain signals by subtracting the mean. Then, we segmented and labeled the time-domain LFP recordings based on DBS amplitude. We discarded segments of LFP data with more than 1 continuous second of packet loss. Time domain samples affected by small packet losses (< 1 second), indicated by NaNs, were replaced with zeros. The mean duration of small packet losses was 110 ± 60 ms in the left hemisphere and 122 ± 68 ms in the right hemisphere, and the total percentage of data affected in the left and right hemispheres was 0.13% and 0.1%, respectively. We further excluded datapoints surrounding stimulation

amplitude changes (5 seconds before and 5 seconds after each change) to avoid including data impacted by artifacts related to the parameter change.

Power spectral density estimations: Individual power spectra were generated for the data collected during each amplitude condition using Welch's Method (MATLAB: *pwelch*) with a 1024-sample Hamming window and 512-sample overlap. We then took the base 10 logarithm of the PSD and multiplied by 10 to convert to decibels. Lastly, we averaged the spectra from each amplitude condition to generate the resulting PSDs shown in Figures 2, 3, Extended Data Figures 2-1, 2-2, 2-3 and 2-4.

Spectrogram visualizations: We used the MATLAB *spectrogram* function with a 500 ms window, 250 ms overlap, and 250-point fast Fourier transform to estimate power over time in each 2 Hz frequency bin from 0 Hz to 250 Hz. To convert to decibels, we took the base 10 logarithm of the magnitude of the time-frequency matrix and multiplied by 10. We smoothed the resulting time-frequency matrix with a 2D Gaussian image smoothing kernel for visualization. Notably, our bin width with this method is 0.5 seconds, so any bleed through of stimulation derived artifact should vanish within 0.5-1 second of stimulation ceasing.

Estimation of high beta power over time: Based on initial spectral analyses, we identified a focal area of interest in the high beta range. To further quantitatively define this spectral band of interest, we used the previously calculated power spectral density estimations to calculate the frequency at which high beta (28 – 34 Hz) power peaked in left and right vlPFC during the high amplitude condition and reported the result for each timepoint in Table 1. Across all time points, the spectral peak in the high beta range occurred of 30.8 Hz and 30.6 Hz in left and right vlPFC, respectively. We therefore focused subsequent analyses on the 31 ± 1.5 Hz frequency band.

Next, in order to compute power over time in our high beta frequency band of interest, we computed time-resolved power in the 31 ± 1.5 Hz band (window size of two seconds with 50% overlap) and corrected for shifts in '1/f' aperiodic background activity. To do so, we used the MATLAB-based SPRiNT toolbox(Wilson et al., 2022) to generate time resolved power estimations, and subtracted the 1/f model fits (Donoghue et al., 2020; Bush et al., 2024) (see next paragraph for fitting parameters). We then recorded the maximum value of this difference over the 29.5 to 32.5 Hz frequency range. The result yielded an estimate of the maximum power above the 1/f aperiodic background activity in our frequency range of interest. Finally, we assigned each maximum power value to a low or high amplitude condition (or speech/no-speech) condition based on the experimental paradigm. Violin plots in Figures 2 and 3 show the resulting high beta power distributions per condition. We further performed a 1/f model for stimulation ON data from the initial experiment using the below described fitting parameters, fitting the time-averaged PSD as opposed to a more time resolved measure. We identified a peak at ~31 Hz, supporting our choice of frequency band for analysis. The result of this fitting is shown in Extended Data Figure 2-4.

We used the following SPRiNT fitting parameters: 2 second window, 50% overlap, 1 window averaged per time point, fitting frequency range [1, 60] Hz, peak width limits [0.5, 2], 1 peak maximum, minimum peak height of 0.6, peak_threshold of 2, 'gaussian' peak type, proximity threshold of 2, 'none' guess weight, 'true' threshold after fitting, and the aperiodic mode was set to 'knee' to account for knees in the spectra (Donoghue et al., 2020).

In Figure 2, Extended Data Figure 2-1, and Extended Data Figure 3-1, we showed an exponential moving average of the 1/f-corrected low beta power in the left or right vlPFC in

black, computed with a 10-sample window. We subsequently computed all statistical tests and correlations using the 1/f-corrected high beta power time series.

In Extended Data Figure 2-3 we visualize power spectral density data immediately preceding or following ON-to-OFF transitions from the Week 0 dataset. We computed PSDs for the following 4 epochs: 10 seconds before to 1 second before the first and second ON-to-OFF transitions, and 1 second after to 10 seconds after the first and second ON-to-OFF transitions. We averaged the PSDs from the first two epochs and the second two epochs separately to obtain a single PSD representing the data immediately preceding the stimulation change and the data immediately following the stimulation change. The PSDs were computed as previously described, but using the shorter segments of data. We took care to exclude the 2 seconds of data immediately flanking stimulation changes as those times were likely to produce artifacts in the PSDs. We show the PSDs from 0 to 250 Hz with insets from 0-55 Hz. Uniquely in the right VS, though the aperiodic activities are not apparently different, a series of sharp peaks occur at various frequencies both between 0-55 Hz and further out at roughly 60 and 80 Hz. These peaks are only present when DBS is on, suggesting again that these changes are likely artifacts of stimulation. We have previously identified artifactual peaks in PSDs recorded from the same devices used in this study and suspect that the observed peaks in our data may be examples of those artifacts. (Alarie et al., 2022)

Audio Data Preprocessing and Analyses

Preprocessing: We extracted the segments of the audio recording containing the speech of the participant using *Praat* software (v 6.3.08) (Boersma and Van Heuven, 2001). We annotated onset and offset of each word spoken by the participant and silenced all other speech and background noise.

Speech rate: To estimate participant speech rate, we used the preprocessed data to compute words per second estimated in two second bins. We showed speech rate overlaid with an exponential moving average (MATLAB function *movavg*, 5-sample window size) in Figure 2, Extended Data Figure 2-1, and Extended Data Figure 3-1.

Acoustic features: In addition to speech rate, we used Praat (Jadoul et al., 2018) to derive the following 8 acoustic features: average syllable duration, articulation rate, mean syllable period, variability of syllable period, number of pauses, mean pause duration, variability of pause duration and speech-to-pause ratio. We also derived 207 low-level acoustic descriptors were also derived using *opensmile* (Eyben and Wöllmer, 2010).

Statistical Analyses

In order to determine whether there were significant differences in high beta power across the low and high amplitude conditions or the speech and no-speech conditions, we performed a 2-sample t-test (MATLAB *ttest2*). Asterisks above the violin plots in Figures 2 and 3 indicate significant differences ($p<0.05$) in high beta power across the low and high amplitude conditions. Statistical results are summarized in Tables 2 and 4. Sample size (n) refers specifically to the number of data points of 1/f-corrected high beta power within each condition.

Likewise, we used the same statistical test to determine if there were significant differences in speech between the low and high amplitude conditions. Statistical results are summarized in Table 3. Sample size (n) refers specifically to the number of time speech rate was quantified within each condition.

Next, we sought to determine whether there was a significant correlation between vlPFC power in the 31 ± 1.5 Hz band and speech rate. We computed Pearson's correlation (MATLAB

corcoef function) between high beta power and speech rate over time. Prior to computing correlation coefficients, we computed the exponential moving average of speech rate using a 5-sample retrospective window to avoid discretization of words per second into whole word bins, and down-sampled power values to match the sampling frequency of speech rate (0.5 Hz). P-values indicating significant correlations between high beta power and speech rate were also computed using the MATLAB *corrcoef* function and are reported in Tables 2 and 4. Scatterplots showing these correlations for the Week 0 experiment are included as Extended Data Figure 2-5.

We used a similar strategy to determine whether there were significant correlations between vlPFC power in the 31 ± 1.5 Hz band and each of the acoustic features we computed. We again computed Pearson's correlation (Python *pandas* package) and P-values indicating significant correlations between high beta power and each acoustic feature (Python *SciPy* package).

Because we computed correlations values for all 215 features, in order to interpret our results, we estimated the false positive rate of significant correlations due to chance. Given a false positive rate of 5%, we would expect roughly 11 features to significantly correlate with high beta power due to chance. In order to test whether the number of significantly correlated features was greater than expected due to chance, we performed a binomial test and computed the associated p-values for each experiment (Python *Scipy* package). Results of the binomial test are included in Table 5.

At weeks 10 and 17 we performed additional bootstrapped statistical testing to determine whether the magnitude of the power increase during the on-off change was greater in the right vlPFC than in the left vlPFC. To compare data between left and right hemispheres, we estimated the magnitude of change ($\Delta_{\text{left-right}}$) in high beta vlPFC activity by randomly selecting one 1/f

corrected power value from the high stimulation periods for each hemisphere and one from the low stimulation periods and subtracting the two values. We repeated this sampling 10000 times to generate a proxy distribution for the effect size and used a 2-sample t-test (MATLAB ttest2) with 1 tail to see if the effect was greater in the left than right vlPFC.

To determine whether DBS produced a greater effect on vlPFC activity than speech alone, we similarly bootstrapped a Δ value for the change in power between speech and silence periods in the vlPFC and compared this change to the change in power between high and low stimulation amplitude on the same day. We only conducted this analysis in the left vlPFC as the right vlPFC no longer showed significant difference in the original paradigm.

Results

The configuration of DBS leads (bilateral VC/VS) (Shofty et al., 2022) and ECoG strips (bilateral OFC and vlPFC) are shown in Figure 1. We recorded from three contact pairs per hemisphere, each in a bipolar configuration. On the DBS lead, we recorded from the bipolar pair flanking the monopolar stimulating contact. On the ECoG strip, we recorded from the medial pair (both in OFC) and the lateral pair (spanning OFC and vlPFC). The ECoG recording contacts were located in very similar positions across hemispheres, with a maximum difference of 4.15mm in absolute value in any (x,y,z) dimension between any left and corresponding right contact pair (mean difference across all pairs: 1.48 mm; mean standard deviation across all pairs: 2.36 mm).

As we do for intraoperative decision-making (Shofty et al., 2022), we used stimulation-induced behavioral changes (i.e., increased approach or improvements in mood/energy) during programming sessions to guide the choice of putative therapeutic contacts. We then performed

an amplitude modulation maneuver on the selected contacts to identify behavioral and neural effects of stimulation adjustments. We varied stimulation amplitude from 0 mA to 5 mA (as shown in Figure 2, Extended Data Figure 2-1, and Table 1) while keeping the participant blind to parameter changes. Stimulation was delivered bilaterally, and stimulation changes occurred simultaneously in both hemispheres. DBS frequency and pulse width were held constant at 150.6 Hz and 120 μs in both hemispheres. During the high amplitude stimulation setting, the participant noted positive effects of stimulation, saying "That was a really nice little wave, and I just wanted to let it run its course… that was really really really good", and "That was a nice little bubble or surge." The study psychiatrist present noted that this behavioral change is consistent with the increase in approach behavior that we typically see after acute VC/VS DBS.

Throughout the experiment, we recorded time domain local field potentials (LFPs) from each of the 6 contact pairs and synchronized the LFP recordings with audio and video. Using these neural and behavioral data streams, our goal was to identify whether there was any neurophysiological signature related to the observed behavioral changes after stimulation increases. To do so, we computed the power spectral density up to 250 Hz (Extended Data Figure 2-2). We did not observe any frequency-specific changes in the VS or OFC (Figure 2A-B). However, in the left VS, we observed a broadband increase in power that we suspected was attributable to stimulation artifact based on our previous experience. (Alarie et al., 2022) To determine whether the broadband change was an artifact of stimulation, we analyzed the spectral content of the signal for the 10 seconds immediately before and after stimulation and found that the aperiodic activity returned to baseline levels immediately after stimulation was turned off (Extended Data Figure 2-3). Therefore, we concluded that the broadband increase in power that we observed in left VS was a stimulation-related artifact.

Conversely, in both the left and right vlPFC we observed a narrow band increase in ~30 Hz power during 5 mA stimulation that persisted after stimulation was turned off (Figure 2C). To demonstrate frequency specificity, we fit a model to estimate periodic activity over the 1/f background activity. Only one peak was identified with a center frequency of ~31 Hz (Extended Data Figure 2-4). To further quantify this effect, we selected our frequency band of interest as 31±1.5 Hz (high beta) based on the frequency corresponding to maximum vlPFC power in the high frequency (beta/gamma) range (see Methods; Table 1) and then estimated power over time in this frequency band. We performed a standard 1/f correction to account for overall changes in the aperiodic background activity.(Donoghue et al., 2020; Wilson et al., 2022) We found that high beta power in vlPFC was significantly greater when DBS was on versus off (left vlPFC: $p<10^{-42}$; right vlPFC: $p<10^{-19}$; Table 2) (Figure 2C). To confirm that this high beta signal was not an artifact related to the VC/VS stimulation, we performed a spectral decomposition of vlPFC power and found that the high beta activity faded over tens of seconds after DBS off (Figure 2D). If the high beta activity were artifactual, we would expect the effect to disappear immediately after DBS was turned off similar to the broadband increase in power we observed in left VS. Given that this effect persisted for more than 10 seconds after DBS was turned off (Extended Data Figure 2-3), and demonstrated spatial specificity to the vlPFC, we concluded that this signal was not a stimulation-related artifact.

Due to the notable increase in talkativeness we observed after increases in DBS amplitude, we quantified the participant's speech rate alongside the high beta activity (Figure 2E). We computed speech rate by annotating the onset and offset of each word spoken by the participant and calculating words per second using a two second window. Speech rate was significantly greater during DBS ($p<10^{-4}$; Table 3) and showed a significant and positive

correlation with high beta power in both the left (R^2 = 0.037, $p<10^{-5}$; Table 2) and right (R^2 = $8.31*10^{-3}$; $p<0.05$; Table 2) vlPFC (Extended Data Figure 2-5). Again, this effect was specific to the vlPFC and not observed in the OFC (left, p=0.41; right, p=0.39; Table 2). While we acknowledge that increased speech rate does not capture all dimensions of our definition of increased approach behavior, we feel that a statistical increase in speech rate in combination with expert clinical observations and subjective reports from the participant supports our claim of increased approach behavior in this participant.

When the participant returned for clinical visits at approximately one, three, and ten weeks after DBS, we repeated the original amplitude modulation experiment. We alternated between a safe low and safe high amplitude (stimulation parameters included in Table 1) and found that both left vlPFC high beta power ($p<10^{-4}$; Table 2) and speech rate ($p<10^{-2}$; Table 3) were significantly greater during the high amplitude condition at all three timepoints. As before, speech rate significantly and positively correlated with left vlPFC high beta activity at each timepoint ($p<0.05$; Table 2). In contrast, these relationships were less consistent in the right vlPFC. Right vlPFC high beta power was greater during high amplitude stimulation at weeks 1 and 3 ($p<10^{-7}$; Table 2), but not at week 10 (Figure 3A-C; p=0.09; Table 2). Activity in the right vlPFC did show a significant correlation with speech rate at week 1 ($p<10^{-2}$; Table 2), but not at weeks 3 and 10 (Week 3, p=0.104; Week 10, p=0.46; Table 2). To investigate this regional specificity, we performed a bootstrapped analysis (see Methods) to compare the change in high beta power in the left and right vlPFC at the 10-week time point and found that the effect was significantly higher in the left vlPFC ($p < 10^{-98}$).

In addition to speech rate, we hypothesized that we would observe neural correlates of acoustic features in the vlPFC. To test this hypothesis, we identified 215 acoustic features in the

speech data (see Methods). Across all sessions, we found that a high proportion (35%) of these acoustic features significantly correlated with high beta power in vlPFC. Notably, the proportion observed in the left vlPFC was greater than the proportion observed in the right vlPFC (44.3% vs. 25.7%; Fisher exact test: $p<10^{-5}$), but both were greater than chance (binomial test: left, $p<10^{-39}$; right, $p<10^{-3}$, Table 5). In contrast, in OFC, we find no significant correlation between these variables. Specifically, the proportion of features significantly correlated over all four sessions (left, 2.7%; right, 4.1%) was not different from the proportion expected by chance (binomial test: left, $p>0.39$; right, $p<10^{-3}$, Table 5).

We carefully monitor increased approach behaviors (including talkativeness/pressured speech) acutely during VC/VS DBS programming as their overabundance could indicate overstimulation that could lead to eventual hypomanic/manic behavior. Indeed, this patient's Young Mania Rating Scale (Young et al., 1978) (YMRS) score increased from 0 to 4 at the 10-week mark. While the increase in YMRS was subthreshold for hypomania, a change of this magnitude (+4) is clinically significant in a patient without a prior history of hypomania or mania. Consistent with this YMRS change, his depression score decreased by 24% (Hamilton Depression Rating Scale (Shear et al., 2001); decrease from 25 to 19) over this interval. As is frequently observed (Goodman et al., 2021), improvement in OCD symptoms lagged behind these mood-related changes (Yale-Brown Obsessive-Compulsive Scale Score changed from 39 to 40 by week 10, then decreased to 31 by week 25).

An alternative interpretation of these findings is that vlFPC high beta power is trivially related to the simple presence or absence of speech rather than to this broader constellation of approach behaviors. To disambiguate these possibilities, we conducted a control experiment at week 17. Rather than varying stimulation amplitude and allowing the participant to speak freely, we did

the opposite – we held stimulation amplitude constant and cued the participant to start and stop talking according to the same block pattern as in the original experiments (Figure 3A, Figure 3-1, Table 1). If the neural signal were being driven simply by the presence/absence of speech, we would expect to see it increase during periods of talking and decrease during periods of silence; recapitulation of our original result. Instead, we did not see a significant increase in left or right vlPFC high beta activity during the speech condition, and speech rate no longer correlated with the neural signal ($p>0.05$; Table 4).

On the same day as this control experiment, we repeated the original amplitude modulation experiment to confirm the original finding and ensure that the control condition was a valid comparison. We again observed significantly increased high beta power in left vlPFC during the high amplitude condition ($p<0.05$; Table 4), suggesting that DBS stimulation amplitude drives neural activity in this spectral band. Similarly, as was the case on previous days, neural activity in the left vlPFC was significantly correlated with speech rate ($R^2 = 0.086$, $p<10^{-4}$; Table 4). We again performed a bootstrapped analysis to compare the left and right hemispheres and found that the high beta increase occurred more strongly in the left than the right ($p<10^{-182}$). To determine whether increased DBS amplitude produced a significantly greater increase in high beta power than increased speech rate alone, we created bootstrapped distributions representing change in power for each condition (DBS ON vs. OFF and speech vs. silence) and performed a one-sided 2-sample t-test to determine significance. The outcome of this test was significant ($p< 10^{-4}$), confirming that increased stimulation produced a greater change in vlPFC high beta power than increased speech.

We also analyzed the number of acoustic features that were significantly correlated with high beta power during the control experiment. We found that the number of significantly

correlated features was not different than the number expected due to chance in either region (binomial test; vlPFC: $p>0.98$; OFC: $p\approx1$; Table 5). However, when the original amplitude modulation experiment was repeated on the same day, we observed a high proportion of features that once again correlated with high beta activity in left but not right vlPFC. The proportion of significantly correlated features was greater than what was expected due to chance (binomial test: $p<10^{-49}$; Table 5).

Discussion

In this case report of a single patient with VC/VS DBS and chronic recording electrodes in the vlPFC and OFC, our results suggest that VC/VS DBS drives high beta activity in the vlPFC, more consistently on the left than right. The consistent relationship between left vlPFC neural activity and speech features, along with the results of the control experiment, suggest that left vlPFC high beta activity is associated with approach behaviors induced by VC/VS stimulation, and not trivially by the simple presence/absence of speech.

Past studies have identified specific patterns of altered neural network activity associated with risk and onset of mania and hypomania. Several of these studies employed reward expectancy paradigms, as a key feature of mania/hypomania is elevated reward sensitivity and goal overvaluation.(Johnson et al., 2012) We have previously shown that fMRI activity in left vlPFC is elevated during reward expectancy in both euthymic and manic adults with bipolar disorder (Bermpohl et al., 2010; Nusslock et al., 2012; Caseras et al., 2013), and in young adults at risk for future mania/hypomania and bipolar disorder (Chase et al., 2017; Edmiston et al., 2020, 2022). We further showed using electroencephalography (EEG) that event-related

synchronization in the beta frequency band (15-25 Hz) over left vlPFC scaled with the expected value of immediate future reward, and positively correlated with sensation seeking (Coffman et al., 2021). These results parallel other findings showing positive relationships between reward-related beta/gamma oscillations and sensation seeking (Leicht et al., 2013).

Elevated prefrontal beta-gamma in response to uncertain reward is thought to reflect phasic recruitment of the dopaminergic system (Kegeles et al., 2006), facilitating fast transmission of signals related to motivational value and coordination of attention, reward, and memory processes (HajiHosseini et al., 2012; Kawasaki and Yamaguchi, 2013; HajiHosseini and Holroyd, 2015; Marco-Pallarés et al., 2015). The left vlPFC/anterior insula (along with striatum) is implicated in immediate future reward expectancy (Tanaka et al., 2004). This finding reflects the role of the vlFPC as a hub region connecting other neural networks, including the prefrontal cortical-ventral striatal reward, central executive, and anterior insula-anterior cingulate cortex-centered salience networks (Suzanne, 2022), enabling links to be made between cues and reward outcomes to optimize decision-making in reward expectancy contexts (Lee et al., 2015; Boorman et al., 2016). The left-sided nature of the vlFPC response in these previously published studies likely reflects the role of the left prefrontal cortex in encoding approach-related emotions (Harmon-Jones et al., 2002; Davidson et al., 2004; Brookshire and Casasanto, 2012). Our present findings follow this spatiospectral pattern of neural activity related to mania. We observed an increase in high beta activity in the vlPFC that was accompanied by bilateral stimulation increases and was more consistent in the left hemisphere. While we observed a bilateral increase in vlPFC activity that corresponded with approach behaviors at early time points, the increase in left hemisphere activity was more consistent than the right over time.

Our vlPFC recording site was in Brodmann area 47/12, which is adjacent to the canonical Broca's area (area 44/45). While we have shown that the changes in vlPFC high beta were not simply related to speech presence, the proximity of our recording site to the classical speech generation site (Fedorenko et al., 2012; Flinker et al., 2015; Matchin and Hickok, 2020) and the greater consistency of the neurobehavioral relationships in the left (typically language dominant) hemisphere is notable. We speculate that our identification of a speech-related feature of stimulation-induced approach behavior in this brain region may not be coincidental. Indeed, acoustic features of speech such as fundamental frequency (pitch) and mean pause duration have been used to distinguish hypomania/mania from euthymia (Faurholt-Jepsen et al., 2016; Low et al., 2020). Future work in a larger cohort will determine whether the speech features that fluctuate with VC/VS stimulation align with the speech features that are predictive of hypomania.

We caution against the over-generalization of these findings given that the neurobehavioral relationships described here were derived from a single subject. However, we would like to highlight that our central findings on the relationship between DBS amplitude, speech rate, and high beta power in the vlPFC replicated over repeated timepoints spanning more than five months. We consider the consistency of these repeated measures as a strong indicator of the validity of this neurobehavioral relationship. Properly conducted studies with appropriate within-subjects power, control, and reproducibility may be sufficient to answer the question "What neurophysiological mechanisms allow this specific brain to achieve the observed behaviors." We believe that the results shown here are sufficient to answer that question in this subject. An important following question remains: "Do all like brains achieve such behavior using similar neurophysiological mechanisms." This question almost always requires

reproduction in or more (depending on the population characteristics, etc.) subjects. (Asaad and Sheth, 2024) Future work is required to determine whether these findings generalize to a larger cohort.

Our results, in the context of these related prior studies, suggest that vlPFC high beta activity (particularly in the left hemisphere) may index features related to affiliative/approach behaviors. These behaviors likely exist on a continuum that ranges from healthy (associated with adaptive reward-based decision-making and euthymia) to pathologically abundant (associated with exuberant reward-seeking behavior and hypomania/mania). These preliminary results suggest that VC/VS stimulation moves behavior along this axis and that vlPFC high beta power is a readout of this behavioral feature. Future efforts are required to test these hypotheses in larger patient samples and determine whether vlPFC could surface as a target for neuromodulation interventions for mania and hypomania (Bertocci et al., 2021; Phillips, 2023).

Author contributions

SAS, WKG, NRP, and JAH conceived of the study. NRP, SVR, and LSP conceptualized data analysis procedures, performed data analysis, interpreted data, and prepared figures and results with support from SAS, MP, BYH, JAH, KAK, GR, RAB, ND, SR, AA, ADG, KEK, KAM, JHB, JRA, SH, NG, and GPB. NRP, SVR, and ND performed data collection in the clinic. NRP, MLP, SAS, and SVR wrote the first draft of the manuscript, and all authors contributed to the writing and revision of the manuscript. WKG, SAS, and EAS performed the clinical care aspects of the study. SAS, BS, and GPB performed the study surgical procedures. SAS, WKG, EAS, and JAH oversaw the collection of data, analysis, and manuscript completion.

Data availability

Data supporting the findings of this study are available from the corresponding author (SAS) upon request. The data will be made public and deposited in the DABI registry.

Code Accessibility

De-identified neural data will be deposited at DABI and made publicly available upon publication. Due to sensitivities surrounding sharing audio data containing speech of the participant, audio data will be made available upon request to the lead contact. Accession numbers are listed in the key resources table. All original code has been deposited on github (https://github.com/shethlab/OCD-30Hz-Analysis) and will be made publicly available upon publication. DOIs are listed in the key resources table. Any additional information required to reanalyze the data reported in this manuscript is available from the lead contact upon request.

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Main Figure Titles and Legends

Figure 1: Anatomical localization of DBS and electrocorticography electrode contacts. (A) Frontal, **(B)** superior, and **(C)** inferior views of the reconstructed cortical surface. The 3D reconstructions show the ventral striatum (green), DBS leads (magenta), ECoG contacts in OFC (yellow) and vlPFC (cyan), and anterior commissure (orange).

Figure 2. High beta power in vlPFC increases with speech rate during DBS. (A) Power spectral density plots showing average activity during DBS on (red; DBS frequency: 150.6 Hz, DBS amplitude: 5 mA, DBS pulse width: 180 μs) and off (blue) period in the left VS, **(B)** OFC, and **(C)** vlPFC. Violin plots in **A-C** show 1/f-corrected high beta power distributions in the DBS on (red) and off (blue) conditions. Left vlPFC shows a significant difference in high beta power between DBS on and off. **(D)** Time-frequency decomposition of left vlPFC power shows the high beta power increase in response to bilateral VC/VS DBS. DBS amplitude is indicated by the blue (0 mA) and red (5 mA) lines above the spectrogram. **(E)** Speech rate (green; words per second) and high beta power in the left vlPFC (black). All data shown in this figure were collected during the amplitude modulation experiment conducted on the same day as DBS activation (Day 0 after DBS). See Figures 2-1, 2-2, 2-3, 2-4, and 2-5 for more details.

Figure 3. vlPFC high beta power is not modulated by the simple presence vs. absence of speech. (A) Experimental paradigm showing bilateral constant DBS throughout the experiment with speech (green) and no-speech (purple) conditions (speech data shown in Extended Data Figure 3-1). **(B, C)** PSD plots showing average activity during the speech (green) and no speech (purple) conditions in the **(B)** left and **(C)** right vlPFC. Violin plots show high beta power distributions in the speech (green) and no speech (purple) periods. See Figure 3-1 for more details.

Extended Data Figure Titles and Legends

Extended Data 2-1. High beta power in vlPFC increases with speech rate during DBS. (A) Power spectral density plots showing average activity during DBS on (red; DBS frequency: 150.6 Hz, DBS amplitude: 5 mA, DBS pulse width: 180 μs) and off (blue) period in the right VS, **(B)** OFC, and **(C)** vlPFC. Violin plots in **A-C** show 1/f-corrected high beta power distributions in the DBS on (red) and off (blue) conditions. Both right OFC and vlPFC show a significant difference in high beta power between DBS on and off. **(D)** Time-frequency decomposition of right vlPFC power shows the high beta power increase in response to bilateral VC/VS DBS. DBS amplitude is indicated by the blue (0 mA) and red (5 mA) lines above the spectrogram. **(E)** Speech rate (green; words per second) and high beta power in the right vlPFC (black). All data shown in this figure were collected during the amplitude modulation experiment conducted on the same day as DBS activation (Day 0 after DBS).

Extended Data 2-2. Power spectra from DBS OFF and ON conditions shown to 250 Hz.

Power spectra calculated for the DBS ON and OFF data as in Figure 2A-C and Extended Data Figure 2-1 A-C shown to 250 Hz to show presence of stimulation artifact at 150 Hz (A: Left Hemisphere; B: Right Hemisphere). DBS ON data shown in red traces, while DBS OFF data shown in blue traces. All data shown in this figure were collected during the amplitude modulation experiment conducted on the same day as DBS activation (Day 0 after DBS).

Extended Data 2-3. Changes in VC/VS power spectra occur at similar timescales to stimulation changes, while vlPFC activity persists even after stimulation is turned off. Power spectra calculated for the DBS ON and OFF data as in Figure 2A-C and Extended Data Figure 2-1 A-C immediately flanking ON-OFF transitions (A: Left Hemisphere; B: Right Hemisphere). DBS ON data (preceding stimulation change) shown in red traces, DBS OFF data (following stimulation change) shown in light blue traces, and baseline data from the first DBS OFF period (prior to any stimulation) shown in dark blue traces. Data shown to 250 Hz to show presence of stimulation artifact at 150 Hz. Insets show data up to 55 Hz. All data shown in this figure were collected during the amplitude modulation experiment conducted on the same day as DBS activation (Day 0 after DBS).

Extended Data 2-4. Identification of frequency band of interest and frequency specificity. Power spectra calculated for the DBS ON condition (red) in left vlPFC as in Figure 2A-C alongside aperiodic (black, dotted) and full model fits (green). Fitting procedure was applied to the full power spectrum, rather than in windows as used in the manuscript to decompose power over time. Fitting parameters are described in the manuscript. Data shown in this figure were collected during the amplitude modulation experiment conducted on the same day as DBS

activation (Day 0 after DBS).

Extended Data 2-5. High beta power in vlPFC correlates with speech rate. Scatter plots showing correlation of the 1/f corrected vlPFC high beta power (x axis) and speech rate (y axis) computed at the same time points (A: Left Hemisphere; B: Right Hemisphere). Data from both DBS ON and OFF conditions are included. Correlation r^2 and p are shown in text. The line of best fit is shown as a red dashed line. All data shown in this figure were collected during the amplitude modulation experiment conducted on the same day as DBS activation (Day 0 after DBS).

Extended Data 3-1: Speech rate over time during continuous stimulation at 5.5 mA. Speech rate of the participant (green; words per second) and high beta power (1/f corrected) in the left vlPFC (black; dB). Black and green lines show the exponential moving average of high beta (31±1.5 Hz) power and speech rate, respectively. Stimulation parameters were held constant throughout the entire experiment, and the participant was prompted to talk for one minute at approximately 100 seconds and 240 seconds. Otherwise, the participant was instructed to remain silent.