

Longitudinal tracking of ventral anteromedial subthalamic nucleus theta bursts in Obsessive Compulsive Disorder: bridging the gap towards a neurophysiological marker

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Abstract

Background: Deep Brain Stimulation (DBS) to treat treatment-resistant obsessive-compulsive disorder (OCD) is still considered off-label in most countries worldwide, despite numerous publications showing significant relief of symptoms and guidelines provided. To enhance therapeutic efficacy, there is an urgent need for further studies to refine stimulation target and promote patient-tailored adaptive DBS by identifying potential neurophysiological markers for OCD. However, limited research has investigated such markers so far.

Methods: In this prospective interventional study, we implanted three refractory OCD patients (2 men and 1 woman) with ventral anteromedial subthalamic nucleus (vamSTN) DBS at the border with the OCD response tract (ORT). We recorded intra- and post-operatively spiking and local field potential (LFP) activity at the target for over two years to evaluate neural markers that correlate with OCD severity and clinical response.

Outcomes: All patients responded to vamSTN DBS with a $54 \pm 5.5\%$ (18.6 ± 1.7 scores) mean reduction in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) at last follow-up. VamSTN LFP activity showed a prominent theta frequency peak. Theta burst duration, power, and entropy significantly correlated with OCD severity and stimulation-induced clinical response. Theta power was more robust and correlated more strongly with clinical scores in the left vamSTN. DBS response also resulted in a wake-sleep diurnal variation in theta power, which was larger in the left vamSTN.

Interpretation: Due to the ease of vamSTN targeting, clinical efficacy, and the strong and stable neural biomarker, we suggest vamSTN theta burst power as a potential neural marker and possible target for adaptive DBS in OCD.

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Introduction

Obsessive compulsive disorder (OCD) has a lifetime prevalence of 1–3% and is the tenth leading cause of disability worldwide. While many patients respond to selective serotonin reuptake inhibitors (SSRIs), anti-psychotic medications, and cognitive behavioral therapy (CBT), up to 40% of affected patients are treatment resistant.(1) These patients may be candidates for advanced treatments, like deep brain stimulation (DBS).(2)

Previous studies of DBS for OCD have demonstrated safety and efficacy with 50% reduction of OCD symptoms.(3) Yet, the lack of funding sources as well as the off-label status of this indication vastly

limits its use and study.(4, 5) Therefore, substantial gaps in optimal targeting and neural markers prevent DBS for OCD from becoming a routine clinical practice, like in the field of movement disorders.(6, 7)

DBS for OCD has been reported across various brain targets, including mostly the ALIC (Anterior Limb of Internal Capsule) and the STN.(8–11) While the anatomic location of the stimulation contacts in the ALIC region is highly variable, the classical STN target is more clearly defined.(12, 13) Similarly, the charge density used for ALIC stimulation is much higher than that used for STN stimulation. Therefore, the trial and error required for STN stimulation is shorter, and the OCD response rate and efficacy is slightly in favor of the STN, while the side effect profile is similar, consisting mainly of transient hypomania.(14–16)

Recently, efforts to refine the “sweet spot” for stimulation along the OCD response tract (ORT) and adjacent subcortical structures were done, using connectivity and DTI-based analysis.(5, 11, 17, 18) Nevertheless, the optimal target remains elusive.(19)

Besides refining the anatomical target, efforts are invested in defining a neural marker for OCD to better understand the pathophysiology of the disease, to monitor alterations in clinical state, to aid programming, and to close the loop in adaptive stimulation.(20–23) Low frequency (delta, theta, alpha and beta) oscillations recorded along the ORT were raised as possible markers.(24–29) In addition, the potential role of nonlinear measures of neuronal signal, such as network entropy, in predicting fluctuations in OCD state was recently emphasized.(30–36) However, the long-term relationship of these measures to OCD state is still not fully understood.

In this open-label prospective study, we implanted three patients with severe, treatment-resistant OCD with bilateral DBS targeting the ventral anteromedial (vam) border of the STN. This location potentially enables us to engage both the ventral STN and the ORT with stimulation. We followed these patients for over 2 years and recorded LFPs throughout this period, focusing on theta power, bursting, entropy, and diurnal variation. Our study demonstrates consistent long-term stability of the recorded theta signal as well as correlation of the theta signal to the symptomatic OCD state of the patients. We therefore suggest the vamSTN theta signal as a potential long-term marker of OCD.

Methods

Study design

This study is a prospective interventional open label cohort clinical trial. The study was approved by the institutional IRB (no. 1005-20-RMC) and the ministry of health of Israel (no. 2002120774).

Patient recruitment and pre-op evaluation

Three adult subjects with intractable OCD (as defined by DSM V criteria; see also supp. Methods) and no other primary psychiatric co-morbidities or suicidality were recruited through the Neurosurgical Department at the Rabin Medical Center and Geha mental health center. All three patients fulfilled the standard inclusion and exclusion criteria for DBS for severe refractory OCD. The patients signed a written informed consent at the pre-surgical visit after the nature and possible consequences of the study and procedure were explained.

Patients' clinical data were collected and included age, gender, OCD severity (Y-BOCS) at first and last follow-up, disorder duration, current medications, mood scores pre- and post-operatively, lead target location, and stimulation parameters.

Surgical procedure

The surgical procedure and sedation protocol were previously reported. (37). Briefly, a CRW frame was used for stereotaxis. The amSTN was targeted on pre-op MRI. Coordinates appear in Table 1. The pre-op MRI was fused with an intra-operative CT scan (O-arm 2; Medtronic Inc.) using the Stealth 8 navigation system (Medtronic Inc.). One or two microelectrodes were used concurrently for Microelectrode recordings. Acute stimulation at the localized target was done using the macroelectrode (0.25 – 4 mA, 60 microseconds, 130 Hz). The patients underwent implantation with bilateral 3389 brain leads (Medtronic Inc.) and PERCEPT PC pulse generator.

Intra-operative recordings and data analysis

Intra-operative microelectrode recordings included local field potentials (LFPs) during rest, along the STN trajectory. Data were recorded and analyzed as previously described(24); see also Supp. Methods.

Therapeutic stimulation and recording configuration

In all three patients, stimulation was activated 2 weeks postoperatively. The second deepest contacts (no. 1 and 9) were used for monopolar stimulation, and the neighboring contacts (0–2 and 8–10) were used for LFP recordings. The initial stimulation parameters were 0.5 mA, 60 microsec and 125 Hz and the amplitude gradually ramped up over a few weeks to months to achieve clinical improvement with minimal side effects. In cases of stimulation induced side effects, the stimulation paradigm was altered accordingly, either by reducing the amplitude of stimulation (mainly in cases of hypomania) or by reviewing other possible contacts and stimulation configuration (e.g., bipolar stimulation, or using the most ventral contact for stimulation).

Outcome measures

The primary aim of the study was to assess the effects of vbmSTN stimulation on OCD symptoms (via the Y-BOCS scale) and to record chronic LFP at the target while analyzing possible neural markers (with emphasis on theta oscillations, bursting, and entropy) to predict OCD symptoms severity and DBS outcome. OCD severity was assessed by Y-BOCS, with 35% reduction (from baseline pre-operative values) predefined as a clinical response, based on previous publications.(38) Close monitoring of the patients for stimulation-induced adverse effects was performed with weekly to monthly visits with the psychiatrist as needed. For comparison of electrophysiology markers between mild and severe OCD states, we defined a cutoff of 25% reduction in Y-BOCS from the pre-operative baseline score.

Chronic sensing and data analysis

PSD analysis

Chronic recordings (LFPs) were acquired at both hospitals (Rabin and Geha) during study visits in an outpatient setting in parallel to the clinical evaluation, using the PERCEPT PC implanted device (Medtronic Inc., Minneapolis, Minnesota, USA). The frequency of study visits and recordings was 1–6 weeks over a period of 24 months.

Time-domain neural recordings were acquired directly from the Percept PC device at a sample rate of 250 Hz. During home recordings with DBS on, we used BrainSense mode to record LFPs in a bipolar configuration around the active stimulation contact (contacts 1 and 9). In-clinic, all recordings were with DBS off, and we leveraged “Survey”/“montage” mode to enable bipolar recordings from each of the six possible contact pairs simultaneously. The duration of each recording was 20–180 sec long.

To compare STN rest spectral activity in OCD, we calculated for each patient the PSD of each rest recording session, using contacts 0–3/8–11 or 0–2/8–10. For power and entropy calculations, theta range was personalized as a 3 Hz band spanning 1.5 above and below the peak theta frequency measured during the first recording session after surgery. These peaks were consistent throughout the study follow-up. In addition to theta frequency, other ranges were analyzed as well, including delta (1–4 Hz), alpha (8–12 Hz), low beta (13–25 Hz), high beta (25–35 Hz) and low gamma (35–50 Hz).

Band-pass filtering between 0.5 and 100 Hz was performed with a 4-pole Butterworth filter. Rest PSD was calculated using the Welch method with a hamming window of 1 s and 50% overlap, and frequency resolution of 0.33 Hz. The spectrum was normalized to the 70–90 Hz band. This normalization method was chosen as there were no peaks of power at that range, only the ‘tail’ of the 1/f exponent, therefore excluding possible contribution of aperiodic activity.

FOOOF analysis was also conducted according to previously published methods (39). Each power spectrum was parameterized into aperiodic and periodic components using the FOOOF (Fitting Oscillations & One Over F) algorithm, fit over the 1–100 Hz range with the aperiodic mode fixed (no spectral knee), a maximum of two periodic peaks, a minimum peak height of 0.0 (in units of the fit’s log-

power space) with a relative peak threshold of 2.0 standard deviations of the flattened spectrum, and peak bandwidths constrained to 1–12 Hz. From each fit we extracted the aperiodic offset and exponent, which together characterize the broadband 1/f-like decay of the power spectrum, and, from the periodic component, the center frequency, power, and bandwidth of any detected peak falling within the theta band, selecting the highest-power peak within this range when more than one was present. Model fit quality was assessed via the FOOOF-reported R^2 and fit error for each spectrum. Theta-band peak power was subsequently normalized to the corresponding aperiodic exponent (theta peak power / exponent) to index theta oscillatory activity relative to the background 1/f slope, for correlation with Y-BOCS and time from surgery. The fit reached statistical significance (for goodness of fit) in all recordings.

Theta burst detection and analysis

Theta bursts were identified from LFP recordings sampled at 250 Hz, as previously described.⁽⁴⁰⁾ The raw signal was first band-pass filtered in the theta range, centered around each patient's individual peak frequency. To estimate the amplitude envelope, the filtered signal was rectified (absolute value) and smoothed using a ~ 100 ms moving window. The smoothing was applied with a step size of 1 sample, without additional normalization.

Bursts were defined as periods in which the smoothed theta envelope exceeded the 75th percentile of its values. Onset and offset times of candidate bursts were identified based on threshold crossings, and only bursts lasting ≥ 100 ms were retained, to limit the contribution of spontaneous fluctuations in amplitude due to noise.⁽⁴⁰⁾

For each burst, the duration and maximum amplitude relative to the local baseline (mean amplitude between bursts) were calculated. Non-burst segments were defined as the intervals between bursts, and their maximum amplitude and duration were similarly recorded.

We quantified the variability of theta burst timing by calculating the coefficient of variation (CV) of the inter-burst intervals.⁽⁴¹⁾ For each session, we extracted the time differences between consecutive bursts and computed their mean and standard deviation. The CV was defined as the standard deviation divided by the mean interval. A CV of 1 reflects exponentially distributed (random, Poisson like) intervals, values below 1 indicate more regular timing, and values above 1 indicate over-dispersion or burst clustering.

Sample Entropy measure

We also used sample entropy, a model-free metric, to capture the change in periodicity and variability of theta activity in the time domain. Sample entropy quantifies the regularity and (un)predictability of time-series data. The implementation of sample entropy was based on a previously described method.⁽⁴²⁾

For each segment, the tolerance parameter (r) was scaled by the standard deviation of the data. The algorithm counted repeated patterns of length m and $m + 1$ and computed Sample Entropy as the negative logarithm of the ratio of these counts. To generate sample entropy values for each clinic visit,

we used normalized theta frequency power values as input and set the input parameters as $m = 2$, $r = 0.2$ times the standard deviation of the data, and $\tau = 1$.(26, 43) We correlated entropy value with OCD severity in various data points along the study period.

Circadian analysis

For circadian theta power calculations, we configured the Percept PC to record a continuous estimate of average LFP amplitude (units of microvolts peak) from a pre-defined theta frequency band. This mode was opened for up to two months for each patient, to preserve IPG battery. We chose the center peak theta frequency according to the patient's initial recordings post-surgery ± 2.5 Hz or at the nearest frequency possible (if the peak was lower than 7.81 Hz, the minimum peak frequency limit of the device for home recordings). These data were automatically saved onboard the device every 10 min (144 samples per day) 24/7 with stimulation on and offloaded upon connection to the Medtronic DBS Clinician Programmer Application on study visits. These chronic data were exported in JSON format during clinic visits. A few gaps in data occurred due to errors in ending the recorded session and, hence, saving the data. Timestamps were in local time zone (UTC + 2).

For the analysis, we included only continuous data segments without missing data points, each lasting at least 48 hours. For circular analysis of theta power across the 24-hour cycle, theta power was first detrended to remove slow baseline drifts, ensuring that analyses captured real fluctuations rather than gradual shifts in the signal. Each data point was assigned a corresponding time of day (00:00–24:00, in minutes), and values were normalized by z-scoring across all available data points. To assess diurnal variation, data were grouped into 60-minute bins, and for each bin the mean z-scored theta power and standard error of the mean (SEM) were calculated. Bin centers were converted to radians ($0-2\pi$) to represent the full 24-hour cycle on a circular axis. (26).

Statistical analysis

Standard descriptive statistics were used. The strength of correlation between theta (and other frequency bands) power/bursting/entropy and Y-BOCS values measured along the follow up period for each patient was calculated using Sperman's rank correlation coefficient due to the ranked nature of the Y-BOCS. In addition, the relationship between theta power and Y-BOCS was assessed using a linear mixed-effects model, with theta power as a fixed effect and patient as a random intercept to account for repeated measures. Time (days since first visit) was included as an additional covariate to control for longitudinal trends. Correlation between electrophysiological measures was conducted using Pearson's correlation. Group comparisons were conducted using unpaired Student's T-tests for normally distributed data and the Mann-Whitney U test for data with non-normal distribution. A threshold of $p < 0.05$ was used to establish statistical significance. Error bars in all figures represent the standard error of the mean (SEM). All analyses were two tailed unless otherwise mentioned. Data analyses were performed using Matlab R2023b (Mathworks, MA, USA) and statistical analyses were performed using GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA).

Role of the funding source

The sponsors of this study had no role in study design, data collection, data analysis, interpretation of the data, writing of the report or decision to submit the paper for publication.

Results

Patient Demographics and symptoms

Demographic data are summarized in Table 1. For clinical details and description of OCD symptoms, see Supp. Results. Long term DBS resulted an average of 54.3% reduction in OCD, 19.2% reduction in anxiety and 12.2% reduction in depression symptoms.

DBS procedure and intra-operative rest recordings

The stereotactic AC-PC based coordinates are detailed in Table 1. An example of implanted leads location at the vamSTN border can be seen in the fused pre-op T2 MRI and post-op CT scans of patient 2 (Fig. 1a), and in the 3D reconstruction of the VTA on top of the inserted lead and the adjacent anatomical structures of the same patient (Fig. 1b).

An example of the normalized root mean square (NRMS) of the recorded STN activity as a function of the estimated distance to the planned target is shown in Fig. 1c - the left trajectory of patient 2 - showing STN entry at 5.5 mm before and exit at 0.5 mm after the pre-planned target. A PSD of the multi-unit activity of the same patient at the level of the targeted vamSTN (0.03 mm superior to the planned target) shows the peak power at the theta range (Fig. 1d). No prominent low beta oscillatory activity was evident, in contrast to standard Parkinson's disease (PD) STN physiology.⁽²⁴⁾ High beta (25–35 Hz) activity was evident in some patients (Fig. 1e). After recordings, intra-operative stimulation test at the selected target (0.25 – 4 mA, 60 microsec, 130 Hz) took place and yielded no acute symptomatic effect on mood, nor were there any side effects. Nevertheless, patients were calm and in a good mood during the surgery, probably due to the dissociative effect of ketamine.⁽³⁷⁾

Clinical follow up

Two patients exhibited an “insertion effect” for 1–2 weeks following surgery, characterized by transiently reduced obsessive thoughts and compulsive rituals, such as reduction in excessive cleaning.

Over time, patients responded to gradual increase (over several weeks to months) in stimulation amplitude (see Table 1 for final parameters), by a sustained and clinically significant reduction in obsessions and compulsions, as well as improvement in mood (see Table 1) and daily functioning. Mean Y-BOCS reduction across patients exceeded 35%, indicating a standard responder-level outcome (Table 1). The therapeutic effects of stimulation were sustained throughout the extended follow-up period in all three patients, with no evidence of attenuation over time. For further clinical outcomes details, see Supp. Results.

Theta oscillations at the vamSTN and its clinical correlations

Bilateral bipolar LFP recordings using the internalized PERCEPT device were clear, without obvious artifacts (e.g., e.c.g., movement, etc.) as illustrated in an example patient for both right and left vamSTNs (Fig. 2a). PSD analysis of the post-operative STN LFP recordings revealed a prominent narrow peak at the theta range (5–8 Hz) in all patients, that increased in intensity along the study follow up (Fig. 2b). No other frequency peaks of activity were consistently noted up to 100 Hz, except for 1–4 Hz delta peak, that was considered part of the 1/f “noise”. High beta activity was evident in some patients. The frequency of theta peak was consistent along the follow-up (Table 1).

All three patients showed a significant negative correlation between theta activity and Y-BOCS scores throughout the study follow up (Fig. 2c; linear mixed-effects model with random intercepts). Higher Theta power was significantly associated with lower Y-BOCS scores (Estimate = -0.72, SE = 0.29, $t(47) = -2.45$, $p = 0.018$), after adjusting for time since first visit. Time itself was not significantly associated with Y-BOCS (Estimate = -0.004, $p = 0.28$). Random intercepts indicated moderate baseline differences between patients (SD = 6.1).

To exclude changes in the presumed theta activity secondary to alterations in aperiodic activity, we analyzed the aperiodic component using FOOOF. The aperiodic activity was variable between patients and within each patient along the follow up, with a slight tendency to decrease over time (Fig. 2d). However, the aperiodic component was significantly correlated with OCD severity (Y-BOCS) only in one patient (Fig. 2e). We therefore re-measured theta peak using the power peak over the exponent in this patient (see Fig. 2f for example). The correlation between theta peak power and Y-BOCS was still highly significant (Fig. 2g). Therefore, theta power seemed to correspond well with all patients’ clinical response.

OCD severity had a waxing and waning course along the follow up, and the variability in Y-BOCS corresponded well with the variations in theta peak power recorded at each clinical visit, gradually increasing over time (Fig. 3a).

This peak was consistently larger at the more ventral contacts (i.e., at the bottom of the STN), as illustrated in Fig. 3b (insets). Total power was more robust on the left STN compared with the right one in all patients along the study follow up (Fig. 3b). The correlation between OCD severity and theta power was more pronounced in the left STN in two patients, and in the right STN in one patient, with laterality unrelated to patient handedness (Fig. 3c).

In addition to theta, we also examined correlations between Y-BOCS and other low frequency bands (see supp. methods). None of which exhibited consistent activity or correlations with Y-BOCS scores across patients.

Theta bursting and its clinical correlation

In the LFP time domain, theta activity appeared to occur in short episodic bursts rather than remaining continuously elevated, as illustrated in the example in Fig. 4a (lower trace; upper trace is the raw LFP). Due to this phasic bursting pattern, we analyzed changes in theta power in the time domain. The raw signal was first filtered to the theta range, a threshold amplitude was set, and bursting events were defined each time the signal crossed the threshold upward (Fig. 4b, second upper trace). These theta bursts were then characterized by their frequency, amplitude and duration during periods of severe versus mild OCD symptoms (Fig. 4b, two bottom traces), and the two groups were compared.

Analyzing all patients' data, we found that the duration of theta bursts were longer in improved OCD states (Fig. 4c), without any significant change in the amplitude (Fig. 3d) or frequency (Fig. 4e) of the bursts. The coefficient of variation (CV) of inter-burst intervals (hence, burst dispersion) did not differ between mild and severe OCD sessions. In both groups, mean CV values were close to 1, indicating approximately random inter-burst intervals and suggesting no significant difference in burst regularity or clustering between the two clinical states (Fig. 4f). The distribution of the burst duration was right shifted in mild OCD states compared to severe states, so that the burst durations were overall longer (Fig. 4g). Nevertheless, there was a strong correlation between theta bursts amplitude and duration (Fig. 4h), similar to previous results on beta bursts in Parkinson's disease patients and primates.^(44, 45)

Theta sample entropy enlarges with clinical effect

Sample entropy is another measure of non-linear irregularity of the neural network activity. A constrained network, limited in its ability to dynamically adapt to various situations, should have a low entropy.

To study theta sample entropy, the raw bipolar recordings obtained at each clinical visit (contacts 0–3 and 0–2, as in the previous figures) were filtered to the theta range, and sample entropy was calculated for each recording session (Fig. 5a). We then correlated these entropy values with the corresponding Y-BOCS scores for each patient. Two of the three patients demonstrated a significant negative correlation between sample entropy and Y-BOCS scores, such that entropy increased as Y-BOCS scores decreased, indicating clinical improvement (Fig. 5b, left and right columns). Interestingly, both theta entropy and power significantly correlated with Y-BOCS in the same hemisphere (Fig. 3c and 5b). We therefore correlated theta sample entropy and theta power in each patient and found a positive correlation between the two measures in all patients (Fig. 5c).

Diurnal variation in theta activity

We next examined the diurnal variability of theta power, as sleep disruption is common in OCD. Each patient had home recordings of theta peak activity in 10 min averages for at least 30 days, using the home sensing capabilities of the implanted pulse generator (Fig. 6a). An example of diurnal variation of theta power is shown in Fig. 6b. For each patient, the data were z-scored within day and then averaged across all recorded days to derive a mean diurnal profile (Fig. 6c). We then visualized these data on a circular 24-hour plot to illustrate the mean theta power and its standard error across the diurnal cycle for each patient (Fig. 6d).

All patients exhibited a consistent daily rhythm of theta power. The diurnal variation of an example patient is shown at baseline (severe OCD state; Fig. 6e, grey) and at a clinical response state after 1 year of stimulation (Fig. 6e, blue). Interestingly, in the response states, there was a marked difference between day and night, with higher theta power amplitudes between 10:00 AM and 20:00 PM, and a decrease in theta power throughout the night, mainly between midnight and 6:00 AM. This “normalization” of day-night diurnal cycle may be a result of better sleep as part of the clinical response to stimulation, as previously suggested.(26) These diurnal changes were observed bilaterally, albeit with a more pronounced decrease at night and increase at noon in the left hemisphere (Fig. 6f).

Discussion

In this study, three patients with treatment resistant OCD were implanted with chronic sensing enabled DBS device and vamSTN LFPs were prospectively recorded. All patients were responders. Theta oscillations appeared in bursts and their duration, power and entropy consistently and long-lastingly increased with DBS response. Clinical response also yielded a reduction in nightly recorded theta power, resulting in day-night differentiation. These findings were stronger on the left STN than on the right.

vamSTN DBS for OCD – “sweet spot”

The aim of high-frequency DBS is to inactivate the dysfunctional circuit involved in the disease state. In OCD, various DBS targets were recently “mapped” along the sIMFB/ ORT white matter tract,(11, 17, 46) with proximity of stimulation to these “sweet spots” predicting clinical response.(12, 13, 47) The potential for chronic recording and adaptive stimulation is naturally greater in grey matter, as was recently suggested also for the ALIC target,(48, 49) making the well-studied STN a favorable candidate. Here, we show clear, stable and reliable recordings of theta peak activity at the vamSTN, rising way above the $1/f^2$ curve, more than 2 years after surgery. The ease of targeting the STN due to extensive surgical experience in PD, the clear anatomical localization using MRI alone, the relatively low current required for significant therapeutic effect, and the low profile of stimulation-induced side effects, all support the vamSTN as an excellent target of choice.(9, 50).

Theta bursting as a possible biomarker for OCD

Theta activity has been recorded in both limbic system structures and limbic regions of the basal ganglia, and it has also been suggested as a biomarker in depression and anxiety in PD patients as well in pos- traumatic stress disorder (PTSD).(51–54) Few previous studies suggested STN oscillatory power as a biomarker for OCD based on single patient analysis,(20, 24) while globus pallidus/ALIC theta-alpha (8–9 Hz) oscillations were recently reported as well.(24, 26, 48, 55, 56) The subtle difference in peak frequency between STN-target studies (ours included) and ALIC-target reports may be target-specific, or, less likely, a matter of post-processing methodology.

In addition, our study suggests an increase in theta power with DBS response, while most ALIC studies suggest the opposite.(53, 57) This difference is probably target-related. Nevertheless, the localization of

theta power to the ventral border of the STN in our study may hint for involvement of the substantia nigra (SN) in the recorded signal, and thus the differential effect of DBS on theta signal represents the opposing role of the SN and the GP at the basal ganglia network.(58) Other possible reasons for this discrepancy maybe the timescale of signal change, the duration of clinical follow up, and the patient state at the time of recordings (rest vs. task-related).

Outside the basal ganglia, increased theta events were documented in the hippocampus during exploration behavior, resulting in increased signal to noise ratio and enhanced cognition.(59) Therefore, a “normal” level of oscillatory bursting may be a physiological phenomenon that plays an important role in cognitive-limbic network function, and DBS may ameliorate pathologically reduced theta synchronization in OCD.

Laterality of OCD encoding

Regarding laterality of the signal, two of the three patients had a stronger correlation of theta power to the clinical state on the left STN, while the third patient had his left lead placed a bit further from the limbic part of the STN (thus more posterolateral), likely influencing our ability to record the theta signal. The diurnal modulation of theta power was more prominent on the left side in all three patients. These results correspond well with previous findings of left lateralization of physiological response to emotional stimuli,(60) stronger correlation of mood scores to theta power on the left STN of PD patients, (53) alterations in functional connectivity and fMRI signal of the left amygdala and OFC in OCD patients, (61, 62) and higher rates of depression in left (vs. right) temporal lobe epilepsy patients undergoing temporal lobectomy.(63, 64) However, the opposite (mood encoding on the right hemisphere) has also been reported,(65) and the different role of the two hemispheres in emotional regulation is still not clear. (66)

Sample Entropy as a possible common marker of STN pathology

In our study, we found theta power to highly correlate with Entropy, and both to increase with DBS response. Network entropy is a non-linear measure of temporal irregularity, randomness or unpredictability, and has long been studied and hypothesized to reflect the information coding capacity and dynamic range of the neural network.(67) In the basal ganglia specifically, changes in entropy have been observed in various neurological and psychiatric disorders.(36, 43, 68) Conflicting results were reported regarding the direction of entropy changes in basal ganglia networks, both in Tourette(68) and in OCD.(26) Also, the periodicity of the theta signal along the diurnal cycle seems to increase with DBS response in our study, differentiating between day and night, while others have shown opposing results. (26) These discrepancies probably reflect the different recording targets within the basal ganglia network, although methodological differences in entropy measurement may also contribute. Nevertheless, Entropy has an obvious advantage over power, as it is less affected by changes in 1/f and artifactual stimulation induced changes over time, and therefore may be favorable for driving adaptive stimulation.

Study limitations

This study is an open, uncontrolled trial including only three patients. While most results were consistent across patients, some variability remained, for example regarding laterality. In addition, data analysis was limited by the bipolar configurations of chronic recordings, by the contact location within the STN, as well as by the lower frequency limit of 5.3 Hz for home recordings in the implanted device. Also, we cannot exclude movement – related artifact as a reason for alteration of diurnal theta rhythm with DBS response (if patients sleep better with DBS and then move less during the night). Larger studies are required to further validate these findings and systematically evaluate the role of vSTN as a preferred target for closed loop DBS in OCD.

Conclusions

In summary, the findings of this study hold promise for a well-defined anatomic and physiologic “sweet spot” for DBS in OCD patients, allowing consistent clinical effect and meaningful neural marker feedback across OCD patients. Further studies are required to validate its potential usability for closed-loop adaptive stimulation in OCD.

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Data sharing: Some data are available in the main text. Otherwise, it is available upon request. Code is not available online.

The use of AI declaration: Some data was generated using generative-AI (Claude platform). The purpose of use was FOOOF analysis. Careful and meticulous oversight of the conducted analysis was taken to assure accuracy, data privacy and comprehensiveness.

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Tables

Table 1 is available in the Supplementary Files section.

Figures

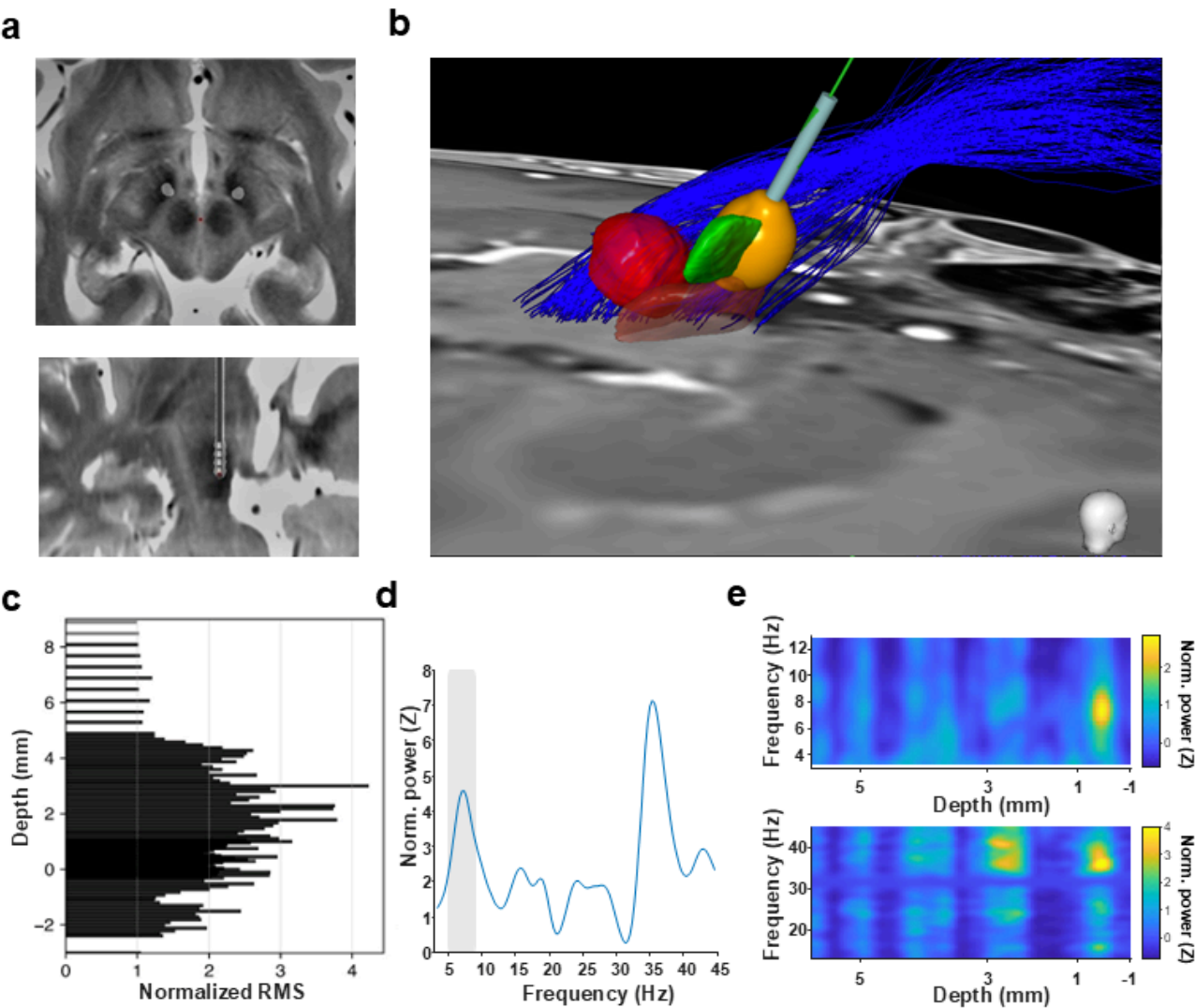


Figure 1

Clinical effect of vamSTN DBS and intra-operative recordings. **a.** axial (up) and trajectory (bottom) view of fused pre-op MRI (T2 sequence) and post-op CT scan showing an example of the location of the implanted lead at the vamSTN target. **b.** 3D reconstruction based on pre-op MRI, post-op CT, and the patient's stimulation parameters at the last follow-up. Light blue cylinder-implanted lead, yellow-VTA, green-STN, dark orange- SN, red-red nucleus, blue-sIMFB fibers. **c.** Normalized Root Mean Square (RMS) of the multiunit activity recorded by the microelectrode along the trajectory (left lead, patient 2). Zero (x-axis) is defined as the planned target. **d.** Normalized LFP PSD of intra-operative recordings at the vamSTN (at depth 0.033 mm relative to the planned target) of an example patient. The power was smoothed with a Gaussian window. The grey area shows a narrow peak at the theta range (7.6 Hz) as well as high beta/ low gamma (35 Hz) power. **e.** PSD of intra-operative recorded data along the lead trajectory of an example patient, divided into low frequencies (3-13 Hz; bottom trace) and high frequencies (13-45 Hz; upper trace). X axis is the distance (in mm) from the planned target at the vamSTN (defined at 0). The color map shows the normalized power (z-scored) intensity in each frequency range.

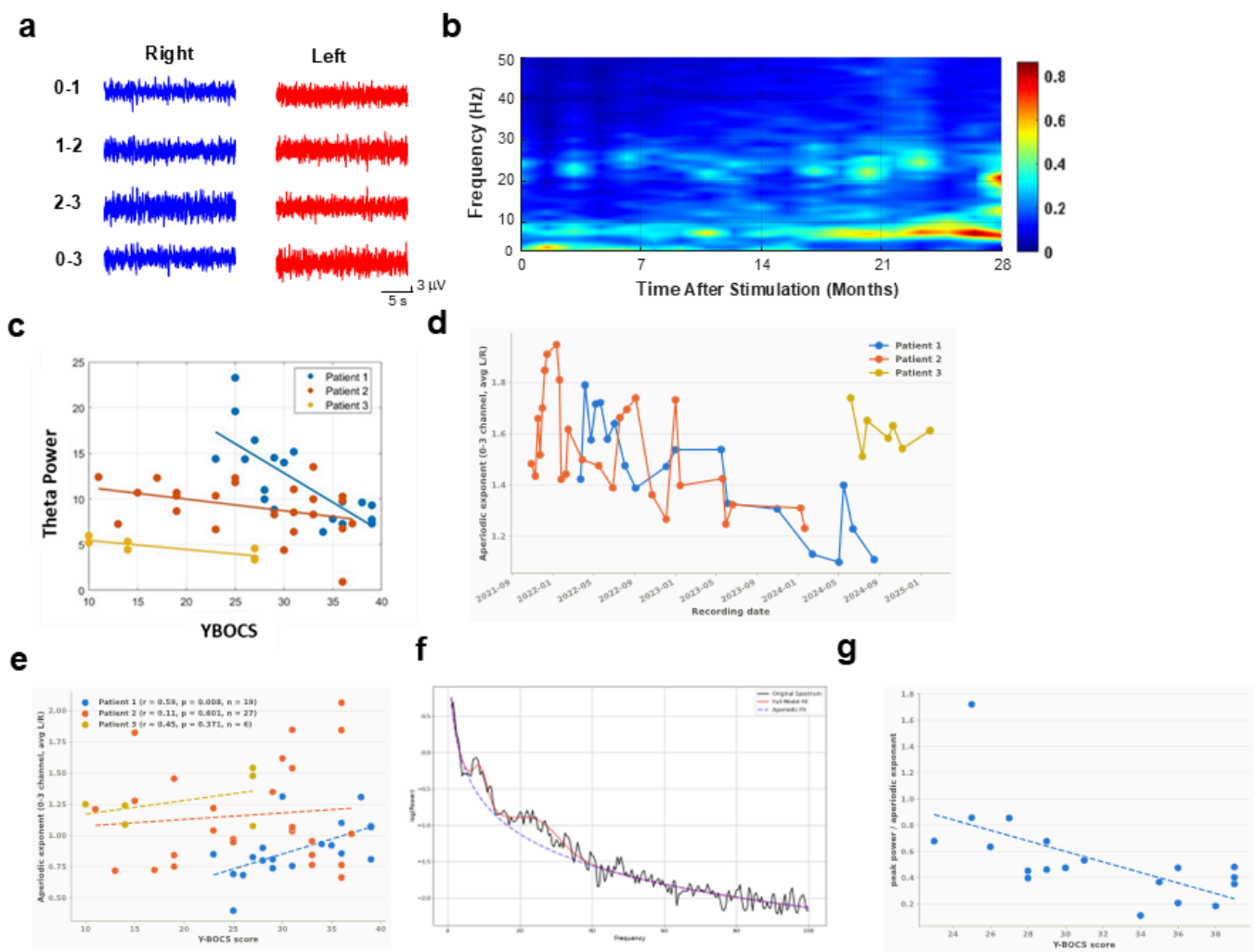


Figure 2

Long-term recordings of theta power and correlations with OCD symptoms. (a) post-operative bipolar recordings at the time domain from all adjacent contact pairs of the implanted leads (right in red and left in blue) of one exemplary patient (patient 1). Scale is 3 μ V and 5 seconds. **(b)** color map of left vamSTN PSD along the post-operative follow up period of patient 1. **(c)** Linear mixed-effect model for each patient correlating Y-BOCS scores and averaged bilateral theta power of all clinical visits. **(d)** aperiodic exponent activity for each patient and each study visit date. **(e)** correlation of aperiodic exponent and Y-BOCS measures of all clinical visits for each patient. **(f)** an example of FOOOF analysis to measure the aperiodic exponent activity and the theta peak over the exponent. **(g)** correlation between theta peak power over the exponent and Y-BOCS in patient no. 1.

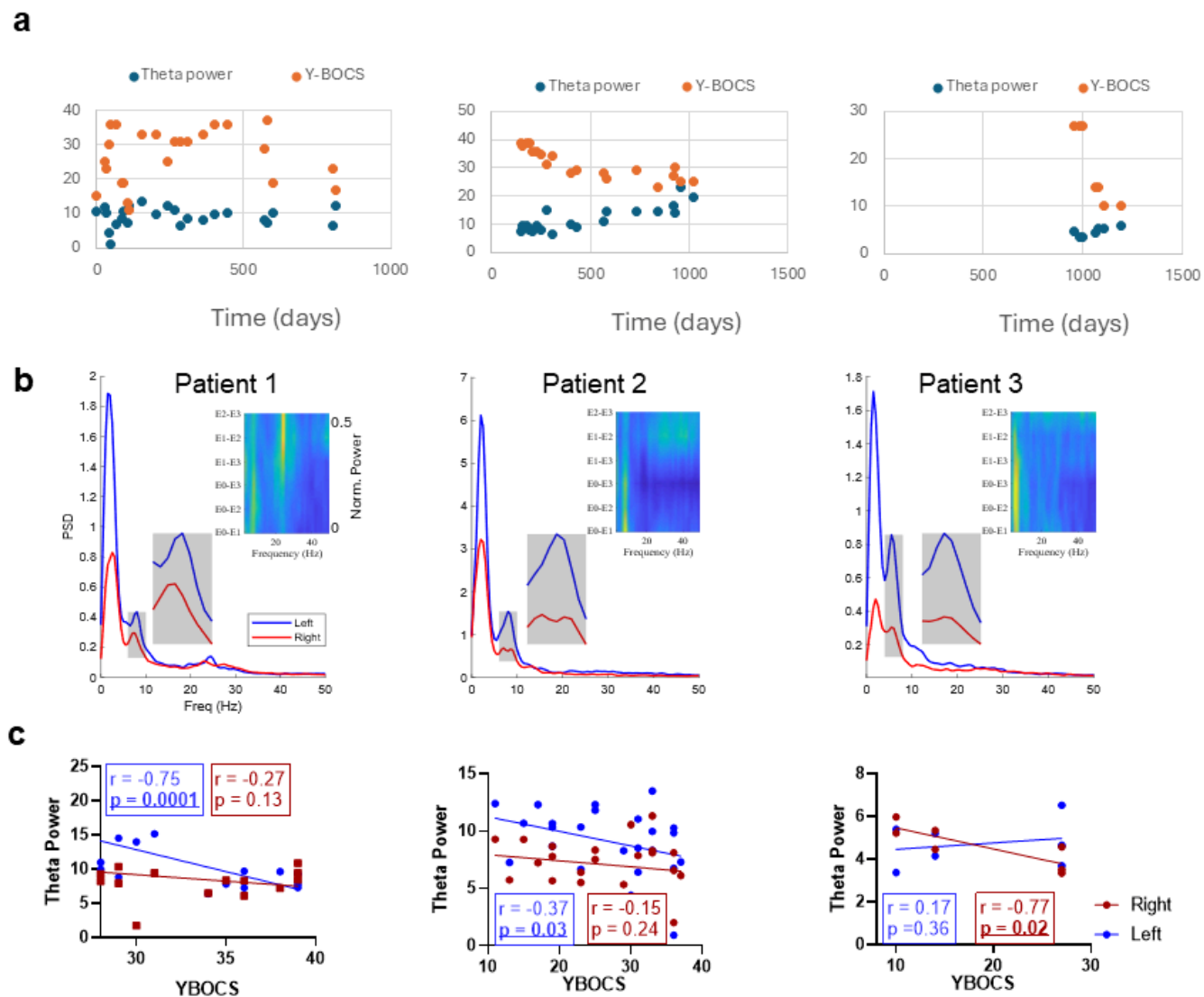


Figure 3

Right-left discrepancies in theta power.

(a) plots of Y-BOCS and theta frequency power co-measures along the post-operative follow up of all three patients. Notably, during follow-up, as Y-BOCS scores decreased (indicating clinical improvement),

theta power increased. **(b)**post-operative PSD analysis of the chronically recorded signal from the 0-2 contact pair of the bilaterally implanted leads of all patients. *Insets*, color maps of the PSD along the left lead trajectory. **(c)** Spearman's correlations of theta power and Y-BOCS of all post-operative visits, for the right and left vamSTNs, separately for each patient.

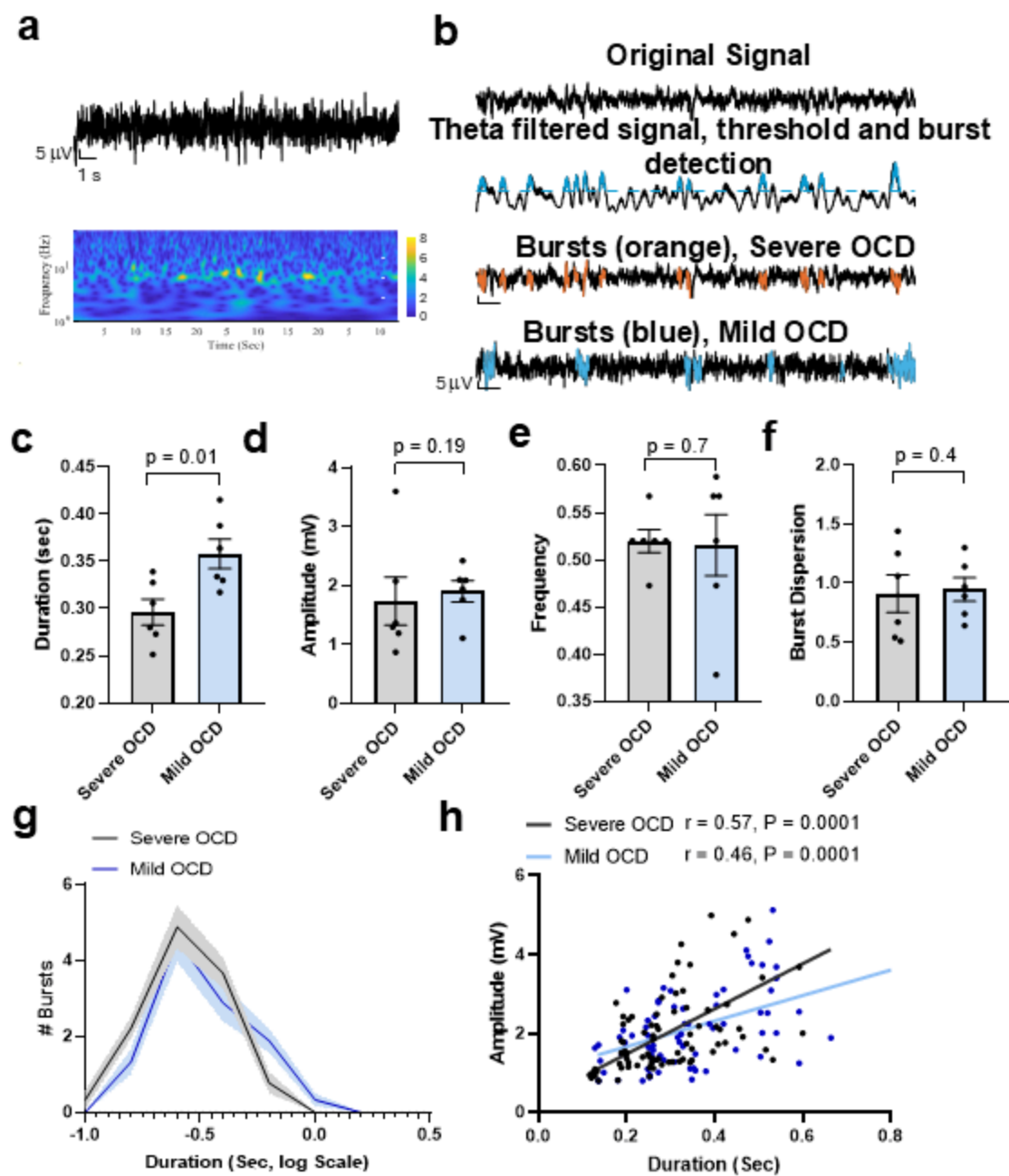


Figure 4

Theta oscillations occur in bursts that prolong with a reduction in OCD severity. **a.** An example of raw LFP recordings in the time domain (upper trace, scale is 5 μ V and 1 second) and after spectral analysis

(low frequencies, logarithmic scale; color map of power) of the same data over time showing the bursts of power in the theta range. **b.** An example of raw LFP recordings in the time domain (upper trace) and after bandpass filtering for theta frequency (second upper trace). The blue dotted line marks the threshold for burst definition. Recordings scale is 5 μ V and 1 sec. Third upper trace, an example of theta bursts as they appear (in orange) in the raw recordings at a severe OCD state (same scale as previous traces) and at a mild OCD state (bottom trace, in blue). **c.** bar graph that compares the duration of theta bursts in severe OCD states (grey) and mild OCD states (blue) in all patients (each point represents one hemisphere of one patient). **d.** bar graph that compares the amplitude of theta bursts in severe OCD states and mild OCD states in all patients. **e.** bar graph that compares the frequency of theta bursts in severe OCD states and mild OCD states in all patients. **f.** Burst dispersion was comparable between groups, with mean CV values near 1, consistent with approximately random burst timing. **g.** Distribution of burst durations across all patients, comparing severe and mild OCD states. The curve of the mild OCD state is shifted to the right, with longer bursts. **h.** Pearson's correlation between theta burst amplitude and duration in severe and mild OCD states across all patients demonstrates a positive association under both conditions.

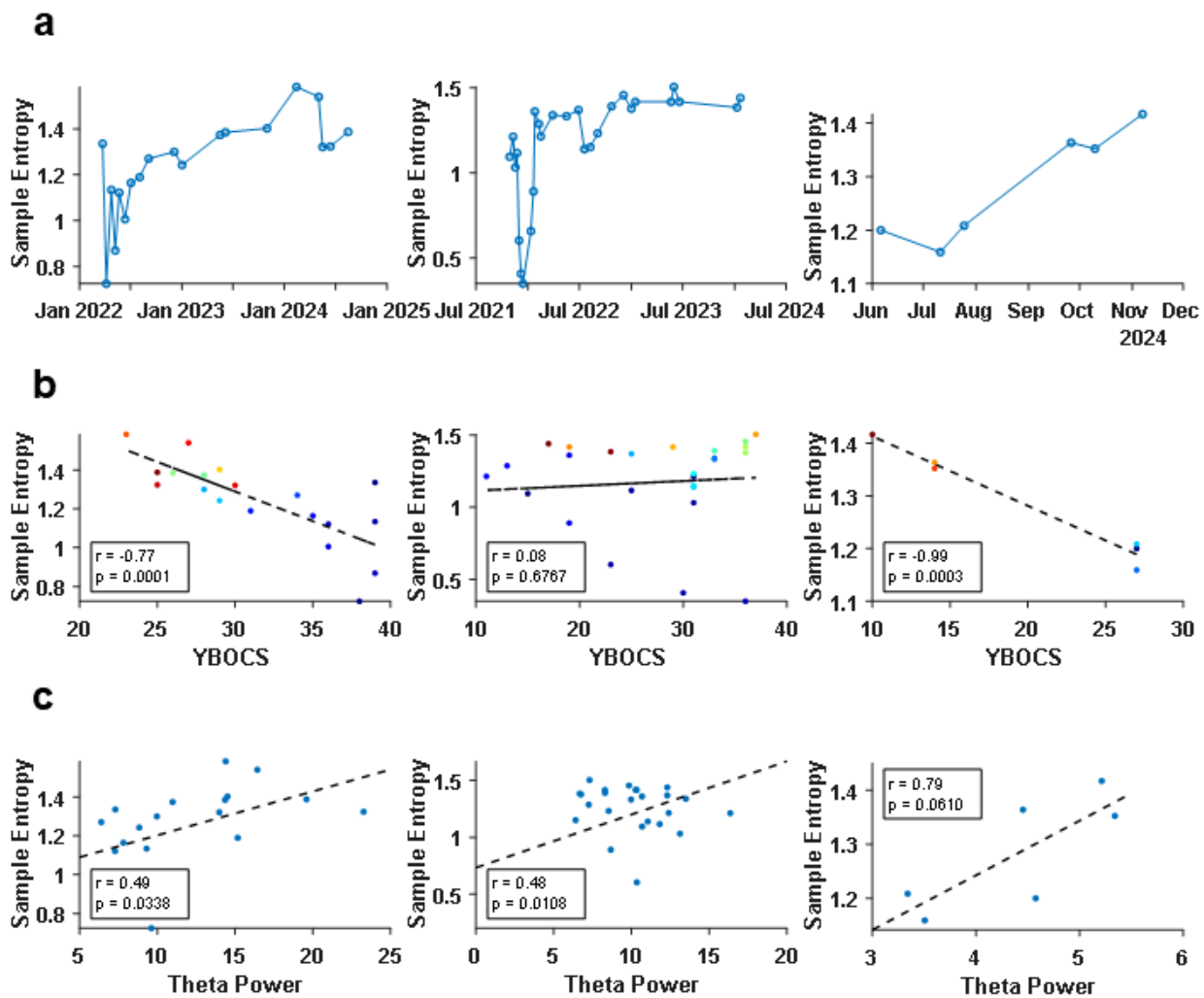


Figure 5

Theta sample entropy and its clinical correlations. **a.** plots of theta sample entropy values along the post-operative follow-up period of the patients (left column=patient one, central column=patient two, and right column=patient three of table 1). **b.** Spearman's correlations between theta sample entropy and Y-BOCS scores of the patients. Data points are color-coded by recording date, with warmer colors (red) indicating more recent sessions and cooler colors (blue) indicating earlier sessions. **c.** Pearson's correlation between theta sample entropy and theta power. Theta power values are derived from the same dataset shown in Figure 3.

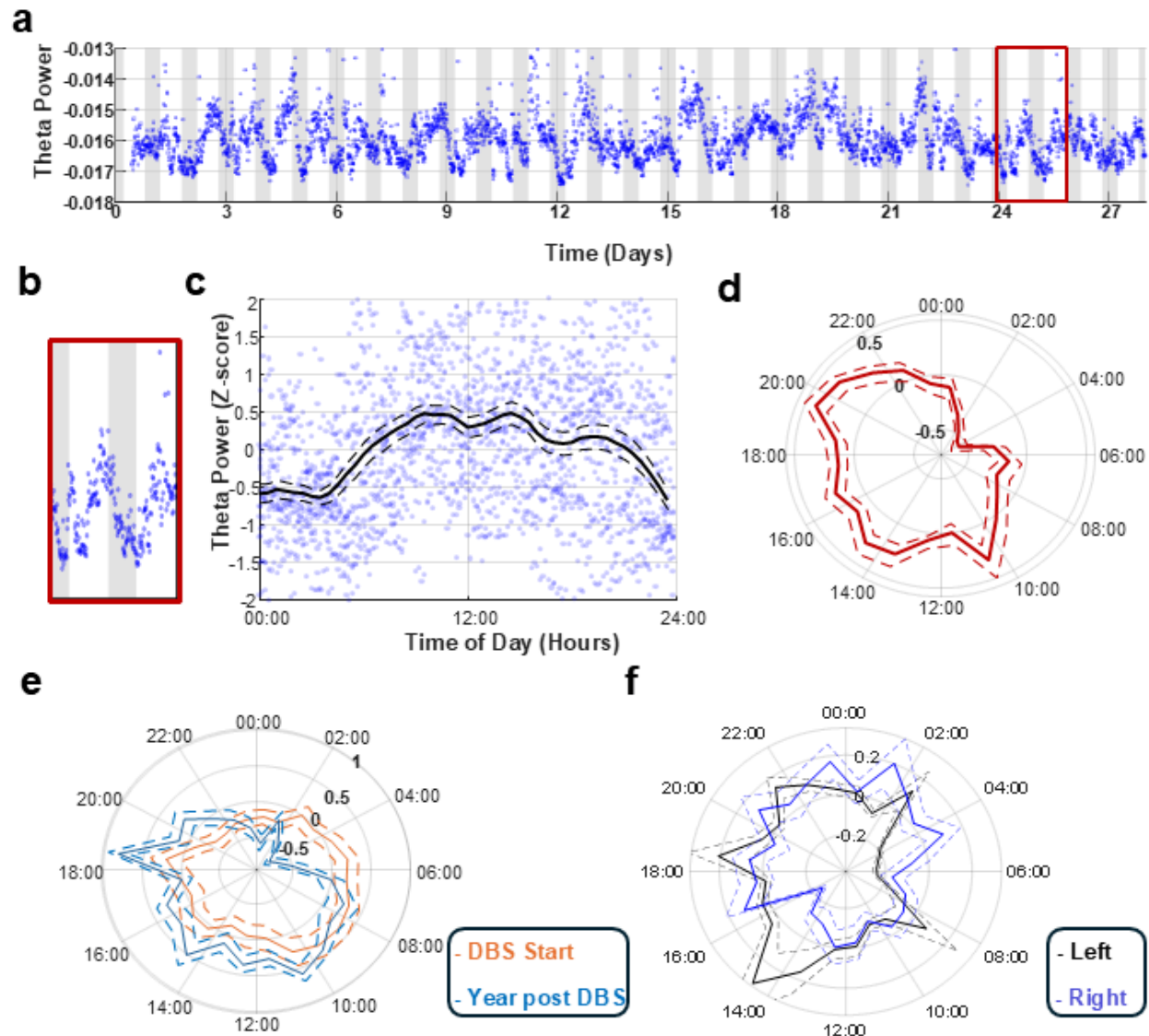


Figure 6

Diurnal variation in theta power normalizes with DBS response. **a.** An example of one month of continuous recordings of theta power at home showing marked diurnal variation of the recorded signal (white background=day, grey background=night). **b.** an inset of two days showing the repeated pattern of theta power variation. **c.** an inset of one month of recordings overlaid on a 24-hour axis. **d.** averaged diurnal variation of theta power of all patients in the mild OCD state. Black line=mean, dotted lines=standard error of the mean. **e.** comparison of average diurnal variation in vbmSTN theta power between severe OCD state (DBS start; black line) and mild OCD state (DBS response 1-year post-op; blue line). **f.** comparison of average diurnal variation in vbmSTN theta power in the mild OCD state between left (black) and right (blue) hemisphere.

Supplementary Files

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- [SupplementaryMethods.docx](#)
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