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Current Biology

Direct Electrical Stimulation of Lateral Orbitofrontal Cortex Acutely Improves Mood in Individuals with Symptoms of Depression

Highlights

- We investigated the effects of brain stimulation on mood state in epilepsy patients
- Lateral OFC stimulation improved mood state in subjects with depression symptoms
- This stimulation induced neural features associated with positive mood states
- Lateral OFC is a promising new stimulation target for treatment of mood disorders

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In Brief

Using direct neurophysiological recordings, Rao et al. show that stimulation of lateral OFC produces acute, dose-dependent mood-state improvement in subjects with baseline depression. This stimulation broadly modulates mood-related circuitry, revealing a new brain stimulation target with strong therapeutic potential.

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Direct Electrical Stimulation of Lateral Orbitofrontal Cortex Acutely Improves Mood in Individuals with Symptoms of Depression

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SUMMARY

Mood disorders cause significant morbidity and mortality, and existing therapies fail 20%–30% of patients. Deep brain stimulation (DBS) is an emerging treatment for refractory mood disorders, but its success depends critically on target selection. DBS focused on known targets within mood-related frontostriatal and limbic circuits has been variably efficacious. Here, we examine the effects of stimulation in orbitofrontal cortex (OFC), a key hub for mood-related circuitry that has not been well characterized as a stimulation target. We studied 25 subjects with epilepsy who were implanted with intracranial electrodes for seizure localization. Baseline depression traits ranged from mild to severe. We serially assayed mood state over several days using a validated questionnaire. Continuous electrocorticography enabled investigation of neurophysiological correlates of mood-state changes. We used implanted electrodes to stimulate OFC and other brain regions while collecting verbal mood reports and questionnaire scores. We found that unilateral stimulation of the lateral OFC produced acute, dose-dependent mood-state improvement in subjects with moderate-to-severe baseline depression. Stimulation suppressed low-frequency power in OFC, mirroring neurophysiological features that were associated with positive mood states during natural mood fluctuation. Stimulation potentiated single-pulse-evoked responses in OFC and modulated activity within distributed structures implicated in mood regulation. Behavioral responses to stimulation did not include hypomania and indicated an acute restoration to non-depressed mood state. Together, these findings indicate that lateral OFC stimulation broadly modulates mood-related circuitry to improve mood state in depressed patients, revealing lateral OFC as a promising new target for therapeutic brain stimulation in mood disorders.

INTRODUCTION

A modern conception of mood disorders holds that the signs and symptoms of emotional dysregulation are manifestations of abnormal activity within large-scale brain networks [1]. This view, evolved from earlier hypotheses based on chemical imbalances in the brain, has fueled interest in selective neural network modulation with deep brain stimulation (DBS). Although the potential for precise therapeutic intervention with DBS is promising, its efficacy is sensitive to target selection. In treatment-resistant depression (TRD), for example, well-studied targets for DBS include the subgenual cingulate cortex (SCC) [2–4] and subcortical structures [5–7], but the benefits of DBS in these areas are not clearly established [8, 9]. A major challenge in this regard relates to the fact that clinical manifestations of mood disorders like TRD are heterogeneous and involve dysfunction in cognitive, affective, and reward systems [10]. Therefore, brain regions that represent a functional confluence of these systems are attractive targets for therapeutic brain stimulation.

Residing within prefrontal cortex, the orbitofrontal cortex (OFC) shares reciprocal connections with amygdala, ventral striatum, insula, and cingulate cortex [11]—areas implicated in emotion regulation [12]. As such, OFC is anatomically well positioned to regulate mood. Functionally, OFC serves as a nexus for sensory integration and has myriad roles related to emotional experience [13, 14], including predicting and evaluating outcomes [15–17], representing reward-driven learning and behavior [18–20], and mediating subjective hedonic experience [21, 22]. Converging lines of evidence from lesion studies, functional neuroimaging, and intracranial physiology point to a role of OFC in emotion processing [10, 23–27]. Clinically depressed individuals have abnormally high levels of activity in OFC as ascertained by functional neuroimaging [28, 29], and recovery from

depression is associated with decreased OFC activity [2, 30]. Repetitive transcranial magnetic stimulation (rTMS) of OFC was shown to improve mood in a single-subject case study [31] and in a series of patients who otherwise did not respond to rTMS delivered to conventional (non-OFC) targets [32], but whether intracranial OFC stimulation can reliably alleviate mood symptoms is not known. Furthermore, OFC is relatively large, and functional distinctions between medial and lateral subregions are known [33], raising the possibility that subregions of OFC may play distinct roles in mood regulation [27]. More generally, it remains poorly understood how direct brain stimulation affects local and network-level neural activity to produce complex emotional responses.

We hypothesized that brain networks involved in emotion processing include regions, like OFC, that represent previously unrecognized stimulation targets for alleviation of neuropsychiatric symptoms. To test this hypothesis, we developed a system for studying mood-related neural activity in subjects with epilepsy who were undergoing intracranial electroencephalography (iEEG) for seizure localization. In addition to direct recording of neural activity, iEEG allows delivery of defined electrical stimulation pulses with high spatiotemporal precision and concurrent measurement of behavioral correlates [12]. Using serial quantitative mood assessments and continuous iEEG recordings, we investigated the acute effects of OFC stimulation on mood state and characterized corresponding changes in neural activity locally and in distributed brain regions. We found that lateral OFC stimulation acutely improved mood in subjects with baseline depression and that these therapeutic effects correlated with modulation of large-scale brain networks implicated in emotion processing. Our results suggest that lateral OFC stimulation improves mood state at least partly through mechanisms that underlie natural mood variation, and they are consistent with the notion that OFC integrates multiple streams of information relevant to affective cognition.

RESULTS

Mood Effects of OFC Stimulation

A modular experimental design (Figures 1A and 1B) and extensive electrode coverage in all subjects (Figures 1C and 1D; Table S1) allowed us to assess the effects of stimulation in numerous brain regions, including limbic and paralimbic structures implicated in mood regulation, with respect to both mood state and mood trait. To assess acute stimulation effects on current mood state, we employed a combination of quantified self-report and word-valence metrics (composite mood score, CMS; lower CMS indicates more negative mood state; see Method Details). To assess stimulation effects with respect to baseline mood trait, we utilized Beck Depression Inventory (BDI) scores obtained prior to surgery.

Subjects had baseline trait depression that ranged from minimal to severe (Figure 2A). Across multiple brain regions and over a wide range of stimulation parameters (0.2–100 Hz, pulse width 100–1,000 μs, 1–10 mA, duration 1–200 s), subjects generally did not report acute stimulation-induced changes in mood state, though stimulation of amygdala occasionally evoked dysphoria or other unpleasant symptoms, as previously described [34, 35]. By contrast, during lateral OFC stimulation (100 Hz, 100 μs pulse width, 1 or 6 mA, duration 100–200 s; hereafter referred to as continuous stimulation), subjects' verbal reports often reflected marked mood improvement (Table S2). For example, one subject (EC84) used mostly negative words to describe their mood state during sham (0 mA) stimulation ("on the sad side," "a little bit nervous") but, during lateral OFC stimulation (6 mA), used mostly positive words ("calm, cool, and collected," "a lot better"). CMS measures reflected such changes, increasing relative to baseline levels recorded during sham stimulation in nearly all subjects (Figure S1A). This effect was driven largely by the word-valence component of CMS, as changes in the quantified self-report component of CMS (immediate mood scaler, IMS [36]; see Method Details) approached but did not reach statistical significance ($p = 0.06$; Figures S1B and S1C). Increase in CMS (i.e., mood improvement) with lateral OFC stimulation was significant in subjects with moderate or severe trait depression, and higher stimulation current was more effective than lower current (Figure 2B, left; 1 mA: $Z = 2.20$, $p = 0.03$; 6 mA: $Z = 2.52$, $p = 0.01$; 1 mA versus 6 mA: $Z = -1.9$, $p = 0.05$). In contrast, we observed no significant change in mood in subjects with minimal or mild baseline mood traits (Figure 2B, right; 1 mA: $Z = 0.45$, $p = 0.65$; 6 mA: $Z = 1.82$, $p = 0.07$; 1 mA versus 6 mA: $Z = -0.65$, $p = 0.51$). This finding is consistent with previous work on TRD showing that patient-specific factors, including measures of disease severity, predict response to brain stimulation [37].

Specificity of Mood Effects

Stimulation of other limbic and paralimbic regions generally did not result in such robust mood-state improvement. However, in line with previous studies [2, 38], cingulate cortex stimulation did improve mood state (Figure S1D), though the effect was more variable than with OFC stimulation. Electrode locations typically permitted stimulation of lateral portions of OFC (Figure 1C, red markers), but we occasionally had the opportunity to stimulate medial OFC as well (Figure 1C, yellow makers). Stimulation of lateral OFC was more effective for mood improvement than medial OFC (Figure S1D), likely due to distinct functions of these subregions [27]. Accordingly, OFC stimulation hereafter refers to lateral OFC stimulation unless otherwise specified.

Speech rate during verbal report did not suggest mania during OFC stimulation (Figures S1E and S1F), though stimulation did specifically elevate speech rate in trait-depressed subjects, resulting in a level similar to that of the non-depressed subjects. Subjects did not display hyperactivity, grandiosity, distractibility, or other symptoms of mania. This indicates that the acute intervention did not produce a supraphysiological mood state, as has been observed with DBS of other brain regions [39, 40]. Furthermore, OFC stimulation generally did not affect CMS of individuals who did not report low mood symptoms during the baseline sham period, suggesting that OFC stimulation normalizes mood state and does not produce non-specific mood elevation.

Neural Activity during Spontaneous Mood Fluctuation

To further understand how OFC stimulation might have this effect, we asked how changes in mood state are reflected in neurophysiology, especially in OFC. Subjects serially reported their mood state using the IMS at variable intervals in the days prior to stimulation studies (Figure 1A; Table S1; mean total

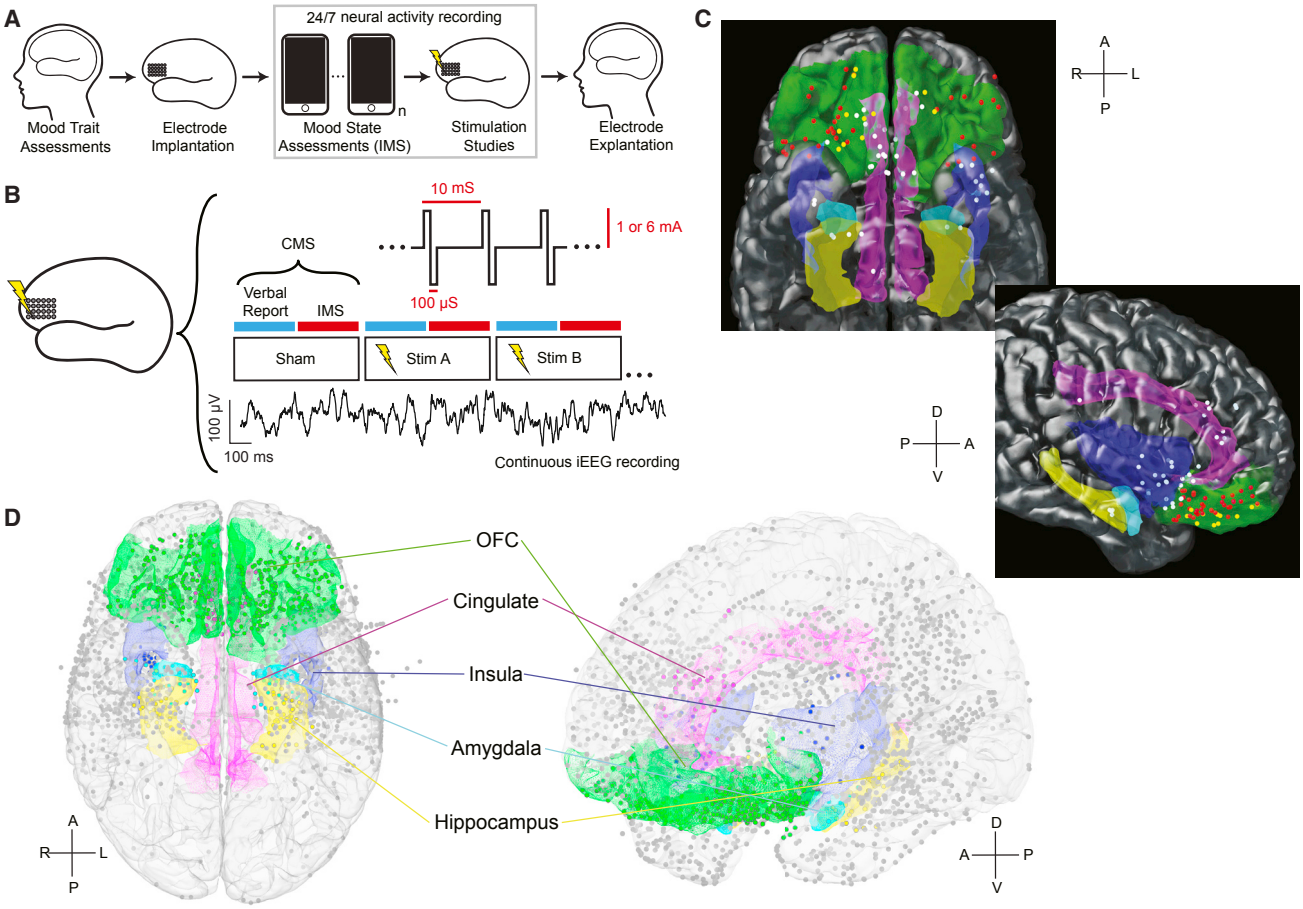

Figure 1. Experimental Design and Locations of Stimulated Sites

(A) Experimental timeline: Subjects completed the Beck Depression Inventory II (BDI) to assay trait depression prior to electrode implantation for seizure monitoring. Mood was assessed during continuous intracranial electroencephalography (iEEG) using the Immediate Mood Scaler (IMS). Stimulation studies were conducted, and electrodes were then explanted.

(B) Overview of stimulation experiments. iEEG was continuously recorded while stimulation was delivered at different sites. For each stimulation site, verbal report and IMS score were combined to provide a composite mood score (CMS) as a measure of current mood state (see Method Details). Bipolar stimulation was delivered in charge-balanced biphasic pulses of 100 µS pulse width, 100 Hz frequency, and amplitudes of 1 or 6 mA.

(C) Montreal Neurological Institute (MNI) template brain with all tested stimulation electrodes across study subjects. Lateral OFC sites shown by red markers, medial OFC sites shown by yellow markers, non-OFC sites shown by white markers.

(D) MNI template brain with all recording electrodes across study subjects. Colored markers indicate electrodes that were verified to be located within the indicated regions based on review of co-registered CT and MRI, while gray markers indicate electrodes outside the indicated regions. Green, orbitofrontal cortex (OFC); magenta, cingulate; blue, insula; cyan, amygdala; yellow, hippocampus.

See also Tables S1 and S3.

number of IMS data points per subject ± SD = 13.2 ± 10.5; mean number of IMS data points per day ± SD = 2.3 ± 2.4). Variability in IMS scores within subjects (Figure S2A) facilitated regression analysis with features of neural activity. We extracted segments of iEEG activity surrounding each IMS data point and examined first-order neural features during this natural (spontaneous) fluctuation in mood (Figure 3A). Normalized OFC power negatively correlated with IMS in theta and alpha frequency bands but not in higher frequencies (Figures 3B, 3C, and S2B). In contrast, the correlation coefficient for the beta band was not significantly different from zero (two-sided z test, $p = 0.11$). This frequency-specific inverse relationship between mood state and OFC power was seen only in subjects with moderate-to-severe baseline mood traits (Figures 3B and 3C). Moreover, we found that for low frequencies, the correlation coefficient was significantly different from zero (two-sided z test, $p = 0.0092$ and $p = 0.018$ for theta and alpha bands, respectively, among $n = 9$ subjects who had at least 10 IMS data points).

Neural Activity in OFC during Stimulation

Having observed that OFC low-frequency power and mood state vary inversely during natural mood fluctuations, we hypothesized that mood improvement would be associated with decreased low-frequency power during OFC stimulation. To test this, we developed an approach to analyze OFC activity during stimulation. Detection of neural responses during electrical stimulation are typically hampered by a stimulus-related artifact that can obscure much or all of the underlying signal. We therefore

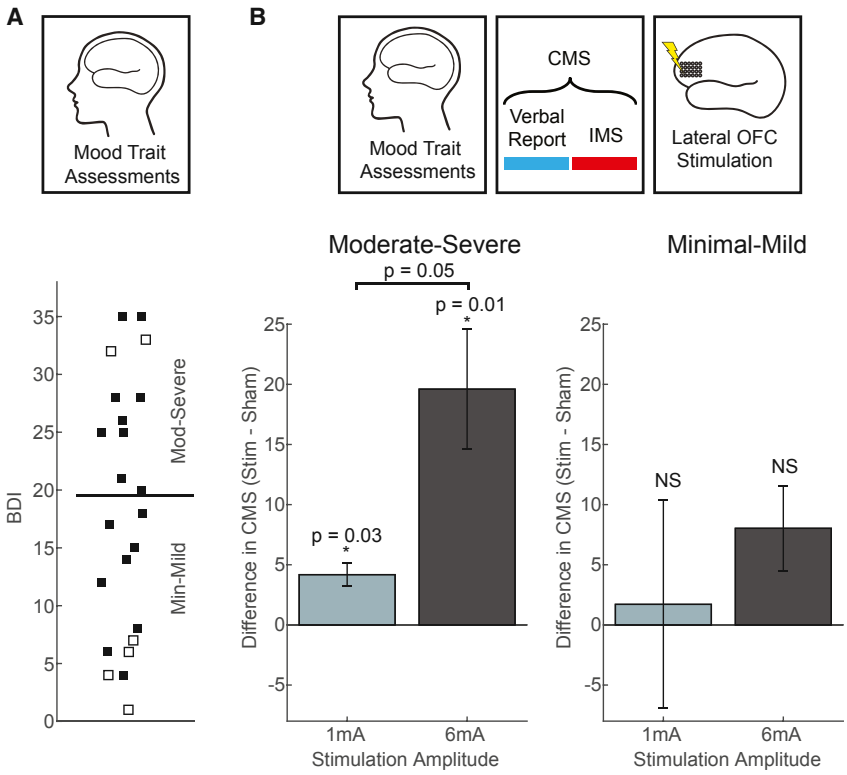

Figure 2. Lateral OFC Stimulation Produces Dose-Dependent Mood Improvement in Subjects with Moderate-to-Severe Baseline Mood Trait

(A) Subjects ranged from exhibiting minimal or mild (Min-Mild) to moderate or severe (Mod-Severe) trait depression.

(B) Mood-improving effects of lateral OFC stimulation were specific to subjects with Mod-Severe trait depression. Bars show mean change in CMS with stimulation relative to sham (0 mA) ± 1 SEM. Significance assessed by signed-rank and rank-sum tests (p values shown in graph).

See also Figure S1 and Tables S1–S4.

developed artifact-rejection techniques (Figure S3; Method Details) that enabled evaluation of low-frequency neural activity during stimulation. Spectral analysis revealed that OFC stimulation suppresses low-frequency power (Figure 4A). This suppression was significant for theta-range frequencies (Figure 4B; pre-stim versus stim periods: $Z = -2.33$, $p = 0.02$; stim versus post-stim periods: $Z = 2.64$, $p = 0.008$), only showed a significant change from stim to post-stim periods in the alpha range (Figure 4C; pre-stim versus stim periods: $Z = -1.65$, $p = 0.1$; stim versus post-stim periods: $Z = 2.22$, $p = 0.03$), and was not significant for beta frequencies (pre-stim versus stim periods: $Z = -0.90$, $p = 0.38$; stim versus post-stim periods: $Z = -0.26$, $p = 0.80$). Thus, local neurophysiological changes during OFC stimulation (decreased theta and, to a lesser extent, alpha frequency power) are opposite those observed during spontaneous negative mood states (Figures 3B and 3C), suggesting that the mood effects of OFC stimulation may involve circuits that mediate natural mood variation. However, OFC power alone does not appear to provide a direct readout of mood state, as Pearson correlation analysis revealed that percent-change in CMS is not significantly correlated to percent-change in OFC theta power from pre-stim to stim periods ($r = 0.41$, $p = 0.16$).

Single-Pulse Stimulation in OFC

To further characterize the neurophysiological effects of OFC stimulation, we probed for changes in cortical excitability by analyzing potentials evoked by current pulses applied immediately before and after continuous stimulation [41]. Trains of high-amplitude single pulses (see Method Details) applied to OFC before OFC continuous stimulation evoked local responses within 100 ms of pulse onset (Figure 4D). After OFC continuous stimulation, identical trains of single pulses evoked potentiated responses (Figures 4D–4F), reflecting increased cortical excitability, as has been described following high-frequency rTMS [42], though given the response latencies, we cannot distinguish between increased local excitability and recurrent activation. Continuous stimulation of a site remote to OFC (precentral gyrus) did not potentiate single-pulse-evoked responses in OFC, ruling out a non-specific effect of cortical stimulation on OFC excitability (Figure S4). Of note, abnormal single-pulse responses have been reported as a marker of epileptogenic cortex [43], but none of our subjects had seizures arising from OFC (Table S1).

Network Effects of OFC Stimulation

Affective states arise from a distributed network of brain regions [12], and given the effects of OFC stimulation on cortical excitability, we next examined effects on activity in other sites sampled by intracranial electrodes (Figure 5A, example subject). Spectral analysis revealed that OFC stimulation suppressed low-frequency power broadly, with greatest effects seen in the theta frequency band in OFC, insula, and dorsal cingulate (Figure 5B). No brain areas had significant increases or decreases in the alpha or beta frequency bands, with the exception of an increase in OFC alpha from stim to post-stim periods (Figure S5A; OFC alpha, $Z = 2.22$, $p = 0.03$). Following offset of stimulation, low-frequency power showed increases that were proportional to the initial decrease across all studied regions (Figures 5B and S5B). By contrast, medial OFC stimulation was not associated with significant changes in theta power in OFC or other studied regions (Figure S5C). Although causality cannot be inferred from our data, taken together, these findings suggest that mood-state improvement observed during lateral OFC stimulation may be mediated through a combination of local and network-level changes in neural activity.

DISCUSSION

Here, we show that human lateral OFC is a promising target for brain stimulation to alleviate mood symptoms. Unilateral

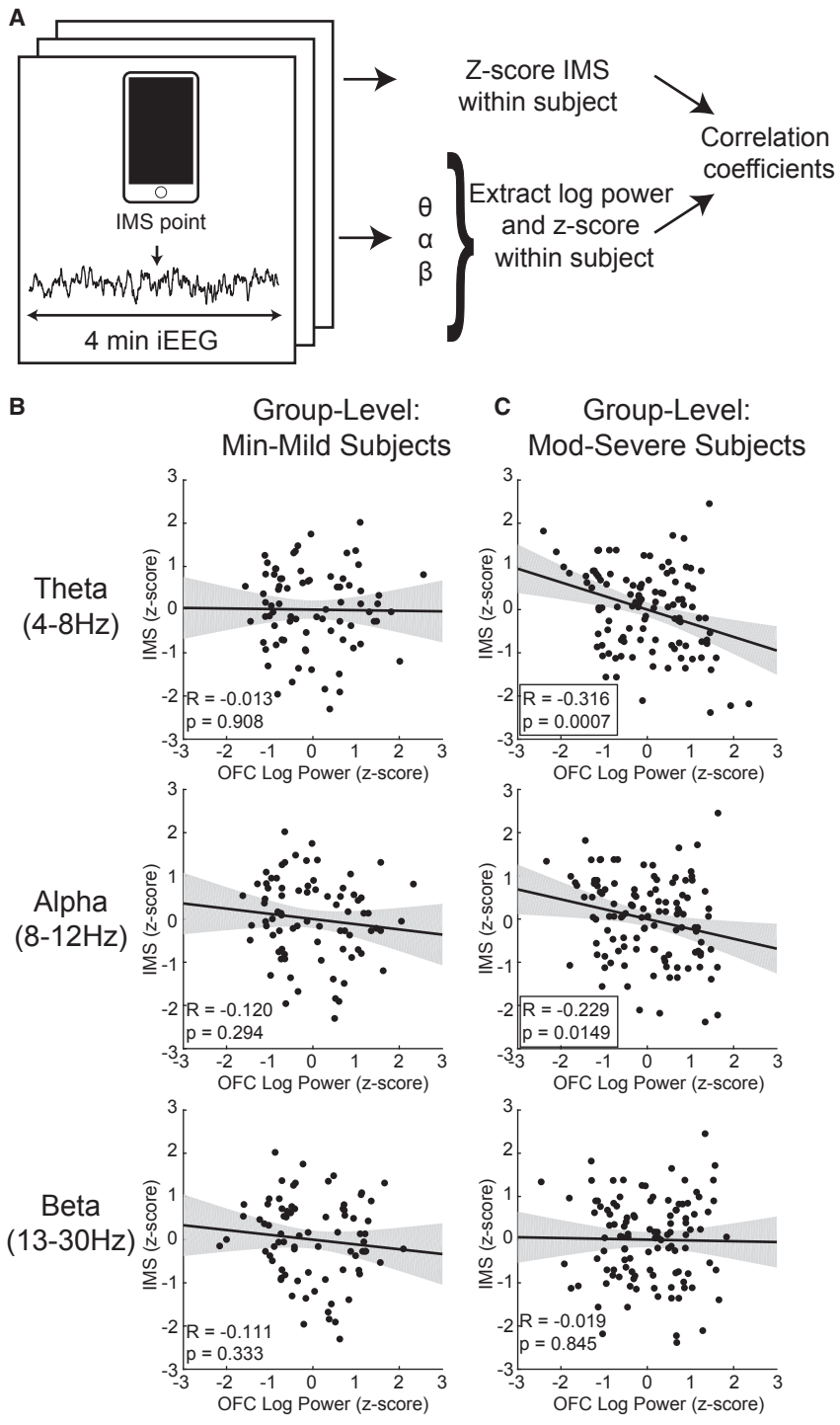

Figure 3. Lateral OFC Low-Frequency Power Negatively Correlates with Natural Mood-State Fluctuation in Subjects with Moderate-to-Severe Baseline Mood Trait

(A) 4 min of iEEG were extracted surrounding each IMS data point. Time-averaged log power (z-scored within subjects) in lateral OFC was calculated for each iEEG segment and correlated with z-scored IMS in order to compare variations in lateral OFC power with variations in IMS. Lower IMS indicates more negative mood state.

(B) Across all IMS data points in subjects with minimal-to-mild depression, there were no significant correlations between IMS and lateral OFC power. R is the correlation coefficient; p is the p value of the correlation coefficient; black lines show the least-squares linear fit; shaded area is the 95% confidence interval of the least-squares linear fit.

(C) In patients with moderate-to-severe depression, theta and alpha lateral OFC powers exhibited negative correlations with IMS. R, p, black line, and shaded area same as above. Number of IMS data points used in correlations for each subject: EC81 (3), EC82 (16), EC84 (16), EC87 (12), EC91 (2), EC92 (3), EC96 (2), EC99 (3), EC108 (12), EC113 (5), EC122 (13), EC125 (12), EC129 (8), EC133 (6), EC137 (18), EC139 (3), EC142 (9), EC150 (20), EC152 (7), EC153 (3), EC162 (11), EC175 (7).

See also Figure S2 and Table S3.

stimulation of lateral OFC consistently produced acute, dose-dependent mood-state improvement across subjects with baseline depression traits. Locally, lateral OFC stimulation increased cortical excitability and suppressed low-frequency power, a feature we found to be negatively correlated with mood state. At the network level, lateral OFC stimulation modulated activity within a network of limbic and paralimbic structures implicated in mood regulation.

Relief of mood symptoms afforded by lateral OFC stimulation may arise from OFC acting as a hub within brain networks that mediate affective cognition. Previous studies identify OFC as a key node within an emotional salience network activated by anticipation of aversive events [44, 45]. Within this network, OFC is thought to integrate multimodal sensory information and guide emotion-related decisions by evaluating expected outcomes [17, 18]. Stimulation of other brain regions that encode value information, such as SCC [2] and ventral striatum [6], has also been found to improve mood, highlighting the relevance of reward circuits to mood state. Here, using iEEG, we extend previous studies that employed indirect imaging biomarkers, such as glucose metabolism or blood oxygen level [46], to show that direct OFC stimulation modulates neural activity within a distributed network of brain regions. Our finding that lateral OFC stimulation was more effective than medial OFC stimulation for mood symptom relief advances the idea that these regions have differential contributions to depression, likely due to differences in network connectivity [47]. We did not observe consistent differences based on laterality of stimulation [22, 32], but future studies powered to discern such differences may reveal additional layers of specificity.

Although few behavioral variables have been identified to predict which individuals will respond to stimulation of a given target

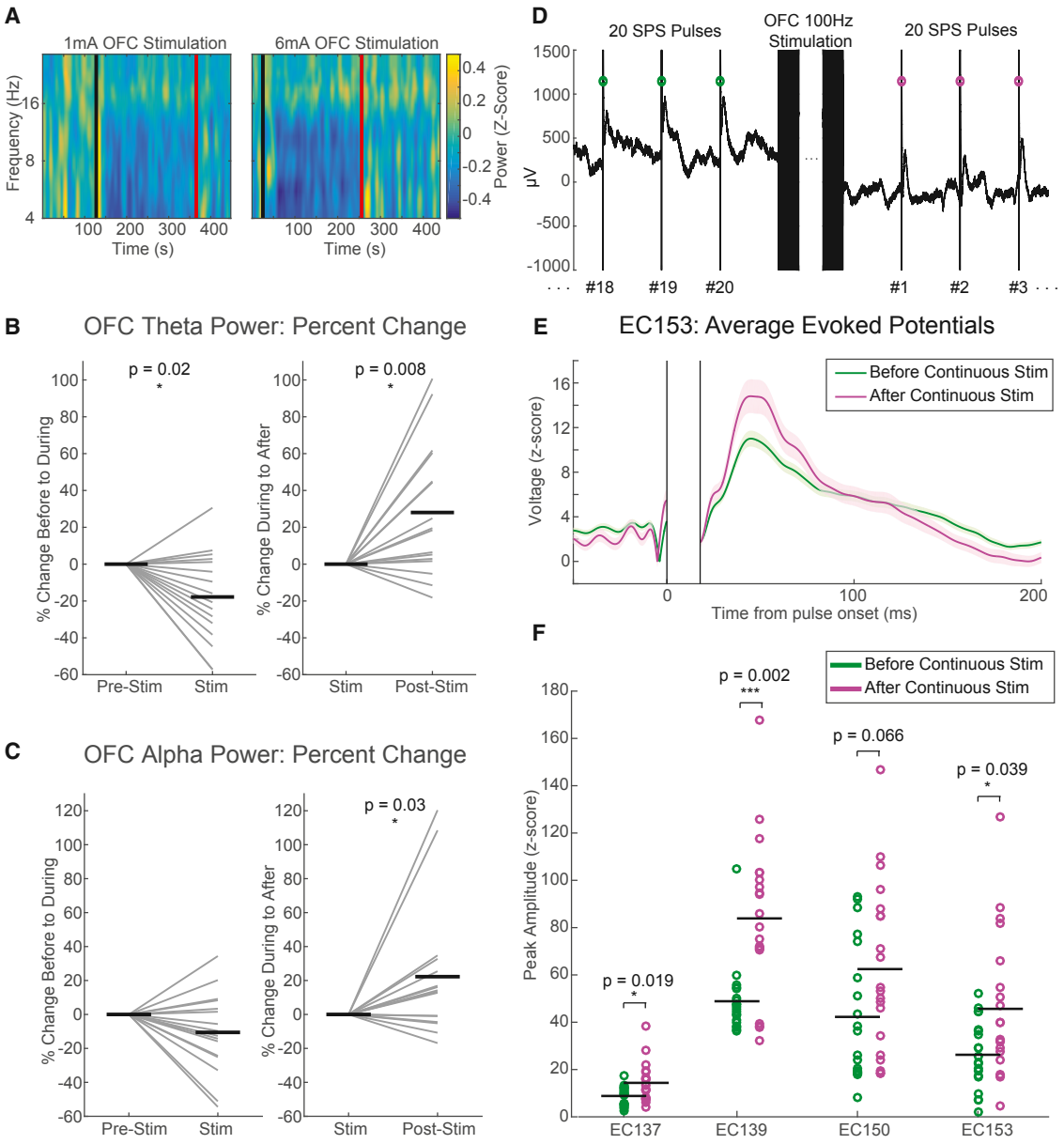

Figure 4. Local Neurophysiological Effects of Lateral OFC Stimulation

(A) Low-frequency power is suppressed during lateral OFC stimulation. Individual subject (EC125) example shown for 1 mA (left) and 6 mA (right) stimulation. Stimulation onset (black line) and offset (red line).

(B) Percent change in lateral OFC power (average of 1 mA and 6 mA responses) from pre-stim to stim (left) and stim to post-stim (right). Theta power significantly decreased from pre-stim to stim and significantly increased from stim to post-stim. Gray lines indicate percent change for each subject; black line indicates group mean.

(C) Same as (B) for alpha power.

(D) Single-pulse stimulation (SPS) in lateral OFC before and after lateral OFC continuous stimulation to assess changes in cortical excitability.

(E) Lateral OFC SPS before (green) and after (magenta) lateral OFC continuous stimulation in a representative subject (EC153), showing that evoked potentials increase after continuous stimulation. Solid lines are mean across 20 SPS pulses; shading shows ±1 SEM.

(F) Across four subjects, peak amplitude of evoked potentials increased after continuous stimulation. Each circle represents evoked potential from an individual pulse of SPS. Black bars show mean across SPS pulses.

See also Figures S3 and S4 and Table S3.

for depression, we found that only patients with significant trait depression experienced mood-state improvement with lateral OFC stimulation. Based on speech-rate analysis, lateral OFC stimulation did not produce supraphysiological mood states, as can be seen with stimulation of other targets [39, 40], but did specifically elevate speech rate in trait-depressed subjects, resulting in a level similar to that of the non-depressed subjects. Local neurophysiological changes induced by stimulation were

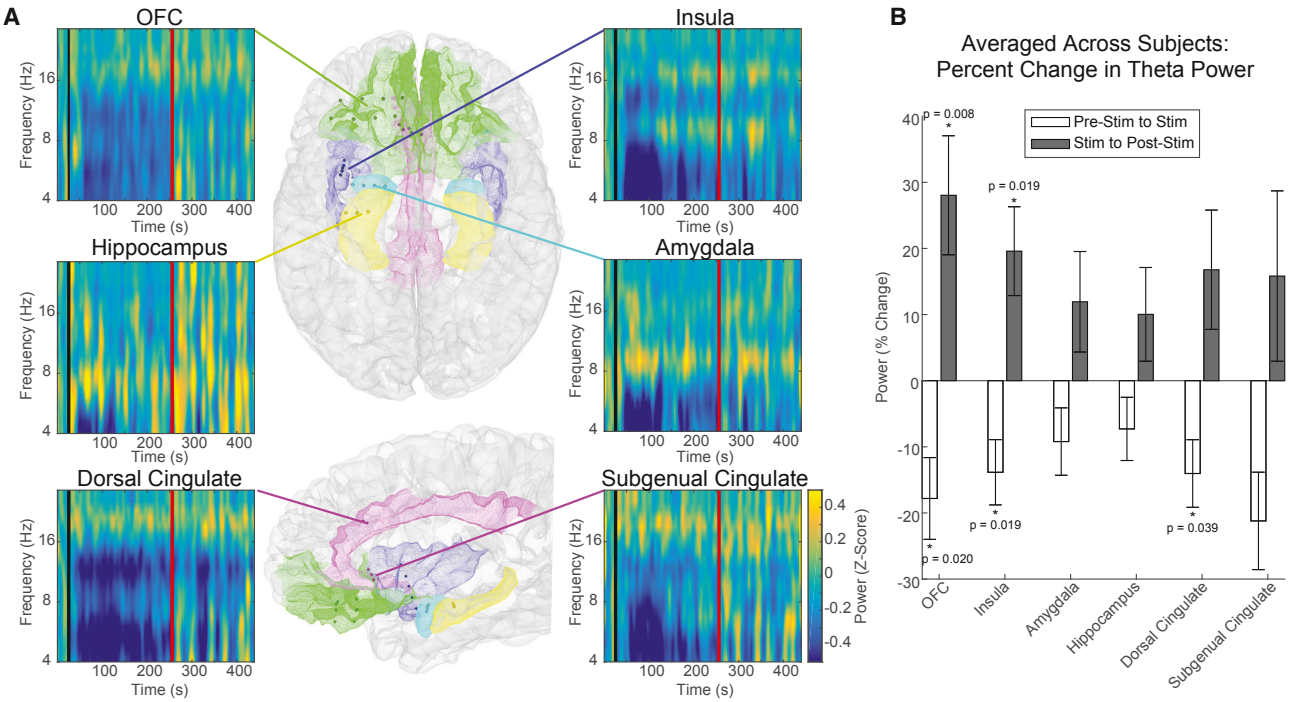

Figure 5. Network-Level Neurophysiological Effects of Lateral OFC Stimulation

(A) Spectrograms from one subject show suppression of low-frequency power in several mood-relevant brain regions sampled by intracranial electrodes. Black and red bars indicate the beginning and end of stimulation, respectively.

(B) Across all subjects, significant changes in power from pre-stim to stim (white bars) and stim to post-stim (black bars) were found in lateral OFC, insula, and cingulate regions in the theta frequency band. Plotting mean time-averaged percent change in power across subjects for both 1 mA and 6 mA stimulation. * indicates significance using a signed-rank test at $p < 0.05$; error bars indicate ±1 SEM.

See also Figures S3 and S5 and Table S3.

opposite of those observed during spontaneous negative mood states. Taken together, these findings suggest that the effect of lateral OFC stimulation is to normalize or suppress pathological activity in circuits that mediate natural mood variation.

Our observations provide potential clues about how lateral OFC stimulation may impact mood. Although functional imaging biomarkers of depression are not firmly established [10], increased activity in lateral OFC is seen in patients with depression and normalizes with effective antidepressant treatment [48], and lateral OFC hyperactivity has been proposed as a mood-state marker of depression [49]. Thus, a speculative possibility is that our stimulation paradigm works by decreasing OFC theta power in a way that may impact baseline hyperactivity [28, 29]. We cannot exclude the possibility that the mechanisms underlying mood improvement with lateral OFC stimulation involve multiple regions and may at least partially overlap with mechanisms responsible for mood improvement with stimulation of SCC [2]. In fact, based on anatomic [50, 51] and functional connectivity [52] between these regions, and the constellation of white matter tracts likely affected by stimulation of these sites [38, 53], some mechanistic overlap seems probable.

Our results have potential implications for interventional treatments for psychiatric disorders like TRD and anxiety. DBS efficacy for TRD is inconsistent [8, 9, 54], and a major thrust of the field has been to understand and circumvent inter-subject variability [38, 53, 54]. For example, the heterogeneous responses seen with SCC stimulation may relate to laterality [55] and precise anatomic electrode position [53]. In our study, positive mood responses were induced by unilateral stimulation of the OFC in either hemisphere, and although stimulation of lateral OFC improved mood more than stimulation of medial OFC, we observed mood improvement with stimulation across lateral OFC and did not see evidence of fine subregion specificity. These findings suggest that lateral OFC may be a more forgiving site for therapeutic stimulation than previously reported targets [53, 54, 56]. Another practical advantage of OFC relative to other targets is that the cortical surface is generally more surgically accessible than deep brain targets and that the ability to forego parenchymal penetration may impart lower risk during electrode implantation. Although seizures are a theoretical risk with any cortical stimulation, this risk is thought to be acceptably low [57], and we did not observe seizures during OFC stimulation.

Despite the widespread use of DBS in clinical and research applications, the mechanisms by which focal brain stimulation modulates network activity to produce complex behavioral changes remain largely unknown. The effects of stimulation are not limited to the targeted region, and stimulation-induced activity can propagate through anatomical connections to influence distributed networks in the brain. Previous studies have shown that target connectivity may determine likelihood of response to DBS [56]. Deciphering the precise mechanism of mood improvement with OFC stimulation requires future study, but

our observation that stimulation suppresses low-frequency activity broadly across multiple sites suggests a possible local inhibitory effect that reverberates through connected brain regions. Consistent with this, inhibitory transcranial magnetic stimulation of OFC was recently reported to improve mood in one depressed patient [31]. Since the OFC is relatively large and bilateral, it is possible that the mood effects we observed could be improved by more widespread stimulation.

Our study has limitations. The sample size was relatively small, reflecting the rare opportunity to directly and precisely target brain stimulation in human subjects. Although electrode coverage was generally extensive in our subjects, basal ganglia structures known to be important for mood [5–7] are not typically implanted with electrodes for the purposes of seizure localization. Subjective self-report of mood has intrinsic limitations but remains the best instrument available to measure internal experience [58]. Our subjects, who had medically refractory epilepsy, may not be representative of all patients with mood disorders. While we cannot rule out the possibility that mood symptoms in our subjects had a seizure-specific etiology, the observed effects of lateral OFC stimulation were robust in a patient group with diverse underlying seizure pathology (Table S1). To establish generalizability, our findings will need to be replicated in other cohorts. Finally, it is possible that the acute effects of stimulation we observed may not translate into chronic efficacy for mood disorders in clinical settings [38]. Indeed, rapid mood changes have been previously reported in TRD patients treated with bilateral DBS of SCC [2] and subcortical targets [59, 60]. Whether chronic OFC stimulation can produce durable mood improvement is an important question for future study, ideally under controlled clinical trial conditions with appropriate monitoring of relevant outcomes and adverse events.

The clinical heterogeneity of mood disorders suggests that brain stimulation paradigms may need to be tailored for individual patients. Importantly, this study is one of few to assess the functional consequences of brain stimulation with direct neural recordings. The approach we used for serial quantitative mood state assessment may be useful for sensitively tracking symptoms of mood disorders during clinical interventions, including DBS trials. Our identification of a novel, robust stimulation target and our observation of stimulation-induced changes in endogenous mood-related neural features together set the stage for the next generation of stimulation therapies. OFC theta power may be useful for optimization of stimulation parameters for non-invasive stimulation modalities targeting the OFC in depression [27], and further characterization of mood biomarkers might enable personalized closed-loop stimulation devices that ameliorate debilitating mood symptoms. Although the OFC is currently among the least understood brain regions [21], it may ultimately prove important for the treatment of refractory mood disorders.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- QUANTIFICATION AND STATISTICAL ANALYSIS
- DATA AND SOFTWARE AVAILABILITY

SUPPLEMENTAL INFORMATION

Supplemental Information includes five figures and four tables and can be found with this article online at https://doi.org/10.1016/j.cub.2018.10.026.

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AUTHOR CONTRIBUTIONS

V.R.R., K.K.S., and E.F.C. designed the study and carried out the experiments. M.B.L. and D.L.W. assisted with subject recruitment and data collection. M.B.L. performed 3D brain reconstructions. M.B. and K.K.S. performed single-pulse stimulation analysis. O.G.S., Y.Y., and M.M.S. analyzed neural activity during spontaneous mood fluctuation. V.R.R. and K.K.S. wrote the manuscript with input from other authors. H.E.D. and E.F.C. supervised the experimental work.

DECLARATION OF INTERESTS

The authors declare no relevant financial disclosures.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited Data		
Raw data	This paper	https://doi.org/10.7272/Q6VD6WM2
Software and Algorithms		
MATLAB	Mathworks (Natick, MA)	R2017a
FreeSurfer	[61]	https://surfer.nmr.mgh.harvard.edu/
EEGLAB	[62]	13_6_5b; https://sccn.ucsd.edu/eeglab/downloadtoolbox.php
Custom processing scripts	This paper	https://doi.org/10.7272/Q6VD6WM2

CONTACT FOR REAGENT AND RESOURCE SHARING

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Edward Chang (Edward.Chang@ucsf.edu).

EXPERIMENTAL MODEL AND SUBJECT DETAILS

The experimental protocol was approved by the Committee for Human Research at the University of California, San Francisco. Written informed consent was obtained from all subjects. Subjects (n = 25, 14 males, ages 20–60; Table S1) had been diagnosed with drug-resistant epilepsy and were undergoing intracranial electroencephalography (iEEG) for seizure localization. Subjects were included in the study if they had electrodes implanted in brain regions of interest and were willing and able to cooperate with study tasks. Subjects were excluded if they lacked capacity or declined to provide informed consent, did not have electrodes implanted in regions of interest, had significant cerebral lesions, and/or had cognitive deficits that precluded reliable completion of study tasks. 'EC(number)' labels used for subject de-identification are non-consecutive because they are applied to all patients in the senior author's clinical practice who have intracranial electrodes, including patients who did not meet inclusion/exclusion criteria for this study. Electrode implantation was guided solely by clinical indications for seizure monitoring and therefore varied somewhat across subjects, but electrodes typically sampled multiple sites implicated in mood regulation, including OFC, amygdala, hippocampus, insula, and cingulate cortex (Table S1). Due to limited time windows for testing, subject tolerance, and other constraints related to the inpatient environment, it was not possible to perform all experiments in all subjects (Table S3).

METHOD DETAILS

Mood trait characterization

Prior to electrode implantation, subjects underwent neuropsychological testing that typically included the Beck Depression Inventory II (BDI) [63]. BDI scores, which ranged from minimal to severe (Figure 2A and Table S1), established baseline mood trait and were binned into two categories (minimal-mild and moderate-severe), based on clinically established cutoff values, to facilitate analysis [64, 65]. In two subjects for whom BDI scores were not available, Patient Health Questionnaire-9 (PHQ-9) was used to determine mood trait categorization with a cutoff score of 10 [66].

Electrode Implantation and Localization

Subdural grid, strip, and depth electrodes (AdTech, Racine, WI, or Integra, Plainsboro, NJ) were implanted using standard neurosurgical techniques. Subjects underwent pre-operative 3 Tesla brain magnetic resonance imaging (MRI) and post-operative computed tomography (CT) scan to localize electrodes. Electrode locations were visualized by co-registering pre-operative T1-weighted MRI with the post-operative CT using Statistical Parametric Mapping software SPM12 [67]. Pial surface 3D reconstructions were created using FreeSurfer [61].

Pre-stimulation Mood Assessment

Following electrode implantation, measurements of mood state were collected serially, multiple times a day, over several days prior to brain stimulation. Subjects used a validated tablet-based mood tracking application, the Immediate Mood Scaler (IMS) [36], which enables momentary assessment of a multidimensional set of symptoms related to depression (Table S4) and thus operationally

defines mood state. Variation in IMS scores (Figure S2A) therefore reflects spontaneous fluctuation in mood state. Subscales within IMS can discriminate between symptoms of depression and anxiety [36] but only total IMS scores were used here.

Electrode Stimulation

Brain stimulation was performed in the window of time after collection of clinical seizure data was completed and before electrode explantation. Typically, anticonvulsant medications that had been tapered to provoke seizures, per standard clinical protocols, were restarted prior to stimulation experiments. Bipolar stimulation was applied to adjacent electrodes using the manually-operated Nicolet^{TM} Cortical Stimulator (Natus Medical, Inc., Pleasanton, CA), which delivers biphasic, constant-current trains of stimulation pulses, and monitored using the Natus EEG viewing software. For continuous stimulation of OFC and other regions, parameters were: 1 or 6 mA, 100 Hz, 100 μs pulse width, 100–200 s duration. 1 mA is at the low end of current intensities deliverable by the cortical stimulator unit, and current intensities above 6 mA were not tested due to safety considerations for long-duration stimulation. For single-pulse stimulation (SPS), parameters were: 10 mA, 1 Hz, 500 μs pulse width, 20 s duration. A board-certified epileptologist (V.R.R.) monitored iEEG recordings in real time for stimulation-induced afterdischarges and electrographic seizures, which did not occur with OFC stimulation.

Mood Assessment during Stimulation

For stimulation studies, subjects were told that various brain regions would be tested, but they were blind to experimental condition, including stimulation parameters, the brain region being tested, and whether stimulation was active. Before each experimental session, subjects were informed that they would be asked questions about their mood but, to minimize expectancy effects, they were not told to anticipate changes in their mood or what other subjects had experienced during similar testing. Sham (0 mA) stimulation blocks allowed subjects to serve as their own controls. Testing conditions in the room were standardized between patients to the extent possible in the inpatient environment. A Sham stimulation block was recorded at beginning of each experimental session, but the sequence of OFC and non-OFC sites was varied across subjects. Due to the idiosyncratic nature of mood self-reports, quantification of stimulation effects on mood state has not been standardized [38]. However, the IMS was specifically developed to capture a range of mood states in the context of clinical interventions [36]. To make mood state assessment during stimulation as quantitative and sensitive as possible, we employed a combination of verbal report and IMS (Figure 1B).

Approximately 30 s after the onset of electrical brain stimulation, subjects were prompted to freely articulate their current mood state. Investigators used neutral, open-ended questions to elicit verbal mood reports (e.g., "How would you describe your mood right now"?). Questions were similar but not strictly standardized across subjects (Table S2), and 30 s was allotted to collect responses. Audiovisual recordings of experimental sessions were transcribed by researchers blind to stimulation condition. Transcribed reports were analyzed for positive and negative words using the validated Language Inquiry Word Count (LIWC) software [68]. A word valence ratio score was calculated and normalized on a scale from 0 (completely negative word use) to 100 (completely positive word use) based on the number of positive emotion words (N_+) and the number of negative emotion words (N_-):

$$\frac{N_+ - N_-}{N_+ + N_-} \times 100$$

We pre-specified that word valence scores would be excluded if there was a change of 50 points or more and transcripts did not reveal sentiment to justify this large change.

Immediately after verbal mood report (i.e., 1 minute after onset of electrical stimulation), subjects answered IMS questions on a tablet. Questions involved seven buttons spanning a pair of negative and positive mood-state descriptor words (Table S4). Subjects tapped the button that best reflected current mood state, with the middle button corresponding to a neutral mood state for the pair of words. The time required to complete all IMS questions varied somewhat across subjects but generally took 1-2 minutes. Stimulation was terminated upon the subjects' completion of IMS, and the next stimulation block commenced 3–5 minutes later. IMS scores for each stimulation block were normalized on a 0 to 100 scale. IMS scores and word valence scores from verbal reports were averaged to obtain a Composite Mood Score (CMS), which served as the primary readout of stimulation-induced mood state changes (higher CMS indicates more positive mood). If either word valence score or IMS was not available, one score was used in place of CMS. Word valence scores were excluded for three subjects (EC99, EC150, and EC152) due to > 50 point change during stimulation, as can occur in subjects who have a paucity of spontaneous speech but occasionally use words with high emotional valence. Of note, two of these subjects (EC150, 152) used generally positive words ("hope… better… engaged…"; Table S2), so the net effect of excluding word valence scores for these three subjects might be underestimation of the positive mood effects of stimulation. IMS score was excluded for one subject (EC105) who is a monolingual Spanish speaker because a Spanish version of IMS was not available at the time, though one was eventually developed and used for EC152.

To determine whether mood state changed during stimulation, we assessed change in CMS (stim – sham) using Wilcoxon signed-rank tests and Wilcoxon rank-sum tests. Each stimulation condition (1mA, 6mA) was tested separately using a signed-rank test to assess if the changes in CMS were significantly different from zero. Rank-sum tests were used to compare effects of 1mA and 6mA stimulation.

Speech Rate Analysis

Video and audio from the stimulation experiments were analyzed for potential effects on speech rate during sham and active stimulation blocks. Subjects' verbal reports were transcribed by blinded researchers and each sentence spoken was timed. Lulls in speech greater than 2 s were not included in the overall time of the sentence. The total number of words for all sentences was divided by the total time of speaking during verbal report to give a speech rate in words per second.

Data Acquisition and Signal Processing

iEEG recordings were acquired at sampling rates ranging from 1kHz to 25kHz using the Natus EEG clinical recording system, Tucker-Davis Technologies PZ5M-512 and RZ2, or the Alpha Omega NeuroOmega. Offline analysis was conducted using custom scripts in MATLAB (Mathworks, Inc., Natick, MA) and EEGLAB [62]. Standard iEEG pre-processing was combined with artifact rejection methods to enable analysis of spectral activity during electrical stimulation. Artifact rejection allowed for analysis of lower frequencies (< 40Hz), but higher frequencies could not be analyzed because artifact rejection procedures change spectral characteristics of the signal in frequencies around the stimulation frequency. Artifact rejection could only be conducted on data acquired at ~3kHz or greater because of the high stimulation frequency (different sampling rates not systematically assessed). The times including stimulation artifact were identified and deleted, and cubic spline interpolation was applied from up to 0.8ms before the artifact peak up to 3ms after the artifact peak; times were chosen empirically based on inspection of signals. Additional pre-processing steps included application of a [2 to 250Hz] bandpass filter, rejection of channels with high noise or multiple bouts of large amplitude artifacts, common average referencing to the mean of all channels remaining after channel rejection, application of notch filters at line noise frequency and harmonics (60Hz, 120Hz, 180Hz, 240Hz) and stimulation frequency and harmonic (100Hz, 200Hz), manual rejection of time periods with non-physiological synchronized activity across channels, and downsampling to 512Hz. Only electrode contacts located in the target region of interest (verified by visual review of MRI and CT) were analyzed.

To determine whether (1) OFC power correlated with mood, and (2) stimulation altered spectral iEEG activity, power was extracted from each electrode by filtering the pre-processed data in frequency bins with logarithmically increasing center frequencies and applying the Hilbert transform. In cases where multiple electrodes were positioned in the region of interest, power was averaged across these electrodes. Where specified, power was averaged within standard frequency bands (theta = 4-8Hz, alpha = 8-12Hz, beta = 12-30Hz, gamma = 30-55Hz).

We tested if OFC power co-varied with mood using Bonferroni-corrected Pearson's correlation coefficient between OFC power and IMS scores. Specifically, 4 minutes of iEEG data were extracted around each IMS data point (2 min before and 2 min after). Data were pre-processed and log power was calculated for standard frequency bands. IMS scores and neural activity metrics were first z-scored within each subject to account for each individual's range of responses, and then combined across subjects. Multiple comparisons were controlled for using Bonferroni correction (3 frequency bands tested, thus correlations significant if $p < 0.0167$). Subjects with fewer than 2 IMS points were excluded, and IMS points tested during stimulation experiments were excluded from analyses of spontaneous mood fluctuation.

We assessed the effects of OFC stimulation on power in standard frequency bands by calculating percent change in power from before stimulation (pre-stim; data prior to the start of the first stimulation block) to during stimulation (stim; starting at onset of stimulation), and from during stimulation to after stimulation (post-stim; all data from the end of one stimulation block to the start of the next block). Power was averaged across relevant time periods (pre-stim, stim, and post-stim time periods were 57.0 ± 65.3, 178.1 ± 90.1, 74.3 ± 57.0 (mean ± SD) [seconds], respectively) and averaged within frequency bands. For visualization in spectrograms only, power was z-scored relative to pre-stim period. A Wilcoxon signed-rank test was used to test if change score was significantly different from zero. Significance was established for p values < 0.05.

In some subjects, SPS was administered before and after continuous OFC stimulation. Pre-processing steps included removing data surrounding stimulation artifact peaks [−5 to 10]ms, application of a [1 to 100Hz] bandpass filter, and notch filter at line noise frequency (60Hz). For each stimulation pulse, evoked activity was z-scored relative to a trial-specific pre-pulse baseline [−300 to −100]ms, the signal was rectified, and the maximum peak was extracted from [13 to 200]ms following the stimulation artifact peak. Significance was assessed with a rank-sum test.

QUANTIFICATION AND STATISTICAL ANALYSIS

All quantitative data were analyzed in MATLAB using custom written scripts and functions in the Signal Processing Toolbox. Due to limited numbers of subjects, males and females were not analyzed separately.

To determine the effect of stimulation on mood, we calculated the change in CMS (stim – sham) and used Wilcoxon signed-rank and Wilcoxon rank-sum tests to test for significant difference from zero and between stimulation amplitudes. Significance was determined by $p < 0.05$. Non-parametric statistics were chosen because we had no *a priori* knowledge that mood change scores would fit a normal distribution. For analysis of stimulation effect on mood, n refers to subjects tested with OFC stimulation at 1mA and/or 6mA. For a given subject, the same amplitude of stimulation was not tested multiple times in the same brain region.

For analyses of neural activity, we examined spectral power averaged in standard EEG frequency bands. To determine if OFC power correlated with mood, power was averaged within standard EEG frequency bands and across electrodes in a given brain region, providing a single number that could be correlated with IMS. Multiple corrections were controlled for using Bonferroni correction (i.e., 3 frequency bands tested, thus correlations significant if $p < 0.0167$). For these analyses, n refers to the number of IMS data

points in each subject. To look for correlations at the population level, data were normalized within subject and correlation was assessed across the collapsed population data. To determine if neural power changed with stimulation, power was averaged within standard EEG frequency bands and across relevant time periods (pre-stim, stim, and post-stim), and percent change was calculated between time periods. A Wilcoxon signed-rank test was used to test if change scores were significantly different from zero.

DATA AND SOFTWARE AVAILABILITY

Data and code used in this study are available for download at: https://doi.org/10.7272/Q6VD6WM2.