

Network dynamics of cognitive control and mood during deep brain stimulation for depression

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Ph.D. Thesis

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Preface

The ideas for my graduate work began as an ambitious effort as part of a clinical trial of deep brain stimulation for treatment-resistant depression, in line with my long-term goals of implementing neurotechnology to drive personalized therapies for psychiatric illness. As a neural engineer and a neuroscientist, the focus of my research aims was to 1) utilize and build on existing neurotechnology frameworks to quantify neural and behavioral states in psychiatric illness 2) implement this framework to expand our understanding of neural mechanisms underlying behavioral responses to deep brain stimulation (DBS) therapy in depression. Chapter one and chapter two outline in detail how existing frameworks for seizure monitoring in subjects with refractory epilepsy can be adapted for patients with depression to build an “NMU” or neurophysiology monitoring unit. Chapter three and four demonstrate quantifiable neural and behavioral characteristics and their response to DBS in limbic hubs. Specifically, chapter three provides novel insights on neural responses between two canonical DBS targets used for psychiatric indications *during resting state*. Chapter four first explores neural mechanisms *during task states without stimulation*. I subsequently connect our findings during resting state with stimulation, and during task states without stimulation to *characterize neural responses to DBS in subjects with depression during task states*, specifically during exertion of cognitive control. This chapter centers cognitive systems or cognitive control as the behavioral domain of interest in depression. My research aims are a part of a broader effort to provide new insights on neural mechanisms during different brain states in depressive networks, and how we can causally manipulate

these neural signals to identify circuit-specific mechanisms underlying improvement of psychiatric symptoms with DBS therapy (Figure 0-1).

I hope that this research effort informs future endeavors in the field of psychiatric neuromodulation in the following ways: 1) enabling researchers to incorporate multimodal measures such as audio, video, self-report and behavioral task performance to inform therapeutic approaches and our understanding of behaviors in depression 2) elucidate our overall understanding of decision-making and cognitive control recruitment in psychiatric disorders.

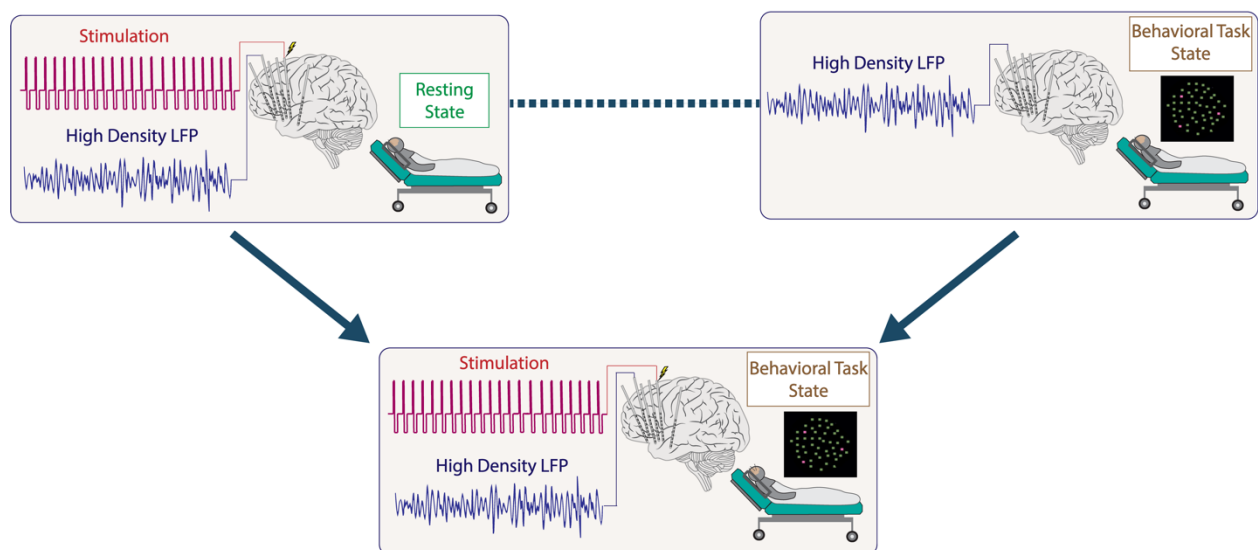


Figure 0-1: Summary of research aims

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meant more than I can express in words. I am a better scientist and overall human after knowing you and I hope I can keep finding ways to continue working with you as long as you will have me.

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1 A Novel Framework for Network-Targeted Psychiatric Deep Brain Stimulation

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1.1 ABSTRACT

Deep brain stimulation (DBS) has emerged as a promising therapy for neuropsychiatric illnesses, including depression and obsessive-compulsive disorder, but has shown inconsistent results in prior clinical trials. We propose a shift away from the empirical paradigm for developing new DBS applications, traditionally based on testing brain targets with conventional stimulation paradigms. Instead, we propose a multimodal approach centered on an individualized intracranial investigation adapted from the epilepsy monitoring experience, which integrates comprehensive behavioral assessment, such as the NIMH-proposed transdiagnostic research domain criteria. In this paradigm-shifting approach, we combine readouts obtained from neurophysiology, behavioral assessments, and self-report during broad exploration of stimulation parameters and behavioral tasks to inform the selection of ideal DBS parameters. Such an approach not only provides a foundational understanding of dysfunctional circuits underlying symptom domains in neuropsychiatric conditions but also aims to identify generalizable principles that can ultimately enable individualization and optimization of therapy without intracranial monitoring.

1.2 INTRODUCTION

Surgical neuromodulation is increasingly utilized for refractory neurological and psychiatric disorders, and deep brain stimulation (DBS) has played an important role in this endeavor. Despite the numerous studies using DBS for various conditions¹, there remain only 3 fully approved indications for DBS (essential tremor, Parkinson's disease [PD], epilepsy), and 2 indications with limited approval in the form of a Humanitarian Device Exemption (HDE) (dystonia, obsessive-compulsive disorder [OCD]) in the United States.

This discrepancy between the number of investigational applications relative to the few approved indications deserves a reappraisal of historical approaches for DBS therapy development. While some conditions have only few published cases reported^{2,3} others have a reference base of hundreds of patients, studied in extensive and costly trials, such as pain⁴⁻⁶ and treatment-resistant depression (TRD)⁷. These latter examples share a history of initially promising open-label studies, followed by controlled trials failing to meet outcome measures sufficient for obtaining regulatory approval (for a review of this trend in psychiatric neurosurgery, see Bari et al.⁸).

We propose that a key reason for the limited success of previous DBS trials is an insufficient understanding of network physiology underlying each disorder and its response to DBS (which is exacerbated by a lack of mechanistic understanding of DBS). This knowledge gap exists at the population level and is exemplified at the individual patient level partially due to clinical symptom heterogeneity across patients. While factors such as patient selection, trial design, placebo effects, among other biases may contribute to unsuccessful trial outcomes, the limited understanding of the symptomatic network will either lead to failure or produce outcomes difficult to reproduce or generalize.

We propose incorporating intracranial monitoring and stimulation as an enhancement of the traditional approach of developing surgical neuromodulation therapies for novel indications. Intracranial monitoring is commonly utilized in medication-refractory epilepsy cases, where patients are admitted to an epilepsy monitoring unit (EMU) to identify patient-specific epileptogenic networks. While seizure onsets result in robust electrographic markers, there exist no evident biomarkers to guide effective individualized therapy for psychiatric disorders. The goal of our suggested approach is

the development of such markers to enable a better understanding of the brain networks underlying the target disorder and their response to stimulation prior to embarking on large clinical trials. Here, we focus on developing this concept and illustrating it in the context of mental health disorders, using TRD as an exemplar.

1.3 CHARACTERIZING BRAIN NETWORKS UNDERLYING DISORDERS OF MENTAL HEALTH

Research in mental illness has undergone a large-scale reorganization in its approach to categorizing disorders. Aimed at resolving impediments to research and therapeutic progress due to patient symptom profile heterogeneity, this new approach uses Research Domain Criteria (RDoC) to formalize and measure behavior and neurobiological indices across domains⁹. Utilizing this approach with major depressive disorder (MDD) serves as a useful example. MDD is a major public health concern, affecting at least 4.4% of the global population¹⁰, with low remission rates¹¹, and demonstrated lack of success in past approaches for treatment optimization¹². Using traditional symptom-based classification, a patient may be diagnosed with MDD by displaying five of nine diagnostic criteria. Thus, two patients may carry the same diagnosis despite overlapping in only one criterion. In contrast, a trans-diagnostic approach focuses on dysfunctional domain systems rather than symptom clusters. For example, patients with OCD and MDD may both experience dysfunction in reward sensitivity, as well as abnormalities of the orbitofrontal cortex, a region involved in processing rewarding stimuli. In MDD, such an approach would aim to first understand the dysfunctional networks underlying reward sensitivity, recognizing that individual patients have varying combinations of different domains. Rather than trying to treat

“MDD” as a monolithic entity, it may be treated as a combination of relevant symptomatic domains (such as negative valence, positive valence, cognitive systems) using the RDoC framework. Each of these domains can be studied and targeted individually with relevant experimental tasks to identify candidate brain areas for finding patient-specific biomarkers. Using this concept of orthogonalizing symptoms onto RDoC-style axes may improve individualized network targeting and hopefully produce better treatment outcomes.

1.4 INTRACRANIAL RECORDINGS FOR TREATMENT INDIVIDUALIZATION

Initial work seeking neural biomarkers of depression using neuroimaging tools has had some success. Differential network connectivity has been found in individuals with MDD such as the cognitive control network^{13,14} and the reward learning network^{15,16}. Scalp electroencephalography (EEG) has also been conducted in patients with depression with the goal of finding biomarkers and predictors of antidepressant treatment response¹⁷. Resulting putative biomarkers included asymmetric regional changes in frontal alpha^{18–20} and changes in theta power²¹, but they have not been consistent or replicable enough to be integrated in a clinical capacity^{20,22}. This outcome can be partially attributed to limitations in spatial and temporal resolution from non-invasive tools. Intracranial recordings, however, would enable spatiotemporally precise sampling across putative networks, including deep structures previously inaccessible using scalp EEG. Applied to TRD, precise neurophysiological intracranial monitoring can shed fundamental insight on dysfunctional networks and provide unique opportunities to execute behavioral tasks in relevant RDoC domains to measure network involvement. If the diversity of phenotypes observed in TRD is a manifestation of varying levels of

disruption in different networks, the ability to precisely measure from these networks and relate them to observed behaviors and subject report would enable understanding of the neurophysiological basis of depression biotypes^{23,24}, driving personalized and effective therapy. Data streams such as synchronized audio/video recordings of the patient and physiological responses indicative of autonomic response can be collected simultaneously to provide an extensive, multi-modal dataset to build a comprehensive understanding of the brain-behavior relationship.

1.5 DBS IN THE MONITORING UNIT

There exists a critical knowledge gap with respect to mechanisms of therapeutic stimulation and biomarkers that can optimize our therapeutic interventions. Little is known about the effects of stimulation parameters on the therapeutic efficacy of DBS for TRD, restricted by an underlying assumption that parameters relevant to DBS for movement disorders can be extrapolated to other psychiatric diseases. Given anatomical and neurophysiological differences in targeted networks, defining dose-response relationships seems imperative to advancing DBS therapies for new indications. The use of simultaneous intracranial recording and stimulation in the Neurophysiology Monitoring Unit or NMU (broadening on the concept of EMU) serves as a therapy development *platform* to address this gap without fundamentally overhauling the therapeutic application of DBS. The value of intracranial recordings for understanding therapeutic mechanisms of DBS is currently exemplified in its application for movement disorders, e.g. PD, where such recordings have yielded putative biomarkers and insight on physiological changes induced by DBS^{25–27}.

Here, we focus on stereo-EEG^{28–30} or depth electrodes as the intracranial technique of choice, given its ability to sample subcortical regions implicated in TRD. Performing DBS in the NMU enables assessment of the network-wide impact of stimulation on (pathological) oscillations and allows correlation of neurophysiological changes with behavior. Importantly, one can address whether therapeutic stimulation is mediated by normalization of “aberrant” activity or by modifying activity in other networks to compensate for abnormal activity in parallel circuits. Extended testing in the NMU also enables evaluation of stimulation dose-response relationships (behavioral and neurophysiological) with large parameter sweeps in an automated fashion, overcoming the significant limitations of prior trials largely assuming equivalence of therapeutic mechanisms despite differences in networks and likely key spectral frequencies. This sEEG-based platform enables characterization of behavioral and neural responses to stimulation at other nodes in physiologically-defined disease-related networks, thereby providing a pathway to defining new potential targets for DBS. In light of the numerous stimulation parameter combinations and number of contacts available for stimulation, investigators must be cognizant of time limitations and proceed in a hypothesis-driven manner to maximize the value of NMU-based investigations. For widespread adoption of such investigations in neuropsychiatric DBS surgery, strong collaborative efforts with psychiatrists in the field are also needed.

Stimulation in the NMU also offers an important venue to validate two major tools used to advance the field of DBS: MR tractography and stimulation field models (SFM, also known as volume of tissue activated). MR tractography can estimate structural brain connectivity of disease-related brain networks and of effective vs ineffective stimulation sites. SFMs can estimate spatial reach and influence of neuromodulation^{31–33}, and DBS

in the NMU can investigate the intersection of MR tractography and SFMs, providing both physiologically-based and imaging-based biomarkers for therapy. These biomarkers are more apparent and meaningful in the context of having characterized the pathophysiological network basis of disease prior to stimulation, in addition to being important for development of future closed-loop therapies.

1.6 IMPLEMENTATION AND VARIATIONS OF THE INTRACRANIAL PLATFORM

In our vision of “sEEG-informed DBS” (Figure 1), patients with the target disorder (e.g. TRD) meeting criteria for neurosurgery undergo two surgical procedures book-ending a stay in the NMU. The first consists of implantation of a therapeutic stimulation system and a separate recording system. The stimulation system consists of DBS leads in historically promising targets. Extensions connected to the other end of the leads are externalized and connected to the research neurophysiology system using standard surgical methods^{34–36}. The recording system consists of sEEG electrodes placed in brain regions implicated in TRD, based on findings from non-invasive methods^{23,24} (Figure 1). In the NMU, the patient undergoes planned testing to build an understanding of the network and its response to stimulation. Following the monitoring period, the patient returns to the OR for a second procedure for removal of sEEG electrodes and tunneling of DBS leads to an implantable pulse generator.

An alternative “staged approach” decouples the stimulation and recording phases, where first only sEEG electrodes are implanted, covering areas of interest for stimulation and recording in the NMU. Following the NMU phase, the patient undergoes removal of sEEG electrodes. After several weeks or months, the patient is implanted with a permanent DBS system in brain targets informed by analysis of acquired data.

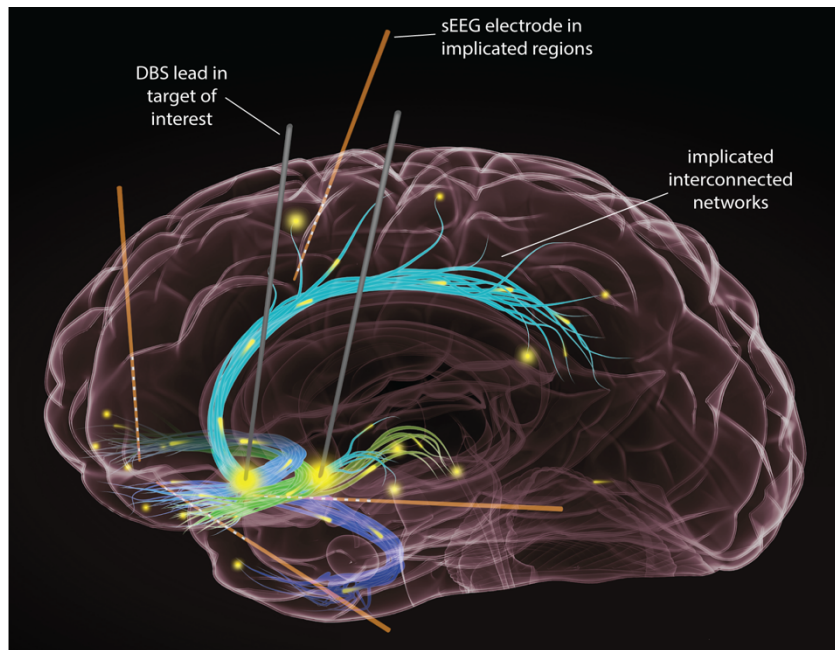


Figure 1-1: Concurrent stimulation and intracranial recordings from sEEG electrodes.

Intracranial recordings from sEEG electrodes in brain regions implicated in TRD, such as the dorsomedial, temporal and ventromedial cortex, as well as the orbitofrontal cortex, to name a few. Ideally, recordings from the aforementioned brain regions would be obtained in gray matter structures at the terminis of white matter tracts, as DBS is typically delivered to white matter fibers. The goal of these electrophysiological recordings is to help understand the pathophysiological network dynamics at the individual patient level. This NMU-based platform also allows appreciation of the network response to stimulation across a broad range of parameters. These two pieces of information can be combined to optimize DBS parameter selection.

This approach has been used previously in pediatric dystonia³⁷. Variations of either approach could also use Electrocorticography(EcoG) strips^{38,39} rather than sEEG, and responsive neurostimulation (RNS)⁴⁰ rather than DBS.

The sEEG-informed DBS approach and staged approach differ significantly in their strategy for permanent stimulation electrodes placement. An advantage to placement during the initial surgery is delivery of stimulation through the same electrode configuration during chronic, long-term management as was delivered in the NMU, as DBS and sEEG leads have different geometries. A potential advantage to the staged approach is the availability of stimulation testing results in the NMU prior to implantation of permanent DBS leads. This information could lead to novel and highly individualized lead placement but is limited by the extent to which acute stimulation effects predict

long-term effects. In movement disorders, such as the dystonia example above, the predictive power may be higher than in psychiatric disorders where this relationship is unclear.

The differences in approaches highlight a major goal of the sEEG-informed DBS approach: identifying generalizable principles and electrophysiological biomarkers to guide future implants *without* the future use of sEEG. This intracranial platform for therapy development is time- and resource-intensive per patient, more invasive, and therefore less appealing to some patients than typical DBS procedures and unsustainable as a permanent approach. We envision this intracranial platform as a bridge spanning the gap of incomplete network characterization of a disorder, only necessary until enough is known to be able to perform future implants successfully without this intracranial intermediate. E.g., intracranial data may correlate well with tractography data for a disorder, such that future implants can be planned and individualized based purely on preoperative imaging. Alternatively, intracranial data may provide electrophysiological biomarkers to enable future closed-loop neurostimulation. The strategy behind the staged approach is to find patient-specific physiologically-informed targets and therapies. It is designed for maximum flexibility, allowing placement of the permanent neurostimulation system almost anywhere in the putative network, at the cost of reduced generalizability. Finding generalizable principles that can later obviate the need for invasive monitoring in each patient with this approach is challenging. The staged approach may therefore be more appropriate for earlier stage and more exploratory, investigations. The sEEG-informed approach may be more appropriate for disorders with more pre-existing evidence, those closer to bridging towards a large, randomized trial.

Finally, the risks in this approach must be considered. sEEG has been used for decades, and recent advances in imaging and stereotactic precision have made this procedure quite safe^{41,42}. Balanced against this small but non-zero risk is the risk of inaction: neuropsychiatric disorders are the leading cause of disability in the US⁴³, and concomitant with increased risk of suicide, especially mood disorders. For severe refractory disorders where non-invasive treatment options have been exhausted, intervention with DBS therapy is a promising consideration. However, to leverage the potential of this therapy, more comprehensive evaluation and multifaceted efforts are needed, as trials of DBS for neuropsychiatric disorders such as TRD have not produced consistent results^{7,47,48}, yielding little new information about the disorder or treatment approaches⁸. We must avoid the temptation of quickly taking results from a small number of uncontrolled studies into expensive randomized trials with all our proverbial eggs in the basket of a single brain target and set of stimulation parameters, while also considering the ethical implications of invasive neuromodulation approaches^{49–51}. Smaller studies utilizing an intracranial platform may help us derive a more complete understanding of the disorder, its variability across patients, and strategies for delivering stimulation to treat it. We hope that judicious use of this approach will usher in an era of a scientific, reasoned approach to surgical modulation for severe neurological and psychiatric disorders.

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2 Implementation of the Neurophysiology Monitoring Unit for Psychiatric Intervention

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2.1 ABSTRACT

Deep brain stimulation for psychiatric disorders is a promising treatment. A paradigm shift towards understanding psychiatric disorders in recent years has suggested domain-based approaches in a transdiagnostic manner to evaluate behavior and symptomology. In line with this approach, we implemented the neurophysiology unit or NMU, to sweep across behavioral domains (such as cognitive systems), symptom measurements and stimulation parameters in subjects with treatment-resistant depression to obtain comprehensive behavioral and electrophysiological responses towards the goal of personalized neuromodulation therapy. We adapted an epilepsy monitoring unit for continuous psychiatric, behavioral and intracranial monitoring and in this chapter we outline the methodological and logistical approaches we executed.

2.2 INTRODUCTION

Over the last decade, the application of neuromodulation therapies such as deep brain stimulation¹⁻³ and transcranial magnetic stimulation^{4,5} has increased for a number of psychiatric indications. However, there remains a fundamental gap in our knowledge of the origins and manifestation of behavioral deficits and circuit dysfunction underlying psychiatric disorders. This gap ultimately influences the extent of therapeutic outcomes, and generalizability of therapeutic approach or parameters from individual patients to larger populations with heterogeneous symptoms. Concurrent with the rise of neurostimulation therapies, research in mental illness has undergone a paradigm shift in its approach to categorizing disease entities, aimed at overcoming the barriers to consistent therapeutic outcomes arising from existing knowledge gaps. Specifically, the use of Research Domain Criteria (RDoC) has been implemented to formalize and measure behavior and neurobiological indices across domains, such as cognitive

symptoms, social processing, positive valence, negative valence, arousal, and regulation^{6,7}. Each domain category is associated with proposed biomarkers ranging across units of analysis from molecules and cells up to neuroimaging and behavioral self-report or task performance.

An underlying assumption of the RDoC approach is that there are distinct brain networks related to each domain, which can be assayed at various levels of analysis, and that therapies can be optimized to these disparate networks in response to individual variations in patient symptom profiles. Building on the proposed framework in Chapter one⁸, we adapted an epilepsy monitoring unit (EMU) for multi-modal neurophysiological and behavioral measurement in patients with psychiatric disorders, specifically treatment-resistant depression (TRD) in our case. Here, we lay out the methods developed for multi-modal measurement of behavior, symptoms, and neurophysiology, with guidance on sweeping across a vast array of behavioral and stimulation states and parameters in the neurophysiology unit (or NMU).

2.3 EXPERIMENTAL SCHEDULE

The NMU approach is modeled on seizure monitoring and treatment of refractory epilepsy, where a patient with epilepsy is implanted with sEEG electrodes for intracranial monitoring alongside video and audio monitoring for detection of seizures. In our case, subjects with TRD are implanted with 10-12 sEEG electrodes in regions hypothesized to contribute to affective and cognitive dysregulation^{9–15}, alongside bilateral segmented DBS leads capable of current steering in the subcallosal cingulate^{2,16,17} and ventral capsule/ventral striatum³. Similar to a patient with refractory

epilepsy admitted to the EMU for seizure monitoring, patients with TRD are admitted for continuous monitoring for 10 days post-surgery in our study.

In order to perform a comprehensive sweep of behavioral, electrophysiological and stimulation experiments, a preemptive schedule is mapped out prior to every patient. It has been critical to utilize each hour of the day carefully while also being mindful of patient safety, comfort and anticipated cognitive state. A typical schedule for a subject is described in detail as follows (Fig. 2-1).

2.3.1 Passive experiments and baseline recording

While the patient recovers from anesthesia for the first 1-2 days, we perform a suite of passive single-pulse experiments¹⁸ across contact configurations, pulse widths of interest and amplitudes to assess effective connectivity. Once the patient has reached a stable and alert state, we perform more cognitively challenging experiments, such as the PACT paradigm, described in Chapter 4 and in Ritz et al.¹⁹, alongside other behavioral tasks probing affect and reward processing. These experiments serve as the baseline or “DBS OFF” condition for within-subject controls.

Across days 3-5, we perform another suite of passive stimulation experiments, designed to probe electrophysiological activity and functional connectivity in response to varying contact configurations, pulse widths, amplitudes and stimulation frequencies per DBS lead. Through these experiments, we are able to sweep across 84 different parameter combinations for each DBS lead. Each trial is 1 second DBS ON followed by 8 seconds of DBS OFF to enable sufficient washout of stimulation effects. No behavioral response is observed or expected to be observed during this time due to the short duration of stimulation.

Across days 6-8, we perform intensive psychiatric and clinical observation in the presence of stimulation. We perform a suite of longer stimulation experiments, designed to probe both electrophysiological activity and behavioral or symptomatic response across stimulation parameters. A more detailed structure of this experiment is described in Chapter 3. A pared down list of stimulation parameters is tested, entailing 3 frequencies (6 Hz, 50 Hz and 130 Hz), 1 amplitude (5 mA), 1 pulse width (180 μ S) and 7 contact configurations per lead, resulting in 21 total combinations tested per DBS lead. Each trial is 15 seconds stimulation ON, followed by 10 seconds stimulation OFF. In subjects A and B, 5 trials per parameter were tested. In subjects C and D, the trial structure was changed from 10 seconds OFF to 6 seconds OFF, to increase the number of trials to 10 total trials per stimulation parameter. While this altered structure reduces the amount of time between trials for stimulation washout, the trade-off was preferable as it allowed us to have enough repetitions to elicit a behavioral response and build in an artifact-free window for analysis of high frequency oscillations during clinical evaluation. To reduce the amount of carryover effect from one stimulation parameter to the next, we performed 1-2 minutes of stimulation OFF recordings before switching between parameters.

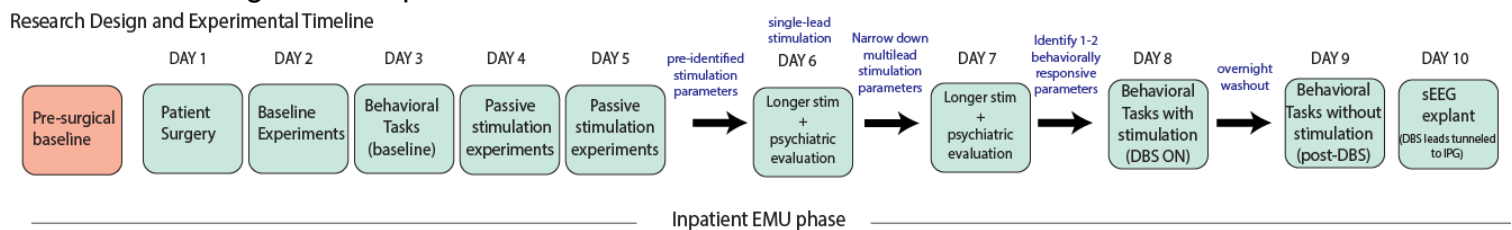
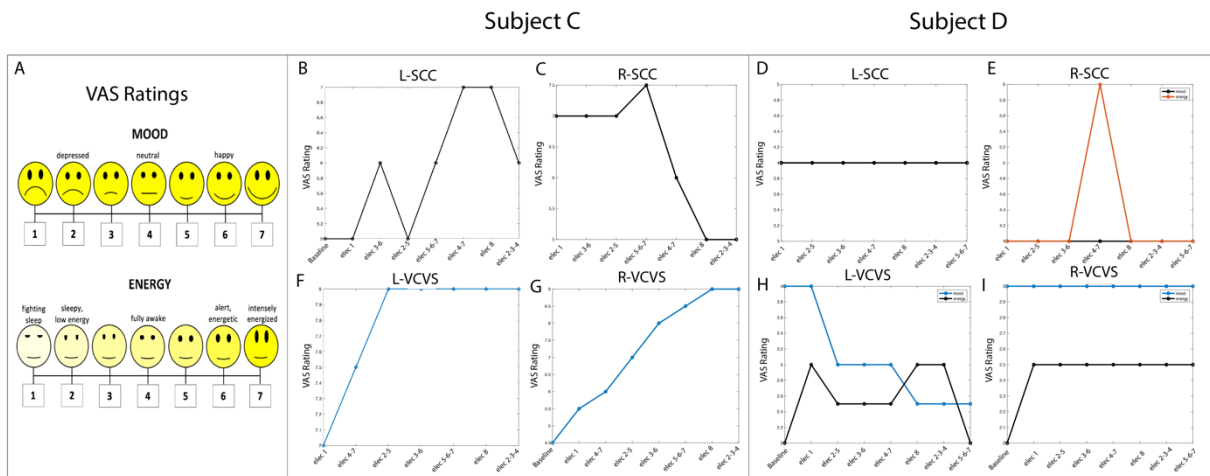


Figure 2-1: Predetermined schedule for a patients admitted for inpatient monitoring

For subjects A and B, qualitative observation of mood and affect was performed by a psychiatrist during testing of each stimulation parameter. For subjects C and D, we

conducted VAS ratings. During the last trial of a given stimulation parameter, patients were asked to report their mood and energy (Fig 2-2a). Depending on baseline anxiety of the patient, and overall responses to stimulation, we could observe a range of this responses (Fig. 2-2b-c; Fig. 2-2f-g) or no overall change irrespective of stimulation parameters (Fig. 2-2d-e; Fig. 2-2h-i). While VAS ratings can be informative for quick assessments or comparison across stimulation conditions, they are prone to lack of dynamic range that captures patient symptoms that may vary on a trial by trial basis. Therefore, we implemented video and audio recordings (described in Section 2.6) as additional modalities of assessment of affect and mood state.



structure as before (15 seconds stim ON, 6 seconds stim OFF) with VAS ratings.

Qualitative behavioral responses as evaluated by the psychiatrist and as noted on VAS ratings are used to inform the primary stimulation parameters used for testing during behavioral tasks (described in more detail in Chapter 4), as another way to probe cognitive and affective regulation.

Using the outlined framework, we are able to probe multiple dimensions of mood, affect, alongside cognitive and psychiatric symptoms in the presence of a vast array of stimulation parameters to inform individualized therapy and biomarker discovery.

We describe the logistical and methodological framework for data collection in the following sections.

2.4 ELECTROPHYSIOLOGICAL RECORDING

The employed electrophysiology system comprises of a Nihon-Kohden clinical recording system, which interfaces the research Blackrock Microsystems Neuroport recording system recording system including 256 channels and Blackrock Cerestim M96 Macro neural stimulation system via custom cabling and adapters. The combination of clinical and recording setup additionally connects to implanted Boston Scientific Cartesia DBS leads via additional custom cabling and adapters (Fig. 2-3b,c) To integrate DBS leads to the system, we incorporated cabling strategies that (1) are compatible with current NMU hardware and sEEG connection methodologies, (2) allow recording from DBS leads.

One goal of the sEEG-informed DBS platform is to be able to flexibly record from and stimulate to any combination of implanted sEEG and DBS contacts, to allow the most precise characterization of the neural activity of the network and its responses to stimulation across multiple nodes. To enable this, the system needs capacity for

recording from a large number of electrode contacts and to include the capacity to stimulate both the sEEG contacts and the DBS leads to effectively sweep through an unexplored parameter and configuration space²⁰.

Integrating the DBS leads into the recording and stimulation configuration with Blackrock requires the use of custom cables that adapt the externalized lead extension on one end to the electrophysiological recording system on the other. We position the DBS lead extensions in a separate bundle from the sEEG connections within the patient's head wrap to facilitate configuration changes. Custom connectors were assembled via Blackrock Microsystems to connect the implanted Boston Scientific DBS leads to enable stimulation delivery via the Blackrock Microsystems Cerestim. Figure 2-3 shows the detail of the recording and stimulation setup. As there are independent grounds for each splitter box on the amplifier, we dedicated one port for stimulation (no recording) to avoid potential grounding loops or a shared ground between the recording and stimulation. Through this connection configuration we are able to sweep through single-lead or multi-lead stimulation parameters during the NMU phase of the study. Additionally, to deliver monopolar stimulation, we use a bovie medical pad applied to the thigh and define that as our "anode", rather than a distant sEEG contact as an anode, to avoid unintentional low-level anodal stimulation.

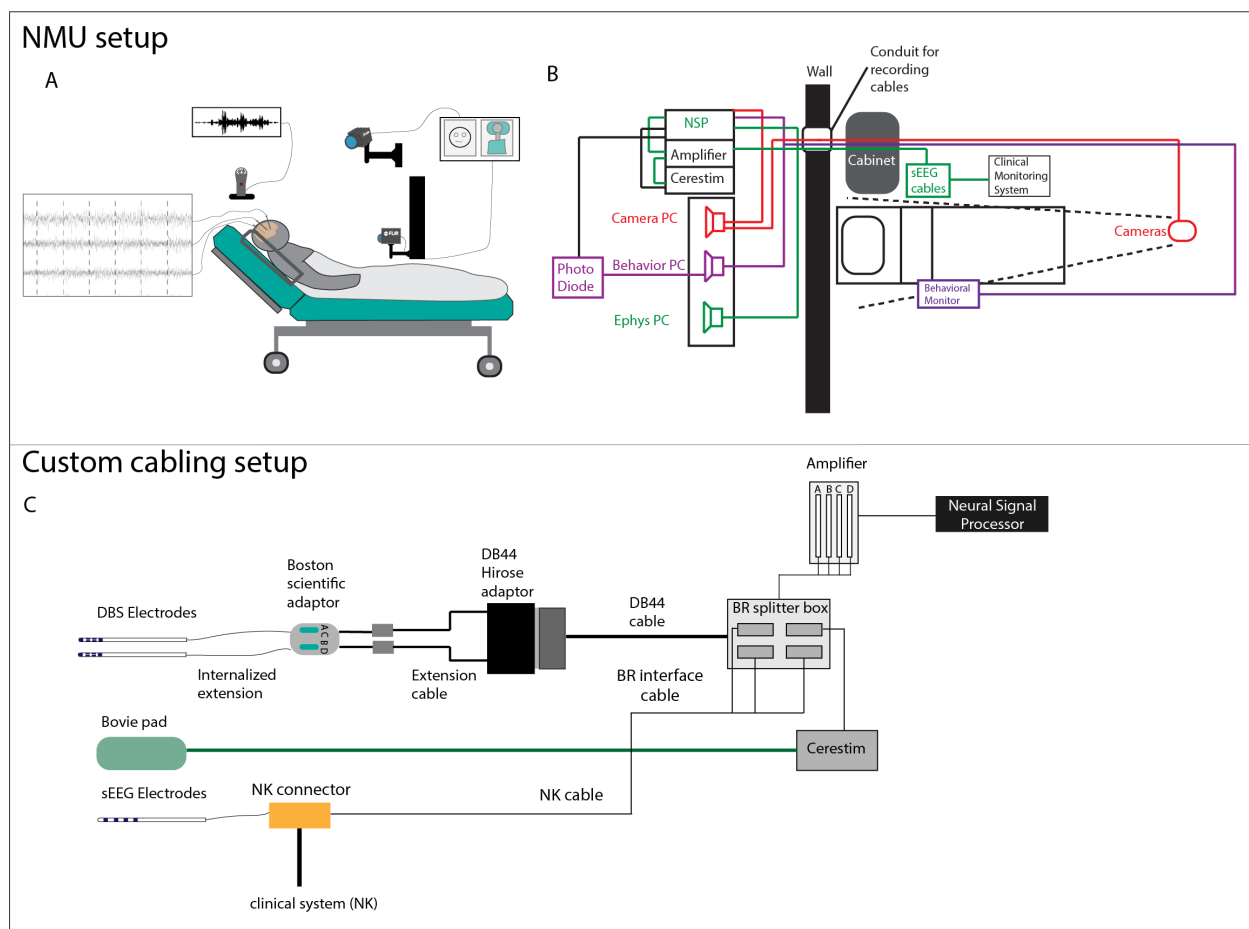


Figure 2-3: NMU setup.

(A) Video, audio, and electrophysiological recording setup in patient room (B) Systems-level overview of equipment and connections implemented for data acquisition and stimulation. (C) Custom-cabling setup to interface Boston Scientific DBS leads with Blackrock recording and stimulation equipment.

We performed baseline recordings (analogous to resting-state fMRI) across all these brain regions while the participant viewed a fixation cross daily, multiple times a day, at the same time each day of the intracranial monitoring period, in addition to task-based electrophysiological recordings. To record across electrophysiology, video, and task-based response items in a unified time base, our computing systems are configured to automatically trigger recording across platforms using cbmex communications (Blackrock Neurotech, Salt Lake City, UT), and synchronized using photodiode recordings and timed synchronization signals across platforms (described in more detail in section 2.6)

2.5 ARTIFACT REMOVAL AND OTHER ELECTROPHYSIOLOGICAL CONSIDERATIONS

2.5.1 Artifact removal

While we perform stimulation experiments of varying lengths during the NMU phase, we will focus on the nature of artifact that is present during periods of longer stimulation as that is of greater relevance for behavioral modulation in psychiatric disorders.

During experiments that entail multi-lead continuous stimulation (e.g. during behavioral tasks performed with high-frequency stimulation ON), the observed artifact has varied across patients for different reasons. Overall, we anticipated the artifact to be centered around the stimulation frequency (130 Hz), with perhaps some harmonics around lower frequencies at 65 Hz, for example. What we instead found that in subject A stimulation artifact was observable at several lower frequencies, highlighted in Figure 2-4. If we are interested in lower frequencies implicated in cognitive control, for example, such as theta or alpha power^{21,22}, we can successfully preprocess the data to obtain a clean signal in lower frequencies. This is accomplished by first bandpass filtering the LFP signal between 1-50 Hz to prevent high-frequency harmonics contaminating lower frequencies of interest. Demeaning, performing bipolar re-referencing and decimating the signal to 1 KHz (in that order) allows us to analyze the data in frequencies between 1-40 Hz without artifact contamination. However, in order to analyze data in high frequencies, additional preprocessing steps will have to be undertaken. Specifically, application of a previously developed artifact removal technique²³ can be applied to remove artifact in higher frequencies in subjects A and B.

In subject C, we observed a similar issue of additional artifact in lower frequencies (Figure 2-3b,e,h,k). However, we also observed an issue of saturation in the signal. As the upper and lower limits of the voltage trace are not entirely clipped (as is expected for a saturated signal), we proceeded to perform our preprocessing pipeline to recover the signal. We observed that while we are able to remove artifact in lower frequencies, on closer inspection the time series signal still appears quite noisy (Fig. 2-3e,h). Artifact mitigation for this subject is still underway.

In subject D, we were able to successfully incorporate optimal recording methods to avoid artifact contamination that is difficult to remove (recording methods outlined in next section). As observed in Figure 2-3, the shape of the artifact is much clearer as the signal is sampled at a higher rate (30 KHz vs 2KHz in subjects A and B) and the underlying LFP is recoverable for analysis across both low and high frequency activity (Fig. 2-3 c,f,i,l).

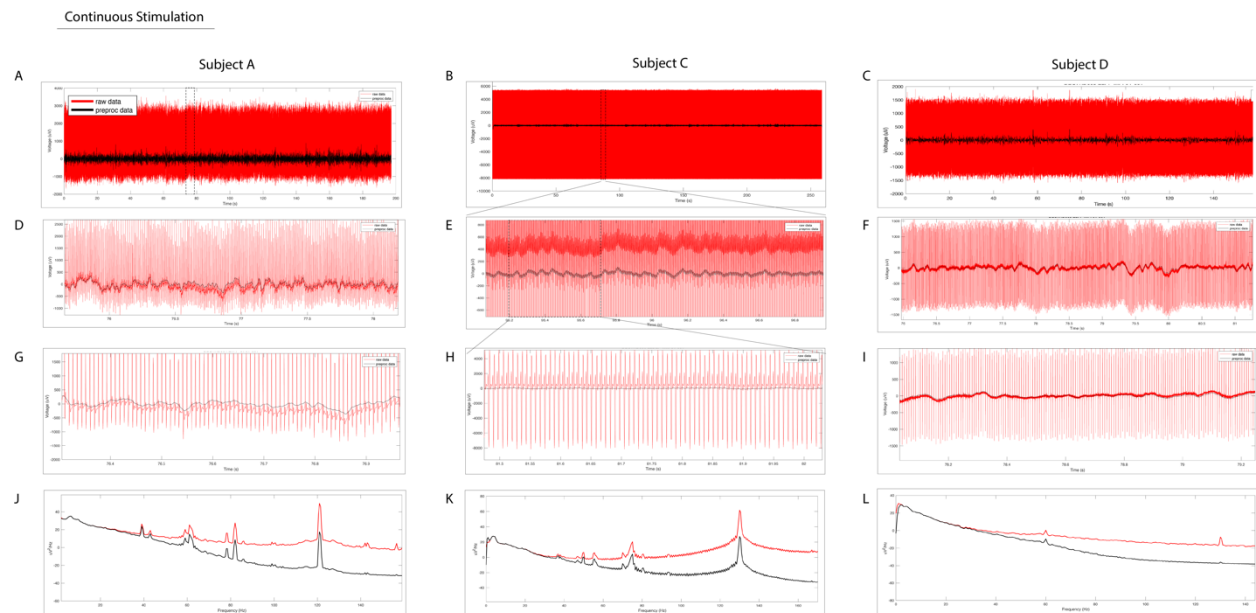


Figure 2-4: Stimulation artifact across TRD subjects.

(A-I) Raw (red) and preprocessed (black) LFP signals along varying time-scales in Subjects A,C and D. Artifact was comparable between subjects A and B, therefore subject B is not shown. (J-L) Periodogram

of the raw(red) and preprocessed(black) signal. For subject A-C, artifact is present in lower frequencies and additional preprocessing steps have to be undertaken to analyze signal in 40 Hz signals and higher.

An additional type of artifact to be mindful of when performing intermittent stimulation (not continuous stimulation as observed in Figure 2-4), is that there can be capacitive discharge or desaturation observed following the tail end of the stimulation ON period for each trial. While this is anticipated to last for a duration of 100-300 ms, we observed this duration to last significantly longer in Subject C, on the order of seconds (Figure 2-5a). While bandpass filtering as described above mostly resolved this issue (as observed in subjects C and D in Figure 2-5), we have taken additional steps (described in the next section) to prevent this issue from reoccurring.

Intermittent Stimulation

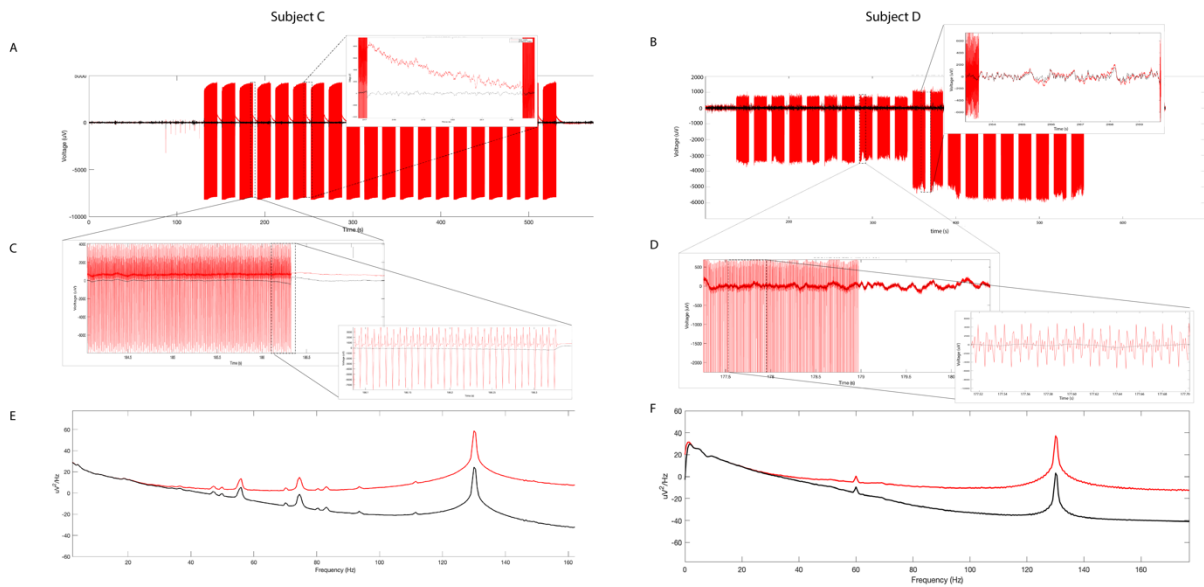


Figure 2-5: Stimulation artifact during intermittent stimulation experiments.

(A-D). Example LFP signals across varying windows of time demonstrating capacitive discharge observed following the end of a stimulation trial. (E-F) Periodograms of raw and preprocessed LFP signals in subjects C and D.

2.5.2 Mitigating artifact during neural data recording

To mitigate the concerns of the nature and frequency of artifact observed across patients during the NMU phase, we have undertaken a few steps. They are outlined in Figure 2-6.

First, prior to the start of any recording or experiment, we perform a quick sweep across channels with a quick bandpass filter (1 Hz -250 Hz) to ensure that there is no noise or unexpected artifact across channels. Second, for experiments that do not involve stimulation, we collect data at 2000 Hz, with an online filter to remove slow drift (at 0.5 Hz). If we are performing experiments that do involve stimulation experiments, we disable all hardware or online filters to collect raw data, and only collect data at 30 KHz. This allows for optimal removal of artifact as there are sufficient samples for implementation of the spline and interpolation method²⁴ or a previously developed artifact removal technique in our research group²³. Third, at the start of every stimulation experiment, we perform “blow-offs”, across DBS leads or more importantly, across sEEG leads. This process entails delivery a small amount of charge or stimulation from every contact, at an amplitude of 200 μ A, frequency of 200 Hz, pulsewidth of 180 μ S for a duration of 100 mS to blow off any tissue that may have accumulated around a contact and led to capacitive discharge, observed during intermittent stimulation. After the first few trials of any stimulation experiment, we perform visual inspection (including filtering and bipolar re-referencing) on the collected data to ensure high data quality. Lastly, when performing stimulation experiments at higher amplitudes (4-5 mA), we visually inspect channels closest to the stimulation source to ensure that there is no signal/amplifier saturation. If there is signal saturation observed, and switching the

ground and reference contact has not mitigated the issue, we decrease our amplitude in increments of 0.5 mA, until we resolve the issue (i.e. no observable saturation).

Through this rigorous approach during data collection, we are able to ensure that the collected data is of the highest quality and requires minimal effort for signal preprocessing and artifact removal post-hoc.

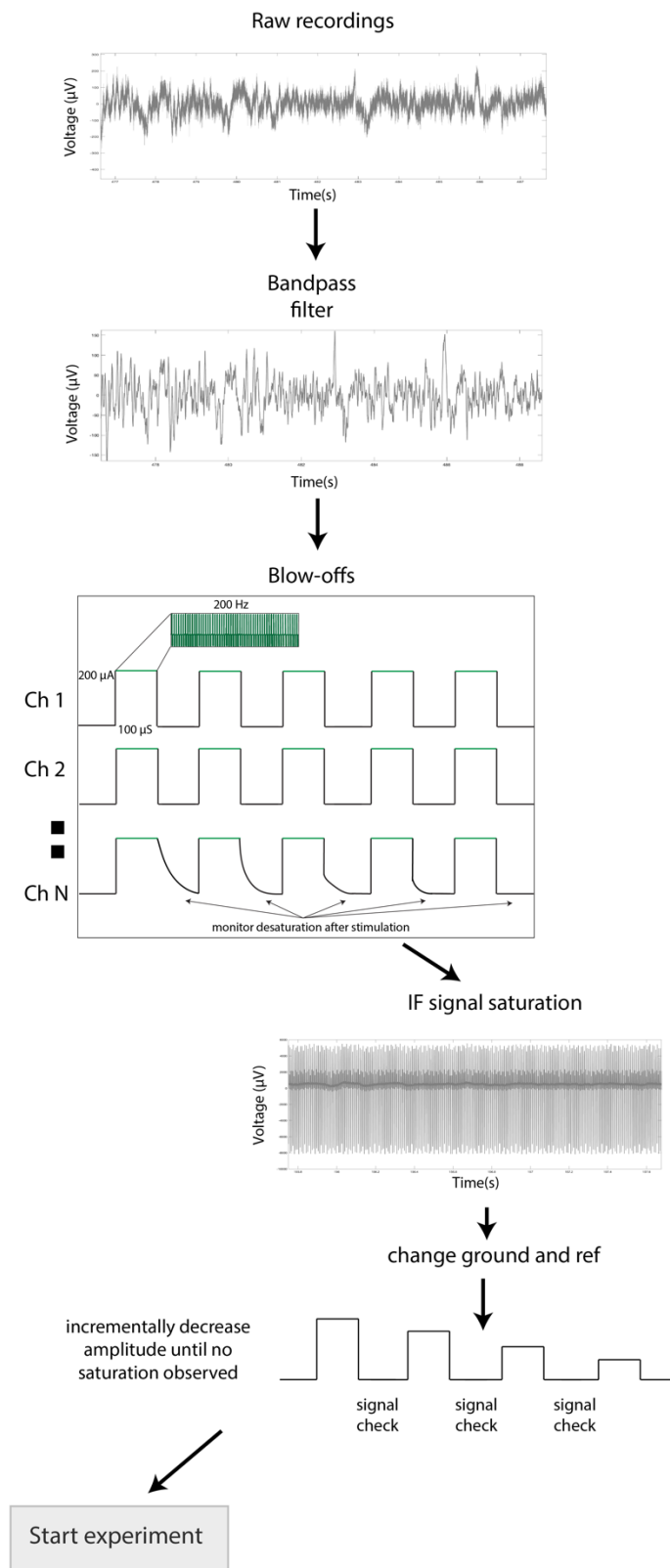


Figure 2-6: Pipeline for recording neural activity during stimulation experiments

2.6 AUDIO, VIDEO AND BEHAVIORAL ASSESSMENT

The NMU setting provides opportunities to implement extensive resting-state intracranial neural recordings, as well as disease-specific behavioral task recordings can support the goal of characterizing network activity relevant to primary symptom domains. This approach can be modulated to whatever symptom domains are of particular interest in a particular patient or disease entity (anxiety disorders, mood disorders, psychotic disorders, chronic pain, etc.). In addition, we integrate naturalistic tasks including self-evaluation, and clinical interview. The three relevant control systems for these experiments are 1) the neural recording system; 2) the central control system; and 3) the video acquisition system. A central computer is used for triggering the start of behavioral tasks and neural recordings and subsequently video and audio data acquisition.

For video data acquisition, we implemented a FLIR GigE Vision Cameras to record video of body posture and face of each subject. The camera for capturing facial expressions is mounted on the monitor used for behavioral tasks to obtain a close-up view of subject face. Video recording of the face camera can be triggered by a single TTL pulse from the Blackrock Microsystems Neural Signal Processor (Fig. 2-7) at the start of every neural recording, or it can be triggered by a TTL pulses at a frequency of 30 Hz, to enable capture of a frame at 30 frames per second (fps). The interface connecting the neural data acquisition and video data acquisition is a printed circuit board previously developed in the lab. Video data is written computer built specifically for video data acquisition. Settings and configurations for video capture (resolution, contrast, etc.) are preset on a FLIR software GUI called Spinview (part of the FLIR

Spinnaker SDK). Video data is captured during behavioral tasks modulating affect, during self-report surveys, and during longform stimulation experiments with psychiatric evaluation.

To collect continuous audio acquisition, a microphone is placed in the patient room and connected to the analog input of the Blackrock microsystems NSP. The sampling frequency for audio recordings is 30 KHz. In this way, audio is collected every time there is a neural recording is initiated (during all stimulation experiments, behavioral tasks, self-report surveys and resting-state recordings).

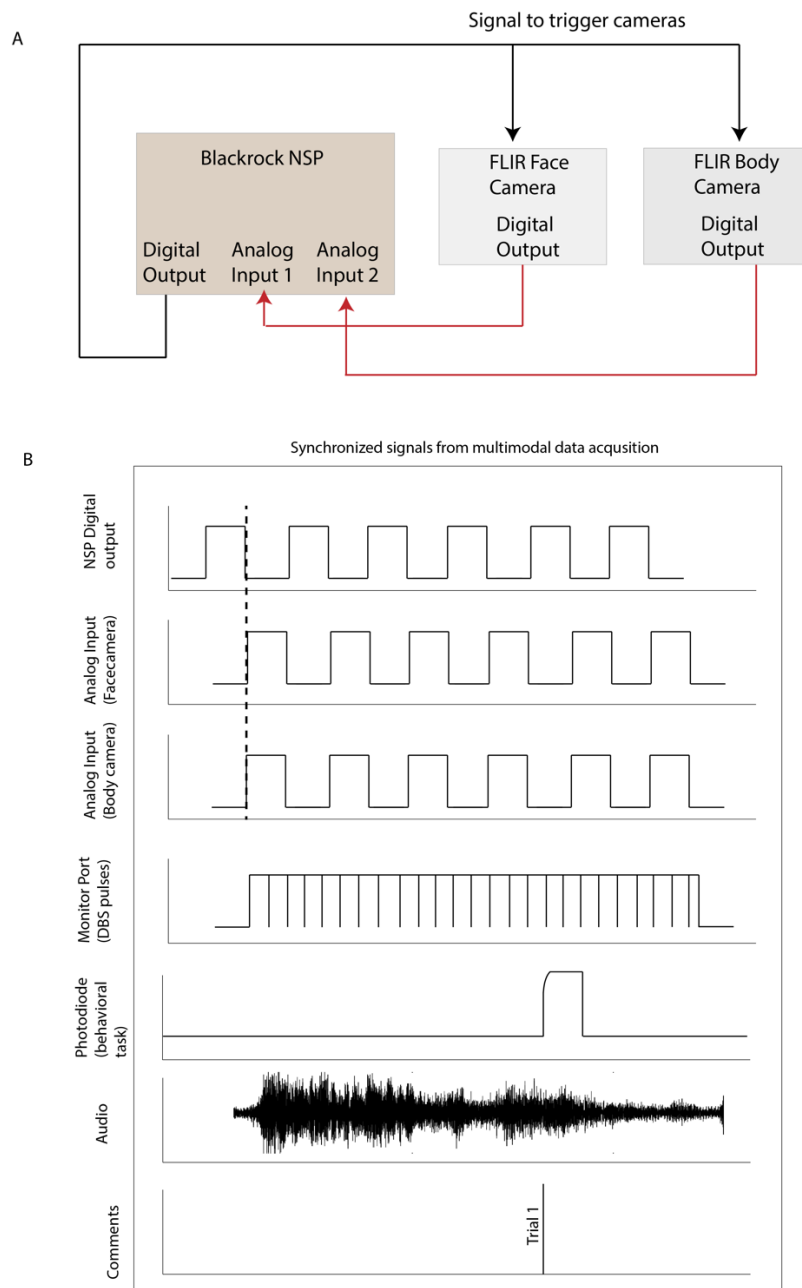


Figure 2-7: Synchronized recordings to capture audio, video, neural activity and behavior

Simultaneously tracking all modalities (video, audio, electrophysiology, behavior; Fig 2-7) requires coordination across platforms with special attention to time synchronization. The complex computing systems used to run data collection are automated to trigger recording across platforms simultaneously with redundancies built in so that if one source of time synchronization fails there is a backup method for obtaining data with

timestamps for synchronization. For example, for behavioral task synchronization, comments are sent via cbmex commands at the start of each trial. Additionally, an analog signal from a photodiode that is placed on the behavioral monitor screen to capture the timestamp of the start of each trial.

With multiple streams of data collection, we can identify biomarkers of affective and cognitive regulation, mood and symptom states, and detect improvement along any axis of measurement during stimulation. Behavioral responses measured via audio, video, tasks or self-reports can guide clinical programming in the outpatient response in a individualized manner.

In summary, we demonstrate that the proposed framework outlined in Chapter one⁸ is implemented in our study for multi-modal continuous recordings of behavior, psychiatric symptom assessments and intracranial electrophysiology during a vast array of stimulation parameters. This rich dataset can then inform personalized therapy for outpatient programming and biomarker discovery for future closed-loop stimulation platforms.

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3 Prefrontal Network Engagement from Deep Brain

Stimulation in Limbic Hubs

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3.1 ABSTRACT

Prefrontal circuits in the human brain play an important role in cognitive and affective processing. Neuromodulation therapies delivered to certain key hubs within these circuits are being used with increasing frequency to treat a host of neuropsychiatric disorders. However, the detailed neurophysiological effects of stimulation to these hubs are largely unknown. Here, we performed intracranial recordings across prefrontal networks while delivering electrical stimulation to two well-established white matter hubs involved in cognitive regulation and depression: the subcallosal cingulate (SCC) and ventral capsule/ventral striatum (VC/VS). We demonstrate a shared frontotemporal circuit consisting of the ventromedial PFC, amygdala, and lateral orbitofrontal cortex where gamma oscillations are differentially modulated by stimulation target. Additionally, we found subject-specific responses to stimulation in the dorsal anterior cingulate cortex and demonstrate the capacity for further tuning of neural activity using current-steered stimulation. Our findings indicate a potential neurophysiological mechanism for the dissociable therapeutic effects seen across the SCC and VC/VS DBS targets for psychiatric neuromodulation and our results lay the groundwork for personalized, network-guided neurostimulation therapy.

3.2 INTRODUCTION

The ability to regulate complex emotions and make controlled decisions are central to the human experience and critical for successful navigation through challenging life circumstances. Neuroimaging and electrodiagnostic studies have implicated prefrontal networks encompassing the dorsal anterior cingulate cortex (dACC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC) and amygdala in affective and emotional regulation^{1–5}, decision making and impulsivity^{2,6,7}, reward evaluation^{8–11}, and

emotional processing^{12,13}. Disruption of neural activity in these circuits is thought to lead to psychiatric disorders of mood, anxiety, and impulsivity, among other behavioral manifestations^{4,14–19}. Neuromodulatory interventions^{20,21} are often used to treat such disorders, but little is known about the human *electrophysiology* of these prefrontal regions and how chronic neurostimulation therapies modify circuit dynamics underlying psychiatric symptoms. Characterizing the specific spatiotemporal prefrontal network activity implicated in affective and cognitive processing in response to therapeutic stimulation can inform stimulation paradigms on a chronic or adaptive basis and aid the prediction of an individual's response to stimulation.

Two well-characterized affective hubs previously demonstrated to be gateways to parsimoniously engage prefrontal and corticolimbic networks through invasive means^{21–24} are the ventral capsule/ventral striatum (VC/VS) and subcallosal cingulate (SCC). The VC/VS and SCC are thought to be hubs²⁵ at the crossroads of white matter pathways hypothesized to influence executive function²³, reward processing^{26,27} and mood processing^{21,28} through their connections of varying degrees to prefrontal and limbic structures (spanning the amygdala, PFC and ACC)^{29,30} with partial overlap^{31–33}.

Modulation of the two targets have shown promising results in DBS studies showing improvement in symptoms of anxiety³⁴, depression^{21,35,36}, treatment-refractory anorexia nervosa³⁷, addiction^{38–40} and obsessive compulsive disorder^{41,42}. In the clinical treatment of treatment-resistant depression (TRD) with DBS, both SCC and VC/VS targets have been extensively used with mixed results. While both targets can have an antidepressant effect, responses to stimulation across the two targets are phenotypically different, and notable qualitative differences in behavioral responses

(“activating” vs “calming”)^{21,28,43–45} have been observed. Prefrontal targets appear to be key in driving a response from both DBS targets^{46–48}.

The aim of our study was to evaluate the network-level effects of stimulation *between* the SCC and VC/VS, two well-established targets used for psychiatric DBS therapy. We took advantage of a unique opportunity afforded through an ongoing clinical trial of DBS for TRD (NCT03437928) where we performed stimulation experiments using segmented DBS leads in the SCC and VC/VS with concurrent high-density intracranial recordings providing high spatiotemporal resolution of neural activity in two participants with TRD. We aimed to characterize the *differences* in neural response across prefrontal networks between the two DBS targets within and across patients with TRD. Given the phenotypic differences that are observable following stimulation of the VC/VS and SCC, and the role of the vmPFC, OFC, dACC and amygdala in neuropsychiatric disorders^{17,49–52}, we hypothesized that we would find differentiable responses to stimulation between the DBS targets in the prefrontal cortex and that this would be unique to anatomical regions in high frequency activity (defined as 13-100 Hz for this study) or low frequency activity (defined as 1-13 Hz for our study) based on previous work implicating frequency-specific neural oscillations in mood^{9,20,52,53}. Our results lay the groundwork for a more mechanistic understanding of the effects of DBS across prefrontal circuits in psychiatric disease, and better equip us to implement optimized, network-guided neuromodulation in the future.

3.3 METHODS AND MATERIALS

3.1.1 Participant and study overview

Data for this study was collected from two subjects (37 year old Latino male and a 57 year old Caucasian female) diagnosed with TRD. The subjects were enrolled in an ongoing clinical trial (NCT 03437928) for DBS for TRD. Each participant gave fully informed consent according to study sponsor guidelines, and all procedures were approved by the local institutional review board at Baylor College of Medicine IRB (H-43036) prior to participation. Subjects underwent stereotactic implantation of four DBS leads (Boston Scientific Cartesia, Marlborough, MA) and 10 temporary stereo-electroencephalography (sEEG) electrodes (PMT, Chanhassen, MN) based on pre-operative scans including patient-specific tractography. Post-implantation, patients underwent a ten-day intracranial monitoring period for evaluation of brain networks involved in depression. Following the intracranial monitoring period, sEEG electrodes were removed and the four DBS leads were internalized and connected to two implanted pulse generators (IPG) (Boston Scientific Gevia, Marlborough, MA). Additional surgical details have been described previously⁴⁵.

3.1.2 Electrode Implantation

Both participants were implanted bilaterally with segmented DBS leads in the VC/VS and the SCC, capable of current steering. The DBS leads used in our study consist of eight stimulation contacts: solid ring contacts at the deepest and shallow positions, as well as three-way segmented contacts located between the ring contacts. Seven total contact configurations of interest were identified per lead, including three stacked configurations listed as follows: (1) anterior-facing contacts 2 and 5, (2) posterior-left facing contacts 4 and 7 and (3) posterior-right facing contacts 3 and 6. The remaining

four configurations tested were ring configurations listed as follows: (1) solid ring contact 1 (2) solid ring contact 8 (3) combination of segmented ring contacts 2, 3 and 4, and (4) combination of segmented ring contacts 5, 6 and 7 (Fig. 3-1b). Intracranial sEEG electrodes for local field potential (LFP) recordings were implanted bilaterally across several cortical and subcortical targets based on previous work implicating their roles in mood, reward, as well as cognitive and affective processing^{3,11,54,55}. Regions sampled included the dorsolateral prefrontal cortex (dlPFC), ventromedial prefrontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC), lateral and medial orbitofrontal cortex (lOFC, mOFC), superior frontal gyrus (SFG), superior and medial temporal gyri (STG, MTG) and the amygdala (Fig. 3-1a). Postoperative CT scans and pre-operative MRI scans were aligned using the Functional Magnetic Resonance Imaging for the Brain Software Library's (FMRIB's) Linear Image Registration Tool (FLIRT). Electrode coordinates were manually determined from the co-registered CT in BioImage Suite and placed into native MRI space. The reconstructed cortical surface, segmented cortical and subcortical structures and electrode coordinates were visualized using the Multi-Modal Visualization Tool⁵⁶.

3.1.3 Electrode Stimulation and Recording

Monopolar cathodic stimulation was delivered through each DBS lead via a Blackrock CereStim R96 (Blackrock Microsystems, Salt Lake City, UT). A stimulation amplitude of 4.8 - 5 mA was delivered at the solid ring contacts, whereas for stacked or ring configurations this amplitude was split evenly among contacts to enable current steering, never exceeding 5 mA in total or at any time a charge density of 30 $\mu\text{C}/\text{cm}^2$. Stimulation was applied at 130 Hz, with a pulse width of 180 μs and interphase gap of 100 μs . In subject A, we tested the seven identified stimulation combinations (3 stacked

configurations, 4 ring configurations) for each DBS lead in the SCC, and five combinations (3 stacked configurations, 2 ring configurations) in each DBS lead in the VC/VS. In subject B, we tested all seven combinations across each of the four DBS leads. Each trial of stimulation consisted of 15 seconds of stimulation on followed by 10 seconds without stimulation (Fig. 3-1c). Trials were repeated 5 times per contact configuration per DBS lead seriatim, resulting in 25-35 trials per DBS lead for subject A and 35 trials per DBS lead for subject B.

3.1.4 Data Acquisition and Signal Processing

Electrophysiological signals from implanted sEEG electrode contacts were recorded using a 256-channel NeuroPort Acquisition System (Blackrock Microsystems, Utah) at a sampling rate of 2 kHz, with a hardware high pass filter applied at 0.3 Hz. Recordings from sEEG contacts were analyzed offline using custom scripts written in MATLAB (Mathworks Inc. Natick, MA) and Python. LFP signals were demeaned, decimated to 1 kHz and bandpass filtered between 1-250 Hz. A butterworth notch filter was applied to remove line noise at 60, 120 and 180 Hz, respectively. Recordings were bipolar re-referenced by subtracting the activity of adjacent electrode contact pairs. Any channels with excessive noise or without a clear neural signal were removed from the analysis. Electrode contacts in gray matter located in the regions of interest were identified and pre-processed signals were then grouped (averaged) per region of interest. The location of electrode contacts in gray matter vs white matter and the labels for anatomical region of interest was verified by visual review of the MRI and CT by an expert rater (BS). To evaluate the response of the sampled networks before and after stimulation, we analyzed the spectral power in the 5 seconds following stimulation to avoid artifact contamination. We identified a window of 600 ms post-stimulation that was additionally

excluded from analysis to avoid residual post-stimulation artifacts in the signal. The multitaper spectral estimation method was used to extract power spectral density (PSD) from the sEEG recording using the *mspectrumc.m* function from the Chronux toolbox⁵⁷. Spectral power was then averaged within standard frequency bands (delta = 1-4 Hz, theta = 4-8 Hz, alpha = 8-12 Hz, beta = 12-30 Hz, low-gamma = 30-55 Hz, high-gamma = 65-100 Hz). The spectral power across the baseline windows and post-stimulation windows across all stimulation experiments were z-scored within subjects. Prior to starting the stimulation experiments, 5 minutes of baseline recording was collected for each subject (Fig. 3-1c). To avoid temporal autocorrelation, the autocorrelation was computed for spectral power within each frequency band of interest and region of interest, across time (Supplementary Fig. 3-S3). The number of lags t where the autocorrelation was at or below 0.1 and all subsequent autocorrelation values were between 0.1 and -0.1. Lag t was then used to generate surrogate “trials” from the baseline recording, where t seconds was skipped every 5 seconds. The resulting 5-second trials were used for analysis to compare against the post-stimulation windows during the stimulation experiments (additional details in Supplementary Fig. 3-S3).

3.1.5 Statistical Analysis

To test the difference between pre- (baseline) and post-stimulation, non-parametric permutation testing was performed on the z-scored data using custom scripts written in MATLAB. Data labels from post-stimulation and baseline windows were randomly shuffled, and then the absolute value of the t-statistic for a two-sample, pooled variance, t-test was computed for each pair of shuffled data. This procedure was repeated 1000 times. We used a single-step maxT procedure to correct for multiple tests^{58,59}, namely, each absolute t-statistic was compared to the distribution (over permutations) of the

maximal absolute t-statistic across all regions of interest and frequency bands of interest in order to obtain corrected p-values that control the familywise error rate (corrected p-values reported in Supplementary Tables 3-S1-4).

To test the difference between PSD changes across the network following unilateral VC/VS stimulation versus SCC stimulation, non-parametric permutation testing was performed on the z-scored data using custom scripts written in MATLAB. We compared the effect of unilateral VC/VS to unilateral SCC stimulation (i.e. left VC/VS was tested against left SCC stim and right VC/VS stim was tested against right SCC stim). Data labels for unilateral SCC stimulation and unilateral VC/VS stimulation were randomly shuffled, and then the absolute value of the t-statistic for a two-sample, pooled variance, t-test was computed for each pair of shuffled data. This procedure was repeated 1000 times. We used a single-step maxT procedure to correct for multiple tests^{58,59}, namely, each absolute t-statistic was compared to the distribution (over permutations) of the maximal absolute t-statistic across all regions of interest and frequency bands of interest in order to obtain corrected p-values that control the familywise error rate (corrected p-values reported in Supplementary Table 3-S5-6)

The goal of our study was to quantify prefrontal network responses to intracranial stimulation between two DBS targets: the SCC and VC/VS. We first evaluated the effects of stimulation for each DBS target (pre- vs. post-stim, p-values adjusted to compensate for multiple comparisons reported in Supplementary Methods and Tables 3-S1-4; Fig. 3-1c) on high-density stereo-EEG (sEEG recordings) in two subjects with TRD (Fig. 3-1a-b; Supplementary Methods). We then compared neural responses (see Supplementary Methods) following stimulation between the two DBS targets (SCC post-stim vs. VC/VS post-stim, adjusted p-values reported in Supplementary Tables 3-S5-6)

on high frequency neural activity (beta, low gamma and high gamma band power) and low frequency activity (delta, theta and alpha band power). A representative example of the electrode coverage is shown in Fig. 3-1d, illustrating bilateral modulation of low frequency power (e.g., theta) and high frequency power (e.g., high gamma) across recording contacts following unilateral stimulation in Subject A. Given the previously established roles of the dACC, amygdala, OFC and vmPFC in affective and cognitive regulation in psychiatric disorders, we focused our analyses across these key four anatomical regions and describe our findings for each key region in detail below.

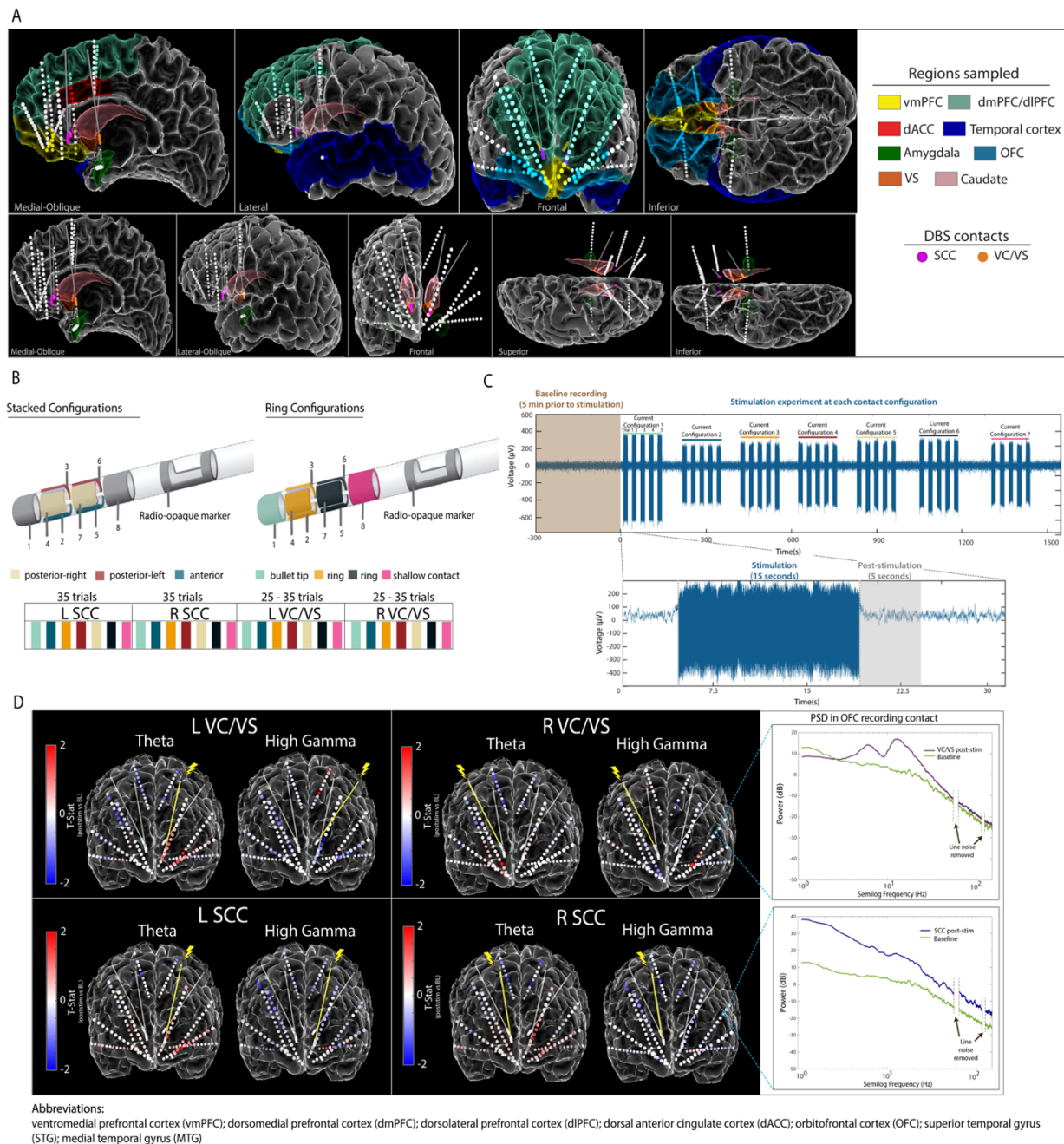


Figure 3-1: Experimental Approach

A) Anatomical reconstruction showing placement of sEEG electrodes (top panel) and DBS leads (bottom panel). Colors in the legend (right) correspond to the region where electrodes were implanted. (B) Steerable DBS leads were used to deliver unilateral stimulation in the VC/VS and SCC respectively. Seven current configurations of interest were identified and tested across subjects. (C) Raw voltage signal recorded on an example sEEG contact during stimulation in the left SCC DBS lead. Subjects were systematically tested at each current configuration for fifteen seconds, with five trials per current configuration at each respective DBS lead. A five-second window following stimulation was used for

subsequent analyses.(D) Electrode diagram showing the mean power change in theta band and high gamma band following stimulation for subject A. Each contact is colored based on the t-statistic value computed between baseline and post-stimulation for each DBS lead (red indicates increase in power following stimulation and blue indicates a decrease in power following stimulation). Inset (top-right) shows log-transformed power spectra from a recording electrode in the OFC during baseline and post-stimulation.

3.4 RESULTS

3.1.6 vmPFC

3.1.1.1 Stimulation-induced response of high frequency activity

We first sought to understand the effect of stimulation on high frequency activity in the vmPFC given its broad involvement in cognitive, affective and emotional processing². Here, we found consistent differences when evaluating neural responses in high frequency bands between SCC and VC/VS stimulation (Fig. 3-2c,f) in both subjects. **Specifically, we found that SCC consistently increased gamma power in both subjects while VC/VS decreased gamma power.** Within Subject A, left SCC stimulation elicited a significant increase in spectral power in high gamma (pre- vs post-stim, $\text{adj.p} < 0.01$). The response to stimulation was significantly different between both DBS targets in high gamma band ($\text{adj.p} < 0.01$) and low gamma band ($\text{adj.p} < 0.01$) irrespective of the hemisphere of stimulation. The inverse relationship in which SCC increased high-frequency activity and VC/VS decreased high-frequency activity was also observed in beta band ($\text{adj.p} < 0.001$) in subject A. In Subject B (Fig. 3-2d), we observed right VC/VS stimulation significantly decreased low gamma power ($\text{adj.p} < 0.05$) and beta power ($\text{adj.p} < 0.001$) from baseline. In the same subject, neural responses were significantly different between the two DBS targets as observed in low gamma ($\text{adj.p} < 0.05$) and high gamma ($\text{adj.p} < 0.01$, corrected; Fig. 3-2f).

3.1.1.2 Stimulation-induced response of low frequency activity

We next explored if the same opposing response between SCC and VC/VS was observed in low-frequency activity. We did observe a significant difference in delta power between SCC and VC/VS stimulation in both subjects (Fig.3- 2c,f). While both SCC and VC/VS stimulation significantly increased delta power from baseline ($\text{adj.p} < 0.01$) respectively, we found that VC/VS stimulation drove a larger increase in delta power than SCC stimulation and the responses between the two DBS targets were significantly different ($\text{adj.p} < 0.05$) in subject A. In subject B, it appears that while both SCC and VC/VS stimulation drive a decrease in delta power from baseline (Fig. 3-

2d), the response between the two targets is still significantly different, where VC/VS drives a smaller decrease than SCC stimulation (adj.p<0.01, corrected; Fig. 3-2f).

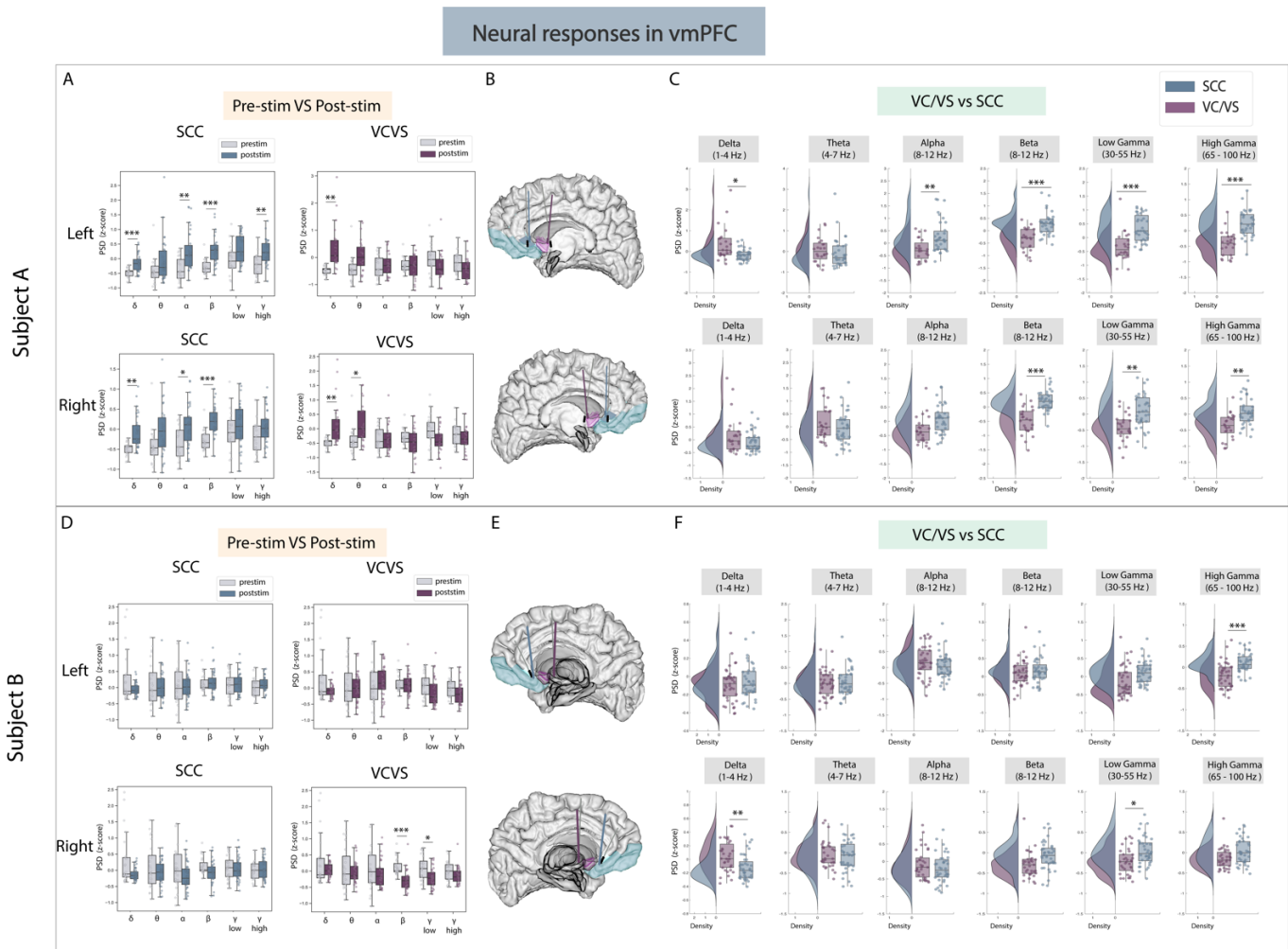


Figure 3-2: Neural responses in the vmPFC following SCC vs. VC/VS stimulation

(A) Distribution of spectral power across all post-stimulation trials vs pre-stimulation (baseline) in the vmPFC after z-scoring in six pre-defined frequency bands (delta, theta, alpha, beta, low gamma and high gamma) following SCC stimulation (left) and VC/VS stimulation (right) in subject A (B) Corresponding anatomical location of the vmPFC highlighted in light blue and corresponding VC/VS and SCC DBS leads highlighted depending on hemisphere of stimulation. Stimulation in left hemisphere is on top, while stimulation in right hemisphere is shown on the bottom. (C) Distribution of spectral power across six pre-defined frequency bands contrasting neural responses following SCC stimulation and VC/VS stimulation. (D)-(F) Replicate of figures in panels (A)-(C) for subject B.

* indicates significance where adj.p-value < 0.05, corrected; ** indicates significance where adj.p-value ≤ 0.01, corrected; *** indicates significance, where adj.p-value ≤ 0.001, corrected.

3.1.7 Amygdala

3.1.1.1 Stimulation-induced response of high frequency neural activity

The next area of interest for this study was the amygdala, given its role in emotional regulation¹². In the amygdala, **while both VC/VS and SCC stimulation elicited**

increases in low and high gamma power, responses in both low and high gamma were still significantly different between the DBS targets in both subjects (Fig. 3-3c,f). SCC stimulation significantly increased high frequency activity from baseline in both subjects (Fig. 3-3a,d). In subject A, SCC stimulation drove a significant increase in beta (adj.p<0.001), low gamma (adj.p<0.001) and high gamma power (adj.p<0.001). In subject B, right SCC stimulation significantly increased low gamma (adj.p<0.001) and high gamma power (adj.p<0.001) while significantly decreasing beta power (adj.p<0.01). VC/VS stimulation also significantly increased high gamma power in both subjects (adj.p<0.05, corrected; Fig 3-3. a,d). In subject A, right VC/VS stimulation also significantly increased low gamma power (adj.p<0.05) and in subject B, left VC/VS stimulation significantly decreased beta power (adj.p<0.05). When contrasting neural responses between the two DBS targets (Fig. 3-3c,f) we observed that SCC increased low gamma (adj.p<0.05) and high gamma power (adj.p<0.05) significantly higher than VC/VS stimulation, and right SCC increased beta power significantly higher than VC/VS stimulation (adj.p<0.01) in subject A. In subject B, beta power and high gamma power were again significantly higher (adj.p<0.05) following right SCC stimulation compared to right VC/VS stimulation, and low gamma power was significantly higher (adj.p<0.001) following SCC stimulation compared to VC/VS stimulation irrespective of the hemisphere of stimulation.

3.1.1.2 Stimulation-induced response of low frequency activity

We were similarly interested to see if significant differences between SCC and VC/VS were prevalent in low frequency activity. We found responses to SCC and VC/VS stimulation were significantly different in theta band in subject B (adj.p<0.01, corrected; Fig. 3-3c,f). Here, SCC drove a decrease in power relative to the VC/VS. However, no

consistent modulation of low frequency activity across the two subjects was otherwise observed.

Neural responses in Amygdala

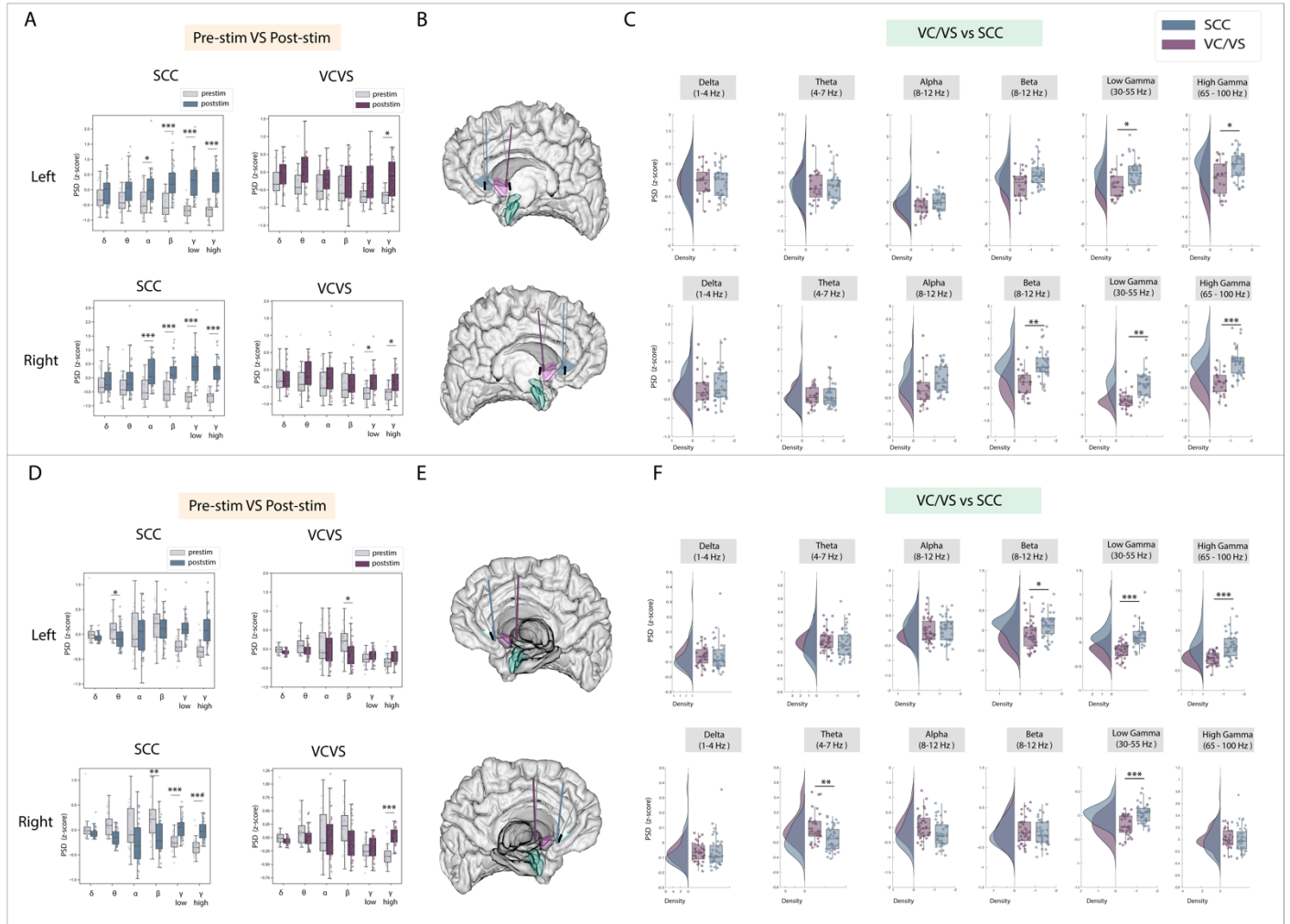


Figure 3-3: Neural responses in the amygdala following SCC stimulation vs. VC/VS stimulation.

(A) Distribution of spectral power across all post-stimulation trials vs pre-stimulation (baseline) in the amygdala after z-scoring in six pre-defined frequency bands (delta, theta, alpha, beta, low gamma and high gamma) following SCC stimulation (left) and VC/VS stimulation (right) in subject A (B) Corresponding anatomical location of the amygdala highlighted in green and corresponding VC/VS and SCC DBS leads highlighted depending on hemisphere of stimulation. Stimulation in left hemisphere is on top, while stimulation in right hemisphere is shown on the bottom. (C) Distribution of spectral power across six pre-defined frequency bands contrasting neural responses following SCC stimulation and VC/VS stimulation. (D)-(F) Replicate of figures in panels (A)-(C) for subject B. * indicates significance where adj.p-value < 0.05, corrected; ** indicates significance where adj.p-value ≤ 0.01, corrected; *** indicates significance, where adj.p-value ≤ 0.001, corrected.

3.1.8 Lateral and medial OFC

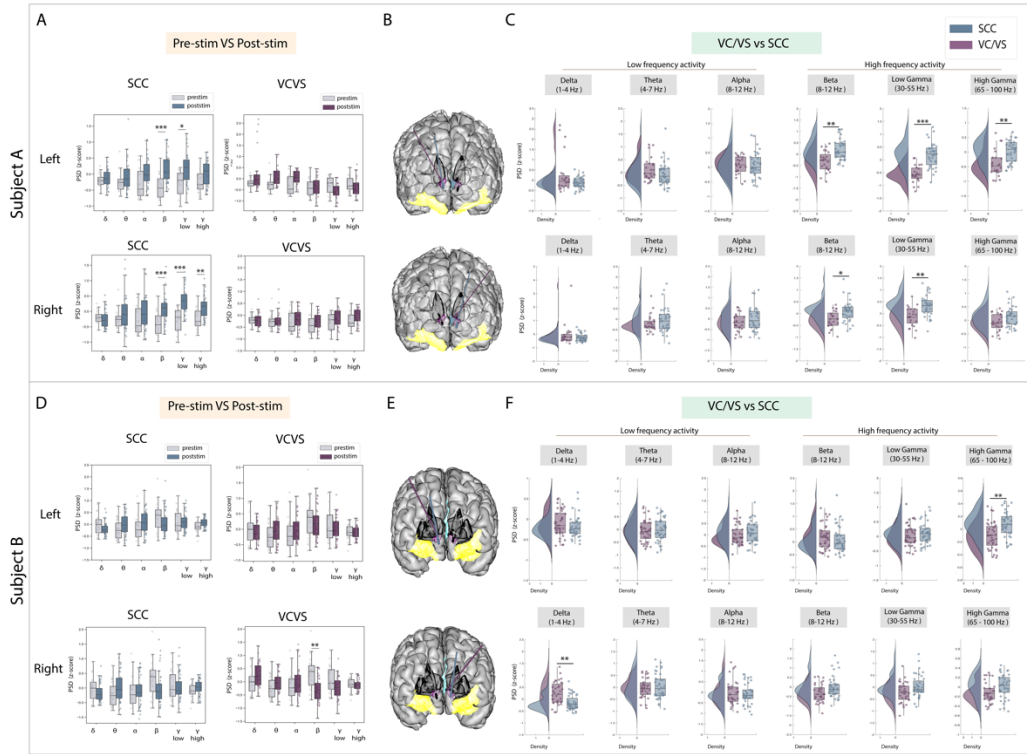
3.1.1.1 Stimulation-induced response of high and low frequency activity (lateral OFC)

The IOFC was a third target of interest because it has been implicated in cognitive and reward processing and recently employed as a target for neuromodulation to improve mood^{44,52}. We found neural responses to SCC stimulation were significantly different from VC/VS stimulation in subject A (adj.p<0.05, corrected; Fig. 3-4c) and once again followed the same inverse relationship seen in the amygdala, **where SCC drove an increase in power in beta, low gamma, and high gamma bands relative to the VC/VS**. In the same subject, SCC stimulation also significantly increased beta, low gamma and high gamma power from baseline (adj.p<0.01). In subject B, the significant difference in response between SCC and VC/VS stimulation was observed in high gamma power (adj.p<0.01, corrected; Fig. 3-4f) following stimulation in the left hemisphere.

We next explored the neural responses of low frequency activity to DBS across the two targets. Surprisingly, we did not find many differences in neural responses to SCC and VC/VS stimulation. Delta band power was significantly modulated, (adj.p<0.01): right VC/VS stimulation increased delta power and right SCC stimulation decreased delta power. The differential delta band power change was, however, subject specific.

Neural responses in OFC

Lateral OFC



Medial OFC

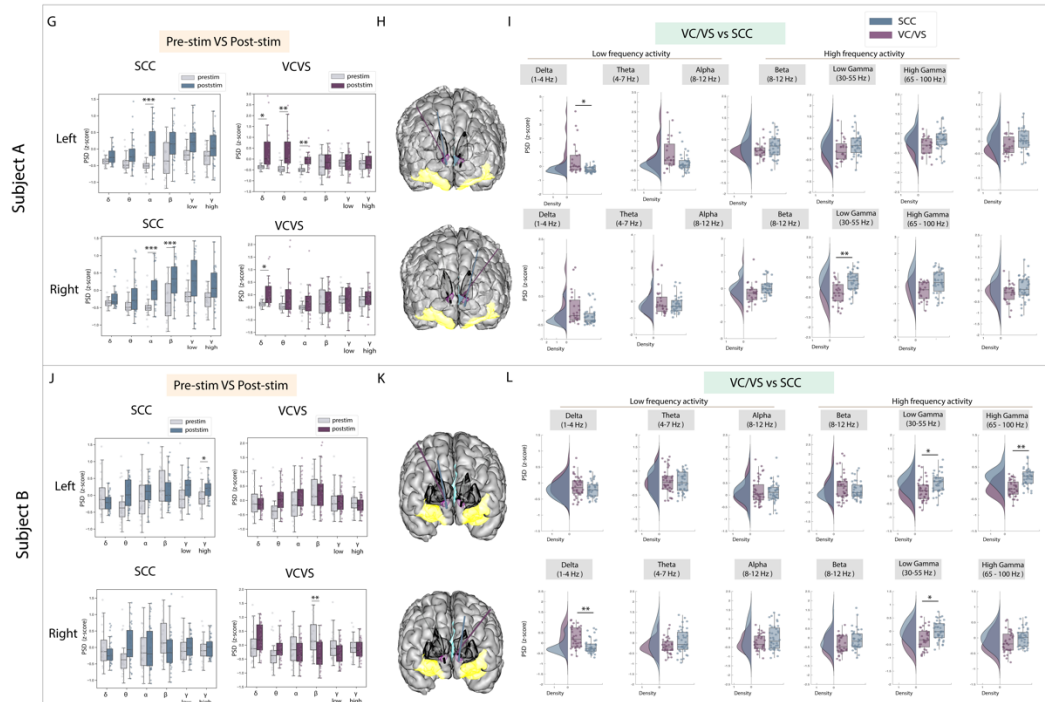


Figure 3-4: Neural responses in the OFC following SCC stimulation vs. VC/VIS stimulation.

(A) Distribution of spectral power across all post-stimulation trials vs pre-stimulation (baseline) in the IOFC after z-scoring in six pre-defined frequency bands (delta, theta, alpha, beta, low gamma and high gamma) following SCC stimulation (left) and VC/VIS stimulation (right) in subject A (B) Corresponding anatomical location of OFC highlighted

in yellow and corresponding VC/VS and SCC DBS leads highlighted depending on hemisphere of stimulation. Stimulation in left hemisphere is on top, while stimulation in right hemisphere is shown on the bottom. (C) Distribution of spectral power across six pre-defined frequency bands contrasting neural responses following SCC stimulation and VC/VS stimulation. (D)-(F) Replicate of figures in panels (A)-(C) for subject B. (G) Distribution of spectral power across all post-stimulation trials vs pre-stimulation (baseline) in the mOFC after z-scoring in six pre-defined frequency bands following SCC stimulation (left) and VC/VS stimulation (right) in subject A. (H) Corresponding anatomical location of OFC highlighted in yellow and corresponding VC/VS and SCC DBS leads highlighted depending on hemisphere of stimulation. Stimulation in left hemisphere is on top, while stimulation in right hemisphere is shown on the bottom. (I) Distribution of spectral power across six pre-defined frequency bands contrasting neural responses following SCC stimulation and VC/VS stimulation. (J)-(L) Replicate of figures in panels (G)-(I) for subject B. * indicates significance where adj.p-value < 0.05, corrected; ** indicates significance where adj.p-value ≤ 0.01, corrected; *** indicates significance, where adj.p-value ≤ 0.001, corrected.

3.1.1.2 Subject-specific response to stimulation observed in high and low frequency neural activity (medial OFC)

We explored stimulation response in the mOFC separately as the lateral and medial orbitofrontal structures have shown to have distinct roles in cognitive and reward processing⁷. We found that differences between responses in high frequency activity following SCC vs. VC/VS stimulation were subject-specific in the mOFC (Fig. 3-4i,l). For example, the inverse relationship where SCC increases high frequency activity and VC/VS decreases high frequency activity was observed in subject A. Here, right SCC stimulation significantly increased beta power from baseline (adj.p<0.001, corrected; Fig. 3-4g), and we observed a significant difference in response to stimulation in beta power between the SCC and the VC/VS (adj.p<0.01, corrected; Fig. 3-4i). In subject B, SCC significantly increased high gamma power from baseline (adj.p<0.05, corrected; Fig. 3-4j). The inverse relationship between SCC and VC/VS stimulation-induced responses of high frequency activity was observed in low gamma (adj.p<0.05) and high gamma (adj.p<0.01), where SCC stimulation increased activity relative to VC/VS stimulation (Fig. 3-4l).

When assessing stimulation response in low frequency activity in the mOFC, we found significant differences between responses to VC/VS vs. SCC stimulation seen across both subjects in delta band (Fig. 3-4i,l). In subject A, left VC/VS stimulation significantly increased power in delta band, and this response was significantly higher than the

neural response following SCC stimulation (adj.p<0.05). In subject B, right VC/VS stimulation significantly increased delta power relative to SCC stimulation (adj.p<0.01).

3.1.9 dACC

3.1.1.1 Subject-specific response to stimulation observed in high and low frequency neural activity

A key region known to play an important role in cognitive control and emotional processing is the dACC^{3,6}. When examining high frequency activity in the dACC, we found that significant differences following stimulation between the SCC and VC/VS were also individual-specific in the dACC but still followed the inverse relationship between the two DBS targets observed in high frequency activity in other ROIs (Fig. 3-5c,f). Right SCC stimulation significantly increased beta power (adj.p<0.01) compared to VC/VS stimulation in subject A. In subject B, left SCC stimulation significantly increased low gamma power from baseline (adj.p<0.01) while stimulation of either hemisphere in the SCC increased high gamma power (adj.p<0.001, corrected; Fig. 3-5d). Left VC/VS stimulation similarly significantly increased low gamma power (adj.p<0.05) while stimulation of either hemisphere significantly increased high gamma power from baseline (adj.p<0.01, corrected; Fig. 3-5d). However, the responses between left SCC and left VC/VS stimulation were still significantly different in low gamma band (adj.p<0.01; Fig. 3-5f) and SCC stimulation drove a larger increase in low gamma power relative to the VC/VS.

When examining low frequency activity in response to stimulation in the dACC, we also observed a significant difference between VC/VS and SCC stimulation in delta power (adj.p<0.001) in subject B - similar to the pattern observed in other ROIs - where SCC decreased power in a low frequency band (delta) and VC/VS stimulation increased power. In subject A, right SCC stimulation significantly decreased delta power

(adj.p<0.05) but no significant difference was observed between SCC and VC/VS stimulation in delta power.

Neural responses in dACC

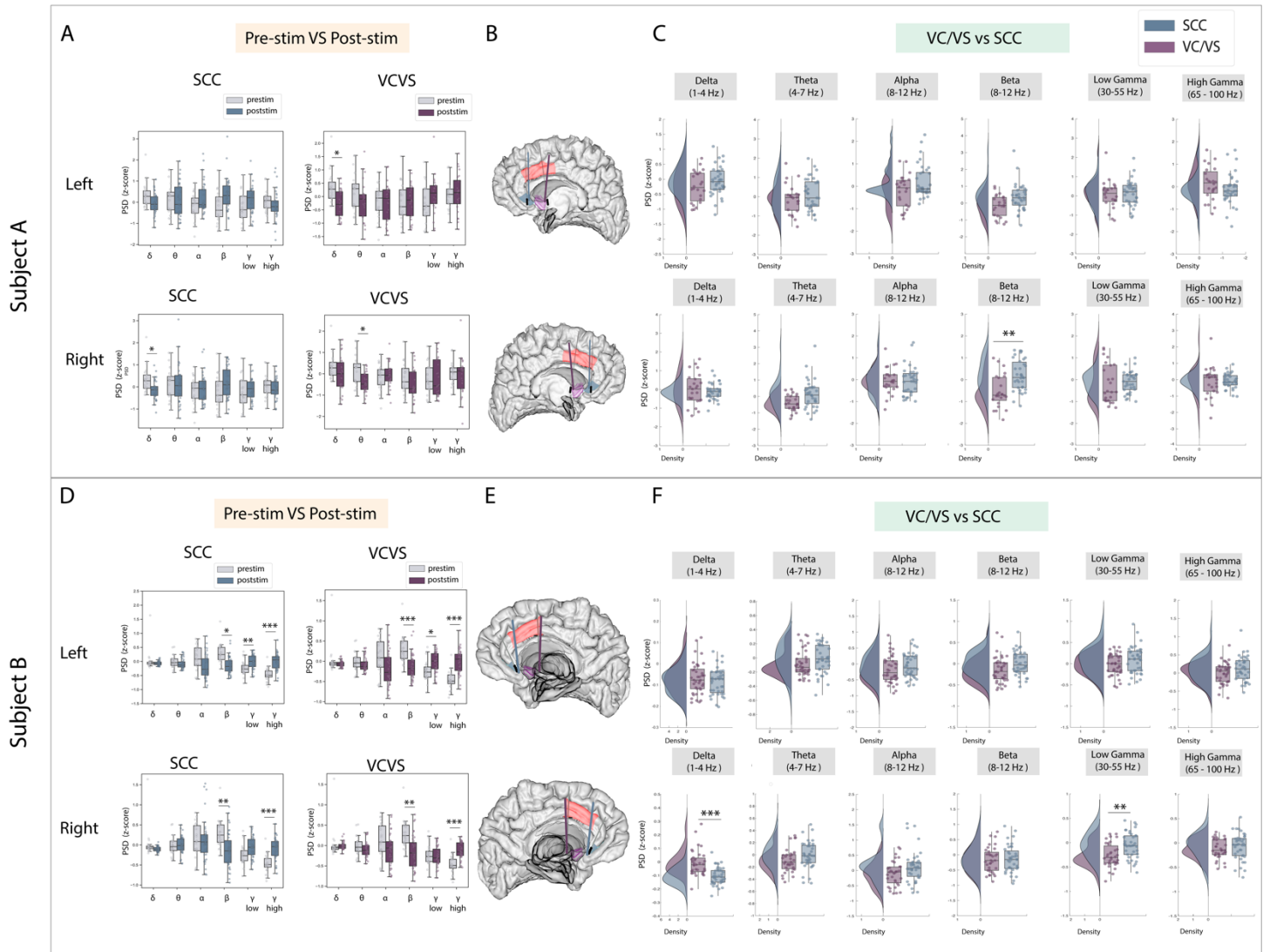


Figure 3-5: Neural responses in the dACC following SCC stimulation vs. VC/VS stimulation.

(A) Distribution of spectral power across all post-stimulation trials vs pre-stimulation (baseline) in the dACC after z-scoring in six pre-defined frequency bands (delta, theta, alpha, beta, low gamma and high gamma) following SCC stimulation (left) and VC/VS stimulation (right) in subject A (B) Corresponding anatomical location of dACC highlighted in red and corresponding VC/VS and SCC DBS leads highlighted depending on hemisphere of stimulation. Stimulation in left hemisphere is on top, while stimulation in right hemisphere is shown on the bottom. (C) Distribution of spectral power across six pre-defined frequency bands comparing neural responses between SCC stimulation and VC/VS stimulation. (D)-(F) Replicate of figures in panels (A)-(C) for subject B. * indicates significance where adj.p-value < 0.05, corrected; ** indicates significance where adj.p-value ≤ 0.01, corrected; *** indicates significance, where adj.p-value ≤ 0.001, corrected.

3.1.10 Current steering can drive dissociable changes across prefrontal networks

To examine whether current steering enabled greater specificity in modulating neural features of interest, we evaluated spectral power for each tested contact configuration within each segmented DBS lead. Given the few trials per contact configuration for each lead, a full statistical investigation controlling for multiple comparisons was not possible. Instead, our results highlights some of the largest differences observed for a pair of DBS leads (in this case, right SCC and VC/VS) when examining the effect of current steering on neural activity to demonstrate potential effects that can be explored more fully in future work. The first feature selected was alpha-band power (see Supplementary Methods), where we found the largest amount of variance across contact configurations in the right SCC (Fig. 3-1b). Current-steered stimulation in right SCC differentially increased or decreased alpha power across ROIs (Fig. 3-6a, left). A significant effect of current steering was seen in the IOFC ($p < 0.05$, uncorrected) and mOFC ($p < 0.01$, uncorrected). Across the right SCC DBS lead, two stacked configurations (posterior electrodes 2-5 and 3-6) and a ring configuration (electrodes 2-3-4) demonstrated a decrease in alpha power in the OFC whereas remaining configurations resulted in an increase in power (the largest mean increase was seen in response to the bullet tip electrode, electrode 1). In response to current-steered stimulation in right VC/VS lead (Fig. 3-1b), mean differences were observed in the dACC and amygdala depending on the contact configuration (Fig. 3-6a, right), but there was no significant effect of current steering.

Our second feature of interest was theta-band power, that showed the largest amount of variance across contact configurations tested in the right VC/VS DBS lead. A significant effect of current steering across the right VC/VS lead was seen only in the IOFC

($p < 0.05$, uncorrected; Fig. 3-6b, right). In the IOFC, the bullet tip electrode (electrode 1) configuration and two stacked configurations (posterior electrodes 3-6 and 4-7) decreased power while the anterior stacked configuration (electrodes 2-5) increased mean power. More broadly, mean differences were observed across other ROIs such as the vmPFC and mOFC between contact configurations as shown Fig. 3-6b (right) following VC/VS and SCC stimulation, respectively.

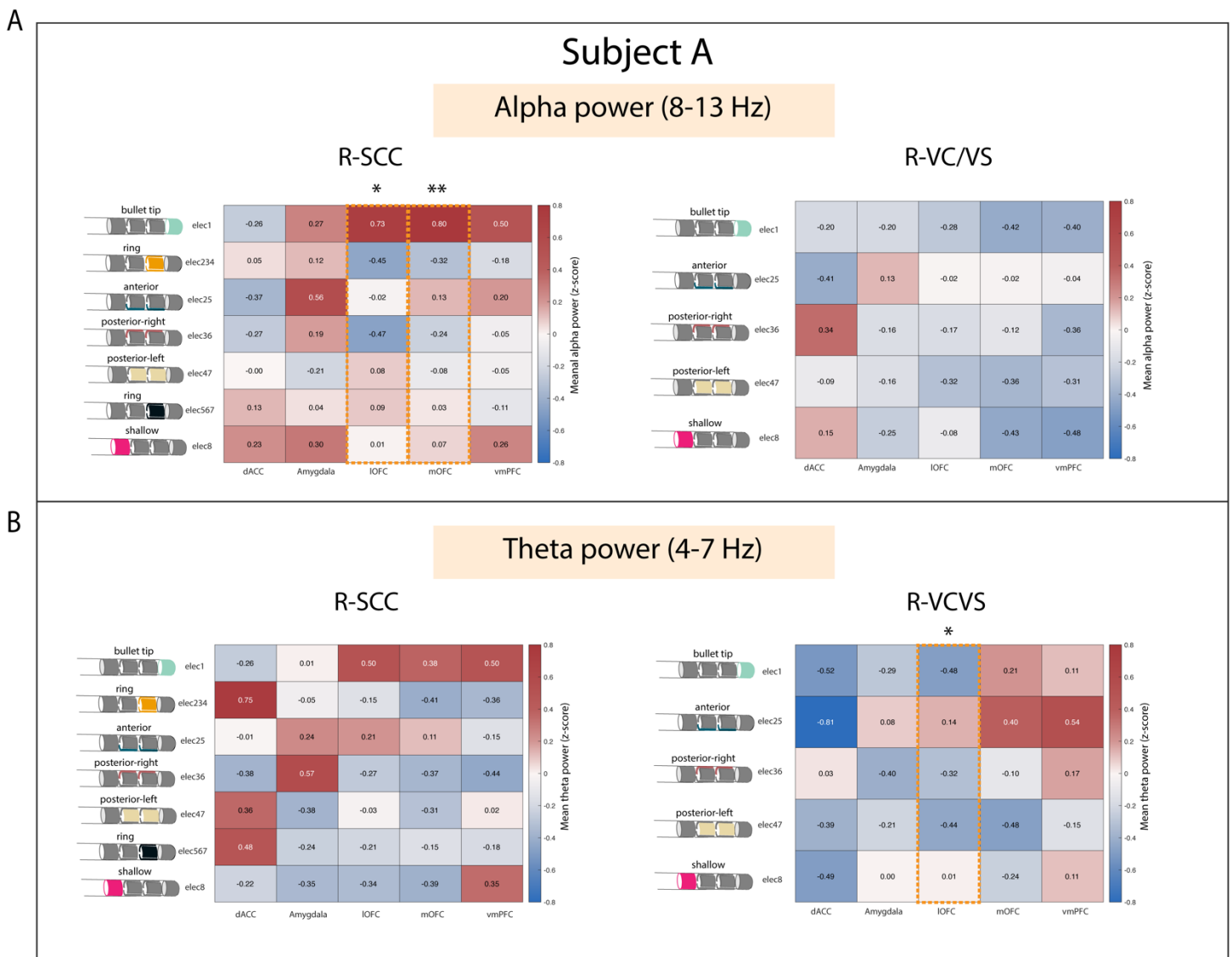


Figure 3-6: Current steering elicits differential effects in neural features implicated in depression.

(A) Mean spectral power in alpha band in response to current steered stimulation in the right SCC (left) and right VC/VS (right) in subject A. Each row corresponds to a tested contact configuration across the respective DBS lead, while each column represents mean spectral power for each ROI. Seven current configurations were tested in the

SCC while five were tested in the VC/VS for subject A. Alpha band was selected based on the neural feature that showed the greatest variance across all ROIs following current steered stimulation across the right SCC DBS lead. (B) Mean spectral power in theta band in response to current steered stimulation in the right SCC (left) and right VC/VS (right) in subject A. Each row corresponds to a tested contact configuration across the respective DBS lead, while each column represents mean spectral power for each ROI. Seven current configurations were tested in the SCC while five were tested in the VC/VS for subject A. Alpha band was selected based on the neural feature that showed the greatest variance across all ROIs following current steered stimulation across the right VC/VS lead.

3.5 DISCUSSION

Through a unique intracranial stimulation and recording dataset collected in two subjects with TRD, we obtained results with three main conclusions (Fig. 3-7). First, we demonstrate that two canonical targets for psychiatric neuromodulation, the SCC and VC/VS, elicit network-wide neurophysiological responses in both high and low frequency activity following stimulation. Second, as hypothesized, we show that stimulation in the SCC and VC/VS drive differentiable neural responses. Specifically, we observed opposite effects on gamma activity in the vmPFC, and differing degrees of modulation on gamma activity in the IOFC and amygdala, where SCC stimulation consistently drives a greater increase in gamma oscillations relative to the VC/VS. Third, we highlight preliminary evidence of subject-specific neurophysiological responses between stimulation targets, and the ability to further modify neural responses using current-steered DBS in the OFC.

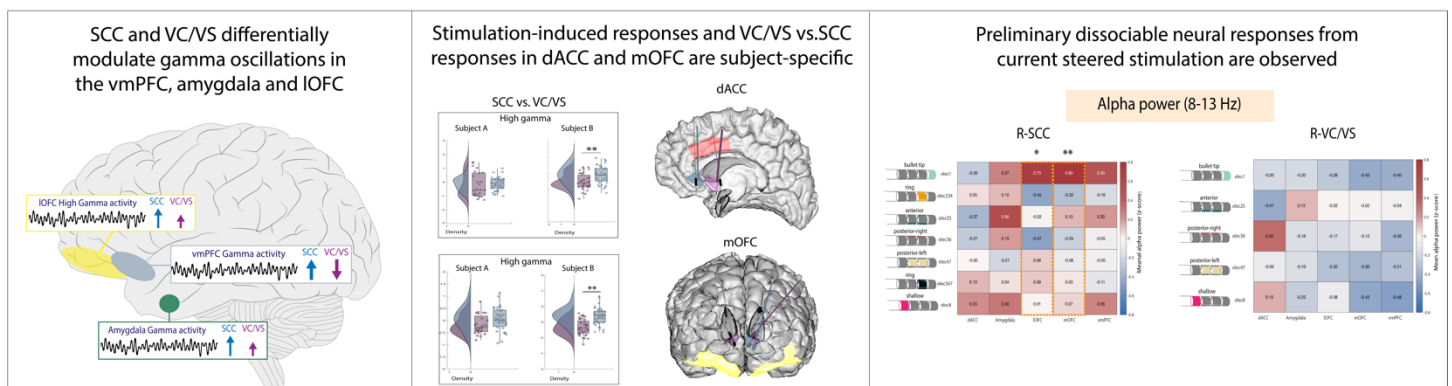


Figure 3-7: Summary of results.

Previous tractography work demonstrates that projections from the SCC and VC/VS overlap in the amygdala and medial PFC, but the anatomical trajectory and pattern of connectivity of these projections are distinct^{32,33}, including the sub-regions that receive projections from the SCC and VC/VS respectively³³. The difference in connectivity patterns may partially account for the distinct patterns of gamma activity in the vmPFC and amygdala between the two stimulation targets. The modulation of gamma activity seen in the amygdala is additionally supported by a recent study implementing amygdala gamma power as a biomarker for closed-loop VC/VS DBS in a case study for TRD²⁰. Interestingly, our results also show modulation of gamma activity in the amygdala following stimulation in *both* targets, but to differing degrees.

Previous studies have also demonstrated anatomical connectivity between the SCC and the OFC, and the VC/VS and the OFC^{60,61}, and initial results from our group have shown differing effective connectivity between the SCC and VC/VS to the IOFC respectively in TRD participants⁶², leading us to expect differences in neural responses between VC/VS and SCC stimulation. While we observed differing degrees of gamma power modulation in the IOFC depending on the DBS target stimulation in both subjects, we did not always observe an overlap in neural responses to stimulation between IOFC and mOFC which might be explained in part by previous work indicating the distinct roles of the lateral vs. medial OFC^{18,52}.

While both VC/VS and SCC stimulation can ameliorate depressive symptoms, they have been described to modulate different dimensions of affective processing and mood: VC/VS stimulation has been reported to increase motivation and energy^{28,63}, while SCC stimulation has reportedly increased calmness, alertness and exteroceptive awareness^{43,64}. It is possible that the dissociable increase/decrease in gamma activity in

the vmPFC and the differing degree of gamma modulation in the amygdala and IOFC may be underlying the differences in SCC vs. VC/VS stimulation described in acute behavioral reports seen elsewhere and further work will elucidate our understanding of this phenomenon.

In the dACC, we expected consistent differences in gamma power modulation following SCC and VC/VS stimulation, given recent work implicating dACC gamma power in positive affective behaviors⁵³ and differential connectivity of the dACC to the VC/VS^{60,65} and SCC⁶¹. However, differences in gamma responses between SCC and VC/VS stimulation were subject-specific. Additionally, within a given DBS lead, we observed subject-specific responses between post-stim and pre-stim in the dACC, as well as all other ROIs. The observed subject-specific stimulation responses both between and within the VC/VS and SCC suggest that increasing efforts to personalize therapy may rely on these within-subject electrophysiological signatures across networks to deliver optimized stimulation. Efforts utilizing subject-specific biomarkers for psychiatric DBS have been recently successfully demonstrated²⁰, alongside network-guided neuromodulation for psychiatric disorders⁶⁶.

Future efforts incorporating behavioral measures corresponding to functional domains within mental illness, alongside electrophysiological measurements to build brain-behavior relationships with stimulation will help identify generalizable principles that can be potentially extended to sub-domains of MDD in the broader population⁶⁷. **Even in the absence of behavioral measurements, characterization of stimulation-induced neural response during resting state, especially between DBS targets, enables tailoring of therapy (i.e. selecting an optimal DBS target and stimulation paradigm) for disorders such as depression, based on a patient's neural**

response to stimulation, putative biomarker of mood, or another functional domain.

Current-steered DBS provides an added parameter for differentially modulating implicated networks and neural biomarkers. A finer grained approach to precisely target anatomical regions implicated in psychopathology of depression for a desired behavioral responses is needed⁶⁸, and the degree of stimulation-induced neural response may plausibly determine a patient's therapeutic response. However, the topography is less well-established across psychiatric targets, in contrast to movement disorders where tracts around stimulation targets are well-understood⁶⁹. Future study is needed to understand the extent of the effect that directionality may have on connectivity across prefrontal networks.

Primary limitations of this study include the small sample size (N=2), and lack of randomization of stimulation conditions within or across the two DBS targets. While a rigorous pipeline for optimal surgical targeting was implemented⁴⁵, one possible reason for inconsistent results within and across subjects is that small variations in targeting may result in modifications in the electrophysiological effects observed. As we were concerned about insufficient time for stimulation washout between trials and stimulation parameters, the baseline window used for analysis was a five-minute recording collected prior to stimulation experiments. To address possible temporal autocorrelation in the baseline recording, we performed a correction procedure (Supplementary Fig. 3-S2). However, delta power in vmPFC and IOFC in Subject B had a larger amount of autocorrelation during the baseline recording that could not be fully corrected with our approach, thus, results for those specific neural features must be viewed provisionally.

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Author Contributions

SAS and KRB initiated the study. ABA, KRB, SAS, DAB designed the experiment. ABA conceptualized analysis procedures, analyzed the data, and drafted the manuscript with support from MH, KRB, SAS and DAB. SAS, NP, VP, WKG, SJM and KRB oversaw the organization of the clinical trial, subject recruitment, and regulatory activities. SAS and NP performed neurosurgical procedures in the subjects' clinical trials. ABA, RKM, KRB, JA and DO performed data collection in the neurophysiology monitoring unit. RKM, BS, MR and KRB performed MRI analysis. ABA, SAS, and DAB wrote the manuscript, and all authors had an opportunity to review the manuscript and provide intellectual feedback.

3.6 SUPPLEMENTARY METHODS

3.6.1 Statistical analysis: permutation testing procedure

The permutation testing procedure and single-step maxT procedure is described in detail as follows:

Let M be a $d \times n$ matrix where M_{ij} denotes the measurement of the i th feature (e.g., α -power on recording electrode 3) on the j th trial. Let C be a $1 \times n$ vector where $C_j \in \{1,2\}$ denotes which of two conditions the j th trial corresponds to (e.g., pre-stim = 1, post-stim = 2). M is held fixed

throughout, so we suppress it in our notation, but all of the statistics defined below operate on M . We do not suppress C in our notation, since we will be permuting the entries of C for the permutation tests described below. Let $T(C)$ be a $d \times 1$ vector where the i th entry $T_i(C)$ is a statistic for comparing trials in condition 1 to trials in condition 2 as indicated by C on the basis of the i th feature measured in M . In the following our statistic will be the absolute value of the classical test-statistic used in the two-sample (unpaired) t-test assuming equal variances, namely,

$$T_i(C) = \frac{|\hat{\mu}_{i1}(C) - \hat{\mu}_{i2}(C)|}{\sqrt{\left(\frac{1}{n_1} + \frac{1}{n_2}\right) \left(\frac{(n_1 - 1)s_{i1}^2(C) + (n_2 - 1)s_{i2}^2(C)}{n - 2}\right)}}$$

where n_b is the number of trials with condition $b \in \{1, 2\}$, namely,

$$n_b = \#\{j: C_j = b\}$$

where $\hat{\mu}_{ib}$ is the sample mean of the measurements of the i th feature in condition $b \in \{1, 2\}$, namely,

$$\hat{\mu}_{ib}(C) = \frac{1}{n_b} \sum_{j: C_j = b} M_{ij}$$

and where s_{ib}^2 is the sample variance of the measurements of the i th feature,

$$s_{ib}^2(C) = \frac{1}{n_b - 1} \sum_{j: C_j = b} (M_{ij} - \hat{\mu}_{ib})^2$$

For clarity, we note that $n_1 + n_2 = n$ and that both n_1 and n_2 depend on C , but not on the order of the entries in C , so we have suppressed that dependence in our notation.

If $\pi = (\pi_1, \dots, \pi_n)$ is a permutation of the numbers $(1, \dots, n)$, then we define the $1 \times n$ vector of permuted condition labels C^π via $C_j^\pi = C_{\pi_j}$. If π is a random permutation (chosen uniformly from all possible $n!$ permutations), then $T_i(C^\pi)$ uses the above two-sample t-test statistic to compare trials randomly assigned to condition 1 to trials randomly assigned to condition 2 on the basis of

the measurements of feature i . The vector $T(C^\pi)$ contains the results of this comparison for each of the d features. Importantly, each entry of $T(C^\pi)$ uses the *same* permutation π .

Consider the null hypothesis H_i that the measurements of the i th feature are unrelated to the condition labels in C . (More formally, the null hypothesis is that $M_{i1}, \dots, M_{in}$ are conditionally exchangeable given C .) A Monte Carlo permutation test can be used to create valid p-values for each of the null hypotheses $H_1, \dots, H_d$ as follows. We sample a total of L independent random permutations $\pi^k = (\pi_1^k, \dots, \pi_n^k)$ for $k = 1, \dots, L$. We use $L = 1000$ in the paper. For each such permutation we compute the t-statistic vector $T^k = T(C^{\pi^k})$. We also compute the t-statistic vector for the original C , namely, $T^0 = T(C)$. A valid p-value for H_i is

$$p_i = \frac{1}{L+1} \sum_{k=0}^L \mathbb{1}[T_i^k \geq T_i^0]$$

where the indicator function $\mathbb{1}[A]$ returns 1 if A is true and 0 if A is false. This p-value gives the fraction of times (among all permutations and the original) that the test statistic for feature i is at least as large as the original observed test statistic for feature i . It is important that the $k = 0$ case is included in the sum and that we use $\geq$ and not $>$ in the comparison to ensure the validity of the test. Note that the smallest possible value of p_i is $1/(L+1)$.

To control for multiple hypothesis tests, we use a single-step version of the max-T procedure that will strongly control the familywise error rate (FWER) across all features subject to a minor caveat described below. For the k th permutation (including the case $k = 0$ corresponding to no permutation), define the maximum statistic as

$$T_*^k = \max_{i=1, \dots, d} T_i^k$$

which is a number, not a vector. A valid adjusted p-value for H_i that controls the FWER over the collection $H_1, \dots, H_d$ is

$$p_i^* = \frac{1}{L+1} \sum_{k=0}^L \mathbb{1}[T_*^k \geq T_i^0]$$

This adjusted p-value gives the fraction of times (among all permutations and the original) that the maximum test statistic over all features is at least as large as the original observed test statistic for feature i . We always have $p_i^* \geq p_i$, but equality is definitely possible (unlike, say, Bonferroni adjusted p-values). These p_i^* are the corrected or adjusted p-values used in the paper. Our rationale for using max-T adjusted p-values instead of Bonferroni adjusted p-values is that max-T adjusted p-values can have much better power for positively correlated p-values (which we expect to see in our context) and also require many fewer permutations to achieve good power.

Unlike the Bonferroni correction, the max-T procedure requires a technical assumption called *subset pivotality* to ensure strong control of the FWER. Roughly speaking, the subset pivotality assumption states that the joint distribution of all features where the null hypothesis is true does not change across conditions. Consider, for instance, the following scenario. The distribution of feature 1 is unchanged between condition 1 and condition 2 so that H_1 is true. Similarly, the distribution of feature 2 is unchanged between condition 1 and condition 2 so that H_2 is true. But features 1 and 2 are more correlated in condition 1 than in condition 2. This situation violates the subset pivotality assumption, since the joint distribution of two or more features is changing across conditions while the marginal distributions of each of these features remains the same. In a situation like this it is possible that either H_1 or H_2 (or both) would be rejected more frequently than expected by chance using the max-T adjusted p-values.

There is no way to know if the subset pivotality assumption is accurate in our context, although we note that it is a strikingly singular manipulation to modify the joint distribution of a collection of variables with absolutely no modification of the marginal distributions of the variables. (In fact, it is impossible to do so if one also requires that the distributions of linear combinations of the variables remain unchanged.) For our scientific purposes, however, we think that the risk of violations of subset pivotality are small for the following reasons.

(1) The primary conclusion of our paper is that there are detectable electrophysiological differences between DBS used in different brain regions and/or using different stimulation parameters. This conclusion is unaffected by the subset pivotality assumption. Indeed, consider the global p-value

$$p_* = \frac{1}{L+1} \sum_{k=0}^L \mathbb{1}[T_*^k \geq T_*^0]$$

This is simply a Monte Carlo permutation test p-value for comparing condition 1 versus condition 2 on the basis of the test statistic T_* , which uses all of the features. Since we have $p_* \leq p_i^*$ for all $i = 1, \dots, d$, then a rejection of any H_i based on the adjusted p-value p_i^* automatically implies a rejection of the null hypothesis that there is no difference between conditions.

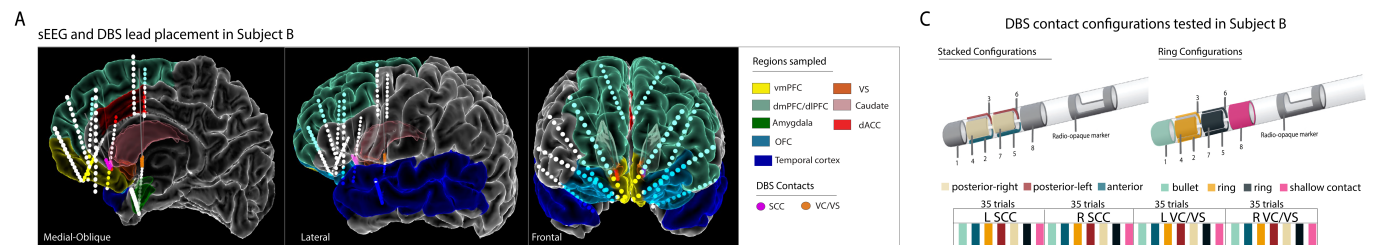
(2) If the subset pivotality condition is not true, the only danger is that we will mistakenly conclude that differences in DBS create differences in some brain region (or frequency band) when, in fact, DBS only creates differences in that region's (or band's) relationship to another region (or band). It begins to border on philosophical whether this is even a mistaken scientific conclusion or not.

(3) Furthermore, since $p_i^* \geq p_i$ for each feature i , our adjusted p-values can only be used to reject null hypothesis H_i when the data provide strong evidence against H_i when viewed in isolation, i.e., when the i th feature measurements are noticeably different across conditions.

To test the effect of current-steering within each DBS lead on neural responses across the sampled networks, we performed a one-way ANOVA (using the *anova1.m* function in the statistics toolbox in MATLAB) for 30 categories comprised of each (region,band) combination using the five regions and six frequency bands of interest on the z-scored data in subject A. To demonstrate the effect of current steering on modulation of neural activity, we chose frequency bands with the greatest amount of variance across ROIs in response to current steered stimulation. We did this by first extracting the f-statistic values computed via a one-way ANOVA

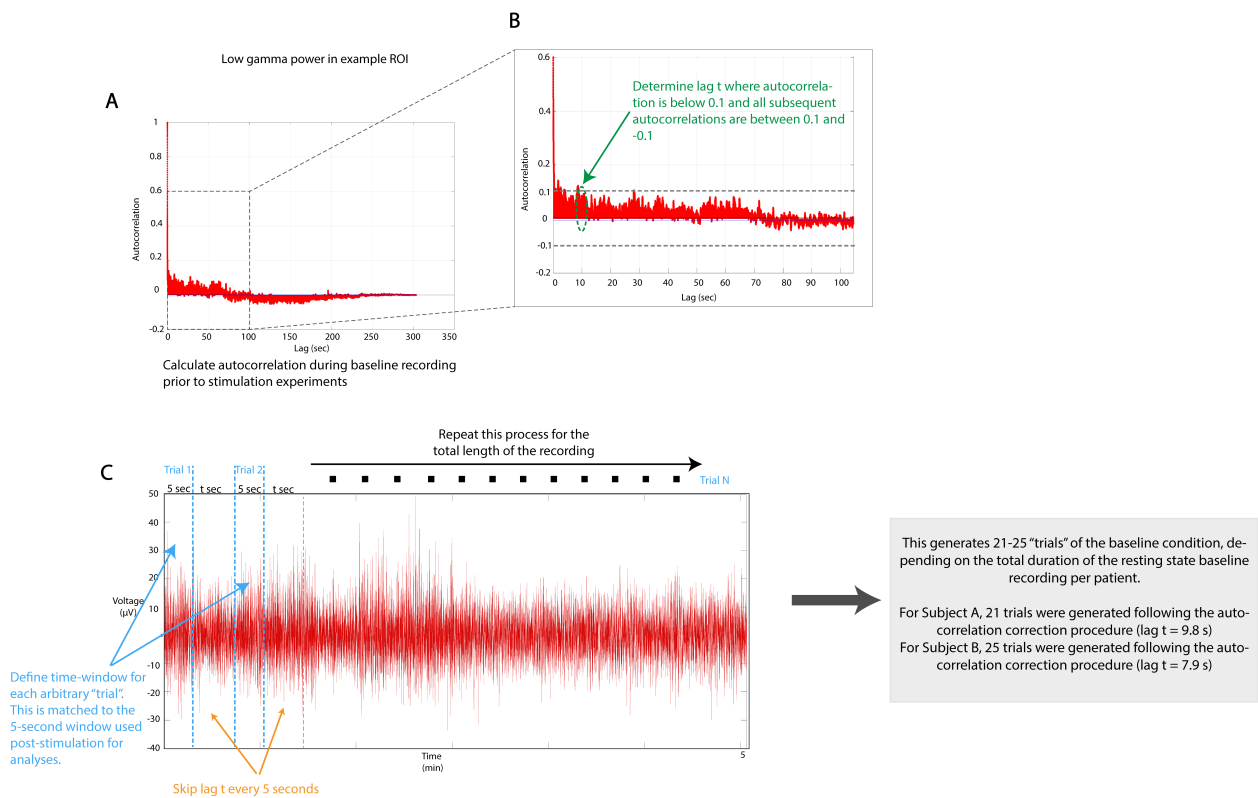
and then summed the f-statistic values for each frequency band across all ROIs and ranked the frequency bands in order of the highest f-statistic values. This resulted in alpha band as the highest ranked frequency band showing the greatest amount of variance across ROIs in response to current steering across the right SCC DBS lead, and theta band as the highest ranked frequency band showing the greatest amount of variance across ROIs in response to current steering across the right VC/VS DBS lead. Uncorrected p-values, f-statistic values and degrees of freedom are reported in Supplementary Table 3-S7. While we performed a one-way anova to compute p-values to determine significance, due to the small number of trials per current configuration per DBS lead (N = 5) we did not perform additional statistical testing.

3.1.11 Supplementary Figures



Supplementary Figure 3-S1:

Location of sEEG and DBS electrodes and tested stimulation configurations in Subject B. (A - B) Anatomical locations of sEEG contacts and DBS leads within Subject B. Both subjects had recording sEEG contacts across the vmPFC, dIPFC



Supplementary Figure 3-S2: Autocorrelation correction procedure for baseline recordings

We performed a correction procedure to account for any autocorrelation in our baseline recordings. We took 5-second windows (to match the length of time for each trial in the post-stimulation data) and skipped t seconds between them to allow for any existing autocorrelation to disappear, and so that we could model surrogate "trials" as independent (which is necessary for permutation testing). In order to choose the appropriate lag t , we performed the following steps: we first computed power spectral estimates across the entire recording, and using the `autocorr.m` function in MATLAB, calculated the autocorrelation for each region of interest (ROI) and frequency band of interest within each subject. For example, autocorrelation values during the baseline recording of low gamma power in an example ROI for Subject A is shown in (A). We then identified a lag t for which the autocorrelation is below 0.1 and all subsequent autocorrelation values are below 0.1 and greater than -0.1 for all frequency bands and ROIs (indicated by dashed lines in (B)). Additionally, for each subject we ensured that lag t that was larger than the majority of the lags identified across all regions and frequency bands, ensuring that the number of samples is the same across all ROIs and neural features. We observed a few exceptions in a few neural features and ROIs where this procedure could not account for autocorrelation – in these cases the autocorrelations were extended for such long lags that we would have to discard a significant amount of data. In such cases, we still used our lag t for these exceptions and results for these exceptions can be viewed provisionally. The exceptions are listed

as follows: delta band in vmPFC and IOFC in subject B. The steps outlined in A-C are performed for each subject separately.

3.1.12 Supplementary Tables

Subject A						
ROIs	Frequency					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
dACC	0.106	1.000	0.657	0.179	0.468	1.000
Amygdala	0.983	0.087	0.035	0.001	0.001	0.001
mOFC	0.123	0.182	0.001	0.019	0.229	0.190
IOFC	1.000	0.860	0.130	0.001	0.019	0.156
vmPFC	0.001	0.609	0.007	0.001	0.171	0.008
Subject B						
ROIs	Frequency					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
dACC	0.783	1.000	0.920	0.014	0.002	0.001
Amygdala	0.444	0.041	1.000	1.000	0.001	0.001
mOFC	0.663	0.147	0.787	0.999	0.132	0.032
IOFC	0.626	0.608	0.667	0.804	1.000	0.050
vmPFC	0.235	1.000	1.000	1.000	1.000	0.872

Supplementary Table 3-S1: Corrected p-values (ISCC vs baseline)

Subject A						
ROIs	Frequency					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
dACC	0.021	1.000	1.000	0.553	0.999	1.000
Amygdala	1.000	0.763	0.001	0.001	0.001	0.001
mOFC	0.440	0.560	0.001	0.001	0.165	0.136
IOFC	0.997	0.964	0.710	0.001	0.001	0.007
vmPFC	0.001	0.266	0.038	0.001	1.000	0.314
Subject B						
ROIs	Frequency					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
dACC	0.511	1.000	1.000	0.003	0.108	0.001
Amygdala	0.538	0.001	0.160	0.005	0.001	0.001
mOFC	0.918	0.230	1.000	0.359	1.000	0.993
IOFC	0.918	0.572	1.000	0.368	1.000	0.751
vmPFC	0.068	0.951	0.822	0.292	1.000	1.000

Supplementary Table 3-S2: Corrected p-values (right SCC vs baseline)

Subject A						
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ROIs	Frequency					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
dACC	0.020	0.945	1.000	1.000	0.917	1.000
Amygdala	0.969	0.308	0.948	0.593	0.063	0.018
mOFC	0.038	0.005	0.004	0.870	1.000	1.000
IOFC	0.565	0.079	0.100	1.000	0.152	0.994
vmPFC	0.002	0.070	1.000	1.000	0.824	0.762
Subject B						
ROIs	Frequency					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
dACC	0.927	0.944	0.291	0.001	0.019	0.001
Amygdala	0.215	0.062	1.000	0.027	0.592	0.084
mOFC	0.988	0.143	0.734	1.000	1.000	0.989
IOFC	1.000	0.870	0.999	0.995	1.000	1.000
vmPFC	0.123	1.000	0.984	1.000	0.400	0.253

Supplementary Table 3-S3: Corrected p-values (left VC/VS vs baseline)

Subject A						
ROIs	Frequency					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
dACC	0.856	0.023	1.000	0.965	1.000	1.000
dIPFC	1.000	0.991	0.908	0.991	0.028	0.017
mOFC	0.016	0.614	0.994	1.000	1.000	0.999
IOFC	1.000	1.000	1.000	0.994	0.999	0.748
vmPFC	0.004	0.023	1.000	0.863	0.215	0.961
Subject B						
ROIs	Frequency					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
dACC	1.000	0.884	0.662	0.003	1.000	0.001
Amygdala	0.473	0.438	1.000	0.092	0.999	0.001
mOFC	0.745	0.965	0.971	0.005	0.454	1.000
IOFC	0.380	0.666	1.000	0.002	0.253	1.000
vmPFC	0.855	0.997	1.000	0.001	0.029	0.575

Supplementary Table 3-S4: Corrected p-values (right VC/VS vs baseline)

Subject A						
ROIs	Frequency					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
dACC	0.983	1.000	0.529	0.216	1.000	0.988
Amygdala	1.000	1.000	0.489	0.058	0.024	0.046
mOFC	0.024	0.111	0.943	0.714	0.453	0.663
IOFC	0.355	0.987	1.000	0.003	0.001	0.009
vmPFC	0.030	1.000	0.026	0.001	0.001	0.001
Subject B						
ROIs	Frequency					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
dACC	1.000	0.921	0.984	0.422	0.877	0.903

Amygdala	1.000	1.000	1.000	0.038	0.001	0.001
mOFC	0.994	1.000	1.000	0.970	0.020	0.001
IOFC	0.981	1.000	0.994	1.000	1.000	0.003
vmPFC	1.000	1.000	0.982	1.000	0.075	0.001

Supplementary Table 3-S5: Corrected p-values (left SCC vs left VC/VS)

Subject A						
ROIs	Frequency					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
dACC	1.000	0.137	1.000	0.009	1.000	1.000
Amygdala	1.000	1.000	0.620	0.002	0.002	0.001
mOFC	0.300	1.000	0.414	0.004	0.058	0.837
IOFC	0.990	0.991	0.992	0.047	0.004	0.391
vmPFC	0.798	0.998	0.071	0.001	0.012	0.004
Subject B						
ROIs	Frequency					
	Delta	Theta	Alpha	Beta	Low Gamma	High Gamma
dACC	0.001	0.694	0.543	1.000	0.015	1.000
Amygdala	1.000	0.010	0.264	1.000	0.001	1.000
mOFC	0.003	0.725	0.768	0.549	0.024	0.491
IOFC	0.002	1.000	1.000	0.209	0.336	0.217
vmPFC	0.012	1.000	0.998	0.097	0.025	0.278

Supplementary Table 3-S6: Corrected p-values (right SCC vs right VC/VS)

Alpha power following stimulation				Theta power following stimulation			
R-SCC				R-SCC			
ROI	df	f-statistic	p-value	ROI	df	f-statistic	p-value
dACC	6	0.54381508	0.770375	dACC	4	1.288509	0.294536
Amygdala	6	1.18697813	0.341678	Amygdala	4	1.402519	0.248526
mOFC	6	4.41423266	0.002922	mOFC	4	2.071399	0.088964
IOFC	6	3.48675677	0.010604	IOFC	4	1.278878	0.29875
vmPFC	6	1.24121801	0.315743	vmPFC	4	1.763105	0.143325
R-VC/VS				R-VC/VS			
ROI	df	f-statistic	p-value	ROI	df	f-statistic	p-value
dACC	4	1.33490557	0.291522	dACC	4	2.570807	0.069391
Amygdala	4	0.2065304	0.931776	Amygdala	4	1.161635	0.357213
mOFC	4	0.43197588	0.783873	mOFC	4	1.003923	0.428749

IOFC	4	0.41683244	0.794511	IOFC	4	3.34029	0.030012
vmPFC	4	0.57318741	0.685224	vmPFC	4	0.634125	0.644018

Supplementary Table 3-S7: Results from one-way ANOVA

Results from Supplementary Table3-S7 show results from one-way ANOVA of different current steering configurations across the right SCC and VC/VS DBS leads on alpha and theta power in ROIs (performed on z-scored data) in subject A. P-values are uncorrected.

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4 Dual-target deep brain stimulation restores fronto-cingulate network activity and enhances cognitive control in psychiatric disorders

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4.1 ABSTRACT

Deficits in cognitive control, defined as the ability to adjust response or attention in the face of competing or changing demands, are linked to inflexible behaviors in neuropsychiatric diseases. To study control, we collected high-density intracranial stereo-EEG recordings across frontocingulate networks in two cohorts. Cohort 1 consisted of subjects with refractory epilepsy and cohort 2 consisted of subjects with treatment-resistant depression (TRD) undergoing a clinical trial of deep brain stimulation (DBS) for TRD. We employed a forced two-choice control task that parametrically varied the strength in the target (task-relevant) coherence and the distractor (task-irrelevant) interference of a visual stimulus. Reaction time (RT) and accuracy worsened with increasing task difficulty across subjects. Single-trial regression analyses revealed spatial encoding of behavioral dimensions (target facilitation and distractor inhibition) in theta activity across subjects in frontocingulate networks and the insula. In cohort 2, high frequency DBS significantly improved behavioral performance, demonstrated by decreased RT and improved accuracy. Enhancement in control was correlated with a significant increase in theta power in frontocingulate networks, indicating a role of theta power in alleviation of cognitive deficits in frontal networks. We additionally found subject-specific evidence of reorganization of frontocingulate networks encoding distractor interference and target coherence during stimulation, indicating that DBS improves cortical function underlying target facilitation alongside distractor inhibition in depression. Leveraging this unique behavioral paradigm with concurrent intracranial recordings and causal manipulation broadens our understanding of neural substrates of controlled decision-making and elucidates the mechanisms of therapeutic action of DBS for depression.

4.1 INTRODUCTION

Major depressive disorder (MDD) is the leading source of disability in the US and a significant source of global economic burden^{1,2}. An estimated one-third of patients with MDD develop treatment-resistant depression (TRD)³. Existing treatments such as DBS for refractory MDD have shown initial promise in smaller pilot studies^{4,5} but follow-up larger randomized controlled clinical trials have demonstrated ambiguous outcomes^{6–9}, indicating the need for revisiting the classical paradigm of DBS therapy for mental health disorders such as depression. Our understanding of the underlying dysfunctional neural circuitry remains limited and prevents therapy from being targeted towards dysfunctional communication across implicated brain circuits related to symptoms of mental disorders.

A paradigm shift in the field of neuromodulation and psychiatry in recent years has suggested moving away from clinical evaluation of symptoms solely via self-report surveys to adding naturalistic and task-based evaluation of behavior across transdiagnostic domains as defined by the NIH Research Domain Criteria (RDoC)¹⁰ framework, intended to incorporate precision psychiatry informed by neurobiology. One promising domain for study in interventional psychiatry is cognitive function and control. Depression is characterized by executive dysfunction and impairments in memory, attention, and cognitive control (i.e. the ability to selectively focus attention on a goal/target and inhibit distractions)¹¹. Deficits in cognitive control and function in MDD are responsible for inflexible behaviors such as rumination, negative automatic thoughts and ideation^{12,13}. Impairments in attention have additionally shown to be associated with worse clinical outcomes¹⁴. The inability to disengage from negative thoughts to perform

goal-directed behaviors makes emotional regulation and adapting to a changing environment more challenging for individuals suffering from depression, resulting in cognitive control as a critical behavioral domain for understanding and treating depression as well as other mental health disorders marked by cognitive deficits^{15,16}.

While cognitive dysfunction is a critical symptom of MDD contributing to disability, it is not well understood, especially in comparison to our understanding of other mood symptoms in MDD. Studies have theorized that impaired cognitive dysfunction in MDD is due to deficits in distractor inhibition or disengagement¹⁷, but an equally likely possibility is that impairments in attentional control in depression are linked to a failure to maintain focus and attention towards current goals (facilitation of target processing), especially in the presence of distractors.

While substantive progress in recent years has shed more light on neural mechanisms underlying control, there remains an inadequate understanding of neural mechanisms specific to brain areas in cortico-striatal and frontoparietal circuits underlying dysfunctional cognitive regulation and how to utilize neural responses to inform and titrate treatment to DBS. Additionally, previous studies incorporating standard attentional or conflict tasks struggle to dissociate processing of distractor inhibition from processing of target facilitation^{18,19}. Such tasks also show participant performance close to ceiling, making it challenging to measure the effects of neuromodulation therapies such as DBS on behavioral measures. Our study mitigates the existing gaps in our knowledge of control deficits in depression by implementing the parametric attentional control task²⁰ (PACT). The PACT paradigm enables the study of how task-relevant information interacts with task-irrelevant information, and measurement of modulation of

behavior during DBS in depressed subjects as this task is not subject to ceiling effects unlike binary or dichotomous tasks²¹. Further, non-invasive methods such as EEG and fMRI while informative, suffer from spatial and temporal smearing that make identification of region or network-specific biomarkers of impaired control in depression challenging. Here, we leveraged high-density intracranial recordings during the PACT behavioral paradigm to study cognitive control in two cohorts: a group of non-depressed subjects with epilepsy admitted for intracranial monitoring, and a group of subjects with treatment-resistant depression admitted for continuous behavioral and intracranial monitoring as part of a clinical trial. In the cohort of TRD subjects, we causally manipulated circuits implicated in cognitive control via delivery of high-frequency DBS in the ventral capsule/ventral striatum and the subcallosal cingulate during the task. The overall objective of this study was to identify intracranial neural correlates of target facilitation vs distractor inhibition in non-depressed subjects and depressed subjects across the frontocingulate networks, and enhance cognitive control performance with DBS in depressed subjects. Our findings show that DBS does indeed improve cognitive control in subjects with depression and identify a clear role for theta oscillations in encoding and processing of target facilitation vs distractor suppression. Additionally, we highlight subject-specific modulation of theta activity across behavioral dimensions during DBS. Together, our results demonstrate a mechanism of action for DBS and a potential biomarker for adaptive or responsive closed-loop DBS therapy for depression.

4.2 METHODS AND MATERIALS

4.1.1 Participants and Study Overview

Data for this study was collected from two cohorts. The first cohort consisted of twelve participants with medically refractory epilepsy undergoing intracranial monitoring to identify regions involved with seizure onset. Subjects underwent stereotactic implantation of temporary depth stereo-electroencephalography (sEEG) electrodes (PMT, Chanhassen, MN), where the location of electrodes was guided by clinical needs for seizure detection for epilepsy treatment. The second cohort consisted of four participants with treatment-resistant depression (two male, two female). These subjects also underwent stereotactic implantation of temporary sEEG electrodes, as well as implantation of four DBS leads (Boston Scientific Cartesia, Marlborough, MA) and 10 temporary stereo-electroencephalography (sEEG) electrodes (PMT, Chanhassen, MN) based on pre-operative scans including patient-specific tractography.

Post-implantation, patients in cohort two underwent a ten-day intracranial monitoring period for evaluation of brain networks involved in depression. Following the intracranial monitoring period, sEEG electrodes were removed and the four DBS leads were internalized and connected to two implanted pulse generators (IPG) (Boston Scientific Gevia, Marlborough, MA). Additional surgical details have been described previously²².

Participants from both cohorts provided fully informed consent according to study sponsor guidelines and all procedures were approved by the local institutional review board (IRB) at Baylor College of Medicine (H-43036) and (IRB-18112).

4.1.2 Experiment Protocol and Task Design

All participants performed the Parametric Attention Control Task (PACT)²⁰, developed previously (Fig. 4-1). Previous versions of this task have been employed in non-human primates^{23,24} and in human neuroimaging studies²⁵ to study decision-making.

Participants faced a display monitor 60 cm away (Wacom cintiq 1080p). Each trial consisted of a 300 ms fixation period with a white fixation cross, followed by a 100 ms fixation period with a grey fixation cross serving as a cue for the start of the trial. The 400 ms total duration served as the baseline window for each trial. Stimulus consisted of an array of moving dots (i.e., a random dot kinematogram), presented in one of four colors. In training blocks preceding the task, participants were taught to match two colors to a left keypress and two colors to a right keypress (with colors counterbalanced across participants). The direction of the dot motion (leftward or rightward) was task-irrelevant and could be consistent with the color response (i.e. distractor congruent trials) or it could be inconsistent with this response (i.e. distractor incongruent trials). The degree of target coherence (i.e. the percentage of dots of one or both colors) and distractor congruence (i.e. percentage of dots moving in the same direction) was parametrically varied. Distractor congruence was linearly spaced between 95% congruence and 95% incongruence, sampled randomly across trials²⁰. Additional details of the task have been previously described²⁰.

Each block of the task consisted of ninety trials, and was interleaved with blocks of 30 trials where the rules were reversed, i.e. participants were instructed to attend to and report the direction of the motion of the dots rather than the color. These blocks were included to maximize the conflict effect based on previous work²⁰. Each run of the task comprised of nine total blocks (five “attend-color” blocks and four “attend-motion” blocks).

In cohort one, participants with epilepsy performed 1-2 runs of the task depending on the current cognitive state and comfort of participants. In cohort two, participants with

TRD performed 2 runs prior to any kind of stimulation, followed by 1-2 runs with DBS ON, and 1 run post-DBS (Fig. 4-1c). The only exception was Subject B in the TRD cohort, who was unable to perform a final run of the task post-DBS, therefore only data before and during DBS was collected. Participants across both cohorts took self-timed breaks between blocks.

4.1.3 Electrode Implantation

In the epilepsy cohort, coverage and location varied on a patient-by-patient basis depending on clinical need. Regions of interest with electrode coverage were the anterior cingulate cortex (ACC), superior frontal gyrus (SFG), dorsolateral prefrontal cortex (dlPFC), Insula, medial and lateral orbitofrontal cortex (mOFC, IOFC), posterior and medial cingulate cortex (PCC, MCC) (Fig. 4-1d).

In the TRD cohort, intracranial sEEG electrodes for LFP recordings were implanted bilaterally across several cortical and subcortical targets based on previous work implicating their roles in mood, reward, as well as cognitive and affective processing²⁶⁻³⁰. Regions sampled included the dlPFC, ventromedial prefrontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC), SFG, IOFC, mOFC, superior and medial temporal gyri (STG, MTG) and the amygdala (Fig. 4-1e). Postoperative CT scans and pre-operative MRI scans were aligned using the Functional Magnetic Resonance Imaging for the Brain Software Library's (FMRIB's) Linear Image Registration Tool (FLIRT). Electrode coordinates were manually determined from the co-registered CT in BiImage Suite and placed into native MRI space. The reconstructed cortical surface, segmented cortical and subcortical structures and electrode coordinates were visualized using the Multi-Modal Visualization Tool³¹. The location of electrode contacts in gray

matter vs white matter and the labels for anatomical region of interest was verified by visual review of the MRI and CT by an expert rater (BS and GB).

4.1.4 Electrode Stimulation and Recording

All four participants with TRD in cohort two were implanted bilaterally with segmented DBS leads in the VC/VS and the SCC, capable of current steering. The DBS leads used in our study consist of eight stimulation contacts: solid ring contacts at the deepest and shallow positions, as well as three-way segmented contacts located between the ring contacts. Seven total contact configurations of interest were identified per lead, including three stacked configurations listed as follows: (1) anterior-facing contacts 2 and 5, (2) posterior-left facing contacts 4 and 7 and (3) posterior-right facing contacts 3 and 6. The remaining four configurations tested were ring configurations listed as follows: (1) solid ring contact 1 (2) solid ring contact 8 (3) combination of segmented ring contacts 2, 3 and 4, and (4) combination of segmented ring contacts 5, 6 and 7. (Fig 1a) . Tested electrode configurations varied across participants, as this configuration was determined by patient behavioral response and symptom state during clinical evaluation by a psychiatrist on days 7-8 of the inpatient stay (see Table 4-S4 for details).

In the TRD cohort, high frequency stimulation with a stimulation amplitude of 4.8 - 5 mA was delivered at the solid ring contacts, whereas for stacked or ring configurations this amplitude was split evenly among contacts to enable current steering, never exceeding 5 mA in total or at any time a charge density of 30 $\mu\text{C}/\text{cm}^2$. Stimulation was always delivered simultaneously across the bilateral SCC and VC/VS leads, respectively. The only notable exception was Subject D, where stimulation was first delivered bilaterally

only in the VC/VS, and then bilaterally across the VC/VS and SCC simultaneously for a separate run of the behavioral task.

4.1.5 Data Acquisition and Signal Processing

Electrophysiological signals from implanted sEEG electrode contacts were recorded using a 256-channel NeuroPort Acquisition System (Blackrock Microsystems, Utah) at a sampling rate of 2 kHz, with a hardware high pass filter applied at 0.3 Hz. Recordings from sEEG contacts were analyzed offline using custom scripts written in MATLAB (Mathworks Inc. Natick, MA) and Python. LFP signals were demeaned, decimated to 1 kHz and bandpass filtered between 1-250 Hz. A butterworth notch filter was applied to remove line noise at 60, 120 and 180 Hz, respectively. To mitigate the influence of volume conduction, channels were bipolar re-referenced by subtracting the activity of adjacent electrode contact pairs. Any channels with excessive noise or without a clear neural signal were removed from the analysis. Only channels located in grey matter were included for subsequent analyses.

Epochs of 4 second durations were cut from the continuous recordings with a buffer of 1 s on each side to avoid edge effects, as all time-frequency decomposition was performed after trials were cut from the continuous recordings. For each electrode, trials with amplitudes (max-min voltage from fixation onset to stimulus off) larger than three standard deviations above the mean amplitude across all trials were considered as containing artifacts or uncharacteristic deflections and excluded from analysis. The percentage of trials excluded by this criterion was ~2-3% across all subjects. The multitaper spectral estimation method was used to extract power spectral density (PSD) from the sEEG recording using the *mspectrumc.m* function from the Chronux toolbox³². Spectral power was then averaged within standard frequency bands (delta = 1-4 Hz,

theta = 4-8 Hz, alpha = 8-12 Hz, beta = 12-30 Hz, low-gamma = 30-55 Hz, high-gamma = 65-100 Hz). For this chapter, only theta band power is reported. Spectral parameters used for theta band are as follows: time-bandwidth product = 2, taper = 3, moving window = 500 ms.

4.2.1.1 Artifact Removal During Stimulation

To remove artifact during stimulation, we modified our preprocessing pipeline when the task was performed with stimulation ON. The LFP signal was first bandpass filtered between 1-50 Hz to prevent high-frequency harmonics contaminating lower frequencies of interest. The signal was then demeaned, re-referenced using bipolar referencing and decimated to 1 KHz. This preprocessing pipeline allowed us to analyze the data in frequencies between 1-40 Hz without signal artifact contamination. In order to analyze data in higher frequency bands previously established artifact removal techniques^{33,34} were tested with some success, but have been excluded as they are beyond the scope of this chapter with primary frequencies of interest for the TRD cohort ranging from 1-30 Hz.

4.1.6 Behavior Data Analysis

The two primary behavioral readouts are accuracy and reaction time (RT). We first analyzed the effect of distractor congruence and target coherence on our behavioral readouts in epilepsy participants to confirm that behavior was parametrically modulated as expected. We performing a robust linear regression using the *fitlm.m* function from the Statistics Toolbox for data pooled across participants:

RT ~ DistCong + TargCoh

Accuracy ~ DistCong + TargCoh

The formula for computing effect size is shown below:

$$d = 2T / \sqrt{df}$$

Where df indicates degrees of freedom and T is the t-statistic obtained from automatically generated outputs from the `fitlm.m` function. Trials with a reaction time less than 200 ms, missing responses or incorrect responses were excluded from the linear regression analyses performed for RT. Trials with missing responses or a reaction time less than 200 ms were excluded from linear regression analyses performed for Accuracy.

We repeated this analyses on behavioral data collected from the cohort of TRD subjects during baseline (DBS OFF) and during stimulation (DBS ON), respectively. To evaluate the effects of stimulation on behavioral data, we first performed a paired t-test to compare the differences between average RT and accuracy during baseline and stimulation.

4.1.7 Neural Data Analysis – iEEG modulation by task variables and DBS

4.2.1.2 Time-averaged regression

Time-frequency data was first normalized by dividing each trial by the average of the preceding fixation period (400 ms duration) for each frequency band and a dB transform was used. The same pre-stimulus baseline period was used for stimulus-locked and response-locked analyses. For stimulus-locked analysis, the window of interest started at the end of baseline and ended 1 second into the trial (0.4 s to 1.4 s). For response-locked analysis, the average reaction time was first computed for each subject. The start of the response-locked window was 500 ms prior to the average reaction time, and 700 ms following the average reaction time (1.1 s duration).

To evaluate whether there was a parametric effect of distractor congruence and target coherence on neural data we performed single trial time-averaged regression on stimulus-locked and response-locked data, respectively. Spectral power for a given frequency band was averaged during the stimulus-locked and response-locked windows and robust linear regression was performed using the *fitlm.m* function:

$$\text{StimlockedPower} \sim \text{DistCong} + \text{TargetCoh} + \text{RT}$$
$$\text{ResplockedPower} \sim \text{DistCong} + \text{TargetCoh} + \text{RT}$$

Single-trial time-averaged regression analysis was repeated in the same manner for the TRD cohort during baseline and stimulation states separately (Supplementary Tables 5-1,5-2,5-3).

4.2.1.3 PCA

Due to the heterogeneity in electrode coverage in epilepsy subjects and variability in behavioral performance across individuals, we sought to identify channels responsive to task parameters by using weighted averages of channels across participants. We first averaged spectral power in a given frequency band across trials for each electrode contact within an ROI, resulting in 11 data points for distractor congruence and 11 data points for target coherence for each channel. We then pooled across all channels for a given ROI across all patients and performed principal component analysis, which provided principal component coefficients and loadings (weights). A weighted average or “normalized” data³⁵ for each ROI was computed by using the loadings from PCA and multiplying this value with the raw data before computing the mean for each condition for a given ROI.

4.2.1.4 Comparison of spectral power during stimulation ON and OFF states

To evaluate whether spectral power in a given frequency band mediated the improvement in cognitive control, we sought to analyze the overall average spectral power during the stimulation OFF and stimulation ON states. We computed the average spectral power for theta and alpha frequency bands across the duration of the entire recording for the TRD cohort during the stimulation OFF state when they first performed the task. Following stimulation artifact removal, we computed the mean theta and alpha power for each ROI during the stimulation ON state when subjects performed the task again. We then used an unpaired t-test to compute statistical differences for each ROI between DBS ON and DBS OFF states.

4.3 RESULTS

In order to measure cognitive control performance, namely target facilitation and distractor inhibition, we employed the parametric attentional control task (PACT). We first validated this task in an inpatient hospital setting, i.e. the epilepsy monitoring unit (EMU) in patients with refractory epilepsy. We then implemented this task in a separate cohort of subjects with TRD undergoing a clinical trial of DBS for TRD. Here, we report our findings on the effect of task variables on theta signals, and modulation of behavior and underlying theta signals with stimulation.

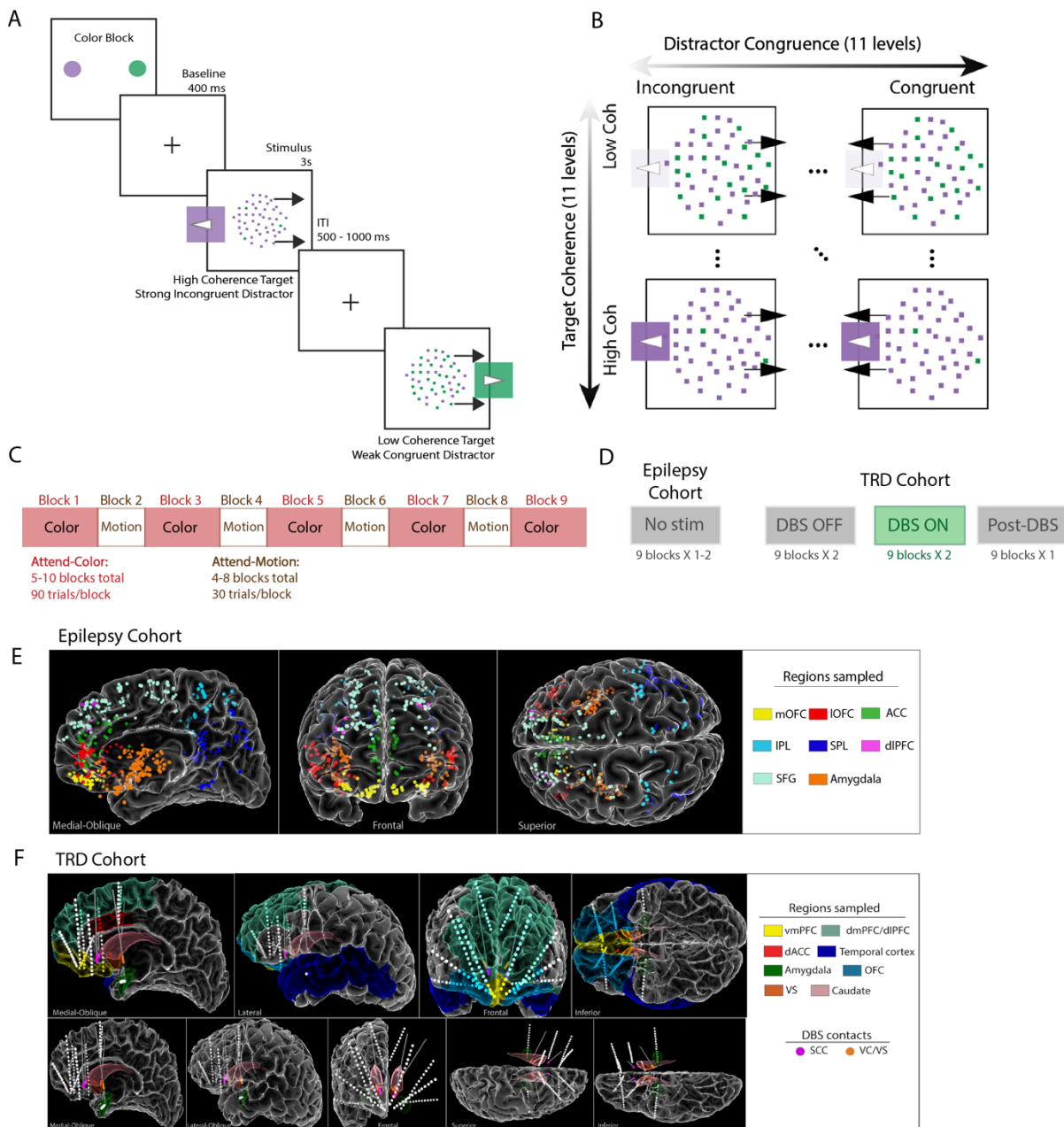


Figure 4-1: Experimental approach and behavioral task

(A) Behavioral task paradigm with example trial structure. (B) Parametric modulation of target coherence and distractor congruence in task. Both task variables have a range of 11 levels to manipulate task difficulty. (C) Block structure for each run of the task. Each run is comprised of 5 blocks with the rule is to attend to the color of the stimuli, and 4 blocks where the rule is to attend to the motion of the stimuli (9 total blocks). (D) Structure of blocks for the epilepsy and TRD cohorts. In the TRD cohort participants perform 1-2 runs of the task with DBS OFF, 1-2 runs with DBS ON, and 1 run post-DBS. (E) Electrode coverage across subjects in the epilepsy cohort (electrode locations are consolidated across subjects) (F) Electrode coverage of subjects in the TRD cohort, including bilateral DBS leads to deliver electrical stimulation.

4.1.8 Behavioral task performance varies linearly with target coherence and distractor congruence in non-depressed subjects

Two cohorts of subjects undergoing high-density intracranial monitoring in an in-patient setting performed this task. Cohort 1 consisted of 11 subjects with refractory epilepsy admitted for seizure monitoring, and cohort 2 consisted of 4 subjects with TRD undergoing a clinical trial of DBS for TRD. We recorded sEEG signals in cohort 1 while they performed PACT with no stimulation. We analyzed the reaction time (RT) and accuracy as the primary readouts of task behavioral performance and found an average reaction time of $996 \text{ ms} \pm 16 \text{ ms}$ (z-score -0.1 ± 0.01) and average accuracy rates of $81\% \pm 0.4\%$ (z-score 0.07 ± 0.0092). Through linear regression models we found that RT and accuracy linearly varied with changing target coherence, i.e. RTs were faster and accuracy was higher with increasing coherence or decreased task difficulty. (cohen's $d_{\text{RT}} = -5.7$, cohen's $d_{\text{Acc}} = 3.6$; Fig. 4-2a). Accuracy also linearly varied with distractor congruence, i.e. higher accuracy was correlated with decreasing interference or task difficulty, and there was a smaller effect of distractor congruence on RT (cohen's $d_{\text{RT}} = 1.31$, cohen's $d_{\text{Acc}} = 11.4$; Fig. 4-2b).

Epilepsy Cohort

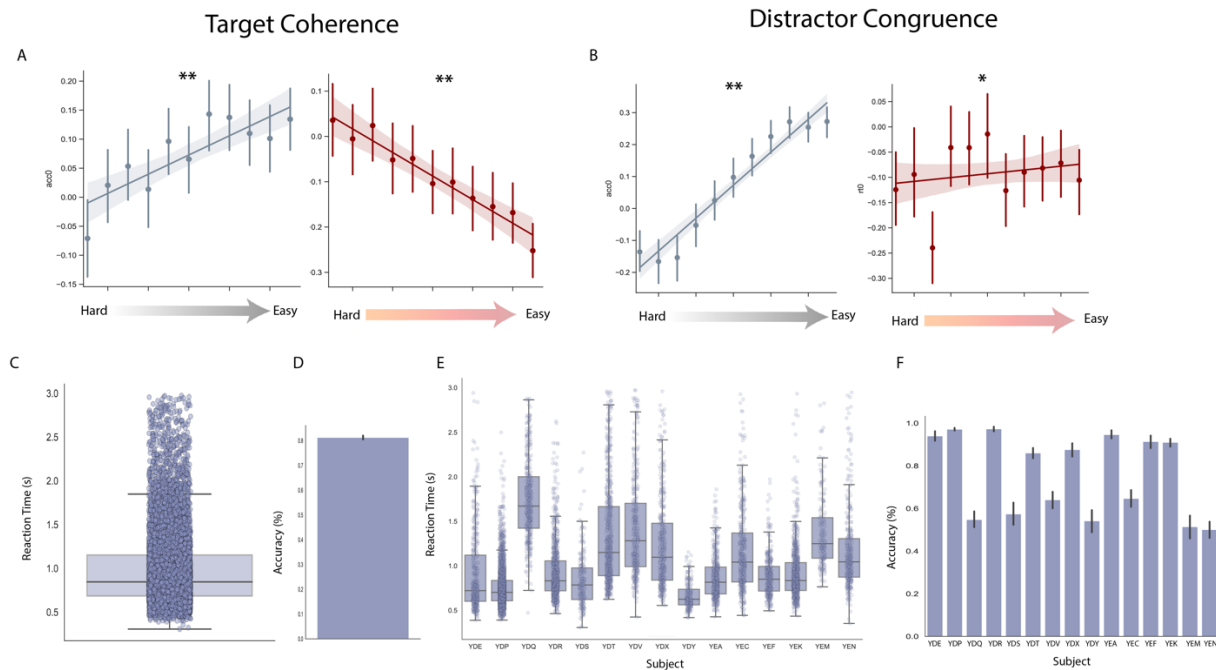


Figure 4-2: Behavioral performance in cohort 1.

(A) Accuracy (left, grey) and RT (right, red) with varying target coherence. (B) Accuracy and RT with varying distractor congruence. (C) Average reaction times across all subjects. Each data point represents an individual trial in each subject. (D) Average accuracy across subjects. (E) Reaction times for each subject in the cohort. (F) Average accuracy for each subject in the cohort. Error bars represent 95% CI; * indicates $p < 0.05$ ** ; indicates $p < 0.01$

4.1.9 Modulation of theta activity during different task demands

We next sought to identify neural substrates of parametric control in our first cohort.

Specifically, we were interested in whether there was differential encoding of target

facilitation vs distractor suppression across non-depressed subjects, and identifying

regions where theta modulation of either task variable would be observable. We

focused our analysis on recordings obtained from the ACC, PFC, OFC, Insula and

Parietal cortex based on previous findings (Fig. 4-1e-f illustrates coverage across both

cohorts) in cohort 1. As the location of electrode implant was determined by clinical

need, there was heterogeneity of electrode coverage across subjects.

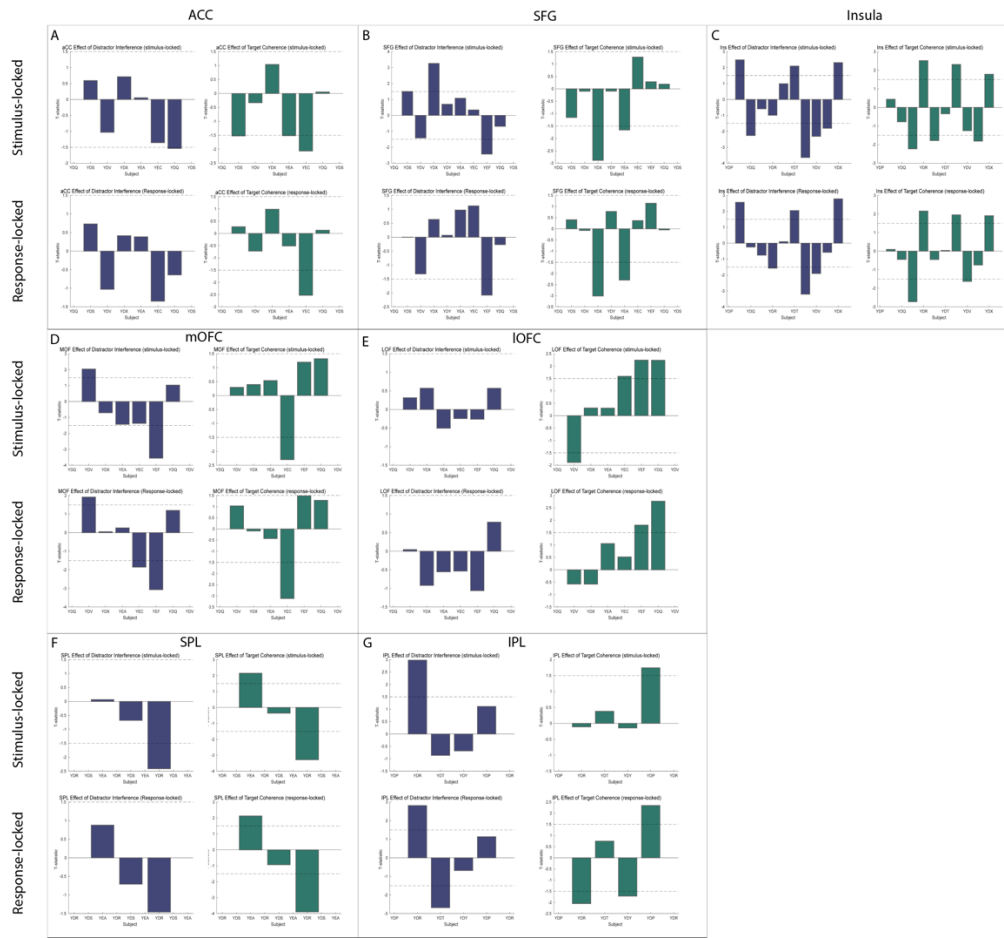


Figure 4-3: Results of single-trial regression of theta power.

(A) T-statistic values obtained from single-trial linear regressions of stimulus-locked (top) and response-locked (bottom), time-averaged theta power against distractor interference (blue) and target coherence (green) for recordings obtained from ACC. Dotted line indicates approaching significance or statistically significant. Replicate of panels for different ROIs are shown in (B) for SFG (C) for Insula (D) mOFC (E) IOFC (F) SPL and (G) IPL.

We centered our findings on theta power (4-7) which has been reliably modulated in response to conflict and decision-making paradigms in both non-invasive EEG and intracranial EEG recordings^{21,36–38}. We analyzed theta power in both stimulus-locked (0-1100 ms) and response-locked (-500 ms to 700 ms post-response time; total duration of 1.4 s) windows using a linear regression model, and both windows were normalized to the same pre-trial baseline window of 400 ms. Regressions of theta power against target coherence and distractor congruence revealed subject-specific modulations of theta power with changing behavioral parameters in the ACC, Insula, OFC, SPL and

IPL. Figure 4-3 shows the resulting t-statistic obtained from linear regressions across contacts. We hypothesized that theta power would increase with increasing conflict (or distractor interference across the ACC, and SFG, given prior work showing theta modulation during conflict tasks^{37,39}). We found that this predicted effect was observed in 2/5 patients with ACC recordings in the stimulus-locked window (Fig. 4-3a, left; Negative t-statistic values indicate increased theta value with increasing conflict and positive t-statistic values indicate decreased theta power with decreasing conflict), and 1/8 patients with SFG recordings (Fig. 4-3b) in either stimulus-locked or response-locked windows. Similarly, we predicted that theta power would increase with increasing target incoherence in the ACC and SFG, and observed that 3/5 subjects with ACC recordings and 2/8 subjects with SFG recordings demonstrated the hypothesized effect. The remaining subjects largely showed no modulation in theta power with respect to target coherence or distractor incongruence.

We next sought to evaluate if theta power across the OFC (Fig. 4-3d-e) or insula (Fig. 4-3c) indicated a common direction of theta modulation across target or distractor dimensions. In the insula, we observed increasing theta power with increasing task difficulty in 4/10 subjects and 3/10 subjects demonstrating the opposing effect (decreasing theta with decreasing task difficulty) in stimulus-locked windows. A similar phenomenon was observed with respect to theta power and target coherence. In the medial and lateral OFC, 1/6 subjects showed increasing theta with increasing distractor interference in stimulus-locked windows. Interestingly, in the IOFC, 3/6 subjects showed the inverse effect (decreasing theta power with decreasing target coherence).

In the SPL (Fig. 4-3g), we found evidence of theta increasing with task difficulty (target coherence or distractor interference) in 1/3 subjects. In the IPL (Fig. 4-3h), we observed the opposite phenomenon of theta decreasing with decreasing task difficulty in 1/4 subjects, and the subject-level differences did not overlap (as the same subjects did not have both superior or inferior parietal lobe electrode contacts).

While we observed the predicted effects in a handful of subjects, the variability in observed effects of theta power indicated that several factors may be diminishing an existing signal. Since electrode location is determined based on clinical need rather than research, the distribution of electrode contacts varies from subject to subject. Additionally, there is substantial variability in behavioral performance across participants as well, which may be reflected in the neural data. For example, a subset of participants are unable to maintain the rules of the task and ignore the motion of the dots (i.e. distractor feature) when performing the task. In order to identify neural substrates commonly represented across subjects, we next performed principle component analysis (PCA), with the goal of amplifying task-related signals in conflict-responsive channels and “de-noising” the data.

4.1.10 Modulation of “normalized” theta signals in selective attention processing

To amplify signal and reduce variability in activity across subjects, we performed PCA (see methods for details). In the Insula, the first component appears to represent stimulus-related changes in theta power (i.e. decrease of theta power during visual perception of stimulus followed by an increase around the time of response; Fig. 4-4a-b). Data was normalized to each principle component respectively and the time-averaged regression analyses repeated. The third and fourth principle components (PC) represent evidence of condition-specific responses. Activity normalized to the third PC

highlight a small effect (cohen's $d = 0.2$) of target coherence, where high incoherence or high task difficulty results in higher theta power. Given the small effect size, it is likely that there is a non-linear effect of target coherence on theta power. Activity normalized to the fourth PC component show an opposing effect where theta power is higher with higher target coherence or task ease.

With respect to distractor congruence (Fig. 4-4c-d), small effects are observed when data is normalized to the second and third PCs, where theta power is observed to increase with increased conflict, and again, the small effect sizes indicate that modulation of theta power may be non-linear. The spatial distribution of channels contributing to weights or loadings for each PC varies between target coherence and distractor congruence (Fig. 4-4e), indicating that there may be differences in which channels show an effect of target facilitation vs distractor interference.

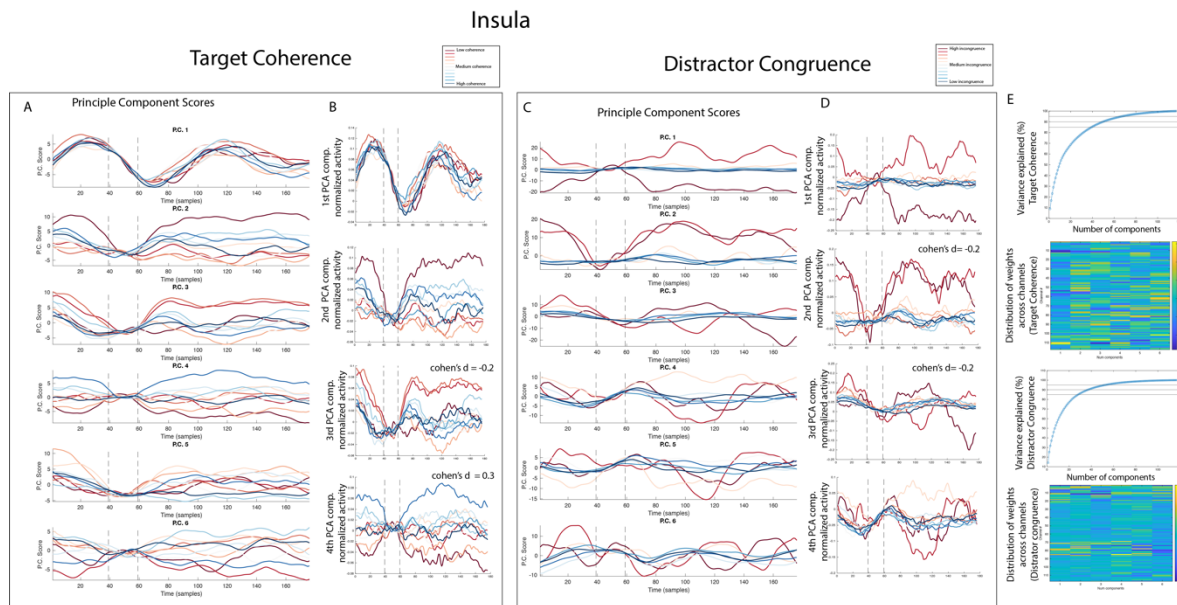


Figure 4-4: Results of PCA of theta activity in Insula recordings across subjects.

(A) Top six principle component scores of trial-averaged data with labels for target coherence, consolidated across channels and patients. (B) Weighted averaged or “normalized” activity for 1-4 PCs in the Insula across time. Red indicates low target coherence (hard trials) and blue indicates high target coherence (easy trials) (C) Top six principle component scores of trial-averaged data with labels for distractor congruence, consolidated across channels and patients. (B) Weighted averaged or

“normalized” activity for 1-4 PCs in the Insula across time. Red indicates low distractor congruence (hard trials) and blue indicates high distractor congruence (easy trials) (E) Percentage of variance explained by number of principle components (first and third row) and distribution of weights across channels for target coherence (second row) and distractor congruence (fourth row; bottom)

In the IPL, while we observe a clear effect of stimulus evoked changes in theta power (Fig. 4-5a-b), no PCs showed modulation of theta power with target or distractor conditions. In the SPL, we again see an effect of the stimulus-evoked changes in theta across time and across conditions in the first PC. There is evidence of theta modulation with target coherence in the second PC, and in the data normalized to the second PC (Fig. 4-6a-b), we observe a small effect (cohen's $d = 0.2$) in theta power with target coherence. However, no effect of distractor congruence is observable in the SPL (Fig. 4-6c-d).

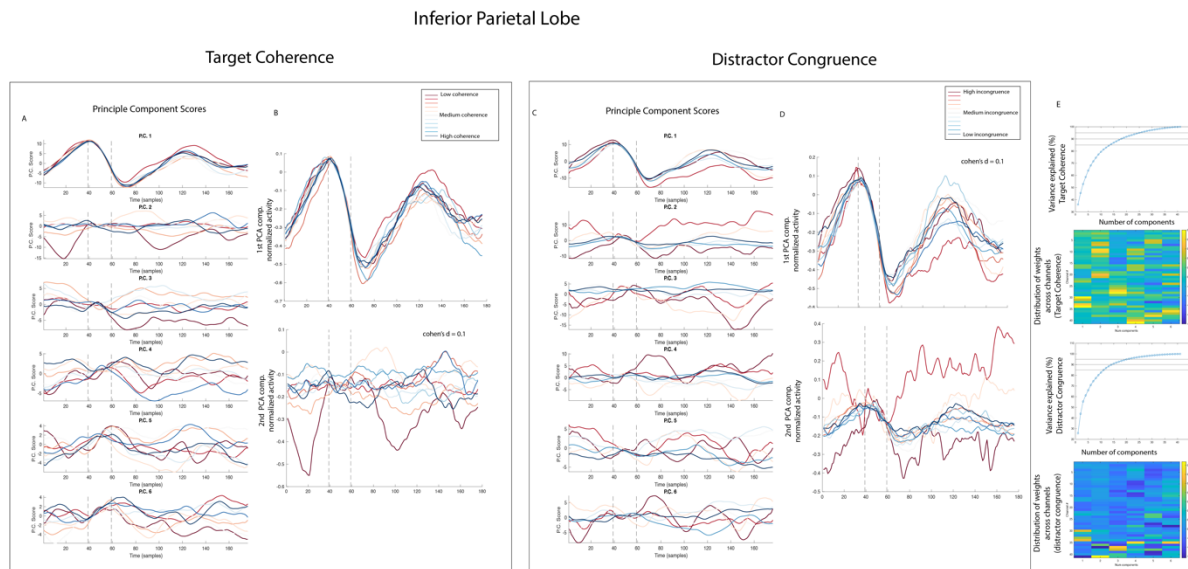


Figure 4-5: Results of PCA of theta activity in Inferior Parietal Lobe (IPL) across subjects.

(A) Top six principle component scores of trial-averaged data with labels for target coherence, consolidated across channels and patients. (B) Weighted averaged or “normalized” activity for 1-4 PCs in the IPL across time. Red indicates low target coherence (hard trials) and blue indicates high target coherence (easy trials) (C) Top six principle component scores of trial-averaged data with labels for distractor congruence, consolidated across channels and patients. (B) Weighted averaged or “normalized” activity for 1-4 PCs in the IPL across time. Red indicates low distractor congruence (hard trials) and blue indicates high distractor congruence (easy trials) (E) Percentage of variance explained by number of principle components (first and third row) and distribution of weights across channels for target coherence (second row) and distractor congruence (fourth row; bottom)

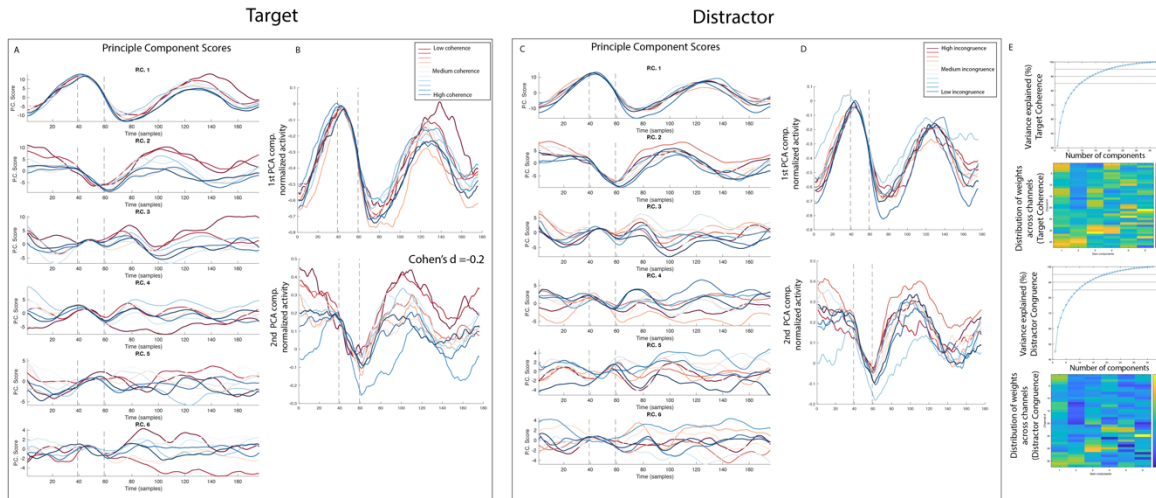


Figure 4-6 - Results of PCA of theta activity in Superior Parietal Lobe (SPL) recordings across subjects.

(A) Top six principle component scores of trial-averaged data with labels for target coherence, consolidated across channels and patients. (B) Weighted averaged or “normalized” activity for 1-4 PCs in the SPL across time. Red indicates low target coherence (hard trials) and blue indicates high target coherence (easy trials) (C) Top six principle component scores of trial-averaged data with labels for distractor congruence, consolidated across channels and patients. (B) Weighted averaged or “normalized” activity for 1-4 PCs in the SPL across time. Red indicates low distractor congruence (hard trials) and blue indicates high distractor congruence (easy trials) (E) Percentage of variance explained by number of principle components (first and third row) and distribution of weights across channels for target coherence (second row) and distractor congruence (fourth row; bottom)

In the mOFC (Fig. 4-7), we observed stimulus and response evoked changes across all conditions in the first and second principle components (Fig. 4-7a-b), and a small effect of increasing theta power with increasing target incoherence in the third PC and in the data normalized to the third PC (cohen's $d = -0.2$). Modulation of theta power with changing distractor congruence is negligible in the mOFC (Fig. 4-7c-d), and a stimulus-evoked changes in power are observed in the third PC. In the IOFC, we also observe stimulus and response evoked changes across all conditions in the first, second and third principle components (target coherence; Fig. 4-8a-b) and the second principle component (distractor congruence; Fig. 4-8c-d). Effects of theta modulation with task difficulty are negligible across both behavioral variables (target/distractor). As observed in the parietal lobe and the insula, there is little overlap in the channels contributing to

the weights of each principle component between the target coherence and distractor congruence conditions (Fig. 4-8e).

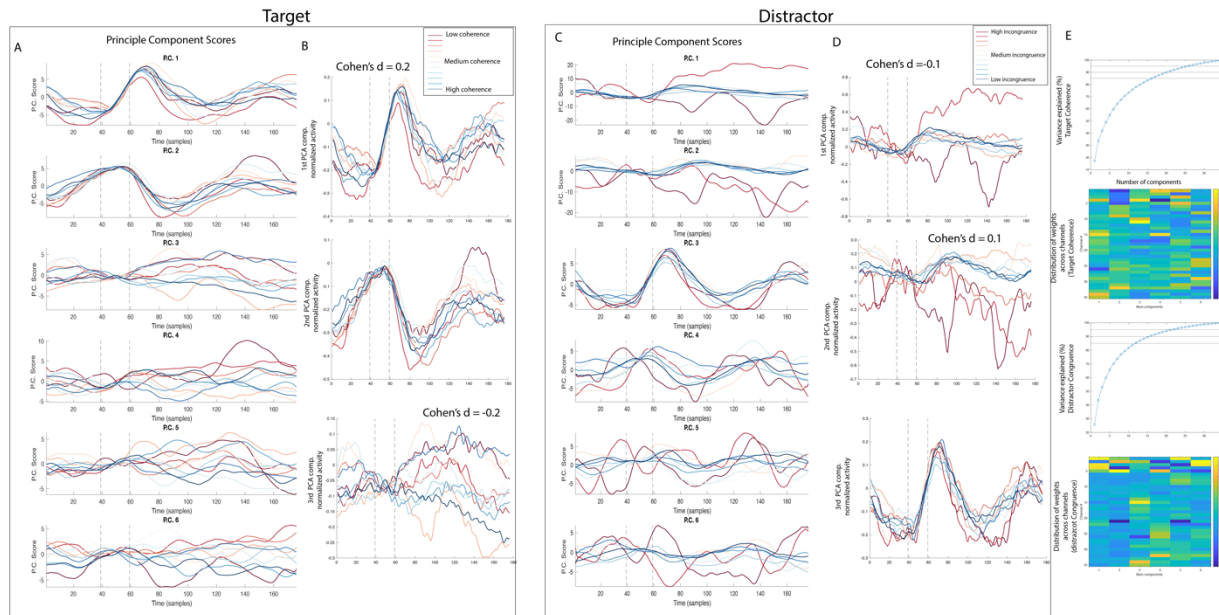


Figure 4-7: Results of PCA of theta activity in mOFC recordings across subjects.

(A) Top six principle component scores of trial-averaged data with labels for target coherence, consolidated across channels and patients. (B) Weighted averaged or “normalized” activity for 1-4 PCs in the mOFC across time. Red indicates low target coherence (hard trials) and blue indicates high target coherence (easy trials) (C) Top six principle component scores of trial-averaged data with labels for distractor congruence, consolidated across channels and patients. (B) Weighted averaged or “normalized” activity for 1-4 PCs in the mOFC across time. Red indicates low distractor congruence (hard trials) and blue indicates high distractor congruence (easy trials) (E) Percentage of variance explained by number of principle components (first and third row) and distribution of weights across channels for target coherence (second row) and distractor congruence (fourth row; bottom)

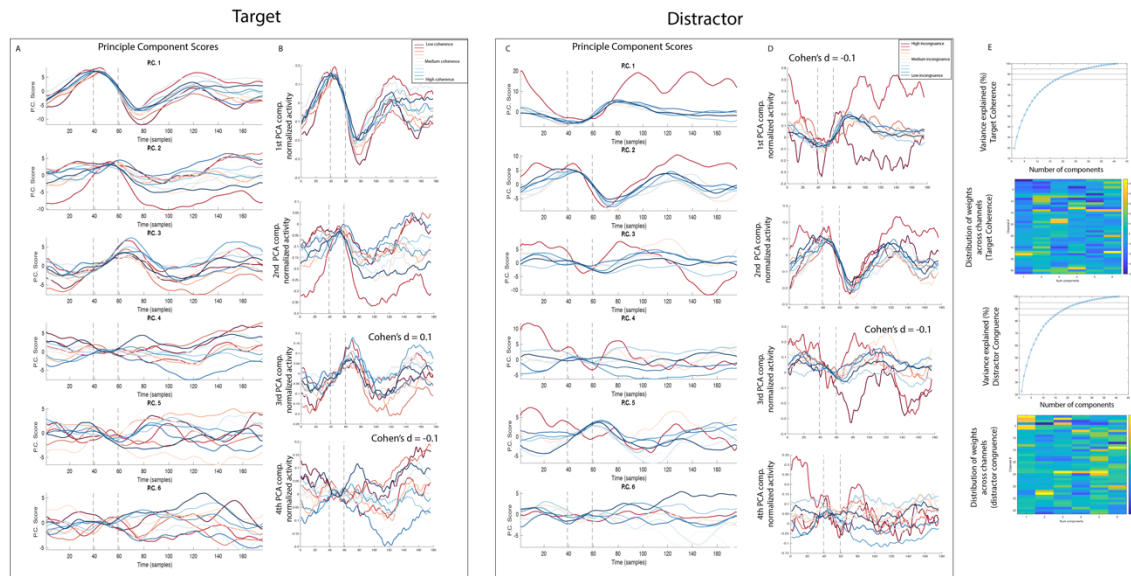


Figure 4-8: Results of PCA of theta activity in IOFC recordings across subjects.

(A) Top six principle component scores of trial-averaged data with labels for target coherence, consolidated across channels and patients. (B) Weighted averaged or “normalized” activity for 1-4 PCs in the IOFC across time. Red indicates low target coherence (hard trials) and blue indicates high target coherence (easy trials) (C) Top six principle component scores of trial-averaged data with labels for distractor congruence, consolidated across channels and patients. (B) Weighted averaged or “normalized” activity for 1-4 PCs in the IOFC across time. Red indicates low distractor congruence (hard trials) and blue indicates high distractor congruence (easy trials) (E) Percentage of variance explained by number of principle components (first and third row) and distribution of weights across channels for target coherence (second row) and distractor congruence (fourth row; bottom)

To summarize, in these analyses we normalized data for each ROI across subjects using principle components indicating evidence of separation between task conditions. The goal was to identify which components showcased linear modulation of theta with behavioral conditions with respect to target or distractor features, effectively “de-noise” the data and identify channels or subjects contributing to linear responses in theta-band with task difficulty. Time-averaged regression analyses indicate largely negligible effects, with some evidence of theta modulation in the OFC, although the effects are very small. This can be due to insufficient data, especially from patients that are able to perform the task and have intracranial coverage of contacts that show conflict-sensitive responses. Another potential reason could be due to the method of regression modeling. The application of linear regression models was informed by previous

analyses on similar task data collected in non-human primates^{23,24}, and it is possible that there is non-linear modulation of theta with task difficulty across regions. Third, we average theta power in stimulus-locked and response-locked windows, which does not consider within-trial dynamics of theta activity. For example, harder trials may result in increase in theta power over a slower course of time relative to an easier trial, and time-averaged responses in our pre-defined windows may not capture these dynamics. Lastly, while only contacts in grey matter within each ROI were included for analysis, previous work has demonstrated responses related to higher cognitive functions can vary along an anatomical gradient^{40–42}, and averaging all channels across an entire ROI in an agnostic manner may equalize these variations. Ongoing analyses and future work will address these limitations to elucidate neural mechanisms of theta oscillations more clearly in this cohort of patients.

4.1.11 Dual-target high-frequency DBS augments cognitive control

Cohort two consisted of four subjects with TRD, that were implanted bilaterally with DBS leads in the ventral capsule/ventral striatum (VC/VS) and the subcallosal cingulate (SCC). We recorded sEEG signals in cohort 2 while they performed PACT with stimulation ON or OFF (Fig. 4-1d). Similar to cohort 1, we analyzed RT and accuracy as the primary behavioral measures (Fig. 4-9). The binary or dichotomous nature of cognitive tasks typically implemented to measure control in an experimental setting make it challenging to measure effects of a therapy such as DBS in a short time-duration. Therefore, we first wanted to validate that behavioral response in our patients could be parametrically modulated by task difficulty on a subject level. During stimulation OFF, RT linearly decreased with increasing target coherence (cohen's $d = -5.4$). Accuracy linearly increased with increasing target coherence (cohen's $d = 2.9$)

increasing distractor congruence (cohen's $d = 2.4$). A relatively small linear decrease as a function of distractor congruence was observed with RT (cohen's $d = -1.2$). During stimulation ON, the effect of target coherence on RT was similar (cohen's $d = -4.7$) as RTs decreased with increasing ease of task/target coherence. The effect of target coherence on accuracy during stimulation ON also followed the same trend as observed during stimulation OFF (cohen's $d = 2.9$). During stimulation ON, there was still a large effect of distractor congruence on accuracy (cohen's $d = 4.1$) and a smaller effect on RT (cohen's $d = -0.98$). These findings suggest that target facilitation and distractor inhibition can be reliably measured through accuracy and reaction time in subjects with depression.

We hypothesized that participants in cohort 2 would overall be slower and less accurate than non-depressed subjects in cohort 1, as a symptom manifestation of cognitive control deficits, and that these impairments would be improved by high frequency stimulation. As expected, participants were faster and more accurate when performing the task with stimulation ON. High frequency DBS reduced the overall average RT when stimulation was OFF from 1081 ± 8.2130 ms (z-score -0.018 ± 0.0082) to 914 ± 7.0648 ms (z-score -0.055 ± 0.007) when stimulation was ON. Overall accuracy was significantly improved from $80 \pm 0.69\%$ (z-score 0.082 ± 0.016) during stimulation OFF to $88.74 \pm 0.56\%$ (z-score 0.013 ± 0.018) during stimulation ON ($p < 0.01$) and was comparable to behavioral performance of non-depressed cohort (cohort 1).

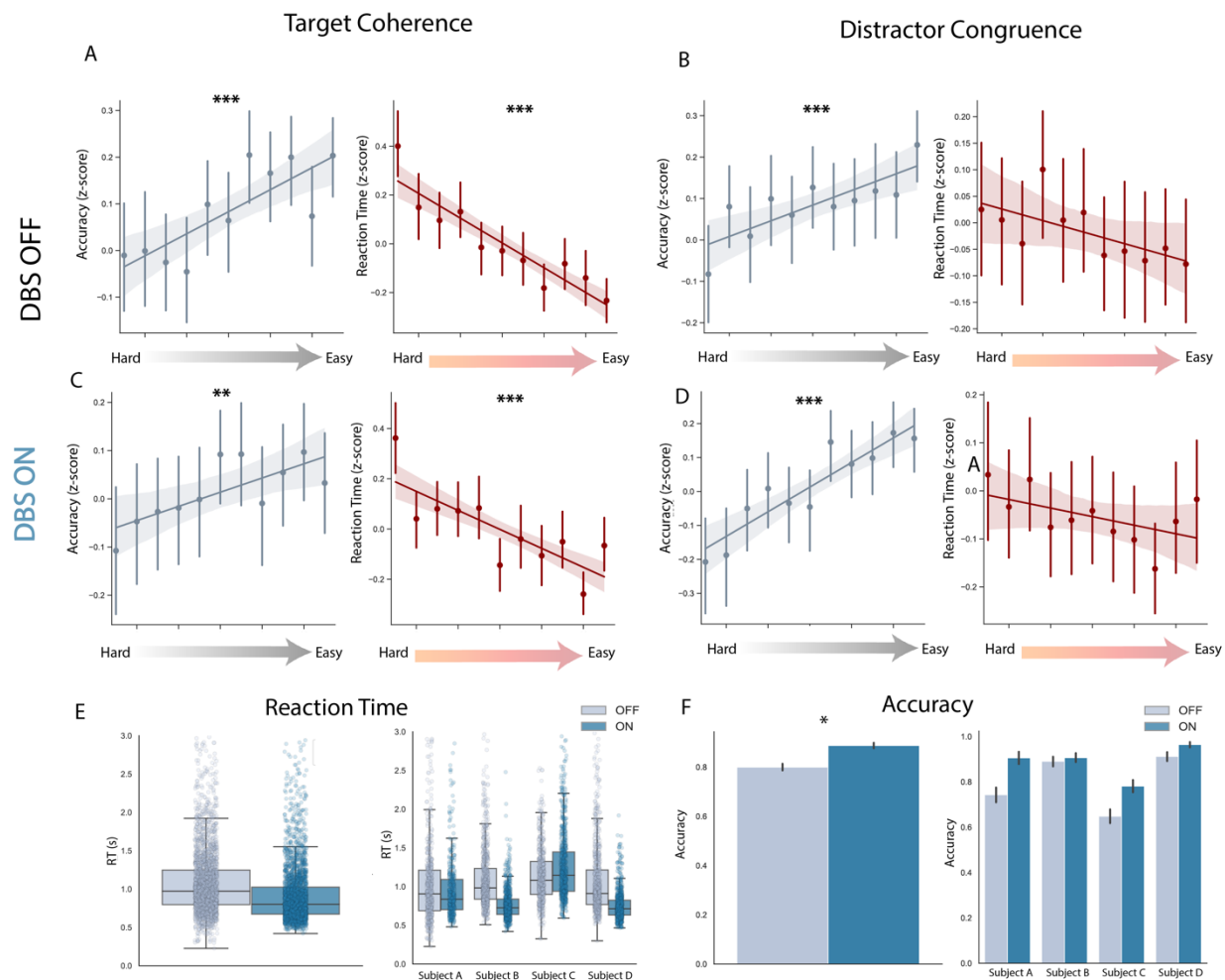


Figure 4-9: Behavioral task performance in cohort of TRD subjects with DBS.

(A) Linear regression of accuracy (grey, left) and RT (red, right) against target coherence and (B) Distractor Congruence with DBS OFF. (C-D) Linear regression of accuracy and RT against target coherence (C) and distractor congruence (D) with DBS ON. There was a significant effect of task conditions (target and distractor) on behavioral performance during stimulation OFF and ON states. (E) Average reaction times across all subjects (left) and for each individual subjects (right) with DBS OFF and DBS ON. DBS reduced RT across patients overall. (F) Average accuracy across all subjects (left) and for individual subjects (right) with DBS OFF and DBS ON. DBS significantly improved accuracy across subjects overall.

4.1.12 Theta oscillations mediate enhancement of cognitive control in depression

After validating that we could parametrically *measure* behavioral response and significantly *improve* behavioral response via stimulation, we next sought to understand neural mechanisms mediating improved behavioral performance. Previous work has implicated theta activity in cognitive processes not only in healthy subjects, but also in

patients with psychiatric disorders and dysfunctional circuitry^{43,44}, specifically indicating elevated frontal theta (as measured via EEG)^{45,46} in mitigating improved cognitive control. We first aimed to replicate these findings, specifically whether theta power is increased during stimulation ON, relative stimulation OFF during the task. Additionally, since EEG suffers from spatial smearing, we wanted to identify specific regions where this phenomenon of increased theta power could be observed across subjects. We hypothesized that we would observe elevated theta power in frontocingulate networks, specifically across the dlPFC, vmPFC and the ACC, given their role in cognitive control and decision-making^{28,47–50}, and potentially in the OFC^{51,52}, because of its role in task representation⁵³.

We analyzed averaged theta power during stimulus-locked epochs with stimulation OFF and ON respectively (theta power was normalized to baseline, see Methods for more details). In subject A, we observed a significant increase in theta power during stimulation ON across the dlPFC, mOFC, SFG, MTG and vmPFC (Fig. 4-10 a-c). In subject B, we observed a significant increase in theta power during stimulation ON across almost all prefrontal and temporal ROIs, including the dlPFC, IOFC, mOFC, dACC and SFG (Fig. 4-10 d-f). However, in subject D, we observed a shift in the opposite direction with stimulation ON. Stimulation decreased theta power across all ROIs, with significant decreases observed in the MFG, MTG, IOFC, ACC and vmPFC (Fig 4-10g-i).

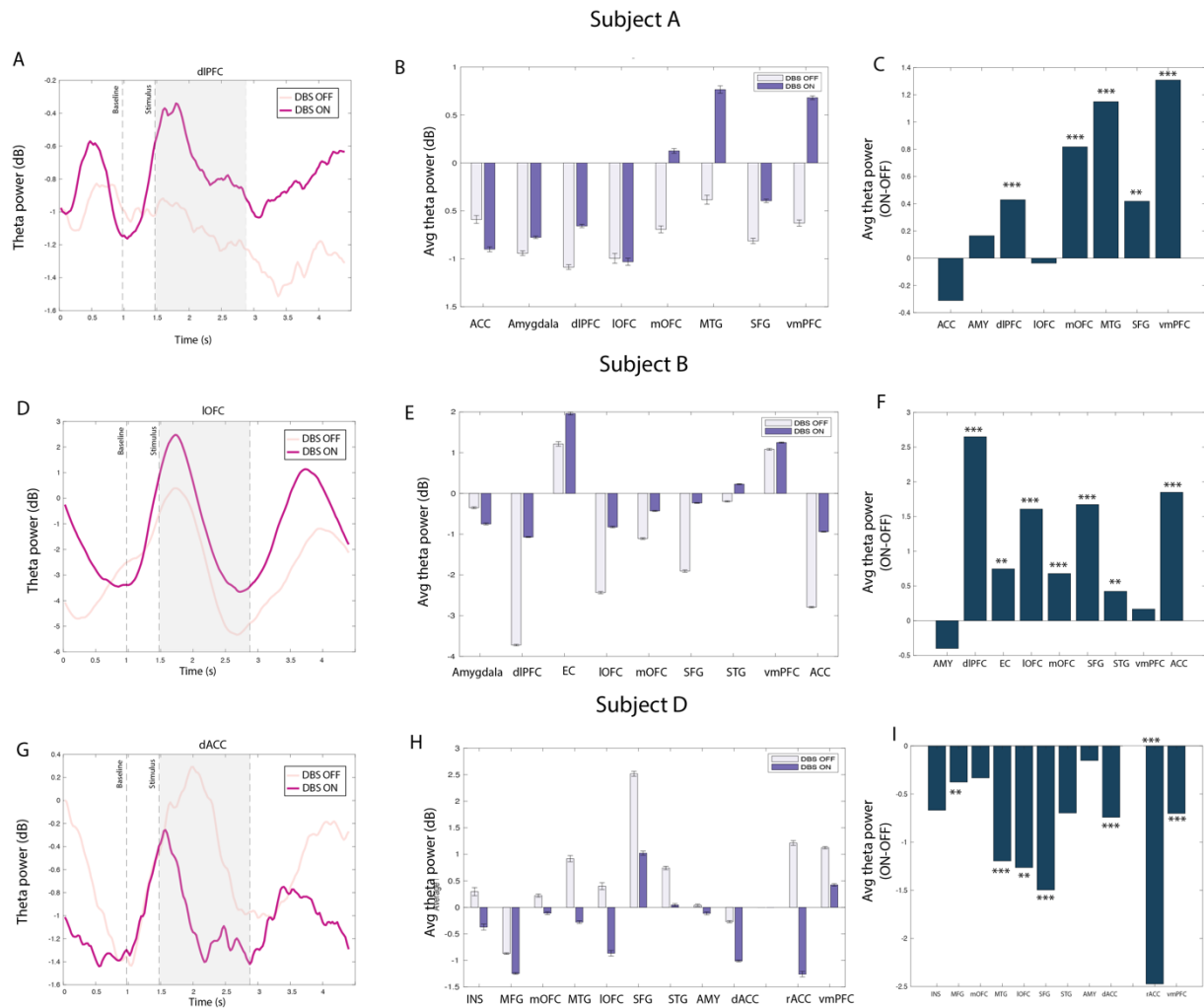


Figure 4-10: DBS modulates overall theta oscillations in subjects.

(A) Trial-averaged theta power across time during DBS OFF and DBS ON in the dlPFC in subject A. Gray shading indicates stimulus-locked window of time used for averaging of theta power. (B) Average theta power across all ROIs in subject A during DBS OFF and ON. (C) Difference in average theta power between DBS OFF and DBS ON. DBS increases theta oscillations across all prefrontal regions except IOFC and ACC. (D) Average theta power across time during DBS OFF and ON in IOFC in subject B. (E) Average theta power across all ROIs in subject B during DBS OFF and ON. (F) Difference in average stimulus-locked theta power between DBS OFF and ON. DBS increases theta power across all frontal ROIs except for vmPFC. (G) Trial-averaged theta-power across time during DBS OFF and DBS on in the dACC in subject D. (H) Average theta power across all ROIs in subject D during DBS OFF and ON. (I) Difference in average stimulus-locked theta power between DBS OFF and ON.

4.1.13 Reorganization of frontocingulate networks during distractor and target processing with DBS

Previous studies have indicated distinct mechanisms for target and distractor encoding during exertion of cognitive control. Because we leveraged a paradigm that is sensitive to continuous variation of targets and distractors that is behaviorally observable, we

were interested in identifying neural mechanisms of selective attention strategies – namely target facilitation and distractor inhibition.

In subject A with stimulation OFF (Fig. 4-11b), we observed an effect of distractor congruence on theta power, where theta signals increased with increasing task conflict, in the dACC (cohen's $d = -0.6$), dlPFC (cohen's $d = -0.4$), IOFC (cohen's $d = -0.6$), mOFC (cohen's $d = -0.7$) and vmPFC (cohen's $d = -1.2$). Modulation of theta in the opposing direction was only seen in the SFG (cohen's $d = 0.6$). With stimulation ON, we observed small effects of distractor congruence, and a reversal in the direction of theta modulation in the dACC (cohen's $d = 0.3$) and SFG (cohen's $d = 0.3$). A smaller effect of distractor congruence was also seen in the vmPFC (cohen's $d = -0.4$) and mOFC (cohen's $d = -0.2$). In the dlPFC, theta power appeared to decrease with increasing conflict (cohen's $d = 0.9$) during stimulation ON.

When evaluating the effect of target coherence on theta power (Fig. 4-11a), we found that theta power increased with increasing coherence in the dACC (cohen's $d = 0.6$), and vmPFC (cohen's $d = 0.9$), and increased with increasing incoherence or task difficulty in the mOFC (cohen's $d = 0.3$) and SFG (cohen's $d = -0.5$). With stimulation ON, we found that the effect of target coherence on dACC was diminished, and theta power was found to increase with increasing coherence in the dlPFC (cohen's $d = 1.1$; Fig. 4-11d), IOFC (cohen's 1.2; Fig. 4-11c), SFG (cohen's $d = 0.8$), with a smaller effect observed in the vmPFC (cohen's $d = 0.4$; Fig. 4-11e) relative to when stimulation OFF.

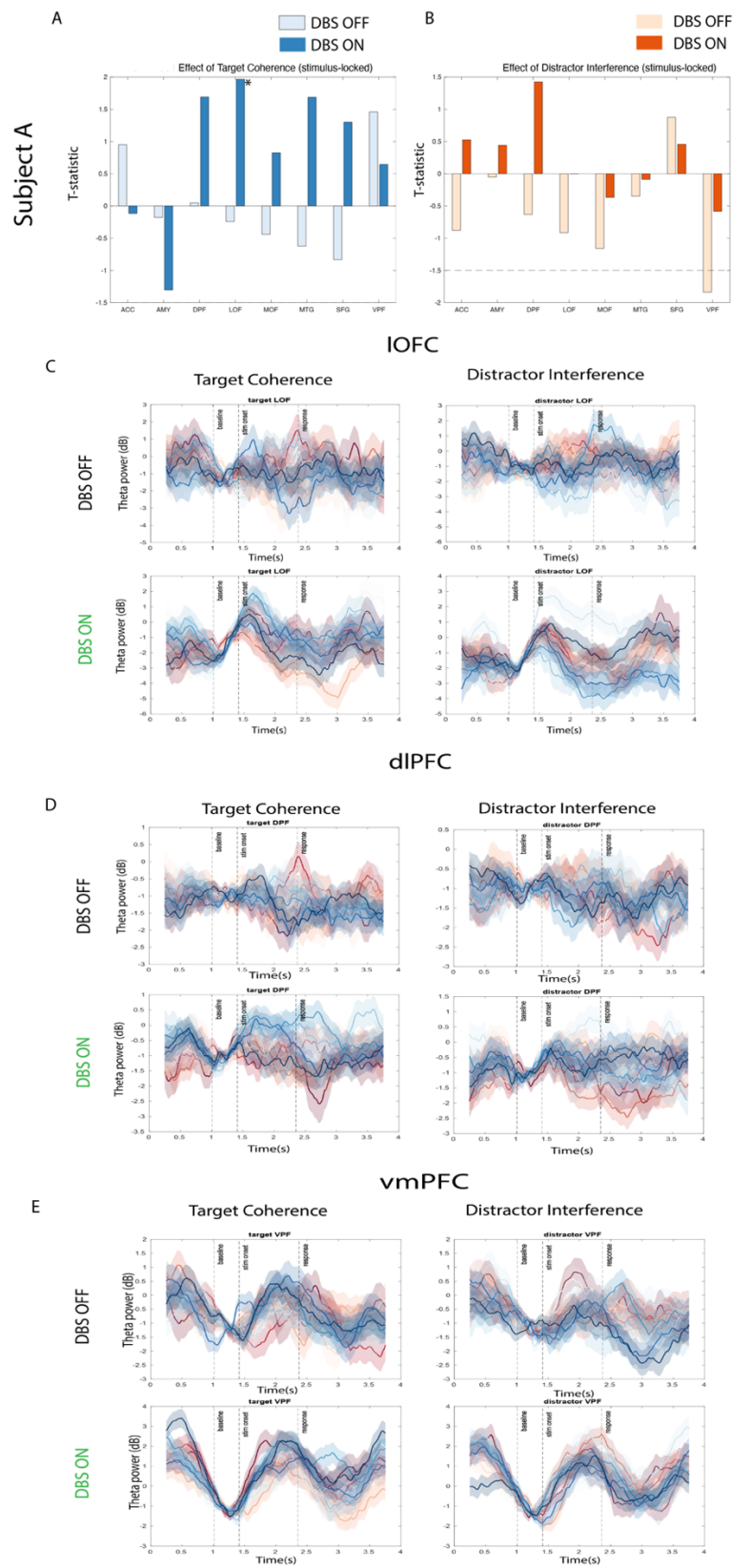


Figure 4-11: Theta modulation with distinct task demands during DBS OFF and DBS ON in subject A

(A) T-statistic values obtained from single-trial linear regression of time-averaged, stimulus-locked theta activity against target coherence during baseline (DBS OFF) and DBS ON for all ROIs for subject A. (B) T-statistic values obtained from single-trial regression of time-averaged, stimulus-locked theta activity against distractor interference during DBS OFF and DBS ON across ROIs for subject A. (C) Trial-averaged theta power across time with varying target coherence (left) and distractor congruence (right) in an ROI where large effects of stimulation on theta modulation were observed, e.g. IOFC (D) dlPFC and (E) vmPFC

In subject B, theta modulation with distractor congruence (Fig. 4-12b) was observed in the dlPFC (cohen's $d = 2.0$), IOFC (cohen's $d = 1.25$) and SFG (cohen's $d = 0.8$), with small effects observed in the vmPFC and dACC (cohen's $d = 0.2$). Across all aforementioned ROIs, theta power increased with increasing congruence or task ease. With stimulation ON, the effect observed in the dlPFC decreased (cohen's $d = 0.2$), was comparable in the mOFC (cohen's $d = 0.7$), IOFC (cohen's $d = 0.98$) and SFG (cohen's $d = 0.8$). In the vmPFC, the effect of distractor congruence on theta power was much larger, where theta power increased with decreasing task conflict (cohen's $d = 1.2$) and a small effect in the dACC was observed in the same direction (cohen's $d = -0.3$).

When assessing the effect of target coherence on theta modulation (Fig. 4-12a), we found small effects in dlPFC (cohen's $d = -0.2$), IOFC (cohen's $d = 0.2$) and mOFC (cohen's $d = 0.4$). We additionally observed the expected direction of theta modulation (increasing power with increasing task difficulty) in the SFG (cohen's $d = -0.8$) and dACC (cohen's $d = 1.2$). With stimulation ON, the effect of target coherence on theta power was observed in the dlPFC (cohen's $d = 0.9$; Fig. 4-12c) and the desired direction of theta modulation (increased power with increased conflict) was indeed observed in the vmPFC (cohen's $d = -0.6$; Fig. 4-12d) and dACC (cohen's $d = -0.6$).

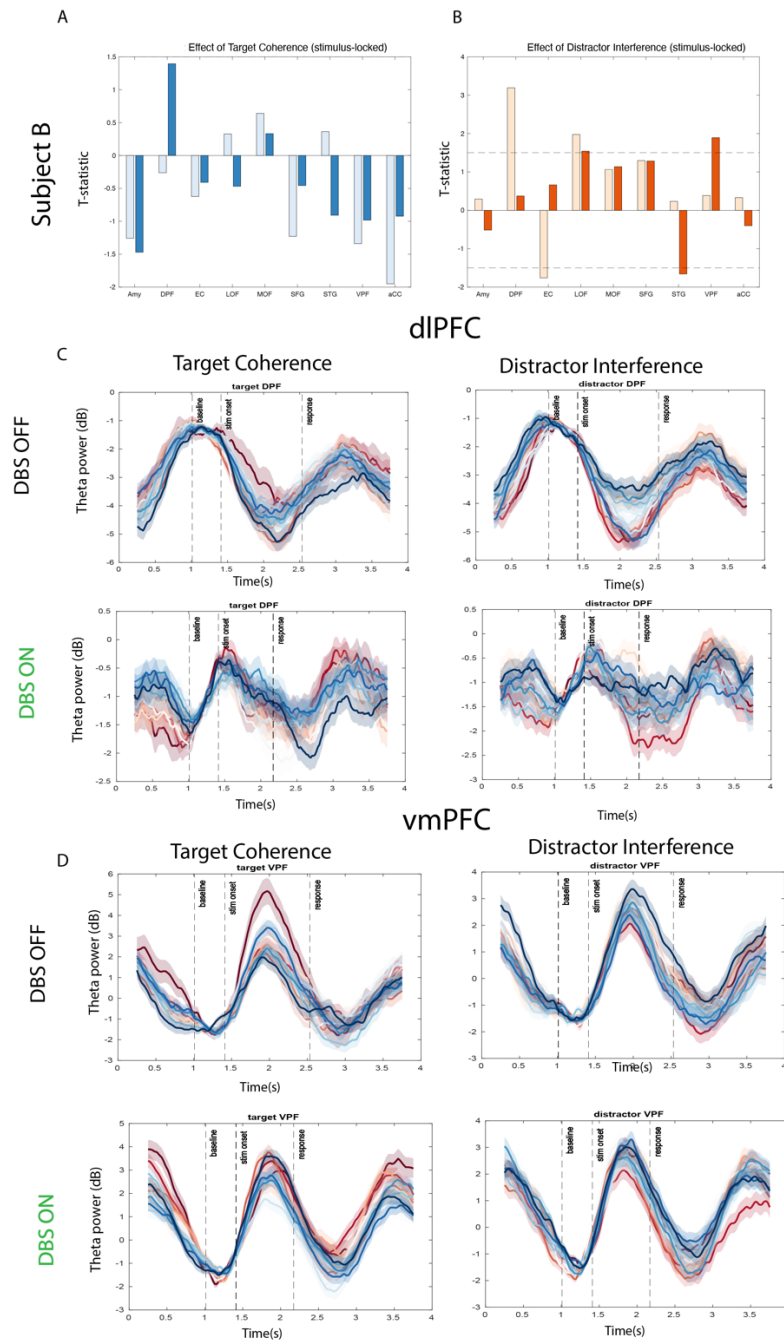


Figure 4-12: Theta modulation with distinct task demands during DBS OFF and DBS ON in subject B.

(A) T-statistic values obtained from single-trial linear regression of time-averaged, stimulus-locked theta activity against target coherence during baseline (DBS OFF) and DBS ON for all ROIs for subject B. (B) T-statistic values obtained from single-trial regression of time-averaged, stimulus-locked theta activity against distractor interference during DBS OFF and DBS ON across ROIs for subject B. (C) Trial-averaged theta power across time with varying target coherence (left) and distractor congruence (right) in an ROI where large effects of stimulation on theta modulation were observed, in dIPFC and (D) vmPFC

In Subject D, we observed small effects (Cohen's $d > 0.2$) of distractor congruence (Fig. 4-13b) on theta power in stimulus-locked epochs across most ROIs. The largest effects were seen in the MFG (Cohen's $d = 1.2$), rACC (Cohen's $d = 1.3$), and medium-sized effects were observed in the mOFC (Cohen's $d = 0.6$). As indicated by the sign of the t-statistic values (Fig. 4-13a-b), theta power appeared to decrease with increasing conflict or task difficulty. During stimulation ON, the direction of theta modulation with distractor congruence was flipped. The effect of distractor congruence on theta power with stimulation ON was observed in the MFG (Cohen's $d = -0.92$), mOFC (Cohen's $d = -0.5$), dACC (Cohen's $d = -0.7$) and vmPFC (Cohen's $d = -2.4$). With stimulation ON, theta power increased with increasing conflict, supporting our hypothesis about the expected direction of modulation (i.e. increased theta with increased recruitment of control).

The effect of target coherence was also evident in theta signals in subject D (Fig. 4-13a). During stimulation OFF, effects of target coherence were observed in the insula (Cohen's $d = -0.8$), MFG (Cohen's $d = -0.9$), mOFC (Cohen's $d = -0.9$), rACC (Cohen's $d = -1.4$). Across all aforementioned ROIs, theta response increased with increasing incoherence or task difficulty. A small effect was also observed in the dACC (Cohen's $d = 0.3$), where theta decreased with increasing task difficulty. With stimulation ON, the direction of theta modulation was largely the same in the MFG (Cohen's $d = -2.4$; Fig. 4-13e) and mOFC (Cohen's $d = -1.1$). However, the direction of theta modulation and effect of distractor congruence on theta power was different in the Insula (Cohen's $d = 0.6$) and rACC (Cohen's $d = 0.73$; Fig. 4-13c). The effect of congruence was also observed in the vmPFC (Cohen's $d = -0.9$; Fig. 4-13d) and SFG (Cohen's $d = -0.5$), where theta power increased with increasing conflict.

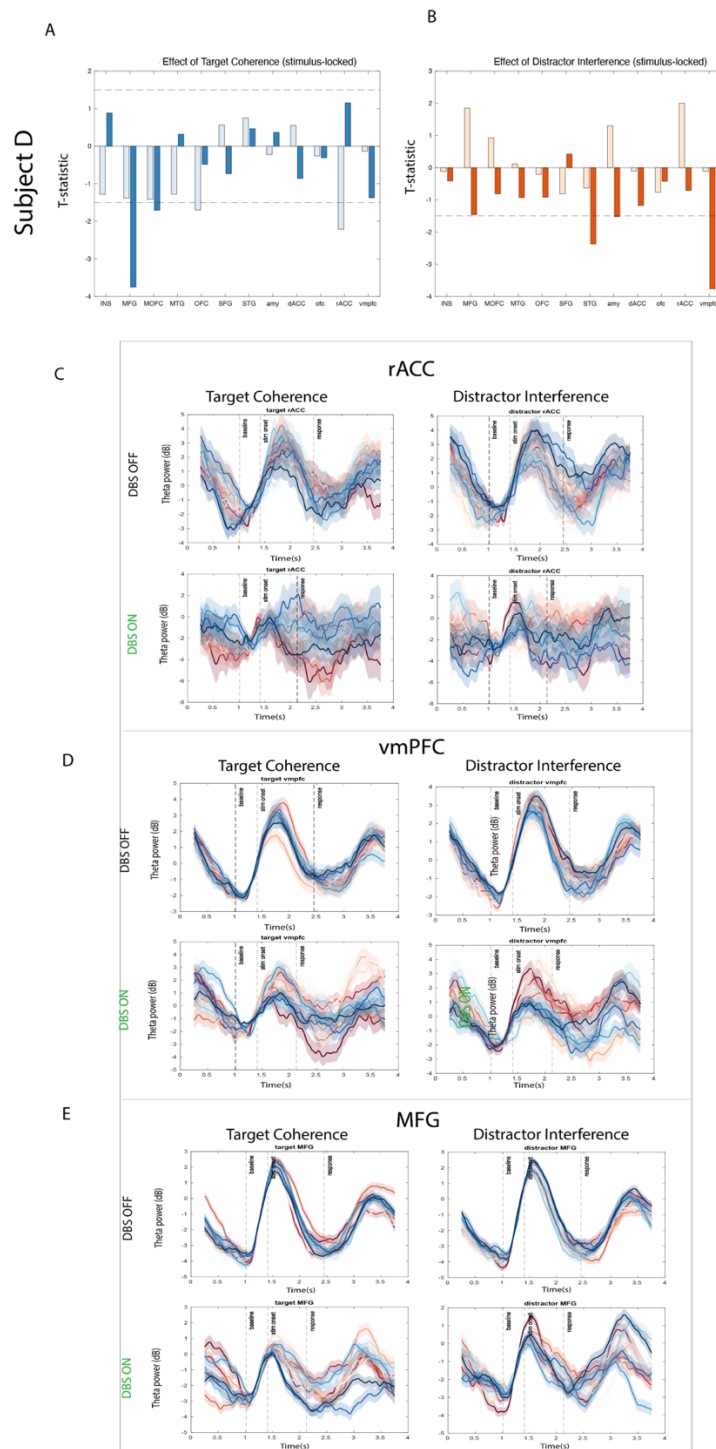


Figure 4-13: Theta modulation with distinct task demands during DBS OFF and DBS ON in subject D.

(A) T-statistic values obtained from single-trial linear regression of time-averaged, stimulus-locked theta activity against target coherence during baseline (DBS OFF) and DBS ON for all ROIs for subject D. (B) T-statistic values obtained from single-trial regression of time-averaged, stimulus-locked theta activity against distractor interference during DBS OFF and DBS ON across ROIs for subject D. (C) Trial-averaged theta power across time with varying target coherence (left) and distractor congruence (right) in

an ROI where large effects of stimulation on theta modulation were observed, demonstrated in rACC (D) vmPFC and (E) MFG

In summary, DBS restored healthy prefrontal/cingulate network activity (i.e. increasing theta with increasing conflict or task difficulty) in subject D in the MFG, mOFC, dACC and vmPFC. Between subjects, there appeared to be variability in both the direction and effect size of theta modulation with task variables during stimulation OFF and ON conditions, especially in ROIs expected to mediate improvement in cognitive control (i.e. the ACC, dlPFC, vmPFC). These findings suggest a subject-specific reorganization of frontocingulate networks underlying exertion of cognitive control during DBS.

4.4 DISCUSSION

Cognitive systems, specifically cognitive control, is a promising behavioral domain for the application of a transdiagnostic framework to aid in the identification of biomarkers of impairments of psychiatric disease^{54,55}, and to measure therapeutic outcomes of neuromodulation therapies such as DBS. In this study, we employed a conflict task with independent modulation of task-relevant and task-irrelevant variables, enabling measurement of target facilitation and distractor inhibition along a continuous axis^{20,40}. We leveraged this task in two cohorts with high-density intracranial recordings, one of which underwent DBS therapy for TRD. In our first cohort of epilepsy patients, we found evidence of differential theta modulation between task demands, i.e. target facilitation and distractor suppression. In our second cohort of subjects with TRD, we successfully implemented the PACT behavioral paradigm to measure the effects of DBS on behavioral performance, bypassing concerns from other conflict tasks where performance is close to ceiling⁵⁶. Third, we showed that DBS enhanced cognitive function in subjects with depression and demonstrated that theta oscillations mediated

enhancement in behavior and frontocingulate function. Finally, we highlight the presence of subject-specific neural mechanisms underlying altered control strategies during DBS.

4.1.14 Theta modulation in non-depressed subjects across the insula and frontal networks

We successfully observed reliable, parametric modulation of behavior as measured via RT and accuracy in both cohorts. Prior work has suggested that neural mechanisms facilitating attention towards a relevant goal are distinct from mechanisms enabling suppression of irrelevant stimuli or distractor interference¹⁸. Theta oscillations have been reliably linked to conflict processing^{37,38,57}, but how theta activity differentiates between cognitive control strategies or distinct task demands is not as well understood. Based on prior neuroimaging work, we hypothesized that theta signals in prefrontal regions implicated in representation and exertion of cognitive control would linearly increase with increased conflict or distractor incongruence, and that this response would be orthogonal to theta modulation with target coherence. In our recordings in the insula, we found that a subset of channels showed increased theta signals with increased incoherence. We also observed that theta modulation with target coherence was not differential from theta responses with varying distractor congruence. The lack of separability in direction of theta modulation between task variables suggests that the theta signals in the insula are also linked to its well-established role in the detection of salient stimuli as part of the salient network⁵⁸, rather than recruitment of control processes. An important distinction to make here is that spatial distribution of electrodes encompasses different subdivisions of the insula. Identification of signals from anterior vs posterior segments will support the existing hypothesis that anterior insula primarily

serves as a node with initiating control signals⁵⁹. In the SPL, we also observed modulation of theta with target coherence. However, we did not observe any modulation of theta with distractor interference, or any strong modulation of theta power in IPL. This was particularly surprising as the IPL is engaged in attentional processes⁶⁰, but the lack of number of participants with sufficient IPL coverage may attribute to the observed outcome.

While the OFC plays an important role in emotional regulation and reward valuation⁶¹, it has been indicated that it may also have executive roles, such as outcome-monitoring⁶², cognitive mapping⁵¹ and rule encoding⁶³. In our study, we did not have apriori hypotheses about theta activity in non-depressed subjects in the OFC, but predicted both target and distractor variables to be represented across both the lateral and medial OFC. We find that both IOFC and mOFC show modulation of theta with target coherence, where a subset of channels show both increasing and decreasing theta power with increasing task difficulty. However, effects of distractor congruence on theta activity were negligible, suggesting that theta activity in the OFC may play a bigger role in attentional control and maintenance of representation of target cues.

Future analysis can highlight whether neuronal encoding of goal-relevant and goal-irrelevant features is orthogonal across frontocingulate and parietal networks.

4.1.15 Neural mechanisms mitigating enhanced cognitive control

A critical goal for this study was to demonstrate improvement of control performance via high frequency DBS and identify putative biomarkers of impaired control in depression alongside neural features mediating improved cognitive function. Plentiful evidence across a myriad of conflict tasks suggests that theta signals are linked to attentional

control and conflict processing^{36,37,45,55,64}, and the idea of theta oscillations as a mechanism mitigating enhanced cognitive control has been previously suggested⁴⁵. Our findings not only support these notions about theta activity, but also demonstrate subject-specific reorganization of theta signals linked to target facilitation and distractor inhibition for optimal control during DBS.

In two subjects with TRD, DBS enhances stimulus-locked theta oscillations across frontocingulate networks. This enhancement in theta oscillations is correlated with significantly improved task performance as measured via RT and accuracy. While this enhancement in cognitive function and associated prefrontal function replicates recent work⁴⁵, it is important to note that this phenomenon of elevated theta was not observed in the third subject, where a significant decrease in theta oscillations was observed in frontocingulate networks instead. This opposing response may be due to a few factors. First, while DBS parameters for stimulation ON is typically chosen based on prior psychiatric evaluation, subject D was the only subject that exhibited no clear overt behavioral response to a stimulation sweep conducted earlier in the study. As a result, the stimulation parameter was informed by a combination of results pertaining to stimulation-evoked responses and tractography and may not have been the optimal stimulation parameter. Second, findings on neural processing underlying cognitive function highlight that individuals with anxiety have elevated neurophysiological neuroimaging responses during conflict/exertion of control¹². Because there is comorbidity between disorders of anxiety and depression, it is not surprising that there are heterogeneous responses across subjects, and patient response may be dependent on the behavioral and underlying neural state of the individual^{65,66}. This theory may potentially explain the attenuated theta response with stimulation in the last subject, as

this subject experienced significantly higher anxiety (relative to other subjects) during the inpatient phase of the study.

While theta power is a reliable marker of conflict and can be used as a neural biomarker to titrate DBS therapy for psychiatry, subject-specific mechanisms for optimization and recruitment of control should be considered. We can leverage the parametric nature of our task that enables measurement of control as a continuous process²⁰ to do so.

Across all subjects, we observed a reorganization in brain networks demonstrating an effect of task variables during stimulation OFF and ON states. In subject A, we observed a decreased effect of target and distractor difficulty on theta activity in vmPFC, and an increased effect of target and distractor difficulty on theta activity in dlPFC. In subject B, we again observed increased target coherence encoding in dlPFC, alongside decreased distractor encoding dlPFC and increased distractor encoding in vmPFC. In subject C, stimulation decreased the effect of target and distractor difficulty on theta activity in rACC, but increased distractor encoding in vmPFC. While the direction of theta oscillations did not overlap across all participants, DBS increased the effect of theta modulation in vmPFC across both subjects B and D, and decreased the effect in subject A. This phenomenon where the effect of goal-directed attention and response inhibition on theta oscillations shifts to a different frontocingulate region during stimulation indicates the possibility of network organization to optimize control within an individual subject. While on average there was an overall reduction in RT and increase in accuracy across participants, there were of course subject specific differences in the behavioral axes that showcased improvement. For example, subject A showed an improvement in RT and accuracy, while subject B and C primarily demonstrated an improvement in RT. The differential theta modulation across the dlPFC, vmPFC and

ACC may serve as evidence of neural substrates reflecting participant specific behaviors and optimization of control strategies. While it is often assumed that there will exist group-level “general” deficits in cognitive tasks and control processing, it is plausible that individual cognitive function or deficits will vary⁶⁵. For example, one subject may have optimal maintenance and representation of goals-relevant information (targets), but an inability to suppress distractors or goal-irrelevant information, whereas another subject may be able to recruit control and facilitate target processing but is unable to exert appropriate response inhibition. Additional analyses and data collection in future subjects will shed light on subject-specific recruitment of control processes.

The anterior cingulate and medial prefrontal cortex have long been considered a hub enabling the interface of affect/emotion and cognitive processing^{15,67,68}. Our results further support the idea that titrating and understanding the interplay of activity in these two regions are important for improving cognitive and affective regulation in psychiatric disorders. Theta activity is a promising biomarker for both impaired cognitive control and within frontocingulate networks for titration and personalization of DBS. Ample evidence from past studies has indicated that theta activity may function as a biomarker or feature of interest for titrating cognitive control not just in MDD or OCD, but also in other neurological disorders where decision-making is altered. For example, theta signals were found to be diminished in patients with parkinson’s disease (PD)⁶⁹. An important phenomenon to consider in biomarker identification is the role of motivation in cognitive processing and related theta signals in depression. During spontaneous clinical interviews following the task, 2/4 subjects reported an increase in motivation when performing the task during stimulation. Therefore, it is also plausible that depressed subjects do not have a reduced ability to employ control, but have lowered motivation,

value and expectations regarding the exertion of cognitive control^{70,71}. Changes in theta activity in the ACC and vmPFC may therefore suggest that inputs to the ACC signal indicate a change in valuation of control rather than an altered ability to leverage control altogether⁷⁰, and this altered signal can be leveraged as a biomarker of mood, motivation and cognitive processing in depression.

There are increasing efforts in the field of neuromodulation to personalize therapy for psychiatric disorders. Endeavors have included identification of neural^{22,66}, physiological⁷², and behavioral^{26,54,73} biomarkers to deliver some form of closed-loop therapy, in either responsive⁷⁴ or adaptive⁷⁵ paradigms. While there has been success^{74,76,77} in identification of personalized biomarkers, the neural mechanisms of impaired cognitive and affective function across behavioral domains and symptoms in disorders such as depression remain elusive. Employing a conflict task that enables measurement of different control strategies (i.e. target facilitation and distractor interference) on a granular level has demonstrated that theta is a promising biomarker. Future work can leverage diminished theta power during distinct contextual or task demands as a biomarker for impaired cognitive function in patients with depression.

4.5 LIMITATIONS

While our study yields significant findings for broadening our understanding of neural-substrates underlying controlled decision-making and putative biomarkers for psychiatric disorders, there are a few limitations to address. First, an important consideration is that neural signals can be multiplexed⁷⁸, i.e. other frequency bands can multiplex computations along different temporal scales. While we have found evidence of theta modulation in target facilitation and distractor inhibition in both cohorts, future

analysis of other spectral features will help elucidate neural mechanisms in frontocingulate networks that reliably encode different cognitive control strategies and task demands. An additional limitation is that temporal modulation of theta activity was not a focus for this study. The lack of differences along target or distractor dimensions in the epilepsy cohort may be attributed to time-averaging of theta power. Future analysis incorporating time-varying theta activity may assist with interpretation of our current findings. Lastly, insufficient data and heterogeneity in electrode coverage may explain some of the between subject variability in cohort one. Data collection in additional subjects with coverage of prefrontal and parietal networks will answer the question of orthogonal or semi-orthogonal encoding of target facilitation vs distractor suppression.

4.6 SUPPLEMENTARY TABLES

ROI	DISTRACTOR OFF	DISTRACTOR ON	TARGET OFF	TARGET ON
ACC	-0.5562813	0.33245149	0.60205126	-0.0738318
AMY	-0.0320083	0.27937348	-0.111401	-0.8233131
DPF	-0.3991373	0.90184625	0.02951259	1.06989566
LOF	-0.577567	-0.0001216	-0.1530466	1.24321397
MOF	-0.733338	-0.231183	-0.277908	0.52225511
MTG	-0.2201438	-0.054989	-0.394019	1.06749766
SFG	0.55405605	0.28951984	-0.5271966	0.82306281
VPF	-1.1607773	-0.3688187	0.92259611	0.40876311

Supplementary Table 4-S1: Results from Subject A. Cohen's d values output from linear regression of theta power against distractor and target during DBS OFF and DBS ON

ROI	DISTRACTOR OFF	DISTRACTOR ON	TARGET OFF	TARGET ON
Amy	0.18535996	-0.3245439	-0.7958879	-0.9298789
DPF	2.01835371	0.2363197	-0.1650684	0.88197869
EC	-1.1124185	0.4192682	-0.3942922	-0.2580324
LOF	1.25078618	0.97501789	0.2072284	-0.2960315
MOF	0.67276267	0.71927553	0.40487372	0.21049837
SFG	0.82031859	0.81256415	-0.7774191	-0.2883211
STG	0.1479721	-1.0482571	0.2295179	-0.5740478
VPF	0.24416534	1.19783463	-0.846598	-0.6212769

Supplementary Table 4-S2: Results from Subject B. Cohen's d values output from linear regression of theta power against distractor and target during DBS OFF and DBS ON

ROI	DISTRACTOR OFF	DISTRACTOR ON	TARGET OFF	TARGET ON
INS	-0.071729	-0.260383	-0.808831	0.55931325
MFG	1.1706	-0.9220641	-0.8748415	-2.3717685
MOFC	0.58473	-0.5137675	-0.8943656	-1.0773238
MTG	0.072173	-0.5871786	-0.8073774	0.20294598
OFC	-0.13238	-0.5805287	-1.0733928	-0.3049722
SFG	-0.51334	0.26554095	0.35619403	-0.4634506
STG	-0.40066	-1.5001861	0.47740994	0.29680895
amy	0.82381	-0.9618828	-0.1406609	0.23338367
dACC	-0.066679	-0.7437617	0.34754021	-0.5427116
ofc	-0.48167	-0.2664538	-0.1632295	-0.1951574
rACC	1.2665	-0.4468653	-1.396673	0.73008977
vmpfc	-0.070619	-2.3790012	-0.0856033	-0.8688701

Supplementary Table 4-S3: Results from Subject D. Cohen's d values output from linear regression of theta power against distractor and target during DBS OFF and DBS ON

Subject	L-SCC contacts	R-SCC contacts	L-VCVS contacts	R-VCVS contacts
Subject A	5-6-7-8	5-6-7	5-6-7	3-6-4-7
Subject B	5-6-7	5-6-7	3-6	1
Subject C	5-6-7	3-6	8	5-6-7
Subject D	8	8	2-3-4	2-3-4

Supplementary Table 4-S4: Contact configurations used for DBS ON during PACT paradigm in TRD subjects

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5 Discussion

5.1 INTRODUCTION

In my dissertation, I have incorporated multiple approaches to advance our understanding of neural mechanisms underlying behaviors in psychiatric disease and their response to DBS. Each chapter is part of a broader effort to elucidate neural mechanisms across different brain states in psychiatric disorders in response to stimulation. In **Chapter 1**, I outline a proposed framework using a transdiagnostic, stereo-EEG informed approach with a broad stimulation parameter sweep for interventional treatment and behavioral evaluation for psychiatric indications. In **Chapter 2**, I described the detailed methodology to *implement* the transdiagnostic framework with multimodal behavioral measurement, via the “NMU” or “Neurophysiology Monitoring Unit”. In **Chapter 3**, I demonstrated the differences in high frequency activity across depressive networks in response to stimulation across two canonical DBS targets employed for psychiatric indications. Findings from this chapter have broad implications for chronic and adaptive DBS and may help explain the observed differential modulation of behavioral dimensions between DBS targets. In **Chapter 4**, I leverage high-dimensional intracranial recordings to characterize the neural substrates of cognitive control in non-depressed subjects. I subsequently demonstrate significant enhancement in cognitive control using DBS and the underlying neural mechanisms in frontocingulate networks mediating the behavioral improvement.

In summary, this dissertation lays the foundation for transdiagnostic, sEEG-driven approaches towards personalized DBS intervention for psychiatric indications. The methodology and findings from this dissertaton will aid in the identification of candidate

biomarkers of mental illnesses for closed-loop stimulation in the future. In this final chapter, I discuss the need for translating intracranial biomarkers discovered in acute inpatient settings for real-world applications, and the utility of using cognitive control as a behavioral domain for psychiatric intervention.

5.2 TRANSLATING ACUTE INTRACRANIAL FINDINGS FOR CHRONIC DBS INTERVENTION

The incidence of intracranial “EMU-inspired” acute recordings and neurophysiology-driven approaches has gained traction for disorders where classic DBS paradigms have ambiguous outcomes. Ongoing studies are implementing this approach for chronic pain and depression^{1,2}. In parallel, acute recordings via intraoperative recordings^{3,4} for psychiatric intervention have been leveraged with much success. Leveraging the use of sEEG in the EMU itself has lent itself well to the discovery of new candidate regions for DBS for psychiatry⁵ and demonstration of closed-loop stimulation^{6,7}. Invasive recordings have major advantages over noninvasive techniques such as fMRI or EEG, due to their spatial and temporal resolution, and a high signal-to-noise ratio. In concert with multimodal behavioral and symptom evaluation, the use of high-density distributed intracranial recordings allows us to measure and causally manipulate multiple nodes in implicated networks to expand our understanding of functional roles of brain networks in psychiatric disorders in the coming years.

An important consideration for our network-minded approaches is how to translate biomarkers or neural mechanisms identified in *acute* inpatient settings to chronic, *longitudinal* therapy. In the case of NMU or EMU-based approaches, intracranial electrophysiology is typically conducted in a duration of 1-2 weeks, or in the span of a few hours in the case of intraoperative recordings. An added layer for consideration

when translating acute findings to longitudinal recordings and stimulation is the mode of chronic DBS, i.e. whether it is responsive, adaptive or open-loop stimulation. Currently, three different avenues are being pursued for DBS intervention of TRD. Our study entails an intracranial platform with high-density recordings across depressive networks with current-steered electrodes in two DBS targets⁸. A separate DBS for TRD study incorporates a similar platform, where high-density intracranial recordings are used to identify optimal DBS targets, as well as candidate biomarkers¹. The chronic stimulation phase entails responsive neuromodulation using the Neuropace RNS system⁹, where stimulation is only delivered after the putative biomarker of interest is detected, thereby not delivering constant chronic stimulation. A third study entails intraoperative recordings and exclusively targets the SCC for stimulation with adaptive DBS^{3,10}. In this scenario, stimulation is always on, but stimulation parameters can be modified depending on the detection of a biomarker. Across these studies, there has been initial success of acute biomarkers successfully informing chronic DBS in case studies. However, for larger clinical populations, the temporal scales across which we expect to measure consistent behavioral responses, and stable electrophysiological biomarkers is important to consider. For example, in depression, symptom improvement with DBS is demonstrated on a longer timescale, on the order of months^{11,12}. While this may be applicable to the specific DBS target (the SCC), it is important to account for the variation in temporal scales as we work towards personalizing and optimizing treatment. One avenue to ensure that we get consistent, reliable measurements of a biomarker and understand whether short-term responses are predictive of long-term responses is to obtain frequent measurements in the same network that we are manipulating and measuring from during the NMU phase. While there are limitations to how many regions

can be sampled from chronically, identifying 1-2 promising targets for continuous measurement and stimulation can allow us to perform frequent data collection. For example, a way to optimize our study in the future may be to use DBS leads that also have recording capability. This way, a combination of the bilateral leads across the VC/VS and SCC can be used for stimulation and biomarker detection, vs detection and stimulation in a singular target.

Additionally, since a multimodal measurement approach during the NMU phase is informative, it is important to implement similar approaches during an at-home setting for the patient to capture recordings during different behavioral states. It is likely that these behaviors will change over time, and incorporating a multi-pronged approach for behavioral measurement as performed in the NMU ensures a better comparison to answer whether acute recordings are predictive of longitudinal neural activity and behavior. Incorporating scenarios that are similar to or feasible for at-home situations in the NMU is another way of evaluating the relationship between acute recordings to longitudinal recordings. An example of this is using spontaneous audio and video for biomarker detection or incorporating items used in daily life such as social media, video games, physical activity, or surveys that probe questions about emotional memories for example, or capture information about daily life outside of the NMU.

A critical piece of the studies currently investigating DBS for TRD is that through multimodal measurements, we can capture biomarkers relevant to different domains. This way, if one acute biomarker is not detected when delivering closed-loop DBS, or is not informative for delivering chronic open-loop DBS, another alternative biomarker corresponding to a different task domain can be used. Maintaining this approach will be

useful for long-term studies and chronic stimulation. Additionally, while studies have primarily focused on changes in spectral power in psychiatric disorders^{1,8,13–16}, it is plausible that measures of functional connectivity such as phase locking¹⁷ are informative biomarkers of behavioral and mood state. Such measures have demonstrated to have immense utility in other intracranial studies of memory^{18–20}, cognitive control²⁰ and reward processing^{20–24}. Indeed, some of our heterogeneous findings in Chapter 3 and Chapter 4 may be due to the neural measures employed. While current implantable devices do not have the capability for extracting phase or performing online functional connectivity analysis for chronic neural recordings, implementing more complex online analyses tools for detection of changes in phase measurements or functional connectivity from LFP signals in future devices will be important.

Lastly, for large-scale feasibility, translating intracranial findings to non-invasive measurements such as EEG or fMRI will likely be necessary. Specifically, it is imperative that we are able to find an analog of intracranially discovered biomarkers or intracranial responses to stimulation for EEG or fMRI measurements. For example, future endeavors could connect spectral markers discovered in iEEG from prefrontal areas to frontal EEG recordings, or functional connectivity between subcortical structures to connectivity measurements via fMRI. Bridging the two modalities will provide a way to translate neural correlates of behavior discovered intracranially to be detected during non-invasive procedures, allowing for network-wide assessment of neural activity and responses to stimulation with greater accessibility. This avenue is important as chronic measurement via high-density electrodes are not currently feasible

in psychiatry, and implantable devices capable of neural measurement may not be feasible for all clinical populations or modes of treatment.

5.3 COGNITIVE CONTROL AS A BIOMARKER FOR TREATMENT INTERVENTION

The use of transdiagnostic approaches for therapeutic applications and elucidating neural mechanisms of psychiatry symptoms has been successful^{6,7,25–27}. However, there are still many challenges ahead with implementing this approach to measure naturalistic behaviors and translating controlled, task-based measures to real-world applications. In subjects with depression, dysfunction or impairment in cognitive control can manifest as automatic negative ideation, rumination, inability to attend to the task at hand, and larger cognitive deficits in executive function. While we were able to enhance cognitive function using DBS through our behavioral paradigm, and hope that this improvement would translate to everyday life, there are still hurdles to overcome to understand 1) where cognitive deficits in depression originate from, 2) which neural mechanisms mediate more efficient recruitment of control and selective attention in everyday life, and 3) how that varies from patient to patient. Within our patients, one subject reported that he was “more motivated” to perform the task, while two other subjects reported that they “had an easier time remembering the task rules” with DBS. These qualitative self-reports indicate that while all subjects performed better on the task, the underlying neural mechanisms related to improved control may vary. Specifically, while neural mechanisms related to selective attention may look similar across subjects with DBS, mechanisms related to motivation, emotional processing and working memory that might attribute to improved control may vary. Understanding these differences and translating them to everyday life for patients will be informative as the field of neuromodulation intervention progresses.

One way to expand our understanding of neural mechanisms mediating improved cognitive function is to include computational modeling to better understand latent states contributing to augmented behavior. Invasive computational psychiatry is a burgeoning field²⁸, and several studies have shown the utility of behavioral and computational modeling to elucidate latent states in describing behavioral modulation^{6,7,29}.

Measuring how emotional and affective regulation intersects with cognitive function is also an important direction for future work, and perhaps a way to bridge task-based measures of control with real-world experiences of cognitive dysfunction. Examples of such tasks include emotional memory tasks^{30,31} that can be performed before or after a conflict task, to measure emotional or affective state around the time that cognitive function is measured. Additionally, self-report scores collected around the time that the behavioral task is performed can be correlated against task performance to identify if there is a direct relationship on mood and energy on behavioral performance.

Another approach is to incorporate more naturalistic measurements in subjects. This approach has been executed successfully in other studies of chronic DBS, but current results remain largely limited to self-report surveys rather than behavioral domain-based measurements¹. For example, in the case of affect, audio recordings collected during clinical interviews with a patient can be used to classify speech into negative and positive affective states³². To measure cognitive load and thinking patterns, we can implement similar paradigms, with audio and video recordings of clinical interviews about daily activity and decisions a subject has made on a given day, including frequency of rumination or negative ideation. An important consideration with obtaining

naturalistic measurements of cognitive control or affect, however, is ensuring that sufficient data points for a given behavioral state are collected for decoding. An additional challenge posed here is that patients often struggle with verbalizing thoughts and responses depending on their mood state, and measuring the inability to articulate a thought process remains a challenge. We experienced this in our current study as well, where a participant's inability to perform a task or tendency to skip trials was difficult to numerically translate to behavioral performance before and after DBS.

A way to potentially get around such limitations is to employ measures of motivation, physical inactivity, or more tailored analysis of naturalistic data (audio, video) and use these measures to inform treatment and symptom state. While motivation may be assessed using a self-report survey, physical activity can be measured chronically using fitness trackers (e.g. an Apple watch or a fitbit), so that we can explore if missing data points on a behavioral task, or inability to articulate emotions is related to anhedonia or lack of motivation (manifested as lack of physical activity). Another example of an informative metric using naturalistic data might be to use acoustic measures to analyze audio recordings from a patient reading scripted, unemotional prompts. In this way, acoustic metrics can inform if there is motor slowing (as measured via speech) or a difference in speech patterns (pitch, volume, etc.) across days. These measures can then be used with depression severity ratings to identify if a patient's inability to articulate themselves or perform tasks are related to a more severe depression state, lack of energy and motivation or another symptom state, and treatment intervention can be modified accordingly.

5.4 CONCLUDING REMARKS

As intracranial human recording opportunities continue to expand, we can expect large advances in capabilities in recording and stimulation techniques, both in density and temporal resolution of recordings³³. It is imperative that as scientists and engineers we thoughtfully approach existing challenges and rapidly advancing technology with precision to maximally utilize patients' time and the large amount of data being generated from ongoing studies. Equally important if not more so, is to remind ourselves of the limitations of controlled experimental settings and be mindful about ensuring that our complex methodologies, experiments, and findings are ultimately informative and applicable for the improvement of the daily lives of patients.

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