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Deep brain stimulation for depression informed by intracranial recordings

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Abstract

The success of deep brain stimulation (DBS) for treating Parkinson's disease has led to its application to several other disorders, including treatment-resistant depression (TRD). Results with DBS for TRD have been heterogeneous, with inconsistencies largely driven by incomplete understanding of the brain networks regulating mood, especially on an individual basis. We report results from the first subject treated with DBS for TRD using an approach that incorporates intracranial recordings to personalize understanding of network behavior and its response to stimulation. These recordings enabled calculation of individually optimized DBS stimulation parameters using a novel "inverse solution" approach. In the ensuing double-blind randomized phase incorporating these bespoke parameter sets, DBS led to remission of symptoms and

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Author Contributions

SAS, NP, WG wrote the grant. SAS, NP, WG, SJM, DB, KB, JFC oversaw organization of the trial, subject recruitment, regulatory activities, and data analysis. AN and CCM provided the holographic planning support. AMS conducted neuropsychological assessments. AA, VP, JAA, BM, JM, RM, DO, ET carried out the recording and stimulation and collected and analyzed data. SAS, NP, KB wrote the manuscript. All authors edited the manuscript and agree with its contents. SAS, NP, WG, and KB have verified the underlying data.

dramatic improvement in quality of life. Results from this initial case demonstrate the feasibility of this personalized platform, which may be used to improve surgical neuromodulation for a vast array of neurological and psychiatric disorders.

Keywords

deep brain stimulation; neuromodulation; stereo-EEG; network; epilepsy; depression

Introduction

The success of deep brain stimulation (DBS) in treating movement disorders such as Parkinson's disease (1) has led to interest in its application to several psychiatric disorders including treatment-resistant depression (TRD). Previous open-label studies of DBS for TRD have demonstrated encouraging results (2–5), but two recent pivotal trials were aborted after interim analyses raised concern for futility (6, 7). These varied results underscore the great challenge and critical need for a strategy to individualize delivery of this therapy for a disorder as heterogeneous as depression (8).

We devised a novel personalized medicine platform for DBS therapy development (9) and designed a clinical trial of DBS for TRD focused on this essential aspect: the need to achieve an individualized understanding of the specific brain networks contributing to a patient's particular depressive phenotype and their response to stimulation. To do so, we borrowed the well-established approach of using intracranial electroencephalography (EEG) to individualize the understanding of epileptic networks (10). Although routinely used in epilepsy, the intracranial EEG platform has rarely been used for other disorders (11, 12). We adapted this platform to serve as a tool for individualized network analysis in TRD, with the hypothesis that doing so would enable personalized delivery of DBS therapy to symptomatic networks and thereby increase the likelihood of clinical success.

Our trial utilizes stereo-EEG (sEEG), a percutaneous method for placing recording electrodes within the brain and interpreting network-wide activity (13). For the first time, we couple this sEEG approach with simultaneous therapeutic DBS lead implantation, thus permitting both recording and stimulation. The implant strategy is individually tailored to the putative networks relevant to TRD based on patient-specific measures of structural connectivity. To fully investigate the distinct contributions of these networks, we targeted the DBS leads to two previously studied regions, the subcallosal cingulate (SCC) (2, 3) and the ventral capsule/ventral striatum (VC/VS) (4, 5). These DBS targets are thought to be hubs at the crossroads of critical white matter pathways that connect cortical and subcortical network regions relevant to the expression of depressive symptoms. The targets seem to have qualitative differences, with SCC stimulation more often reducing negative feelings (e.g., anhedonia, helplessness) and VC/VS stimulation increasing positive feelings (e.g., motivation, energy) (4, 14). Recent evidence correspondingly suggests that the brain networks associated with these two targets overlap but have distinct components (15–17).

We use this dual-target strategy to maximize accessibility to as much of the relevant TRD network as possible. We then use the intracranial sEEG recordings to narrow the

possible stimulation parameter space and choose those parameters that engage network sub-regions most effectively for the individual subject. Thus, this strategy initially casts a wide net and then uses the uniquely available electrophysiological data to focus stimulation delivery using bespoke parameter sets. This "sEEG-informed DBS" platform enables therapeutic development with an emphasis on individualized understanding of network (patho-)physiology. Here, we present results from the first patient treated with this approach in this FDA-approved (IDE G180300) trial (ClinicalTrials.gov number NCT03437928). The subject is a 37-year-old Hispanic male with a history of severe treatment-resistant Major Depressive Disorder who met inclusion criteria of severity, chronicity, and treatment-refractoriness and provided informed consent (BCM IRB H-43036) (Supplementary Information).

Methods

Network-Minded Implant Surgery

The initial surgery consisted of intracranially implanting 4 DBS leads (bilateral SCC and VC/VS) and 10 sEEG electrodes (Supplementary Information). To allow mapping of relevant brain networks and connections, target locations for both sEEG electrodes and DBS leads were determined based on high-resolution structural connectivity imaging. DBS leads were positioned to span the region of SCC and VC/VS with the joint maximal probability of connectivity with white matter tracts critically associated with each respective target, as we have previously described (18) (Supplementary Information). The DBS leads were externalized (19) to provide access for stimulation delivery. sEEG electrodes targeted downstream depression-relevant frontotemporal network regions: bilateral dorsolateral prefrontal cortex (dlPFC), ventrolateral and ventromedial prefrontal cortex (vlPFC, vmPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and mesial temporal lobe (MTL) (20, 21).

For the first time, our study supplemented traditional stereotactic planning tools with a holographic augmented reality platform that enabled interactive visualization of the DBS and sEEG targets and white matter tracts connecting them. This "HoloSEEG" platform created a collaborative planning environment and provided a more complete three-dimensional appreciation of the extended networks that were targeted with this approach (Fig. 1).

Neurophysiological Data-Driven Stimulation

Following the initial surgery, the patient was admitted to the epilepsy monitoring unit, which we conceptually renamed the neurophysiology monitoring unit (NMU). We performed 9 days of continuous high-resolution recordings from the 180 intracranial channels during unconstrained behavior, performance of specific behavioral tasks designed to assess affect and cognition, and delivery of stimulation across a wide parameter space (Supplementary Information). At the conclusion of the NMU period, we performed a second surgery to remove the sEEG electrodes and internalize the DBS leads to implanted pulse generators.

The critical goal of the NMU phase was to gather data to enable generation of personalized stimulation parameter sets to implement and evaluate during chronic outpatient DBS. The traditional method of choosing optimal parameters–trial-and-error exploration of the stimulation parameter space – would be infeasible for several reasons. The first is the sheer size of the parameter space. Conventional two-lead monopolar DBS with 4-contact leads allows 2^8 possible contact configurations. Factoring in multiple possible stimulation frequencies, pulse widths, and amplitudes, the possible combinations number in the thousands. Dimensionality of the parameter space in this case is exponentially larger: because we use four rather than two DBS leads, and because each segmented DBS lead has eight rather than four contacts, there are 2^{32} (>4 billion) possible contact configurations alone. Another reason is the mismatch in temporal dynamics between DBS parameter adjustments and observable changes. In DBS for movement disorders, DBS adjustments often have immediately measurable effects (e.g., tremor suppression). In psychiatric DBS, however, the time delay and consistency between adjustments and observable effects are unpredictable. Thus brute force exploration of this high-dimensional parameter space would be extremely time-consuming and may only lead to the identification of somewhat effective parameters (local maximum) but perhaps not the most effective parameters (global maximum).

This trial replaces the effort-intensive, trial-and-error conventional method (Fig. 2A "Forward" solution) with a data-driven, rigorous approach utilizing the critical feature unique to this platform: the intracranial recordings. These recordings provide measures of network activity across a range of mood states occurring through natural variation or induced by specific behavioral tasks. They also provide measures of the network's response to stimulation across the vast parameter space, which can be efficiently explored with this platform. Combining this information, we can calculate an "Inverse" solution (Fig. 2A): the set of computed stimulation parameters determined most likely to produce the desired behavioral outcome.

In this case, we calculated the inverse solution by defining a desired brain state and identifying the stimulation parameter set that produced a network-wide electrographic pattern that most closely matched it (Supplementary Information). We created correlation matrices between this desired brain state and the multiple stimulation parameter combinations tested per DBS lead, where each matrix correlated spectral power across all intracranial contacts. This process produced a rank-ordered list of parameter sets across the four DBS leads. Then, to determine the relative contributions of stimulation parameter features to the correlation match value, we modeled each component as a beta weight in a generalized linear model and used iterative model fitting to identify the most-contributing components.

Outpatient Phase

We implemented the NMU-derived stimulation parameters in the outpatient phase of the trial. We began with an 8-month period of open label optimization, in which we observed the effects of the chosen stimulation parameters without blinding. The subject then entered the double-blind discontinuation phase. We saw the patient in clinic weekly during this

time for close monitoring. At a timepoint unknown to the subject and blinded raters, we began reducing stimulation by 25% per visit on a randomly chosen DBS target pair. A 25% increase in the Montgomery-Asberg Depression Rating Scale (MADRS) over 2 consecutive visits, relative to pre-discontinuation, and Clinical Global Impression – Improvement scale (CGI-I) of 6 (“much worse”) were escape criteria that would trigger exit from the discontinuation phase and reinstatement of open label stimulation. Subject blinding was maintained by asking the subject to not access the patient programmer and to recharge the DBS pulse generator daily so that they would be unaware of differences in recharge duration that would tip off amount of battery usage.

Results

Inverse Solution for DBS Parameter Generation

We delivered stimulation across a wide range of parameter space, including single pulses and pulse trains of 1 sec, 15 sec, 5 minute, and 20 minute duration (Supplementary Information). The 1-second stimulation data were used for inverse solution generation. These short stimulation trains did not produce an observable behavioral response, but 15 second stimulation and longer did. In general, SCC stimulation effects, when present, consisted of feelings of calmness and mental clarity. VC/VS effect, when present, were more energizing, consisting of increased talkativeness and feeling “online”. His symptom scores decreased rapidly during the 10 day NMU stay, decreasing by 56% (MADRS) to 67% (HAM-D) relative to his baseline severity (Figure S1).

We performed the inverse analysis in three ways to identify and confirm a solution. We first chose the subject’s baseline resting activity on day 9 of the NMU stay as the desired state. His symptom ratings were most improved at this point, and his performance on behavioral tasks was at its best (Supplementary Information). Subjectively, he stated that if he were able to consistently feel this way, he would function much better in life, emotionally and cognitively. Whether he had reached this state due to the accumulated stimulation delivery by that time or due to other non-stimulation-specific effects, it represented a desirable state. From the rank-ordered list generated by the inverse analysis targeting this state, we chose the top-ranked set as our prioritized set of stimulation parameters. This modeling approach does not allow us to quantify the significance of the difference between items in the list, however, so we are agnostic regarding the potential effect of choosing any other high-ranking set.

We performed two additional analyses to add confidence to this choice. First, we chose an alternate desired state: activity during one of the behavioral tasks that induced a positive mood state. This choice provided an objectively defined target state to balance the subjectivity of the original choice. The highest ranked match using this alternative was identical in all but one stimulation parameter to the original set. Second, we followed the same steps to match to an undesired brain state, which we chose as the baseline recording on day 2 in the NMU when his depression severity was still elevated (Supplementary Information). This rank-ordered list was in nearly the exact inverse order of the other two, providing further confirmation of the result.

Evaluation of the beta weights in the general linear model provided further information regarding the stimulation parameters that most influenced the match score. Contact configuration – the combination of DBS contacts through which stimulation was delivered – was consistently the most significant contributor. The second most significant contributor was stimulation frequency. Pulse width and amplitude were consistently least significant.

Clinical Outcome

We implemented the NMU-defined stimulation parameter sets during an initial eight-month period of open-label DBS. Of note, this sEEG-informed strategy changed the workflow for clinical programming visits. Because the stimulation sets were generated based on NMU data, little clinic time was spent exploring the parameter space to build stimulation sets for this complex 4-lead configuration.

During this time, the participant reported steady improvements in mood, increased interest in pleasurable activities, and closer emotional connections to loved ones. Professionally, he noticed increased concentration and improved performance at work, and decreased anxiety when making presentations to colleagues and clients. His partner reported increased talkativeness, emotional engagement, and interest in shared activities. Standard rating scales demonstrated progressive improvement in depression severity leading to remission of symptoms by week 22 relative to the initial surgery, or approximately 18 weeks following initiation of chronic DBS (Fig. 2B). He did not report treatment-emergent adverse events such as anxiety, hypomania, or suicidal ideation. Neuropsychological testing at the end of open-label optimization revealed improvement in semantic fluency, abstract visual reasoning, and long and short delay recall of non-contextual verbal material. Whether these cognitive improvements were a direct result of stimulation or secondary to mood improvements is difficult to determine.

At 37 weeks he entered the double-blind, randomized discontinuation phase of the trial to distinguish between true and sham response. He was randomized to SCC discontinuation first. Stimulation amplitude was reduced by 25% per visit beginning on the 3rd visit in double-blind fashion. The stability of his scores during this lead-in period (lack of nocebo effect) argues against unblinding. During the discontinuation, he reported steadily worsening mood and anxiety. His symptom scores increased during this period until he met rescue criteria. At this point, stimulation was reinstated at pre-discontinuation levels, and his depression symptoms again quickly remitted. He did not undergo discontinuation of the VC/VS target, as our protocol limits the discontinuation phase to a single target for patient safety.

Discussion

We present a novel platform for DBS therapy development and the first case of clinically effective “sEEG-informed DBS” for TRD. Our novel dual-target DBS strategy increased our access to a wider brain network than achievable by a single target. The intracranial monitoring platform of the NMU allowed first-of-its-kind rigorous electrophysiological characterization of depression-relevant networks and their response to a wide range of stimulation parameters. This approach enabled data-driven determination

of optimal stimulation parameters to engage the symptomatic network. The double-blind discontinuation results suggest that the observed robust response, which led to symptom remission, was a true stimulation-induced response and not a sham/placebo response.

Beyond the utilitarian purpose of enabling calculation of optimal DBS parameters, these results shed light on the relative influence of the various stimulation parameters on network activity. We consistently observed contact configuration as the most significant feature. These results argue for the value of using directionally steerable DBS leads, which allow finer grained control over the pattern of evoked neural activity (Supplementary Information). Stimulation frequency was consistently the next most significant feature. Of note, whereas the effect of contact configuration may be estimated using imaging methods (e.g., Fig. 1), the effect of stimulation frequency cannot. Pulse width and amplitude were consistently the least significant features in our model. Their lower significance does not mean that these parameters are unimportant, but rather that they have the least influence on the pattern of evoked activity and therefore the match to the target network state.

This report is the first to combine VC/VS and SCC DBS for TRD. When tested individually in the NMU, SCC and VC/VS stimulation produced behavioral effects as described in previous reports: SCC stimulation reduced “mental noise” and produced calmness and attention; VC/VS stimulation injected energy and motivation (5, 7, 14, 16, 22). A possible concern is that an inappropriate combination of these diverging effects could be antagonistic, but our results suggest otherwise. Before exiting the discontinuation phase, the subject’s symptom scores were approximately halfway back to his pre-surgical baseline. We cannot speculate how he would have fared for a longer time without SCC stimulation, but it is likely that stimulation in the two targets was constructive. Further experience with dual-target stimulation will shed light on this balance.

We envision this platform as one for DBS therapy development and optimization for challenging disorders during a critical period of knowledge acquisition, not as a replacement for standard DBS surgery. The goal of this trial is to determine whether an sEEG-based approach is feasible and whether the information obtained from the sEEG recordings can be used to select effective DBS stimulation parameters. In this first subject, we demonstrate initial feasibility and utility of the platform. Importantly, we did not try to prove that the sEEG-informed DBS parameters were *better than* parameters derived from other/conventional methods. Such a test would require well-designed head-to-head comparisons, which may be done in the future should interest in this platform increase.

One possible future implementation of this sEEG platform may be for patients who do not respond to conventional DBS (for TRD or other disorders). Those who respond to conventional methods would have done so without intracranial recordings, but those who do not respond could undergo this process to gain the network-wide electrophysiological data that would permit derivation of new solutions and hopefully improve their outcome. Future work will also undoubtedly improve the inverse solution methodology. The specific computational form used to generate the inverse solution here is just the first example. Increasingly sophisticated techniques for decoding mood states from electrophysiological measurements and using intracranial stimulation to modulate them are the subject of active

investigation (23–25). Implementation of these methods will likely improve our ability to find optimal solutions.

The increased invasiveness of this platform over conventional DBS is meant to be a bridge to future less invasive approaches. This successful case is a necessary first demonstration of this novel strategy using direct intracranial measurements. Future work can test the success of substituting non-invasive techniques as readouts of neural activity (Fig. 2A, part 4) as they become increasingly reliable. More generally, an important advantage of this platform is that stimulation configurations derived from future analyses can be readily implemented as new sets of stimulation parameters to employ and test. This approach enables repeated iteration between computational analysis and clinical testing, providing a long-term testbed for the neuroscientist and continued hope for symptomatic relief for the patient.

In summary, our initial results demonstrate the feasibility of this novel platform for personalized DBS. We propose that this approach, if consistently demonstrated safe and effective, can be used to develop and improve surgical neuromodulation for a vast array of neurological and psychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures

SAS is a consultant for Boston Scientific, Neuropace, Abbott, and Zimmer Biomet. NP is a consultant for Boston Scientific and Abbott. WG has received donated devices from Medtronic and is a consultant for Biohaven Pharmaceuticals. SJM has served as a consultant for Alkermes, Allergan, Axsome Therapeutics, Clexio Biosciences, Engrail Therapeutics, Intra-Cellular Therapies, Janssen, Neurocrine, Perception Neurosciences, Praxis Precision Medicines, and Sage Therapeutics. CCM is a consultant for Boston Scientific and receives royalties from Hologram Consultants, Neuros Medical, Qr8 Health, and is a shareholder in the following companies: Hologram Consultants, Surgical Information Sciences, CereGate, Autonomic Technologies, Cardionomic, Enspire DBS. All other authors report no biomedical financial interests or potential conflicts of interest.

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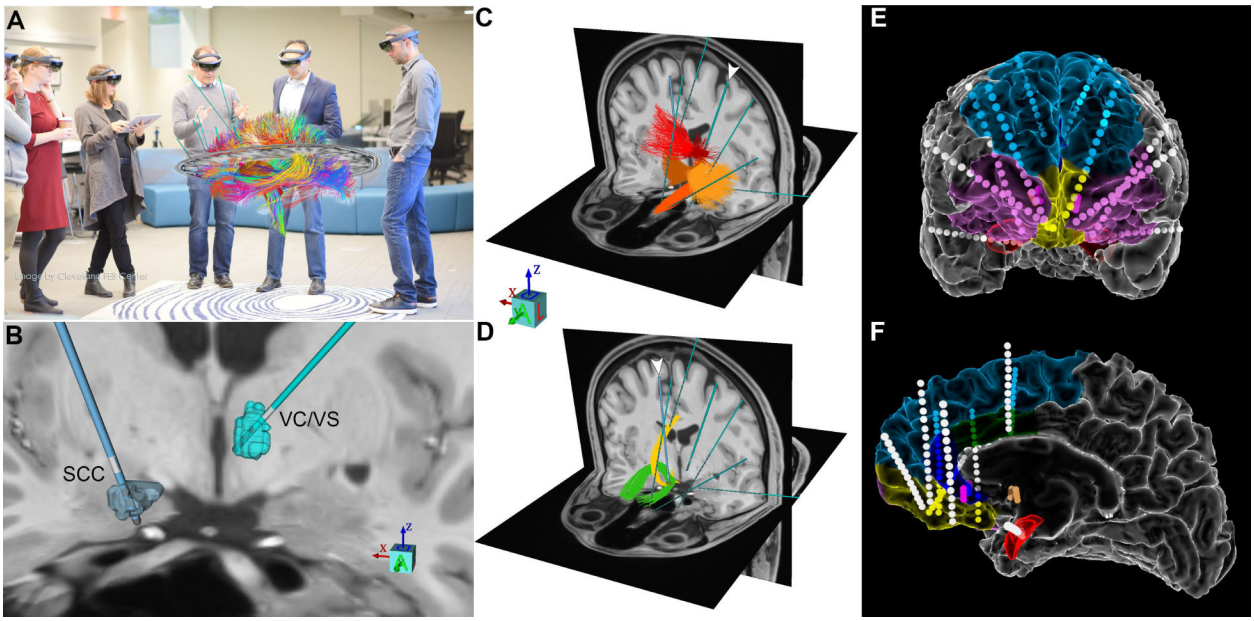

Figure 1. Network-guided implant planning.

A) Interactive trajectory planning for 4 DBS leads and 10 sEEG electrodes using structural connectivity hypotheses to guide the electrode positions. This process was performed using holographic augmented reality facilitated by custom software (HoloSEEG). **B)** VC/VS and SCC DBS leads target regions defined by patient-specific tractography (Supplementary Information). For clarity, we only show the left VC/VS and right SCC target regions. **C, D)** We used axonal pathway activation estimates of stimulation through the DBS leads (white arrowheads) to guide placement of the sEEG electrodes. Streamlines from VC/VS (**C**) and SCC (**D**) connect to distinct but partially overlapping frontotemporal regions. For sEEG trajectory planning, dorsal and lateral cortical termination regions of streamline estimates (e.g., dlPFC, vlPFC) were chosen as sEEG entry points. Ventral, medial, and orbital streamline termination regions (e.g., dACC, vmPFC, OFC) were chosen as sEEG target points. We thus tried to maximize sampling of relevant cortical areas while minimizing the number of sEEG electrodes. **E,F)** Frontal view and mesial view(26) showing actual implant locations in this subject. Stereo-EEG recording contacts (white) sample regions within depression-relevant frontotemporal networks, including dlPFC and dmPFC (blue), dACC (green), vmPFC (yellow), OFC (pink), and MTL (red). DBS lead contacts are also shown in pink (SCC) and orange (VC/VS).

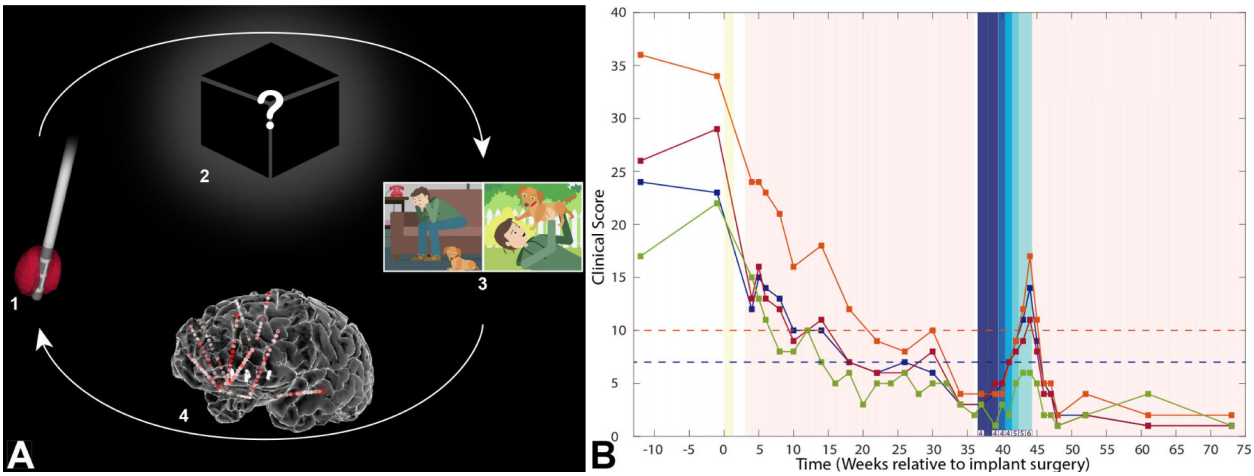

Figure 2. "Inverse" DBS programming strategy and clinical outcome.

A) The NMU recordings uniquely enable us to generate data-driven "Inverse" solutions for DBS programming. Selection of programming parameters in conventional DBS progresses in the "Forward" (upper arrow) direction: **1)** Using a trial-and-error strategy, the clinician chooses different combinations of input stimulation parameters, including contact configuration, frequency, pulse width, and amplitude. **2)** These parameters produce unknown changes in the brain, which in turn lead to (3) measurable behaviors (e.g., mood changes in the case of DBS for TRD). As described in the text, optimizing this Forward solution is challenging even in conventional DBS for TRD because of the mismatch in time constants and inconsistencies between programming adjustments and behavioral changes. Exploring the vast possible stimulation parameter space using this brute force approach is extremely time consuming and inefficient. Our trial uses NMU-derived intracranial recordings to pioneer the "Inverse solution" (lower arrow). The recordings allow us to measure and define various "network states", electrographic patterns characterizing various mood states, and the network's response to stimulation (4). Armed with this information, we can select a desired behavioral outcome (3), identify its associated network state (4), and then compute the combination of stimulation parameters (1) that are most likely to achieve it. This approach will become progressively more effective with future improvements in our understanding of brain-behavior relationships – in particular, the neural encoding of mood states. It is also readily translatable to a non-invasive future, as less invasive methods of network state measurement improve and can be substituted in (4).

B) We tested the stimulation parameters derived from the NMU (yellow bar) during the outpatient open-label optimization phase (pink). Depression scores decreased steadily to remission (HAM-D<=7, blue dashed line; MADRS<10, orange dashed line). At week 37 the subject initiated the double-blind, randomized discontinuation phase. He was randomized to SCC discontinuation first. Stimulation amplitude was reduced from 100% to 0% in 25% increments per week (corresponding to shades of dark to light blue). Only the unblinded programmer knew the stimulation amplitude; the subject and remainder of the research team, including symptom rater, were blinded. For the first three weeks when stimulation was maintained at 100% (dark blue), the subject's scores did not appreciably change, indicating lack of a nocebo effect that would have confounded interpretation. As amplitude was reduced over subsequent weeks his scores worsened, suggesting that his response to

DBS was a true response, not a sham/placebo response. He met rescue criteria at week 44 (MADRS >25% increase and CGI-I [values shown along x-axis] of 6 [‘much worse’] relative to pre-discontinuation). At this point the discontinuation phase ended and unblinded stimulation resumed. VC/VS stimulation was not tapered, as dictated by our study protocol, to reduce risk to the subject (see Supplement). He again quickly remitted following DBS reinstatement. Abbreviations: HAM-A, Hamilton Anxiety Inventory (magenta); MADRS, Montgomery-Asberg Depression Rating Scale (orange); HAM-D, Hamilton Depression Inventory (blue); QIDS-SR, Quick Inventory of Depressive Symptomatology Self Report (green); CGI-I, Clinical Global Impression-Improvement.