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Bilateral epidural prefrontal cortical stimulation for treatment-resistant depression

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Abstract:	We describe the targeting, surgical technique, intraoperative testing, and post-operative programming strategy for the invasive neuromodulatory technique termed epidural prefrontal cortical stimulation (EpCS). While EpCS has been explored by several groups, the unique approach described involves surgical placement of four epidural cortical stimulation paddles - two over the bilateral dorsolateral prefrontal cortex (DLPFC) and two over the frontopolar cortex (FPC). 5 subjects were implanted with EpCS (3 with major depression, 2 with bipolar affective disorder I, depressive type) and their depressive symptoms were followed for five years. Application of chronic electrical stimulation (10-15mA) across all four of these paddles produced a durable antidepressant response for 3 of 5 subjects at the five-year follow-up. This manuscript discusses the unique intraoperative testing strategy as well as the programming approaches employed in this study. We aim to give guidance into improving the effect size of this novel form of stimulation, which may be more promising than noninvasive brain stimulation techniques in cases of severe forms of treatment-resistant depression (TRD) while simultaneously decreasing the surgical risk

	of more invasive forms of stimulation such as deep brain stimulation (DBS). Given the overall safety, efficacy, and ability to be tailored to dysfunctions in functional connectivity on an individual level, EpCS of the FPC and DLPFC has the potential to fill a current gap in available treatments for severe TRD.
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Cover Letter

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Jan 31, 2017

To Whom It May Concern:

Please find: Bilateral epidural prefrontal cortical stimulation for treatment-resistant depression attached. We appreciate the invitation to submit this manuscript.

Nolan Williams, MD

TITLE:
Description of a Novel, Surgically Implanted Neuromodulatory Technique Known as Bilateral Epidural Prefrontal Cortical Stimulation (Epcs) for Treatment-Resistant Depression (TRD)

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KEYWORDS:
Deep brain stimulation, treatment-resistant depression, epidural cortical stimulation, epidural prefrontal cortical stimulation, dorsolateral prefrontal cortex, brain stimulation, interventional psychiatry

SHORT ABSTRACT:
We describe the implantation of 4 epidural stimulation paddles directly above the dura mater over both the left and right frontopolar and dorsolateral prefrontal cortices. Placement was verified using postoperative computed tomography (CT) coregistered with presurgical magnetic

resonance imaging (MRI).

LONG ABSTRACT:
We describe the targeting, surgical technique, intraoperative testing, and postoperative programming strategy for the invasive neuromodulatory technique termed epidural prefrontal cortical stimulation (EpCS). While EpCS has been explored by several groups, the unique approach described here involves surgical placement of four epidural cortical stimulation paddles - two over the bilateral dorsolateral prefrontal cortex (DLPFC) and two over the frontopolar cortex (FPC). The safety and efficacy of this technique for treatment-resistant depression has been described previously by the authors. 5 subjects were implanted with EpCS (3 with major depression, 2 with bipolar affective disorder I, depressive type) and their depressive symptoms were followed for five years. Application of chronic electrical stimulation (10-15mA) across all four of these paddles produced a durable antidepressant response for 3 of 5 subjects at the five-year follow-up. This manuscript discusses the unique intraoperative testing strategy as well as the programming approaches employed in this study. We aim to give guidance into improving the effect size of this novel form of stimulation.

INTRODUCTION:
Nonpharmacologic brain stimulation therapies have emerged as potentially promising treatments for a variety of illnesses, including depression[1]. Depression is a disabling psychiatric disorder of melancholia that not only affects an individual's daily life and social functioning[2], but is a leading cause of premature mortality and disability worldwide[3]. Large clinical trials have shown that pharmacologic interventions have limited success in treating depression[4]. Roughly 41% of patients fail to respond to two adequate trials of pharmacologic treatment, which is the definition of treatment resistant depression (TRD)[5,6].

It is for these patients that interventional psychiatric approaches have emerged[1], though they vary widely in methodology, with some options being significantly more invasive than others[7]. Guiding these therapies is the emerging understanding of mood disorders as functions of anatomic interconnections within brain regions[8]. Depression is a model illness for studying cooperative brain stimulation treatments, as studies have suggested that the left dorsolateral prefrontal cortex (DLPFC) is hypoactive while the right DLPFC is hyperactive[9,10]. The frontopolar cortex (FPC) is another region of interest due to its role in the mood regulatory circuit[11] and is consistently found to have increased resting-state activity in patients suffering from depression[12].

Research over the past decade has demonstrated the efficacy of epidural cortical stimulation (ECS)[13,14] in managing intractable pain syndrome[15-18], aiding in stroke recovery[19], and improving Parkinson's disease and movement disorders[20]. These studies generally utilized chronic unilateral ECS of the primary motor cortex[21]. In addition, several cortical nodes including the anterior cingulate cortex, left temporoparietal junction, and dorsolateral prefrontal cortex have been targeted for tinnitus[22-24]. A form of ECS, epidural prefrontal cortical stimulation (EpCS) has been utilized to treat depression. Like subdural prefrontal cortical stimulation[25,26], EpCS provides constant stimulation to cortical network nodes of interest[27-29]. EpCS is safer than subdural cortical stimulation from the standpoint of seizure induction and hemorrhage risk[13,30].

In this protocol, we describe the method of bilateral EpCS, a unique therapeutic approach for cooperative stimulation of multiple brain regions of interest[28]. The electrical device remains separated from the cortex by the arachnoid space, making it potentially safer than deep brain stimulation (DBS), where electrodes lie within brain tissue[31]. EpCS may therefore be preferred over more invasive stimulation techniques in patients at high risk for surgical complications, including intracranial hemorrhage[32]. We observed the efficacy, safety, and durability of chronic intermittent EpCS of the DLPFC and FPC over a five-year period in 5 patients[28,33].

PROTOCOL:

These experiments were conducted at the Medical University of South Carolina (MUSC) in compliance with an Investigational Device Exemption issued to Ziad Nahas and later transferred to Edward Baron Short under US Food and Drug Administration (FDA) guidance. The MUSC Institutional Review Board approved the protocol.

1. Participants

1.1. For each subject, conduct comprehensive assessment including detailed neuropsychological testing at baseline and repeatedly after implantation. Fuse the patient's brain MRI with a digital 3D Brodmann area map prior to surgery.

1.2. Keep patients on stable medication regimens for a minimum of 4 weeks prior and for 5 months following surgery.

1.2.1. Dose reductions are permitted if improvements are seen and the patient is able to maintain clinical benefit or decrease current or newly expressed side effects without worsening of symptoms. Increases in medication dose are advised against as higher doses of concurrent medications pose unknown combinatory risks.

1.3. If patients are implanted with a vagus nerve stimulation (VNS) therapy device, turn the device off for at least 6 months prior to, and 1 year following, their enrollment. The acute use of concurrent implantable neuromodulation techniques has not been explored and therefore we advise turning off prior implanted devices to avoid unknown synergistic negative effects, and to minimize safety risk to patient.

Note: In the longer 5-year follow-up period, VNS stimulation parameters and medications may be changed in type or dose however ECT, TMS and DBS should not be provided. This is to conservatively minimize risk to the patient. Also, given the placement of the implant, we believe that the electrode may potentially be damaged by external magnetic or electrical stimulation targeting of nearby or underlying cortical areas. VNS is excluded from this list as it is implanted outside of the skull and its direct cortical effects are relayed polysynaptically rather than directly as in ECT, TMS, and DBS.

1.4. A minimum 2-week recovery period follows implantation.

2. Surgical Planning and Procedure

2.1. Perform the entire surgical procedure while using complete hemodynamic monitoring consisting of electrocardiography, pulse oximetry, end-tidal CO_2, and non-invasive blood pressure monitoring.

2.2. Phase 1

2.2.1. Sedation

2.2.1.1. Induce moderate sedation in the patient using intravenous fentanyl (50-250 micrograms) as well as a propofol infusion (25-100 micrograms/kg/min).

2.2.1.2. Have the surgeon inject 2 cc of 2% lidocaine with epinephrine locally at the site of the burr hole and surgical headrest pin locations on the scalp to the periosteum. Mark the location for bicoronal incision and infiltrate the area with local anesthetic, about 5 ccs of an equal mixture of 1% lidocaine with epinephrine 1:100,000 and bupivacaine 0.5%.

2.2.1.3. Orient the patient in a supine position on the operating table.

2.2.2. Placement planning

2.2.2.1. To maintain head stability and limit movement, use a skull clamp with surgical pins. Position the patient supine with the head elevated and neck slightly flexed. Determine the stereotactic placement of the 4 paddle leads using the 3D tagged MRI image and surface landmarks of the patient's head, previously imported into a neuronavigation system.

2.2.2.2. Use the linear "look ahead" function to indicate the underlying cortical area of interest. Map targeted cortical areas using a pointer wand.

2.2.3. Placement

2.2.3.1. Sterilely drape the patient. Make a bicoronal incision behind the hairline using a scalpel (surgeon's preference). Peel the flap forward.

2.2.3.1.1. Using a generic 4-mm spherical diamond drill bit, make two slit-shaped craniotomies, one over each frontal hemisphere, (each 3 cm by 0.5 cm) parallel and anterior to the coronal suture. Wax the bone edges.

2.2.3.2. Insert the sterile paddle leads epidurally (the anatomical space between the dura and the inner table of the skull, known as the epidural space) over the desired areas.

2.2.4. Placement verification

2.2.4.1. Use the neuronavigation equipment and intraoperative fluoroscopy in conjunction to coregister and verify accurate lead placement. When the pointer wand coincides with the Brodmann map domain of interest on the computer screen and with the position and orientation of the electrode paddle on the plain X-rays in multiple planes, the placement is correct.

2.2.4.2. Following these final adjustments, anchor the paddle leads to the edge of the craniectomy slit openings. Use "dog-bone" style plates and micro-screws to anchor the leads.

2.2.4.2.1. At this point, note the tails of the paddle leads will exit the skull at a soft angle via grooves sunk in the posterior edge of the craniectomies; these grooves are created as part of the craniotomy to reduce wire tension. Secure the tails to the bone surface with "dog-bone" microplates and screws.

2.2.5. Proceed to intraoperative testing.

3. Intraoperative Testing

3.1. Lift the moderate propofol sedation by discontinuing the infusion. Begin testing once the patient regains full alertness[34].

3.2. Conduct patient masked, sham-controlled parametric testing of the bilateral anterior or midlateral leads.

3.2.1. Connect all four leads to external stimulators. Turn on the external stimulators, apply stimulation at 0 V, 2 V, and 4-5 V at 60 Hz. Randomize the order, with "no simulation condition" (0 V) always occurring first and at a minimum once more during testing. Apply each train of stimulation for 3 min.

3.2.2. During each 3 min train of stimulation, record the subject's subjective experience through responses to a series of 13 questions on a visual analogue scale (0 = extremely sad or depressed and 100 = extremely happy or great mood.

3.2.2.1. Present the questions using a laptop. Phrase the questions along the lines of "I feel SAD," "I feel ANXIOUS," "I feel SETTLED emotionally," and "I feel ATTENTIVE to my surroundings."

3.2.2.2. Allow the patient to express any perceived changes in mood, attention, or cognition if they so desire.

3.3. Phase 2

Note: The second phase of surgery immediately follows the above testing. Patients were placed under general endotracheal anesthesia to allow for the implantation of a pulse generator with 2 channels on each side in the chest wall, 2 cm inferior to the clavicle. The generators were

connected individually to two ipsilateral leads using extension leads that were tunneled subcutaneously behind the ear, down the neck, and to the infraclavicular pockets. Right and left Channel 1s were connected to the ipsilateral anterior frontal pole. Right and left Channel 2s were connected to the ipsilateral lead over the mid-lateral prefrontal cortex. The final step of the intraoperative procedure involved testing the system's impedance and finally, turning it off. It was not re-activated until two to three weeks later.

3.3.1. Perform this phase immediately after **intraoperative testing.**

3.3.2. Discard lead extensions. Insert paddle tails under the parietal galea.

3.3.3. Irrigate the bicoronal incision with bacitracin solution. Sprinkle the bone openings with vancomycin powder and fit with ribbons of sterile compressed sponge (*e.g.*, gelfoam). Close the scalp with polyglactin (*e.g.*, vicryl) and nylon sutures with inverted interrupted 2-0 polyglactin sutures to galea and running 3-0 nylon to skin. Place a sterile dressing over the area. Remove the drapes and head holder.

3.3.4. Place the patient under general endotracheal anesthesia, as dictated by the patient's previous anesthesia history and comorbidities as well as the anesthesiologist's preference and expertise, for bilateral pulse generation implantation.

3.3.5. Implantation of pulse generators

3.3.5.1. Implant a pulse generator with 2 channels on each side in the chest wall, 2 cm inferior to the clavicle.

3.3.5.1.1. Make skin incisions over the parietal scalp and below the clavicle on both sides to the depth of subcutaneous fat using a standard scalpel (or surgeon's preference). In this layer, pass a hollow tunneling rod between the parietal and infraclavicular incisions. Thread the individual extension cords for each paddle through the hollow lumen of the tunneling rod then remove the tunneling rod.

3.3.5.2. Connect generators individually to two ipsilateral leads using the extension leads.

3.3.5.2.1. Tunnel the leads subcutaneously behind the ear, down the neck, and to the infraclavicular pockets.

3.3.5.2.2. Connect right and left Channel 1s to the ipsilateral anterior frontal pole.

3.3.5.2.3. Connect right and left Channel 2s to the ipsilateral lead over the mid-lateral prefrontal cortex.

3.3.5.3. Create subcutaneous pockets below the clavicles using blunt dissection.

3.3.6. Connect and turn on the system using the associated clinician programmer device, per device instructions. Once active, select each lead individually and use the "Impedance" section to test contact impedance. Record values for future reference. Turn off the system. Do not reactivate until two to three weeks post-surgery.

3.3.7. Close the incision using 3-0 interrupted polyglactin suture to fascia and running 4-0 nylon to skin. Apply sterile dressings over the area. Extubate the patient and take them to recovery.

4. Postoperative Inpatient Recovery

4.1. Keep patients on an inpatient ward for at least 48 hours post-surgery for observation. Obtain a high resolution spiral CT scan without contrast (FOV=256 mm, slice thickness=1.5 mm, gap=0, number of slices=110, pitch (table-scan ratio = 2:1 and reconstruction scan slice increment = 2 mm)) to confirm lead placement and monitor for intracranial bleeding.

4.2. Provide patients with opiate analgesics, which may be continued as needed on an outpatient basis.

5. Postoperative Testing and Stimulation Optimization Period

5.1. Perform brief psychological screenings of patients approximately 2 to 3 weeks post-implantation

5.1.1. Assess general cognitive functioning, including executive functioning and memory.

5.1.2. Assess psychological (attention, mood and social relatedness) and biological (electroencephalogram) correlates. Use the information from these assessments to inform the optimal voltage settings for clinical follow-up; these will ultimately correspond to various stimulation parameters of the different leads.

5.2. 20 min after these evaluations, activate the EpCS device for the first time after implantation. Determine the optimal voltage settings, and repeat neuropsychological testing 1 h following EpCS lead activation.

5.2.1. Discharge patients with chronic and intermittent bilateral stimulation at the following settings: 130 Hz, 4.5-6.5 V, 210 µs, across all 4 paddles for each lead; these general settings are the authors' recommendations from previously published 5 year follow-up data[33].

5.2.2. To determine optimal voltage settings in the 4.5-6.5V range, assess previously determined psychological and biological correlates to best estimate the required voltage for each particular patient.

Note: Further optimization will occur in the long-term follow-up phase.

5.3. Set stimulation to 30 min on / 2.5 h off (from the hours of 8 AM to 10 PM). Set stimulation to “off” throughout the night.

Note: These intermittent settings are strikingly different from most DBS or ECS protocols, which employ constant stimulation 24 hours per day. Patients receive an approximate total of 36,000 stimuli per day, as opposed to 345,600 had stimulation been continuous. Intermittent stimulation is chosen to attempt to optimize durable long-term change that does not relapse with cessation of treatment (*i.e.*, when the battery expires).

5.4. Stimulation optimization

5.4.1. Perform optimization from weeks 2 to 4 post-implantation. Use data previously gathered from psychological and biological correlates (see step 5.1.2) to inform choices regarding parameter adjustment and interval selection. Ultimately, use active patient input to guide parameter changes during this time, particularly thoughts regarding what appears to help the most in alleviating depressive symptoms, increasing attention, or increasing energy.

5.5. At the end of the 4th week, set stimulation parameters and hold constant for 17 weeks.

6. Chronic Stimulation Parameters

6.1. During the follow-up period, change stimulation parameters over time to continue providing optimal therapy.

6.1.1. Log the patient’s frequency, intensity, and pulse width settings over time as well as corresponding psychological and biological correlates.

6.1.2. As required by the patient’s symptoms, increase/decrease voltage parameters by modest and equal increments during each follow-up session, such as 0.5V.

Note: Changing stimulation frequency and/or pulse width is less likely to be necessary. The author’s recommendations for these parameters are listed above and are based on studies of deep brain stimulation for obsessive-compulsive disorder[35] and were altered during years 2-5 of therapy.

6.2. During the follow-up period, see participants on a **quarterly** basis. If clinically indicated, see participants more frequently, such as weekly. In addition to a clinical assessment of their functioning and symptomatology, interrogate their current stimulation parameters and adjust as needed.

6.2.1. To evaluate and adjust settings, place the extension of the programmer wand directly over an IPG (located 2 cm inferior to the clavicle) to interrogate ipsilateral paddles. Participants may leave their clothing on for programming.

6.2.2. Select **NAME OF MENU ITEM** to bring up the device stimulation parameters; this includes information on battery charge and use, cycling, frequency, voltage, contact impedance, and therapeutic delivery.

6.2.2.1. Using the "Therapeutic Delivery" section, one can measure the true level of current being delivered by each lead at that moment.

Note: As impedance may vary between subjects and even between the contacts/leads of an individual subject, this approach allows a much more accurate assessment than simply looking at voltage alone.

6.2.2.2. Because the neurostimulator does not allow for a constant current setting if more than one of the contacts is activated, use the therapy delivery to determine current delivery at a given voltage then monitor the impedance/current delivery at that set voltage over time.

Note: Impedance generally varies less than 20-50 Ω over the course of a year in a given paddle lead. The optimized range of current in past participants has been 10-15 mA.

6.2.3. Incorporate the clinical assessment and patient feedback, and make adjustments to the stimulation parameters as required. Reevaluate the effectiveness of these changes at the next clinical encounter.

Note: As one increases therapeutic delivery current between 10-15 mA, participants may eventually experience a blunting of affect and cognition. By lowering the therapeutic delivery by.5-1 mA, participants can achieve a maximal antidepressant response without the blunting of affect or cognition. These settings may be representative of the optimal stimulation range that can be individualized to the participant. This inverted U-shaped curve has been observed in movement disorder DBS programming as well[36].

6.3. Use the following settings for years 2-5 of stimulation: chronic, bilateral stimulation to the left and right frontopolar cortex and dorsolateral prefrontal cortex using a total of 4 paddle leads at 130 Hz, 4.5-6.5 V, 210 µs across all 4 paddles for each lead.

NOTE: The change from an initial 60 Hz to 130 Hz represents a difference from another study using a single paddle[27], and reflects a programming strategy more similar to DBS[37]. This change continued to reflect ideas of intermittency[38].

6.4. Continue to utilize cycling of the stimulation, including turning the stimulation off at night. Optimize the cycled stimulation on/off periods through a process of trial and error.

Note: Subjects may receive continuous stimulation, however rapidly alternating on/off cycles (on 0.1 s, off 0.1-0.2 s) may prolong battery life while simulating continuous stimulation.

6.5. Monitor batteries for depletion and replace as necessary.

REPRESENTATIVE RESULTS:

Sample Characteristics: A total of 6 patients were enrolled in this trial. 1 withdrew prior to EpCS implantation. A total of 5 patients (3 female, mean age=44.2 years, SD=9.4 years) received EpCS implantation and completed the trial through the 5-year follow-up period. Sample characteristics are summarized in **Table 1**. A total of 3 subjects had a diagnosis of MDD while the 2 remaining participants had a diagnosis of bipolar affective disorder I, depressive type. All patients were unemployed at the time of implantation and 3 continued to receive disability benefits. Depressive illness duration was on average 25.6 (± 8.3) years (mean ± SD), with the length of the current depressive episode of 3 years and 7 months (± 38 months) on average. These patients had received on average 9.8 (± 5.3) unsuccessful clinical treatments (various psychopharmacological interventions prescribed by their physician, ECT, TMS, VNS) during the major depressive episode prior to implantation. Of these pharmacologic agents, an average of 5.8 (± 2.05) met our criteria as adequate trials of antidepressant therapy[39]. At enrollment, patients were taking a mean of 6 (± 2.3) psychotropic drugs. At the time of 5-year follow-up, they were taking an average of 4.4 (± 1.34). This is a reduction in psychotropic drugs.

A total of 4 patients had received prior neuromodulatory treatments, including ECT, TMS or VNS. Only during the final 4 years of the study was VNS reactivated; it was reactivated in all 3 patients. However, no patient received ECT or TMS during EpCS treatment, given concerns regarding treatment interactions.

Intraoperative Testing: Testing during this phase consisted of a single-blind sham-controlled experiment, roughly 30 min in duration, in which active EpCS was associated with significant decreases in patients' subjective sadness ($p=0.05$) and anxiety levels ($p=0.034$) compared to baseline. Effects on self-reported attention, ability to feel pleasure, levels of trust, and levels of anger were not statistically significant. No sham conditions led to significant changes from baseline.

Clinical Outcomes: Patient scores at predetermined study landmarks are outlined in **Table 2**. At 7 and 60 months of active stimulation, the group displayed a mean Hamilton Rating Scale for Depression-24 (HRSD24) improvement of 55% (standard deviation ± 38) and 42.9% (± 38.4), respectively. All but one patient had an HRSD24 score at 60 months that was within 3 points of the 7 month score. ANOVA calculations showed a significant difference in mean HRSD24 scores across time points ($F_{5,4}=6.12$, $p<0.01$). This contrasts with post-hoc paired *t*-tests, which revealed a significant difference from baseline to 7-months ($p<0.05$), but failed to detect significance at 60 months.

Secondary Outcomes: Secondary measures included the Montgomery-Asberg Depression Rating Scale (MADRS) and the Inventory of Depressive Symptomatology, Self-Report (IDS-SR) and are outlined in **Table 3**. Both scores were significantly improved from baseline.

Functional Measures: Participants completed the Quality of Life, Enjoyment and Satisfaction Questionnaire[40], as well as the Medical Outcomes Study Short Form-36. No changes in the

patients' physical functioning, pain, and general health were noted overall 60 months post-implantation.

Neuropsychological Testing: **Table 4** outlines neuropsychological testing scores at baseline, postoperatively at 20 (± 9) weeks as well as at 60 months. No significant changes were noted at any of these time points.

Adverse Events: Distinct adverse events were noted at different stages of implantation. Intraoperatively, a small tear in the dura was created when passing a paddle through the epidural space. To mitigate this, the paddle was placed in such a way as to cover the slit defect and prevent leakage of subgaleal cerebrospinal fluid. Not accumulation of fluid was noted in the postoperative stages. During intraoperative testing, one patient experienced mild subjective dissociation when stimulated at 6 V over the anterior frontal poles.

One serious adverse event resulting in hospitalization occurred at 12 weeks post-implantation. The research team received delayed notification from the patient of oozing pus at the left scalp incision site. When the team was notified, 1 week after the patient first noticed symptoms, she underwent emergent debridement and antibiotic therapy. Conservative management was favored and the team chose to explant the affected leads. The patient experienced a temporary worsening in symptoms 2-3 weeks following lead removal, though she was otherwise asymptomatic. She displayed a 42% decrease from her baseline HRSD24 score at the 7 month follow up.

Other less severe long-term side effects were noted. Two patients with a history of migraines experienced periodic migraine attacks, however these were without notable change in frequency as compared to baseline. Another patient experienced new urinary incontinence, which improved on oxybutynin chloride extended-release. Unfortunately, this addition caused worsening of the patient's underlying essential tremor.

There were no seizures, incidents of hypomania, impulsivity, or disinhibition. No cognitive deficits were reported as compared to baseline, nor did detailed cognitive testing reveal any deficits attributable to stimulation itself (refer to **Table 4**)

TABLE LEGENDS:

Table 1. Sample demographics of all participants. The following abbreviations are used: ATHF, Antidepressant History Treatment Form; BPAD, bipolar affective disorder; ECT, electroconvulsive therapy; F, female; HRSD24, Hamilton Rating Scale for Depression 24-item; M, male; MDD, major depressive disorder; TMS, transcranial magnetic stimulation; VNS, vagus nerve stimulation. The following superscripts are used: *a* Excluding psychotherapy*; b* Mean (±SD). This table has been modified from Williams *et al.* (2016)[33].

Table 2. Individual 24-item Hamilton rating scale for depression scores. EpCS refers to epidural prefrontal cortical electrical stimulation. This table has been modified from Williams *et al.*

(2016)[33].

Table 3. changes in average group scores over time for primary (hrsd24) and secondary (MADRS and IDS-SR30) outcome measures with corresponding statistical values. The following abbreviations are used: HRSD24, Hamilton Rating Scale for Depression 24-item; MADRS, Montgomery-Asperg Depression Rating Scale; IDS-SR30, Inventory of Depressive Symptomatology 30-point Self Report; ANOVA, analysis of variance. For each of these assessments, a higher score corresponds to greater severity of depressive symptoms. This table has been modified from Williams *et al.* (2016)[33].

Table 4. Neuropsychological testing scores at baseline and post-treatment. Scores before, after 20 (±9) Weeks, and after 5 years of Epidural Prefrontal Cortical Electrical Stimulation. The following superscripts are used: *a* Mean (SD), *b* t tests compare baseline to 5-year follow up. This table has been modified from Williams *et al.* (2016)[33].

DISCUSSION:

In this manuscript, we describe the method of EpCS of the bilateral DLPFC and FPC for the treatment of TRD. This first iteration of bilateral EpCS of DLPFC and FPC resulted in a remission rate of 60% at five year follow-up, and 80% shortly thereafter, in a group of severely depressed patients[33]. Despite years of chronic stimulation of the FPC and DLPFC, no changes were noted in neuropsychiatric measures of cognition and this method was generally well tolerated by all participants.

Critical steps within the protocol**:** The current paucity of patients treated with this technique prevents strong conclusions regarding critical steps in this method. However, there are several steps that deserve consideration. Foremost is that a relatively large area of prefrontal cortex was targeted using bilateral stimulation with four paddle leads on both the bilateral DLPFC as well as the bilateral FPC. There is currently no validated technique of functional targeting for determining optimal cortical target selection for EpCS. Studies exploring rTMS of the DLPFC for treatment of depression suggest that there may be more effective targets than others within the DLPFC[41,42], but this has not yet been sufficiently explored for EpCS. Similarly, there is inadequate evidence to inform targeting of a specific subregion of FPC. As no consensus exists on how the DLPFC or FPC can be optimally targeted to treat TRD, implanting a sufficiently large area of cortical territory remains a necessary step to ensure that the relevant cortical pathways are modulated by the implanted stimulators. Indeed, suboptimal lead placement of EpCS has been shown to be associated with worsened clinical outcomes[27,43]. Until more sophisticated methods of target verification are available, intraoperative test stimulation with patient feedback will likely remain a critical step in determining the final location of EpCS lead placement[34]. Although no changes were made in lead location from this testing in the current report, participants' subjective accounts during sham-controlled intraoperative testing were related to their reports during postoperative chronic stimulation[44], indicating that this could be a viable and currently available method of predicting efficacy. Additionally, intraoperative impedance testing is necessary to ensure effective current amplitudes can be delivered to cortical nodes[45]. As detailed in the Modification and troubleshooting section, excessive impedance accounts for two

treatment failures.

Modifications and troubleshooting**:** After implantation, the bulk of troubleshooting took place within programming the neurostimulators to maximize efficacy. Through an iterative process of adjusting parameters, it was determined that a higher frequency (*i.e.,* 60Hz increased to 130Hz) and higher amplitude stimulation were associated with greater efficacy. Although stimulation amplitude was tracked as lead potential (voltage), in Subject 4 the lead impedance was found to be especially high, and the potential had to be increased sufficiently to raise the current to a level similar to the other participants (*i.e.*, 10mA). After Subject 4's stimulator potential was increased, their symptoms of depression remitted; however, this modification did not occur until after the termination of the five-year follow-up study. This observation also seems to hold significance across studies, as another report of EpCS for treatment of TRD reported a lower current of approximately 6mA and had a lower remission rate (25%)[27,43], indicating that future studies may benefit from programming amplitude based on current instead of potential[46]. This troubleshooting suggestion is further supported by the case of Subject 3, the only other participant who did not demonstrate a treatment response at the five-year follow-up. Subject 3 had progressive prefrontal volume loss with cortex receding from dura, thereby increasing the distance between cortex and the stimulator paddles and reducing the electrical current delivered to the cortex. These observations indicate that the amplitude of current delivered to the cortex is likely a crucial parameter in treating TRD with EpCS.

Limitations of the technique**:** There are several limitations to treating TRD with EpCS using the methods described herein. Foremost, the methods reported are based on a small, open-label trial with no comparison group. Thus, these methods need to be interpreted with caution, and strong conclusions regarding critical steps cannot be made. Moreover, EpCS is limited by the need for a surgical procedure and an implanted device that, like all devices, is capable of malfunctioning. Indeed, over a five-year period in our cohort of five patients, there was one infection and four device malfunctions that lead to hospitalizations. The infection occurred in Subject 3 three months after implantation and required debridement, antibiotic therapy for one week, and explantation of the patient's ipsilateral leads. Three of the four device malfunctions were battery depletion and another involved the device's connectors. These device failures were associated with a rapid loss of antidepressant efficacy, which has also been noted in a controlled trial of DBS for TRD[47]. This is an important consideration for use of this approach, as patients require close and potentially life-long follow-up with providers trained in EpCS. In the latter years and after implantation of the implantable pulse generators (IPGs), the rate of malfunctioning dropped considerably. Additionally, there remains an immediate feedback parameter that predicts later efficacy that can be used to optimize device programming; thus, similar to other implantable devices for treatment of TRD such as DBS, programming continues to require an iterative process in which parameters are modified and the effect on depression is then observed over the subsequent days to weeks before another parameter change is attempted. This also requires providers familiar with both device programming as well as management of TRD.

Significance with respect to existing methods**:** This first iteration of bilateral EpCS of DLPFC and FPC resulted in a remission rate of 60% at five-year follow-up, and 80% shortly thereafter, in a

group of severely depressed patients[33]. This remission rate is similar to current open label trials of DBS for TRD[47]; however, EpCS has fewer surgical risks than DBS, with a negligible risk for intracranial hemorrhage[48]. Although EpCS exposes patients to greater surgical risk than less invasive approaches such as rTMS, ECT, and pharmaceuticals, it is difficult to compare remission rates to these methods, as the patients selected for implanted device trials suffer from the most severe TRD and have failed multiple drug trials as well as ECT. However, EpCS is a more targeted approach than pharmaceuticals, which non-selectively affect multiple organ systems and produce numerous side effects. Further, despite the possibility that high frequency stimulation of deep grey matter targets may produce a functional lesion[49], high frequency stimulation through EpCS did not produce abnormalities in the neurocognitive testing battery[50]. Indeed, another group found improved working memory[51], which is a significant improvement from the neurocognitive deficits associated with ECT[52,53]. A potential sequential treatment approach may start with the least invasive methods (*e.g.*, pharmaceuticals, psychotherapy, and TMS, and then progress to increasingly invasive therapies from ECT to EpCS to DBS for more treatment-resistant patients).

Future applications**:** The next important step in the development of EpCS of DLPFC and PFC for treatment of TRD is to test this approach in a larger, controlled, and blinded trial. Additionally, as with all neurostimulation treatments, a major lingering question is how to individualize cortical targeting and stimulation parameters. Cortical targeting based on individualized measures of cortical function and connectivity has already begun to show promise for ECS treatment of central pain[54] and tinnitus[55,56]. As studies of ECS of the motor cortex for treatment of central pain have demonstrated, even for the motor cortex, with its tight correspondence between topology and function, functional targeting is necessary to define the particular cortical function on an individual basis[48]. Similarly, the precise anatomical location of DLPFC and FPC can be determined via MRI, and this imaging data allows for precise anatomical placement of leads using a neuronavigation system, as demonstrated in the current report. Yet, there remains room for improvement in response rates for EpCS for treatment of TRD[27,33], and placement has been identified as a factor separating responders from non-responders[27,43]. Advancements in the understanding of downstream secondary targets of stimulation for both the DLPFC[57,58] and the FPC[59] targets suggest that functional connectivity-based targeting for EpCS placement would be the next logical step[41,60]. For example, cortical locations within the DLPFC and FPC that are most functionally anticorrelated with subgenual cingulate activity may be optimal locations for EpCS placement[41,57-60]. Although there continues to be hope for effective neurostimulation-based treatments for TRD, and EpCS offers a less invasive method than DBS, an effective approach using epidural cortical stimulation has yet to be validated. The methods described in this report can be used to replicate and build upon this incipient work.

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Table 1

	Subject 1	Subject 2	Subject 3
Gender	F	M	F
Diagnosis Recurrent	MDD	BPAD Depressed	BPAD Depressed
Current Age	42	57	47
Length of Illness (years)	17	32	31
Current Depressive Episode (months)	N/A	N/A	84
HRSD Score (24 item)	23	33	33
Previous Brain Stimulation Therapies	ECT, VNS, TMS	ECT, VNS, TMS	ECT
Past Psychotherapy	Yes	Yes	Yes
Family History of Depression	Yes	Yes	No
Number of Psychiatric Treatments in Current Depressive Episode[a]	12	18	6
Current ATHF	8	8	4
Number of Psychotropics at Baseline	9	5	6
Number of Psychotropics at 5 years	5	2	5

Subject 4	Subject 5	Group
F	F	4 F/1 M
Recurrent MDD	Recurrent MDD	3 MDD/2 BPAD
31	45	44.4 (±9.7)[b]
16	32	25.6 (±8.3)
8	N/A	46 (±53.7)
29	24	28.4(±8)
VNS, TMS	None	4 Yes/1 No
Yes	Yes	All
Yes	Yes	4 Yes/1 No
8	5	9.8 (±5.3)
5	4	5.8 (±2.05)
3	7	6 (±2.23)
5	5	4.4(±1.34)

Table 2

Time	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Preoperative Baseline	23	33	33	29	24
Week of EpCS Activation	22	32	38	29	28
2 Weeks post-EpCS Activation	14	36	38	24	14
4 Months	2	33	23	29	10
7 Months	4	3	19	30	9
5 Years	7	1	38	27	8

Table 3

	Patients (n = 5) Mean Scores (SD)						
	Preop	**Activation**	**2 Weeks**	**4 Months**	**7 Months**	**5 Years**	***df***
HRSD (24 Item)	28.4 (4.8)	29.8 (5.8)	25.2 (11.5)	19.4 (13)	13.0 (11.4)	16.2 (15.6)	4
MADRS	32.0 (7.6)	31.2 (9.6)	27 (6.2)	22.0 (6.6)	14.6 (6.1)	17.0 (14.6)	4
IDS-SR (30 Item)	45.8 (16.2)	43.0 (12.9)	36.8 (19.1)	31.4 (25.3)	19.0 (18.5)	25 (18.7)	4

Repeated-Measures ANOVA			Paired t Test *p* Values		
F	***p***	**Observed Power**	**Preop vs. 4months**	**Preop vs. 7 months**	**Preop vs. 5 years**
4.867	0.009	0.879	0.092	0.037	0.13
3.886	0.022	0.683	0.075	0.043	0.052
4.419	0.014	0.842	0.1	0.023	0.065

Table 4

	Baseline	20 (±9) Weeks Follow-up
Choice Reaction Test (No. Correct)	58.80 (1.30)[a]	50.80 (20.02)
Choice Reaction Test (msec)	836.08 (432.68)	508.72 (322.89)
Choice Reaction Test (No. Incorrect)	1.20 (1.30)	9.20 (20.02)
Simple Reaction Time (ms)	402.40 (138.80)	361.82 (96.53)
Continuous Performance Task (No. False Alarms)	3.00 (2.45)	3.75 (0.96)
Continuous Performance Task (False Alarm Time—ms)	602 (90.39)	625.37 (183.61)
Continuous Performance Task (No. Hits)	18.75 (7.09)	21.50 (6.03)
Continuous Performance Task (Hit Time—ms)	536.21 (30.23)	519.59 (45.65)
Cognitive Failures Test	51.25 (10.50)	37.75 (18.37)
Modified Mini-Mental Status Examination (Total Score)	60.25 (6.95)	63.50 (0.58)

5 Year Follow-up	t^b	*df*	*p*
59.5 (0.58)	-1.41	3	0.252
605.51 (116.60)	0.75	3	0.508
0.5 (0.58)	1.41	3	0.252
393.51 (122.98)	-1.66	3	0.196
5.8 (3.77)	-0.69	3	0.539
514.27 (60.30)	1.65	2	0.241
22.2 (5.36)	0.37	3	0.734
526.32 (64.78)	0.37	3	0.734
33.2 (22.30)	2.12	4	0.101
64.6 (2.3)	-1.09	4	0.336

Table of Materials/Equipment

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Item	Name (if applicable)
3T MRI Scanner	
Computer workstation	
Imaging software	MRIcro
Electrocardiography	
Pulse oximetry	
End-tidal CO2	
Non-invasive blood pressure monitoring	
Fentanyl (50-250 micrograms)	
Propofol infusion (25-100 micrograms/kg/min	
2% lidocaine with epinephrine (2ccs)	
Equal mixture of 1% lidocaine with epinephrine 1:100,000 and bupivacaine 0.5%	
Skull clamp with surgical pins	Mayfield
Neuronavigation system	VectorVision
Paddle leads with extensions	Resume
Pulse generater with 2 channels	Synergy
Neurostimulator	Activa PC/RC
Standard aesculap power-drill	
Generic 4mm spherical diamond drill bit	
Plates and microscrews	Leibinger "Dog-bone" style
Bacitracin solution	
Vancomycin power	
Gelfoam	
2-0 vicryl sutures	
3-0 nylon sutures	
Sterile dressing materals	
Endotracheal anesthesia	
3-0 vicryl sutures	
4-0 nylon sutures	
High resolution spiral CT scan without contrast	
Opiate analgesics	
Programmer wand	N'Vision Clinician Programmer

Company/Institution (if applicable)	Other Information
Siemens	
University of South Caroline	http://www.sph.sc.edu/comd/rorden/mricro.html
(5ccs)	
IntegraTM, Plainsboro, New Jersey	
BrainLab, Westchester, Illinois	
Medtronic Inc., Minneapolis, Minnesota	
Medtronic Inc., Minneapolis, Minnesota	
Medtronic Inc., Minneapolis, Minnesota	
Stryker, Kalamazoo, Michigan	
	As dictated by patient's history and anesthesiologist's
Medtronic Inc., Minneapolis, Minnesota	

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Title of Article: Bilateral epidural prefrontal cortical stimulation for treatment-resistant depression

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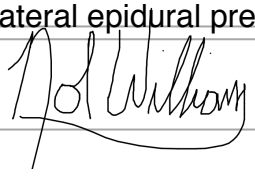
Article Title: Bilateral epidural prefrontal cortical stimulation for treatment-resistant depression

Signature:  Date: 1/31/2017

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Dear Alisha DSouza:

We hope this letter finds you well. We are contacting you with regard to our manuscript [JoVE56043] previously entitled "Bilateral epidural prefrontal cortical stimulation for treatment-resistant depression." We thank you for the kind words on our manuscript, and we are delighted that you found it potentially worthy of publication in *JoVE*. We have edited the manuscript to address all of the insightful points raised by reviewers, and these edits are listed below with the corresponding point that each addresses. We hope that you find these edits satisfactory, and we remain open to further suggestions as you see fit.

JoVE Scientific Review Editor:

The manuscript titles appears to match an existing publication, please edit the title. Please ensure that the manuscript title best reflects the filmable content (i.e. the portions you highlight).
Response: We have edited the title accordingly.

Abstracts: Your Short Abstract exceeds our 50-word limit. Please revise the Short Abstract so that it clearly states the goal of the protocol within 50 words. Please re-word the Long Abstract to more clearly state the goal of the protocol.
Response**:** We have edited the short abstract to 40 words and have reworded the long abstract to more clearly state the goal of the protocol.

Protocol Language: Please ensure that all text in the protocol section is written in the imperative tense as if you are telling someone how to do the technique
Response: We have changed all statements in the protocol section to imperative tense.

Protocol Detail: Please add more details to the following protocol steps (15 steps indicated).
Response: We have added detail to the steps indicated.

Protocol Highlights: please highlight ~2.5 pages or less of text (which includes headings and spaces) in yellow, to identify which steps should be visualized to tell the most cohesive story of your protocol steps
Response: The steps that should be visualized are highlighted for filming.

Discussion: JoVE articles are focused on the methods and the protocol, thus the discussion should be similarly focused. Please ensure that the discussion covers the following in detail and in paragraph form: 1) modifications and troubleshooting, 2) limitations of the technique, 3) significance with respect to existing methods, 4) future applications and 5) critical steps within the protocol.
Response**:** The discussion has been reformatted to focus on these areas.

Figure/table legends: Each figure or table must have an accompanying legend including a short title, followed by a short description of each panel and/or a general description. Please place the legends at the end of the results section.
Response: A legend as described has been added for each figure/table.

References: Please make sure that your references comply with JoVE instructions for authors.
Response**:** We have updated the manuscript to use the JoVE EndNote template.

Commercial language: Locate and replace all commercial sounding language in your manuscript with generic names. Figure: Since this is an image of a commercial instrument without a clear view of the settings, it may be preferable to remove it or edit to block out the commercial name "n'vision".
Response: We have removed commercial sounding language. We have also removed the referenced image from the manuscript as it does not provide accurate a clear view of the settings.

Table of Materials: Please revise the table of the essential supplies, reagents, and equipment. The table should include the name, company, and catalog number of all relevant materials/software in separate columns in an xls/xlsx file. Please include items such as surgical tools. Instruments, imaging instruments, neuronavigation system.
Response: Such a table has been created and added as Table 5.0. It is included in our updated manuscript as an xlsx file.

Other comments: Please define abbreviations. Please use standard abbreviations and symbols for Si units.
Response**:** Abbreviations have been standardized and defined.

Please add a Disclosures section.
Response**:** Disclosures section is now included following Acknowledgements.

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Please also cite the figure appropriately in the figure legend, i.e. "This figure has been modified from [citation]."
Response: A statement to this effect has been added to the relevant tables.

Reviewer #1:

Discussion: In general, not very focused and highly speculative. Would consider just summarizing the results and addressing the major outstanding questions not answered/raised by this study.
Response: As suggested by the Editor and Reviewers, the Discussion has been reformatted with subheadings to help focus the content and guide the reader. Speculative sections have been removed. A brief summary appears at the start of the Discussion, and major outstanding questions not answered/raised by this study appear in the *Future applications* subsection.

Discussion: …the fact that with EpCS over these locations, none of the neuropsych measures changed, should be emphasized more.
Response: We agree. This is now emphasized in the summary of results at the start of the Discussion as well as in the *Significance with respect to existing methods* section.

Discussion: I think you could reduce discussion to three very focused paragraphs, with the third being the 'Limitation's section. In the limitations section, make sure to emphasize that the results must be cautiously interpreted given that 1) only 5 patients are included, 2) this is an open label trial and 3) no comparison group is included.
Response: The Discussion has been significantly reduced; however, three paragraphs would not allow for the use of the subheadings recommended by the Editor and Reviewer 2. The limitations, including the above suggestions, are now under the *Limitations of the Technique* subheading.

Discussion: Consider discussing differences between MDD and BP Type I and whether these would be predicted to respond to EpCS similarly or not.
Response: We included patients with unipolar and bipolar depression. This was not associated with efficacy, but there were too few participants to draw any meaningful information beyond that this technique seems to work in both.

Discussion: Are there any other studies that provide evidence of synergistic effect of VNS and EpCS?
Response: We are not aware of any other studies that provide evidence of a potential synergistic effect of VNS and EpCS. Our study did not provide evidence of synergy, nor was it structured to assess synergy. Discussion comments about VNS have been removed to maintain focus as suggested by all Reviewers.

Discussion: Which subject had the cortical atrophy? Please indicate.
Response: Subject 3. The Discussion now includes references to specific subjects where relevant.

In 5.3.2, no explanation is given as to why 36,000 stimuli per day is superior to 345,600 stimuli per day.

Response: Intermittent stimulation is chosen to attempt to optimize durable long-term change that does not relapse with cessation of treatment (i.e. when the battery expires). In some applications (e.g., DBS for tremor), the clinical changes occur immediately after switching the stimulator on or off. This argues for stimulus-locked activation or inhibition of neural cells or modification of a pattern of desynchronization within specific neural pathways or loops (62). In contrast, other applications (e.g., DBS for dystonia or depression, ECS for chronic pain, or the unilateral EpCS study listed earlier) show delayed and gradual clinical improvements. In these cases, time-consuming processes are needed to alter synaptic plasticity critical for long-term treatment of major depression. Similarly, we have observed longer antidepressant onset with VNS applied intermittently with on/off duty cycles. This has ben included in the manuscript.

In 5.4, how the parameters were adjusted (reasoning, interval selection, etc) is not addressed.
Response**:** Further detail has been added to sections 5 and 6 detailing the adjustment of the stimulation parameters. Not all parameters need be adjusted, and we realize this was not clear in the initial draft of the manuscript. Recommended frequency and pulse width settings are now stated in these sections, and cite previous 5-year follow-up data in which these settings were refined. The setting that may need adjustment is voltage, and this setting is therefore stated as a possible range (4.5-6.5V).

No example imaging from the study is included to be able to evaluate exactly where each contact is located, which some might find useful.
Response**:** Unfortunately no example imaging from the original study is available, however we will make every effort to include exact contact placement in the video to be filmed for this publication.

Minor concerns: grammatical corrections noted.
Response: The grammatical corrections listed under Minor Concerns have been included.

Not clear what 'unsuccessful clinical treatments' means.
Response: It refers to various psychopharmacological interventions prescribed by their physician, including ECT, TMS, VNS. This has been included in the manuscript.

Is the difference between 6 and 4.4 psychotropic drugs significant?
Response: This was a non-significant difference and has been noted as such in the manuscript.

Intraoperative Testing: If many of these are not significant, consider leaving them out and simply describe in text.
Response: For clarity we have followed this recommendation and altered table 3 to focus on the most important findings, all other findings are described in text.

Intraoperative Testing: for p-values, please provide n and type of test.
Response: N and type of test has been included in the column headings for table 3 and in table legend for table 4.

Intraoperative Testing: Not familiar with most of these assessments, does higher or lower mean improvement? Should indicate this for each test in table legend.
Response: We have indicated if higher or lower means improvement for the clinical assessment tools described in table 3.

Intraoperative Testing: Why are some test results blank? Why are some test results 0? What does zero vs blank mean?
Response: Some test results are blank because they were not performed at the indicated time point. Test results are 0 are only associated with the Medical Outcomes Study 36 Item Short Form Survey (MOS-SF36), where a score of 0 indicates maximum disability and a score of 100 indicates no disability. This has been clarified in the table legend.

Consider listing the parameter settings for each patient at preop, 2 weeks, 4 months, 7 months, and 5 years.
Response: For clarity, and given the methods focus on this paper, we have included our recommended parameter settings that were developed over our previous 5-year study period. We believe our final parameter settings are most appropriate for future studies using this methodology, given that they were extensively fine-tuned during this period. However, we do include references to past publications that detail how settings changed from the 2 week to 5 year period.

Reviewer #2:

Discussion: This section requires significant revision and reduction. One approach would be the use of subheadings to guide the reader regarding which topic is being addressed, and to help them understand the context of the techniques and associated

findings.
Response: As suggested by the Editor and Reviewers, the discussion has been reformatted with subheadings to help focus the content and guide the reader.

In general, the Discussion is very lengthy, and most of it is speculative. I would strongly suggest the authors trim this section and focus on the lessons learned from their EpCS work and not venture into speculation.
Response: The Discussion has been significantly reduced in length. Speculative sections have been removed with exception of the *Future applications* subsection, which is inherently speculative.

Furthermore, the Discussion section must include the authors' reflection and interpretation of the serious adverse events.
Response: The adverse events can be found under the *Limitations of the technique* subsection. This section has been expanded.

I was surprised to discussion of these results and how they compare to other forms of invasive stimulation (e.g., sgACC DBS, VC/VS DBS, DBS to the MFB) occurred very briefly and only at the end of this section.
Response: This content can now be found under the *Significance with respect to existing methods* subsection. As the content of the Discussion has been significantly reduced, the relative size of this content is now balanced with the other subsections; thus, little has been added to this subsection.

Discussion, Page 3, middle paragraph: The section on connectivity-based optimization is very speculative for EpCS, and should be deleted. TMS focality (or lack thereof) would not be sufficient to inform EpCS electrode use/placement.
Response: The content on connectivity-based optimization appears now exclusively under *Future applications* and in a reduced form. We feel strongly that this is the next logical step in optimizing EpCS; hence, we continue to include a small discussion on this topic in this relevant subsection. Comments concerning how TMS relates to this work have been removed.

Furthermore, the manuscript appears to make claims about accelerated TBS that are not substantiated. Reference 94 showed very modest antidepressant effects, and reference 95 reported reduction in suicidality was unrelated to active or sham status.
Discussion, Page 3, last paragraph: The sentence regarding TBS is confusing; do the authors expect that EpCS will be used to calibrate later use of TBS, in the same patient? Is EpCS safe in combination with TBS?
Response: Comments regarding TBS have been removed.

Abstract - statements that EpCS may be more promising than noninvasive stimulation should be deleted.
Response: The statement to this effect has been removed.

Abstract - functional Connectivity is addressed at the end, but is otherwise not introduced nor explained. This should also be deleted or paraphrased to omit this technical term.
Response: Reference to functional connectivity has been deleted.

Short Abstract - the description of pulse generators is unnecessary in this section. This would be very confusing for those not familiar with the issue. It is appropriately included later in the manuscript body.
Response: Description of pulse generators has been deleted.

Introduction, first page, last paragraph - the manuscript states that EpCS allows more direct stimulation than noninvasive methods/ECT, creating a false dichotomy. This is not technically correct; in tCS and ECT, current flows through the tissue and in TMS current is induced.
Response: This statement has been removed.

Protocol, 1.2.1 - Please clarify that medication dose reductions are permitted, but also clarify for what reasons they can be reduced. In their experience, do EpCS patients require medication reduction after implantation?
Response: Dose reductions were permitted if improvements ere seen and patient was able to maintain clinical benefit or decrease the current or newly expressed side effects without worsening of symptoms. Increases in medication dose were advised against as higher doses of concurrent medications pose unknown combinatory risks. This has been included in the manuscript. We comment on medication reduction in EpCS patients in the Discussion, as including it in the Protocol would not follow JoVE's guidelines.

Protocol, 1.3. - please explain the rationale behind modifications to VNS use.
Response: We advised that if patients were implanted with a vagus nerve stimulation (VNS) therapy device, they turn the

device off for at least 6 months prior to, and 1 year following, their enrollment. The acute use of concurrent implantable neuromodulation techniques has not been explored and therefore we advise to turn off prior implantable devices to avoid unknown synergistic negative effects, including minimizing safety risk to patient. This has been included in the manuscript.

Protocol, 1.3.1 - please explain why ECT/TMS/DBS should not be provided (I assume the authors are thinking about potential safety issues). They do state later that DBS is MRI-safe, so this later statement will need to be reconciled with what is described here.
Response: In the longer 5-year follow-up period, VNS stimulation parameters and medications were allowed to be changed in type or dose however ECT, TMS and DBS were not be provided. This is due to conservatively minimizing risk to the patient. Also, given the placement of the implant, we believed that the electrode could potentially be damaged by external magnetic or electrical stimulation targeting nearby or underlying cortical areas. VNS is excluded from this list as it is implanted outside of the skull and its direct cortical effects are relayed polysynaptically rather than directly as ECT, TMS, and DBS do. This has been included in the manuscript.

Protocol, 2.1. - spell out abbreviations used for the first time.
Response: Abbreviations used for the first time have been spelled out.

Protocol, Phase 2 - please describe impedance and the importance of impedance testing.
Response: The importance of impedance testing has been elaborated in the Modifications and Troubleshooting section, where we outline how excessive impedance accounted for two treatment failures and how to avoid this in future studies.

Protocol, 5.2 - describe how to determine optimal settings. Much more description is needed about the trial and error nature of desirable frequency/pulse width. Please describe how this is done for these patients and provide any thoughts on how best to approach this important issue. This should include keeping a log of parameters tested.
Response: Further detail has been added to sections 5 and 6 detailing the adjustment of the stimulation parameters. Not all parameters need be adjusted, and we realize this was not clear in the initial draft of the manuscript. Recommended frequency and pulse width settings are now stated in these sections, and cite previous 5-year follow-up data in which these settings were refined. The setting that may need adjustment is voltage, and this setting is therefore stated as a possible range (4.5-6.5V). Logging parameters has been included as well.

Protocol 6.3.2 - please remove the phrase "which less like DBS stimulation." Not only is this grammatically incorrect, some DBS centers will turn off the device at night.
Response: This phrase has been removed.

Representative Results/Sample Characteristics - this section should read like a CONSORT diagram, i.e., the section should start by saying 6 patients were enrolled, 1 withdrew prior to implantation.., etc. Also, for this paragraph, sentences should not start with a number.
Response: We have corrected all sentences that begin with a number and have adjusted paragraph flow to better fit the CONSORT diagram format.

Table 3 - CGI differences between Preop and 5 year outcomes are reported to be significantly different ($p = .043$), yet baseline CGI is 5.6 (1.1) and 5-year outcome is 5.4 (3.3). Please explain/elaborate.
Response: This was an error and has been omitted.

Reviewer 3:

In Discussion, 2nd paragraph, "If coupled with a more quantitative approach for capturing affect change such as a quantitative intraoperative facial musculature(60-62) assessment(63) that could be linked to an acute antidepressant assessment(64), this may lead to further optimization of placement and dose". I do not understand to what Refs. 60-62 refer to and why you add another one after "assessment". Further on, "Particularly is TBS is utilized later, the intraoperative motor threshold would be of use in further determination of %MT for chronic stimulation(70)", the first is should presumably be if. You did not abbreviate theta-burst stimulation as TBS on your first occasion and then went on using both terms promiscuously. Please be sure to abbreviate as soon as possible (about page 17) and then to use only TBS.
Response: These sentences were removed in an effort to trim the Discussion as suggested by the other Reviewers.

You should stress stronger that this technique could be used after noninvasive techniques, like rTMS, dTMS, and tDCS have failed. So, the resistant patients you select for this technique should be more resistant than the ones selected for noninvasive methods.
Response: We agree. This comment has been added the *Significance with respect to existing methods* subsection of the Discussion

In your methods, it's not clear what were the criteria for TRD. Did you refer to any particular definition? Any reference to provide?
Response: The criteria for TRD have been included in the last sentence of the first paragraph of the Introduction: "Roughly 41% patients fail to respond to two adequate trials of pharmacologic treatment, the definition of treatment resistant depression (TRD)."

Was the participant who withdrew a man or a woman? Please, specify.
Response: Unfortunately we no longer have demographic information on the participant that withdrew from the original study.

In Adverse events, before the Tables, you state "nor did detailed cognitive testing reveal any deficits" and so on. Since you don't name the tests used, you should refer to Table 4 at this point.
Response: Reference to table 4 has been included.

You did not abbreviate theta-burst stimulation as TBS on your first occasion and then went on using both terms promiscuously. Please be sure to abbreviate as soon as possible (about page 17) and then to use only TBS.
Response: Mentions of theta-burst stimulation and TBS have been removed from the manuscript.

We hope that you find our edits satisfactory, and we look forward to hearing from you.

Sincerely,

Nolan Williams, MD *et al.*