

Video Article

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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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 depression¹. Depression is a disabling psychiatric disorder of melancholia that not only affects an individual's daily life and social functioning², but is a leading cause of premature mortality and disability worldwide³. Large clinical trials have shown that pharmacologic interventions have limited success in treating depression⁴. 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 emerged¹, though they vary widely in methodology, with some options being significantly more invasive than others⁷. Guiding these therapies is the emerging understanding of mood disorders as functions of anatomic interconnections within brain regions⁸. 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 circuit¹¹ and is consistently found to have increased resting-state activity in patients suffering from depression¹².

Research over the past decade has demonstrated the efficacy of epidural cortical stimulation (ECS)^{13,14} in managing intractable pain syndrome^{15,16,17,18}, aiding in stroke recovery¹⁹, and improving Parkinson's disease and movement disorders²⁰. These studies generally utilized chronic unilateral ECS of the primary motor cortex²¹. In addition, several cortical nodes including the anterior cingulate cortex, left temporoparietal junction, and dorsolateral prefrontal cortex have been targeted for tinnitus^{22,23,24}. 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^{27,28,29}. 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 interest²⁸. 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 tissue³¹. EpCS may therefore be preferred over more invasive stimulation techniques in patients at high

risk for surgical complications, including intracranial hemorrhage³². 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. 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.
2. Keep patients on stable medication regimens for a minimum of 4 weeks prior and for 5 months following surgery.
 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.
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.
4. A minimum 2-week recovery period follows implantation.

2. Surgical Planning and Procedure

1. Perform the entire surgical procedure while using complete hemodynamic monitoring consisting of electrocardiography, pulse oximetry, end-tidal CO₂, and non-invasive blood pressure monitoring.
2. **Phase 1**
 1. Sedation
 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. 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%.
 3. Orient the patient in a supine position on the operating table.
 2. Placement planning
 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. Use the linear "look ahead" function to indicate the underlying cortical area of interest. Map targeted cortical areas using a pointer wand.
 3. Placement
 1. Sterilely drape the patient. Make a bicoronal incision behind the hairline using a scalpel (surgeon's preference). Peel the flap forward.
 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. 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.
 4. Placement verification
 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. 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.
 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.

5. Proceed to intraoperative testing.

3. Intraoperative Testing

1. Lift the moderate propofol sedation by discontinuing the infusion. Begin testing once the patient regains full alertness³⁴.
2. Conduct patient masked, sham-controlled parametric testing of the bilateral anterior or midlateral leads.
 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.
 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).
 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."
 2. Allow the patient to express any perceived changes in mood, attention, or cognition if they so desire.
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.
 1. Perform this phase immediately after **intraoperative testing**.
 2. Discard lead extensions. Insert paddle tails under the parietal galea.
 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.
 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.
 5. Implantation of pulse generators
 1. Implant a pulse generator with 2 channels on each side in the chest wall, 2 cm inferior to the clavicle.
 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.
 2. Connect generators individually to two ipsilateral leads using the extension leads.
 1. Tunnel the leads subcutaneously behind the ear, down the neck, and to the infraclavicular pockets.
 2. Connect right and left Channel 1s to the ipsilateral anterior frontal pole.
 3. Connect right and left Channel 2s to the ipsilateral lead over the mid-lateral prefrontal cortex.
 3. Create subcutaneous pockets below the clavicles using blunt dissection.
 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.
 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

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

5. Postoperative Testing and Stimulation Optimization Period

1. Perform brief psychological screenings of patients approximately 2 to 3 weeks post-implantation
 1. Assess general cognitive functioning, including executive functioning and memory.
 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.
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.

1. Discharge patients with chronic and intermittent bilateral stimulation at the following settings: 130 Hz, 4.5-6.5 V, 210 μ s, across all 4 paddles for each lead; these general settings are the authors' recommendations from previously published 5 year follow-up data³³.
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.

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

6. Chronic Stimulation Parameters

1. During the follow-up period, change stimulation parameters over time to continue providing optimal therapy.
 1. Log the patient's frequency, intensity, and pulse width settings over time as well as corresponding psychological and biological correlates.
 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 disorder³⁵ and were altered during years 2-5 of therapy.
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.
 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.
 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.
 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.
 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.
 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 well³⁶.
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 μ s 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 paddle²⁷, and reflects a programming strategy more similar to DBS³⁷. This change continued to reflect ideas of intermittency³⁸.
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.
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 ($\pm$ 8.3) years (mean $\pm$ SD), with the length of the current depressive episode of 3 years and 7 months ($\pm$ 38 months) on average. These patients had received on average 9.8 ($\pm$ 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 ($\pm$ 2.05) met our criteria as adequate trials of antidepressant therapy³⁹. At enrollment, patients were taking a mean of 6 ($\pm$ 2.3) psychotropic drugs. At the time of 5-year follow-up, they were taking an average of 4.4 ($\pm$ 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 $\pm$ 38) and 42.9% ($\pm$ 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 Questionnaire⁴⁰, 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 ($\pm$ 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. No 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**)

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Group
Gender	F	M	F	F	F	4 F/1 M
Diagnosis Recurrent	MDD	BPAD Depressed	BPAD Depressed	Recurrent MDD	Recurrent MDD	3 MDD/2 BPAD
Current Age	42	57	47	31	45	44.4 (± 9.7) ^b
Length of Illness (years)	17	32	31	16	32	25.6 (± 8.3)
Current Depressive Episode (months)	N/A	N/A	84	8	N/A	46 (± 53.7)
HRSD Score (24 item)	23	33	33	29	24	28.4(± 8)
Previous Brain Stimulation Therapies	ECT, VNS, TMS	ECT, VNS, TMS	ECT	VNS, TMS	None	4 Yes/1 No
Past Psychotherapy	Yes	Yes	Yes	Yes	Yes	All
Family History of Depression	Yes	Yes	No	Yes	Yes	4 Yes/1 No
Number of Psychiatric Treatments in Current Depressive Episode ^a	12	18	6	8	5	9.8 (± 5.3)
Current ATHF	8	8	4	5	4	5.8 (± 2.05)
Number of Psychotropics at Baseline	9	5	6	3	7	6 (± 2.23)
Number of Psychotropics at 5 years	5	2	5	5	5	4.4(± 1.34)

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 ($\pm$ SD). This table has been modified from Williams *et al.* (2016)³³.

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 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.

	Patients (n = 5) Mean Scores (SD)						Repeated-Measures ANOVA				Paired t Test p Values		
	Preop	Activation	2 Weeks	4 Months	7 Months	5 Years	df	F	p	Observed Power	Preop vs. 4 months	Preop vs. 7 months	Preop vs. 5 years
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	4.867	0.009	0.879	0.092	0.037	0.13
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	3.886	0.022	0.683	0.075	0.043	0.052
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	4.419	0.014	0.842	0.1	0.023	0.065

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.

	Baseline	20 (±9) Weeks Follow-up	5 Year Follow-up	t^b	df	p
Choice Reaction Test (No. Correct)	58.80 (1.30) ^a	50.80 (20.02)	59.5 (0.58)	-1.41	3	0.252
Choice Reaction Test (msec)	836.08 (432.68)	508.72 (322.89)	605.51 (116.60)	0.75	3	0.508
Choice Reaction Test (No. Incorrect)	1.20 (1.30)	9.20 (20.02)	0.5 (0.58)	1.41	3	0.252
Simple Reaction Time (ms)	402.40 (138.80)	361.82 (96.53)	393.51 (122.98)	-1.66	3	0.196
Continuous Performance Task (No. False Alarms)	3.00 (2.45)	3.75 (0.96)	5.8 (3.77)	-0.69	3	0.539
Continuous Performance Task (False Alarm Time—ms)	602 (90.39)	625.37 (183.61)	514.27 (60.30)	1.65	2	0.241
Continuous Performance Task (No. Hits)	18.75 (7.09)	21.50 (6.03)	22.2 (5.36)	0.37	3	0.734
Continuous Performance Task (Hit Time—ms)	536.21 (30.23)	519.59 (45.65)	526.32 (64.78)	0.37	3	0.734
Cognitive Failures Test	51.25 (10.50)	37.75 (18.37)	33.2 (22.30)	2.12	4	0.101
Modified Mini-Mental Status Examination (Total Score)	60.25 (6.95)	63.50 (0.58)	64.6 (2.3)	-1.09	4	0.336

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 patients³³. 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 placement³⁴. 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 stimulation⁴⁴, 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 nodes⁴⁵. 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 potential⁴⁶. 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 TRD⁴⁷. 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 patients³³. This remission rate is similar to current open label trials of DBS for TRD⁴⁷; however, EpCS has fewer surgical risks than DBS, with a negligible risk for intracranial hemorrhage⁴⁸. 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 lesion⁴⁹, high frequency stimulation through EpCS did not produce abnormalities in the neurocognitive testing battery⁵⁰. Indeed, another group found improved working memory⁵¹, 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 FPC 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 pain⁵⁴ 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 basis⁴⁸. 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 FPC⁵⁹ 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^{41,57,58,59,60}. 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.

Disclosures

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