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## Bilateral Epidural Prefrontal Cortical Stimulation for Treatment-Resistant Depression

Ziad Nahas, Berry S. Anderson, Jeff Borckardt, Ashley B. Arana, Mark S. George, Scott T. Reeves, and Istvan Takacs

Department of Psychiatry (ZN, BSA, JB, ABA, MSG), Mood Disorders Program and Brain Stimulation Laboratory, and the Departments of Neuroscience (ZN, MSG, IT), Anesthesia and Perioperative Medicine (JB, STR), Neurosurgery (IT), and Radiology (MSG), Medical University of South Carolina, and the Ralph H. Johnson VA Medical Center (MSG), Charleston, South Carolina.

### Abstract

**Background**—Treatment-resistant depression presents a serious challenge to both patients and clinicians. The anterior and midlateral prefrontal cortices play complementary roles in integrating emotional and cognitive experiences and in modulating subcortical regions. Both regions offer a distinct opportunity for targeted antidepressant treatments. We chose to pilot the safety and therapeutic benefits of chronic and intermittent epidural prefrontal cortical stimulation (EpCS) in patients with treatment-resistant depression.

**Methods**—We enrolled five adults with an average of 5.8 failed antidepressant treatments in their current depressive episode. All subjects underwent comprehensive clinical assessments, detailed neuropsychological testing, and presurgical magnetic resonance imaging. Four cortical stimulation paddle leads were stereotactically placed bilaterally over the anterior frontal poles and midlateral prefrontal cortex. We also acquired a postsurgical computed tomography scan and repeatedly assessed clinical outcomes over time of EpCS as an adjunctive treatment to constant medications.

**Results**—All patients tolerated the therapy. At 7-month follow-up, the average improvement from preimplant baseline on the Hamilton Rating Scale for Depression and the Inventory of Depressive Symptoms—Self-Report were 54.9% ( $\pm 37.7$ ) and 60.1% ( $\pm 34.1$ ), respectively. Three implanted subjects reached remission. One patient's left hemisphere leads were explanted 12 weeks postsurgery because of a scalp infection.

**Conclusions**—Bilateral EpCS over anterior and midlateral frontal cortex is a promising new technology for treatment-resistant depression. Future double-blind studies are warranted.

### Keywords

Anterior poles; brain stimulation; cingulate; depression; epidural cortical stimulation; frontal lobes; medial prefrontal cortex

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Treatment-resistant depression (TRD) is a recurrent psychiatric illness and a leading cause of premature mortality due to suicide and associated medical conditions (1,2). It is also associated

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Address correspondence to Ziad Nahas, M.D., M.S.C.R., Institute of Psychiatry, 67 President Street, Charleston, SC 29425; nahasz@musc.edu.

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with high social impairments and direct and indirect health care costs (3,4). In the United States, more than 3.2 million patients are diagnosed with TRD, but only a small percentage are adequately treated following expert guidelines (5–7). Large clinical studies (8) demonstrate the fairly limited success of psychopharmacologic interventions, and new treatments are needed.

Nonpharmacologic brain stimulation therapies (BSTs) have emerged since the mid-1990s as potentially efficacious treatments for TRD (9). They vary widely in their approach, brain targets, and stimulation parameters but have all been guided by the emerging knowledge of mood-regulating systems based on known anatomic interconnections (10). Some have suggested that the anterior and midlateral prefrontal cortices play different but complementary roles in mood regulation. The frontal pole is part of a distributed network extending caudally that is now commonly referred to as the “default-mode” network (11) and has rich connections directed to the anterior cingulate cortex, precuneus, and posterior cingulate (12) and orbitofrontal and dorsolateral prefrontal cortex (13,14). It appears to be an integrative center for cognitive and emotional processing with higher-level mnemonic control operations and control of emotions, memory, and motivation. It is also involved in self-reference (15), reflective self-awareness (16), and in attributing mental states to others (17). Conversely, the midlateral frontal regions maintain preferential bidirectional connections with multimodal temporal areas, on one hand, and paralimbic cortical areas such as the cingulate, the retrosplenial cortex, and the rostral temporal cortex, on the other hand (18). The dorsal regions (of the midlateral or medial parts) are involved in the monitoring of information in working memory and the ventral regions are involved in active judgments concerning information held in posterior cortical association regions that are necessary for active retrieval and encoding of information. The lateral frontal regions also play a critical role in organizing, monitoring, and verifying information; in attending to emotional stimuli; and in reappraisal. Both anterior and midlateral prefrontal regions offer a distinct opportunity for targeted antidepressant treatments.

Epidural cortical stimulation (ECS) (19) is a unique therapeutic approach. Leads are placed through a burr hole in the skull but above the dura mater and thus remain separated from the underlying cortical region by the arachnoid space. ECS is more direct than transcranial magnetic stimulation (TMS) (20,21) or vagus nerve stimulation (VNS) (22,23) and potentially safer (24) than deep brain stimulation (DBS), which involves passing the electrodes through brain tissue (25,26). ECS generally offers a wide range of stimulation configurations that can ultimately affect the size of the induced electrical field, its directionality, and the specificity in activated neuronal elements by varying pulse width, intensity, and frequency parameters. Chronic ECS of the motor or sensory areas has been used over the past 10 years to treat intractable pain syndromes (24,27–29), enhance recovery from stroke (30) and for motor disorders such as Parkinson's disease (19). An industry-sponsored study recently reported on the feasibility of constant stimulation unilateral left dorsolateral prefrontal ECS (EpCS) in TRD with modest but encouraging results (31). We hypothesized that chronic and intermittent anterior frontal poles and midlateral prefrontal cortex EpCS could modulate both medial and lateral networks and lead to improved mood in a treatment resistant depressed cohort.

## Methods and Materials

### Recruitment and Consent

This study was conducted at the Medical University of South Carolina (MUSC) in compliance with an Investigational Device Exemption issued to Z.N. under US Food and Drug Administration (FDA) guidance. The MUSC Institutional Review Board approved the protocol. To address the ethical concerns of providing an experimental and untested intervention that required surgery, the inclusion criteria limited enrollment to depressed participants with definite histories of substantial treatment resistance. An expert psychiatrist,

independent of the study team, evaluated all patients to ensure that they were well informed of their clinical options. Written consents were obtained in the presence of a patient advocate also independent of the study team. All subjects underwent comprehensive assessments including detailed neuropsychological testing at baseline and repeatedly after implantation (details in Supplement 1).

## Participants

Eligible participants presented with a nonpsychotic, nonatypical major depressive episode (MDE) as part of either bipolar (I or II) disorder or major depressive disorder (MDD), defined by DSM-IV criteria (32). All participants scored  $\geq 20$  on the 24-item Hamilton Rating Scale for Depression (HRSD<sub>24</sub>) (33,34) before implantation and following the 2- to 3-week postimplantation recovery period, after which time the EpCS leads were activated.

Participants were included if, during their current MDE, they had not benefited sufficiently to adequate trials of at least four classes of antidepressant medications or other somatic treatments as defined by the Antidepressant History Treatment Form (ATHF) criteria (35). Further, a minimum of 6 weeks of prior psychotherapy during any MDE was required.

A minimum 2-week recovery period followed implantation. The surgical procedure (Figure 1) is detailed in Supplement 1. The EpCS paddle leads (Medtronic, Minneapolis, MN) were then activated and adjusted over 2 more weeks, after which the stimulation parameters were fixed for the subsequent 15 weeks. Participants were on stable medication regimens for at least 4 weeks before and for 5 months following implantation, except that dose reductions were allowed during this period (primary outcome). If patients were already implanted with VNS therapy, their device needed to be off for a minimum of 6 months before and 1 year after their enrollment. During the longer-term follow-up study, which followed the acute phase, stimulation parameters and medications could be changed in type or dose. ECT, TMS, and DBS could not be provided. In effect, the bulk of treatment during changes during the study consisted of EpCS dose modifications (e.g., current, frequency, duty cycle, different leads stimulated) with minimal changes in medications.

## Intraoperative Testing

After all four leads were in place (see Supplement 1 for details), they were, by extension wires, connected to external stimulators. The moderate sedation was then lifted by discontinuing the propofol infusion. After the patient was fully alert, the surgical table was adjusted with head and back elevation for better patient interaction, and testing began. We conducted a patient masked sham-controlled parametric testing of bilateral anterior or midlateral leads at 0, 2, and 4–5 V and 60 Hz. Order was randomized, with “no stimulation condition” (0 V) always occurring first and at least once more during testing. Two patients were also tested at 6 V, but their data are not included here for consistency across sessions. Each train of stimulation lasted approximately 2 to 3 min, and patients were instructed to record their subjective experience by responding to 13 questions in the form of a visual analogue scale. Questions were presented on a laptop computer placed on the patient's abdomen and were typically phrased “I feel SAD,” “I feel ANXIOUS,” “I feel SETTLED emotionally,” “I feel ATTENTIVE to my surroundings,” and so on. All patients had the opportunity to familiarize themselves with the format and content of these subjective inquiries during their preoperative baseline visits. They were also encouraged to express any perceived changes in mood, attention, or cognition.

## Postoperative Testing and Stimulation Optimization Period

The EpCS lead activation to determine stimulation parameters for chronic therapy took place on average 2 to 3 weeks postimplantation. Participants underwent a brief psychological screening 20 min before device activation. The screening measures were designed to assess

general cognitive functioning quickly, including memory and executive functioning. Patients also underwent a series of experiments to investigate the psychological (mood, attention, and social relatedness) and biological correlates (electroencephalogram) of various stimulation parameters of the different leads to determine the optimal settings for clinical follow-up. These challenge results of this baseline acute stimulation are reported separately. After optimal settings were determined, patients underwent a repeat of the neuropsychologic testing with the EpCS leads active for at least 1 hour. In general, all paddle leads with their corresponding four contact electrodes were set to “-” (the most distal contact), “+,” “-” and “+” (the most proximal contact). Patients were discharged with a chronic and intermittent bilateral stimulation of all four paddle leads at 60 Hz, 2–4 V, 30 min on/ 2.5 hours off from 8 AM to 10 PM (stimulation was “off” during nighttime). The following 2 weeks, parameters were adjusted according to patients’ input of what appeared to help the most in alleviating depressive symptoms or increasing attention and energy and then were held constant for 17 weeks. On average, patients received a cumulative 36,000 stimuli per day, as opposed to 345,600 if stimulation were continuous for 24 hours per day. (Note that these intermittent settings [30 min on, 2.5 hours off] are radically different from other DBS or ECS protocols, which have employed constant stimulation 24 hours/day.)

## Data Analyses

Response was defined a priori as a 50% or greater reduction in mean HRSD<sub>24</sub> scores relative to the average of the baseline (preimplantation) visits or, for secondary analyses, a 50% or greater reduction in the mean of baseline Montgomery-Asberg Depression Rating Scale (MADRS) score, or a 50% or greater reduction in the mean of baseline Inventory of Depressive Symptoms—Self-Report (IDS-SR) score. Remission was defined a priori as an HRSD<sub>24</sub> score of 10 or lower. We employed a last observation carried forward analysis for missing data.

All data were quality checked and queries clarified before final analyses were conducted. The intraoperative subjective visual analogue scales were specifically scrutinized and matched to notes taken during testing. Certain values were reversed when there was a documentation that the patient intended to rate the opposite immediately after pressing the mouse pad key. Several responses were deleted when there was an indication in the output files that the questions skipped rapidly before the patient was able to respond accordingly. More than 80% of the values remained unchanged. Subject 2 was dysphoric and psychomotorically slowed during testing and was unable to complete the computerized VAS. His responses were conservatively entered as 0% change from baseline for all 13 questions.

The following techniques were used: descriptive statistics (including mean and standard deviation), Shapiro-Wilks Test for normality, Kruksal-Wallis Test, one-sample *t* test for normed intraoperative subjective visual analogue scales, repeated-measure analysis of variance (ANOVA) with repeated contrasts for clinical outcomes with post hoc analyses contrasting baseline to 4-month scores and baseline to 7-month scores, and graphical displays. For cognitive and neuropsychologic testing data, paired-sample *t* tests were used to assess for change over time. All statistical tests were two-tailed at .05 alpha level.

## Results

### Sample Characteristics

Of six initially enrolled participants, five received EpCS and participated in this study. One participant withdrew consent before implantation. Table 1 summarizes the sample characteristics. The mean age was 44.2 ( $\pm$  9.4) years. Four were women, and three were diagnosed with recurrent MDD; two others had bipolar affective disorder I, depressed type. All were unemployed, and three were receiving disability. The average length of depressive

illness was 25.6 ( $\pm$  8.3) years. The average length of the current depressive episode was 3 years, 7 months ( $\pm$  38 months). It is noteworthy that participants had received an average of 9.8 ( $\pm$  5.3) unsuccessful clinical treatments during the current MDE. Of these central nervous system-active compounds, an average of 6.2 ( $\pm$  2.1) were classic antidepressant treatments of which 5.8 ( $\pm$  2.05) met ATHF criteria for trial adequacy (7). Two patients had failed a trial of a monoamine oxidase inhibitor or buprenorphine augmentation (36); one failed intravenous ketamine infusion (37), a trial of clozapine (38), and another trial of mifepristone for nonpsychotic depressive symptoms (39). Four of the patients had received prior treatments with ECT, TMS, or VNS. They enrolled in the study taking on average 6 ( $\pm$  2.3) psychotropic drugs.

### Accuracy of Lead Placement

The postoperative computed tomography scan coregistered with a presurgical magnetic imaging resonance scan identified four contact electrodes for each paddle lead. In all subjects, contact electrodes were over the anterior frontal pole or midlateral prefrontal cortex (Table 2). Note that Subject 4 had both anterior paddle leads extending more ventrally to overlap Brodmann's area (BA) 11, and Subject 5's ventral portion of the left lateral lead was directed slightly more posterior and arching over BA 45.

### Intraoperative Testing

In this single-blind sham-controlled experiment, which lasted on average 30 min, active EpCS was associated with significant decreases compared with baseline in patients' subjective sadness ( $p = .05$ ) and anxiety levels ( $p = .034$ ) despite this small sample size (Table 3). Active stimulation was also associated with more than 100% improvement in self-ratings of "improved pleasure," "sense of involvement," and "attention," but these effects were specifically pronounced in two subjects, which led to a large standard deviation and were not statistically significant. Of note is "I feel ANGRY," and the average percent change from baseline is primarily driven by one subject whose rating increased from 4/100 to 15/100, representing a 300% increase despite its relative small absolute change. Patients' trust was high at baseline and was not changed throughout the session. None of the sham conditions led to significant changes from baseline. The changes attributable to specific active leads were not exclusive, although two patients distinctly noted improved attention, increased brightness, and alertness with lateral stimulation. They commented: "I feel attentive," "feel better and I can talk now," "I can think clearer." A patient noted during anterior frontal pole stimulation feeling as if a "weight [was] lifting off my shoulder," "I feel calm"; another stated, "and although I am worried, I feel dissociated from it. I can think back at my worry." Interestingly, this last comment of subjective dissociation was observed at 6 V. The same patient would later experience similar effects during postoperative stimulation optimization period. Subject 2 failed to notice or report any positive changes across all tested parameters and became disappointed, discouraged, and dysphoric. His testing was interrupted early.

### Clinical Outcomes

Table 4 details the individual scores at study landmarks following device activation. Patients did not improve clinically 2 to 3 weeks postoperatively with the EpCS leads turned off but rather showed a 5% worsening of symptoms. However, after the leads were activated, patients showed a significant improvement over time ( $df = 4$ ,  $F = 4.867$ ,  $p = .009$ ). After 4 months of active stimulation, the group showed a mean HRSD<sub>24</sub> improvement of 36% ( $\pm$  39), which increased to 55% ( $\pm$  38) at 7 months (Figure 2, Table 5). Two patients achieved remission at 4 months, and three of five were remitted at 7 months.

## Secondary Outcomes

Mean scores of the MADRS and IDS-SR are provided in Table 5. MADRS percent change from baseline significantly improved over time (ANOVA:  $df = 4$ ,  $F = 3.886$ ,  $p = .022$ ). The IDS-SR scores at baseline, 4 months, and 7 months were also significantly improved (ANOVA:  $df = 4$ ,  $F = 4.419$ ,  $p = .014$ ). One patient reached remission after 2 weeks of stimulation based on IDS-SR of 15 or less and remained well until her 7-month follow-up. Two additional patients reached remission, one at 4-month and the second at 7-month follow-up.

## Functional Measures

Participants completed the Quality of Life, Enjoyment and Satisfaction Questionnaire (40) at baseline and at 4 and 7 months (Table 5). They also completed the Medical Outcomes Study Short Form-36 (41). At 4 months after implant, no changes were noted as a group in physical functioning, pain or general health.

## Before and After First Day of Activation

Scores for each of the brief screening measures are presented in Table 6. Significant improvement was observed on the Stroop Color–Word Test and the Sentence Repetition Test after the devices were turned on [ $t(4) = 3.81$ ,  $p = .019$ , and  $t(4) = 3.16$ ,  $p = .03$ , respectively]. No significant changes were observed across any of the other brief screening measures (Table 6).

## Baseline and Postacute Phase

No significant changes were seen after 20 ( $\pm 9$ ) weeks of bilateral EpCS compared with baseline (Table 7).

## Adverse Events

In one subject, on surgically passing one of the paddles down the epidural space over the left frontal pole, a small rent in the dura was caused. The lead paddle was successfully placed epidurally and covering the slit defect. There was no leakage or subgaleal cerebrospinal fluid collection postoperatively. Between the initiation of stimulation (turning on the device) and the 7-month follow-up, one serious adverse event occurred that required a rehospitalization at Week 12 postimplant. The patient failed to notify the research team until 1 week after noticing oozing of pus at the site of the left scalp incision. She immediately underwent debridement and antibiotic therapy for 1 week before the team elected to act conservatively and explant the patient's ipsilateral leads. She was asymptomatic otherwise. Her clinical depressive symptoms worsened temporarily for 2 to 3 weeks but began to show gradual signs of improvement afterward. At 7-month follow-up, she demonstrated a 42% drop from her study-entry HRSD<sub>24</sub> score. Two patients with a history of migraines continued to have periodic attacks without any documented changes in the frequency of their occurrences compared with baseline. One patient experienced urinary incontinence and was placed on oxybutynin chloride extended-release and had a worsening of essential tremor. One patient experienced a mild dissociative state when stimulated at 6 V over the anterior frontal poles, which was reversible upon reducing the EpCS intensity. There were no seizures, incidents of hypomania, impulsivity, or disinhibition, nor were there reports of emergent cognitive deficits compared with baseline. Of note is that the detailed cognitive testing did not reveal any deficits attributable to the stimulation itself.

## Discussion

Our primary objective was to test the potential safety, tolerability, and potential therapeutic benefits of bilateral anterior and lateral EpCS in TRD patients. We developed a unique



presurgical planning method that rendered our stereotactic surgical implant accurate and safe. In this small sample, acute stimulation during surgery of anterior and midlateral leads was associated with significant mood changes under blinded conditions. By 7 months, adjunctive intermittent open-label EpCS was well tolerated and was associated with marked and sustained improvement in three of the five severe TRD patients.

Despite the invasive nature of EpCS and the functional impairment of these patients at the time of enrollment, patients tolerated the surgical procedure and chronic stimulation with no worsening of cognition, especially tasks that involved the frontal lobes. The infection of the left surgical site at 3 months in one patient was unexpected, especially that late after implant. In one recent large study of neurosurgical postoperative infections, the mean latency between surgery and infection was 34 days, ranging from a minimum of 8 days (cerebral spinal fluid infection) to a maximum of 4 months (42). Nevertheless, the subsequent removal of the leads is a reminder of the risks associated with device implantations and craniotomies. In a recently published series, 3 of 20 (15%) DBS-implanted depressed patients had to be explanted because of infection (43), and depressed patients do have abnormal immune system function (44,45). Detailed neuropsychologic examination showed that the patients did not exhibit any cognitive impairment in attention, working memory, or problem solving that could have been possible with targeted prefrontal cortical regions. There was nonspecific increased subjective alertness and attention with both targets. The reversible dissociative experience with high-intensity stimulation in one patient was only seen with anterior pole EpCS. This is intriguing given this cortical region's role in self-reference (15), reflective self-awareness (16), and abstract integration of affective and cognitive inputs (13). All patients were continuing with the therapy at last follow-up.

Over the past decade, there have been several studies that explored subconvulsive brain stimulation for TRD. VNS therapy was one of the first to be systematically tested and is now U.S. FDA approved for TRD. In early reports on its feasibility and putative efficacy ( $n = 30$ ), adjunctive antidepressant responses at 3 and 6 months were 40% and 55%, respectively. Remission rates were up to 37% at 6 months (46). A subsequent double-blind placebo-controlled study in a larger sample and 21 clinical sites showed more modest effects with 15% response and 9% remission at 3 months (47). Six months open data were associated with 18% response and 9% remission (48). It is noteworthy that experience has shown that VNS therapy appears to have a slow onset, with response and remission rates achieving 27.2% and 15.8% at 1 year (49,50). Longitudinal imaging studies also support the gradual modulation of critical brain regions implicated in mood regulation, including medial prefrontal cortex and insula (23). In general, studies investigating VNS therapy have included 10% (51) to 27% (52) of patients with bipolar affective disorder and showed comparable response rates to the general cohort (22,47,53). There are several uncontrolled reports with small samples of successfully treating TRD using high-frequency DBS to the caudate nucleus (54), anterior thalamic nuclei (55), subgenual cingulate (26,43), the anterior limb of the internal capsule (56), or the nucleus accumbens (25). The clinical effects range between 20% and 35% remission rates at 6-month open-label follow-up (43). To our knowledge, the only other EpCS study to date involved 12 TRD patients who were randomized to active or sham single-blind treatment for 8 weeks with an adaptive open design follow-up (31). No significant difference across conditions was noted after 2 months. At 4 months, active left dorsolateral prefrontal cortex EpCS demonstrated a  $21\% \pm 23\%$  improvement in depressive symptoms. One of 12 patients reached remission at 4 months. Additional follow-up will provide critical information on further changes over time in this cohort. Importantly, this study had two major differences compared with our report: the Dougherty 2008 study involved only stimulation of the left prefrontal region, not bilaterally with four paddle leads, and the stimulation was applied in a constant manner, not intermittently.

Assuming these results are more than merely placebo, the antidepressant mechanisms of action of EpCS are yet to be elucidated. ECS over the motor cortex appears to induce its therapeutic effects at stimulation intensities below the threshold for overt motor responses. Stimulated axons could be short fibers of small inhibitory interneurons within the frontal cortex, as well as afferent or efferent fibers connected with distant cortical or subcortical structures (57). We approached stimulation targets and parameters guided by known functional neuroanatomy and previous experience in intermittent brain stimulation therapies with TMS (21,58–60) and VNS (61). It is possible that EpCS, when applied at 60 Hz, exerts strong inhibition on the underlying cellular network in the prefrontal cortex itself, locally modulating its output. The duty cycle (on/off trains of stimulation) is a key parameter because the pathophysiology of depression may benefit from intermittent stimulation to optimize durable long-term changes that are not subject to immediate relapse upon the interruption of treatment (i.e., when 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. Our current study does not yet fully address this critical theoretical hypothesis, but to the degree that we may have found some efficacy, we provide evidence that intermittent stimulation may work.

Our study has clear limitations owing to its small sample size and open design. The patients were motivated, but their treatment resistance was unquestionable. Use parameters (which combination of leads, intensity, frequency) were guided by acute subjective changes, but it is not clear whether these will predict later responses. We are using electroencephalogram and diffusion tensor imaging to understand better the structural and functional connectivity associated with EpCS (63). At this stage in the development, it is not clear why the functional measure did not show significant improvements. This is likely related to the relatively small sample size and baseline variability in functional disability. It is also not known whether a bilateral approach is always necessary to optimize treatment outcomes.

In summary, bilateral anterior pole and midlateral EpCS for TRD appears relatively safe, feasible, and, most important, has shown open-label improvement consistent with other functional neurosurgical approaches in a treatment resistant cohort. More studies are needed.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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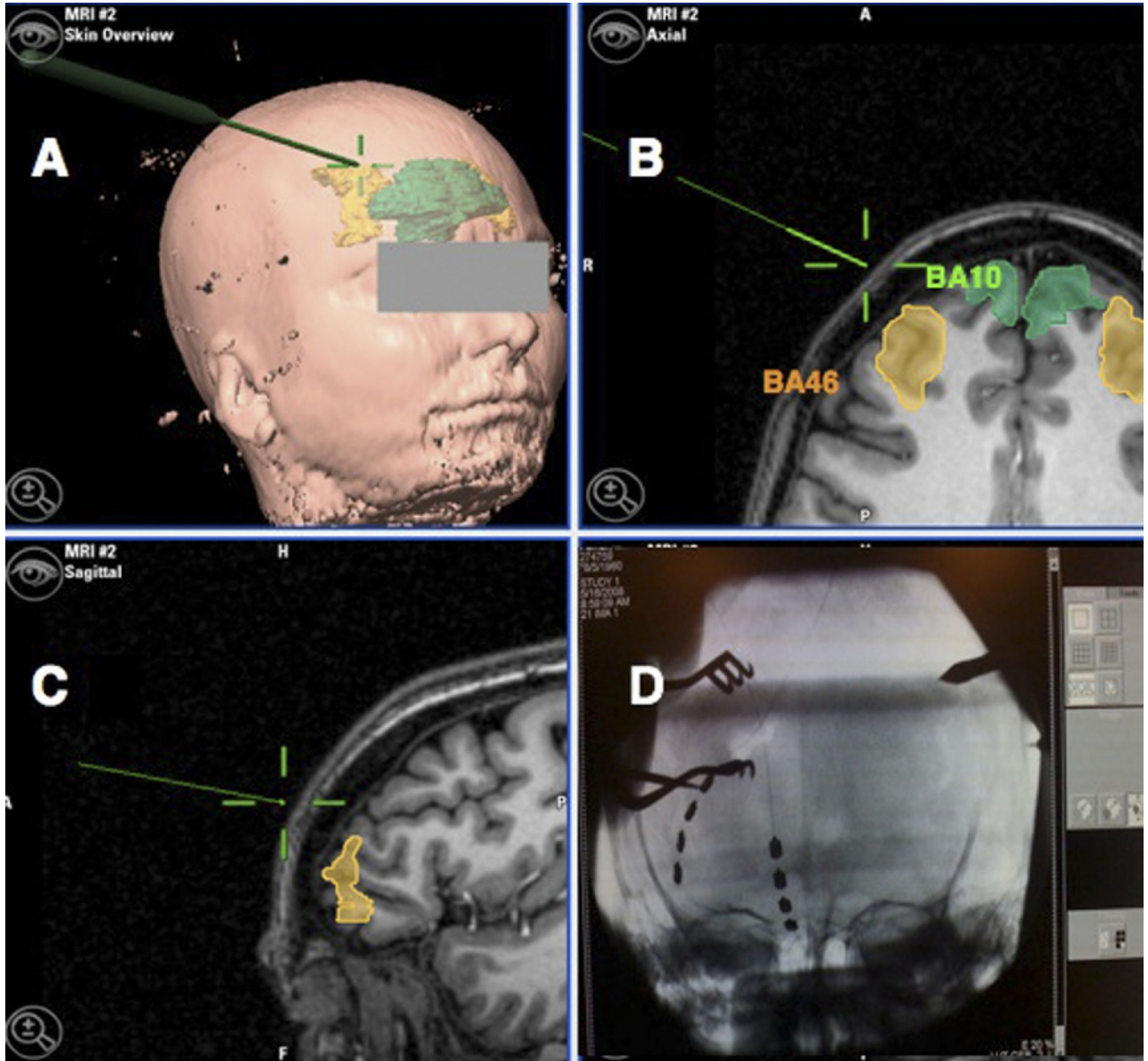
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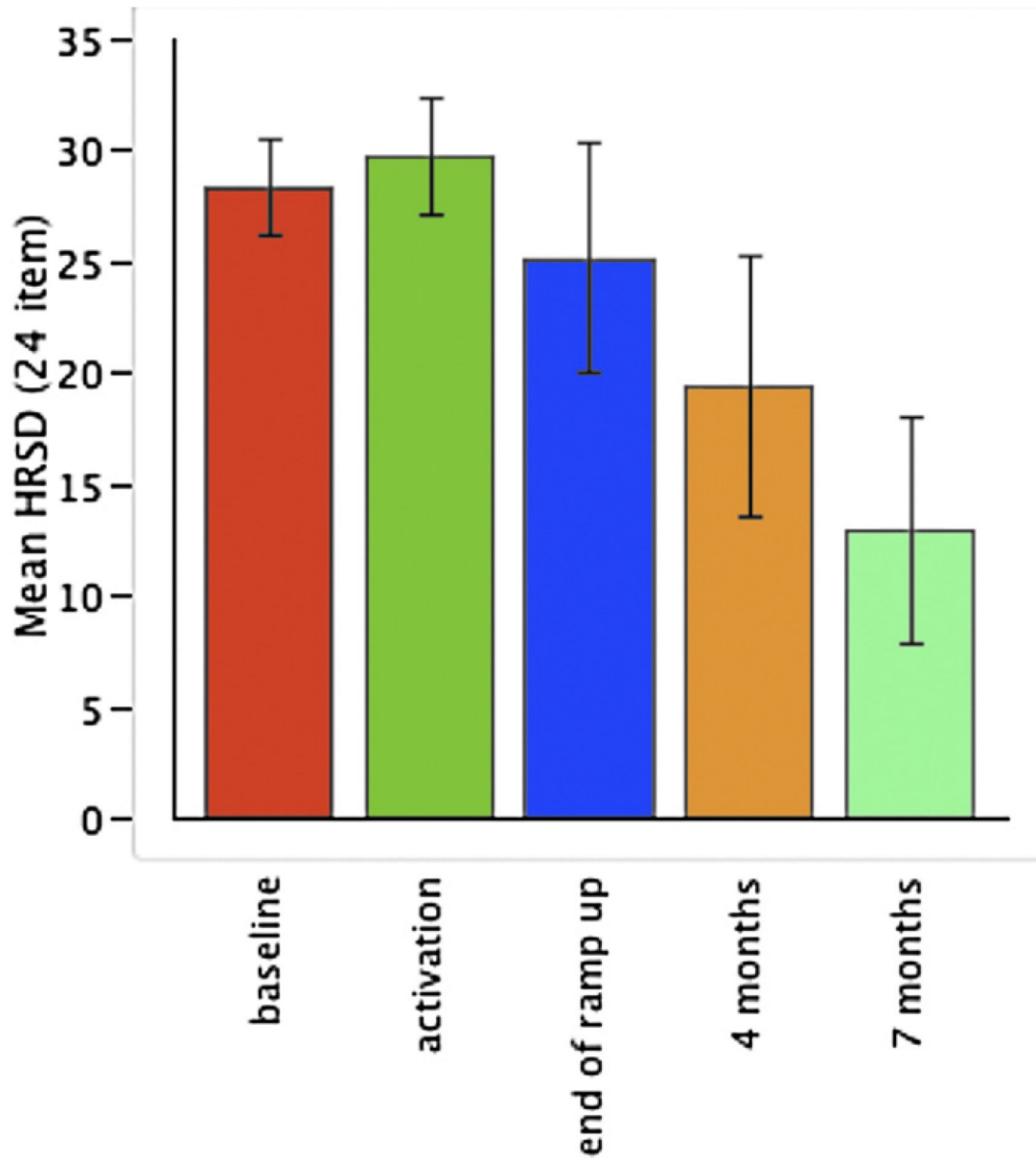
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**Figure 1.** Surgical planning and electrodes placement. Before surgery, the region of interests (Brodmann's areas [BA] 10 and 46 bilaterally) were identified and highlighted on each subject's magnetic resonance imaging (MRI) scan (**A and B**). In the operating room, the patient's head was coregistered with the MRI image using a stereotactic frameless system (BrainLab, Westchester, Illinois). A three-dimensional rendering displayed the head surface anatomy in native space with bilateral BA 10 and 46 in distinctive colors. An external wand helped identify landmarks of interest for accurate position of the leads. (**A–C**) The external wand pointing at the right midlateral region of interest (BA 46). The surgical team used intraoperative fluoroscopy (**D**) in conjunction with the stereotactic frameless system to optimize targeting accuracy.





**Figure 2.** Mean and standard error in 24-item Hamilton Rating Scale for Depression patients over time in five treatment-resistant depression-treated with adjunctive anterior pole and midlateral epidural prefrontal cortical electrical stimulation.

**Table 1**

Sample Demographics

	Subject 1		Subject 2		Subject 3		Subject 4		Subject 5		Group
	F	M	M	F	F	F	F	F	F	M	
Gender	Recurrent MDD		BPAD Depressed	BPAD Depressed	Recurrent MDD	Recurrent MDD	Recurrent MDD	Recurrent MDD	Recurrent MDD	3 MDD/2 BPAD	
Diagnosis	42	57	31	47	31	31	31	31	45	44.4 (± 9.7)	
Current Age	17	32	31	31	31	16	16	16	32	25.6 (± 8.3)	
Length of Illness (years)	31	83	83	84	84	8	8	8	8	42.8 (± 38.3)	
Current Depressive Episode (months)	23	33	33	33	33	29	29	29	24	28.4(± 8)	
HRSD Score (24 item)	ECT, VNS, TMS		ECT, VNS, TMS	ECT	ECT	VNS, TMS	VNS, TMS	VNS, TMS	None	4 Yes/1 No	
Previous Brain Stimulation Therapies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	All	
Past Psychotherapy	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	4 Yes/1 No	
Family History of Depression	12	18	18	6	6	8	8	8	5	9.8 (± 5.3)	
Number of Psychiatric Treatments in Current Depressive Episode <sup>a</sup>	8	8	8	4	4	5	5	5	4	5.8 (± 2.05)	
Current ATHF	9	5	5	6	6	3	3	3	7	6 (± 2.23)	
Number of Psychotropics at Baseline											

ATHF, Antidepressant History Treatment Form; BPAD, bipolar affective disorder; ECT, electroconvulsive therapy; F, female; HRSD, Hamilton Rating Scale for Depression; M, male; MDD, major depressive disorder; TMS, transcranial magnetic stimulation; VNS, vagus nerve stimulation.

<sup>a</sup>Excluding psychotherapy.

**Table 2**

Spiral Computed Tomography Scan Acquired Postoperatively Allowed the Identification of Each Paddle Lead and Its Four Contact Electrodes: Individual Correspondence Between Contact Electrode and Underlying Cortical Brodmann Area in All Five Subjects

	Left Midlateral Frontal Cortex	Left Anterior Frontal Pole	Right Anterior Frontal Pole	Right Midlateral Frontal Cortex
Subject 1				
Contact 4	9	9	9	9
Contact 3	46	10	10	46
Contact 2	46	10	10	46
Contact 1	46	10	10	46
Subject 2				
Contact 4	46	10	10	46
Contact 3	46	10	10	46
Contact 2	46	10	10	46
Contact 1	46	10	11	45
Subject 3				
Contact 4	46	10	10	46
Contact 3	46	10	10	46
Contact 2	46	11	11	46
Contact 1	46	11	11	46
Subject 4				
Contact 4	46	9	9	46
Contact 3	45	10	10	46
Contact 2	45	10	10	46
Contact 1	45	10	10	45
Subject 5				
Contact 4	46	10	10	46
Contact 3	46	10	10	46
Contact 2	46	10	10	46
Contact 1	46	10	11	46

**Table 3**

Intraoperative Testing

Subjective	t	df	p Value (2-tailed)	Mean Change from Baseline	95% CI of the Difference	
					Lower	Upper
Sad	-2.768	4	.050	-34.65%	-69.41	.10
Secure	1.564	4	.193	31.01%	-24.05	86.08
Tense	-.481	4	.656	-9.26%	-62.72	44.20
Angry	.761	4	.489	103.04%	-272.70	478.78
Anxious	-3.082	4	.037	-45.81%	-87.08	-4.54
Comfortable	1.857	4	.137	58.38%	-28.89	145.66
Worried	-2.376	4	.076	-36%	-78.05	6.06
Confused	-2.600	4	.060	-45.72%	-94.55	3.11
Trustful	-.373	4	.728	-1.712%	-14.47	11.05
Settled	1.845	4	.139	73.34%	-37.05	183.74
Pleasure	1.015	4	.367	102.22%	-177.31	381.75
Involved	1.611	4	.182	137.73%	-99.60	375.06
Attentive	1.573	4	.191	103.85%	-79.44	287.14

CI, confidence interval.

**Table 4**

Individual 24-Item Hamilton Rating Scale for Depression Scores over Time

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

EpCS, epidural prefrontal cortical electrical stimulation.



**Table 5**

Changes in Average Group Scores over Time for Primary (HRSD<sub>24</sub>) and Secondary (MADRS, IDS-SR<sub>30</sub>, and CGI-C) Outcome Measures with Corresponding Statistical Values, Functional Measures (Q-LES and MOS-SF36), and Average Psychotropic Drugs<sup>a</sup>

	Patients (n = 5) Mean Scores (SD)					Repeated-Measure ANOVA				Paired t Test	
	Preop	Activation	2 Weeks	4 Months	7 Months	df	F	p Value	Observed Power	Preop vs. 4 Months p Value	Preop vs. 7 Months p Value
HRSD (24 Item)	28.4 (4.8)	29.8 (5.8)	25.2 (11.5)	19.4 (13)	13 (11.4)	4	4.867	.009	.879	.092	.037
MADRS	32 (7.6)	31.2 (9.6)	27 (6.2)	22 (6.6)	14.6 (6.1)	4	3.886	.022	.683	.075	.043
IDS-SR (30 Item)	45.8 (16.2)	43 (12.9)	36.8 (19.1)	31.4 (25.3)	19 (18.48) <sup>a</sup>	4	4.419	.014	.842	.1	.023
CGI	5.6 (1.14)	5.2 (.8)	4.8 (1.3)	3 (1.2)	3.4 (1.67)	4	7.647	.0001	.981	.075	.043
Q-LES	40 (7.1)	—	—	52 (20.9)	50.4 (16.9)						
MOS-SF36											
Physical functioning	62 (21.96)	—	—	71 (25.83)	81 (12.94)						
Role limit due to physical health	0	—	—	0	0						
Role limit due to emotional problem	0	—	—	0	0						
Energy/fatigue	13 (10.36)	—	—	32 (19.55)	40 (22.63)						
Emotional well-being	36.8 (22.16)	—	—	56.8 (38.09)	67.2 (25.2)						
Social functioning	22.5 (18.54)	—	—	50 (47.59)	60 (45.41)						
Pain	67 (31.29)	—	—	65.5 (23.41)	69.5 (30.68)						
General health	50 (28.06)	—	—	50 (31.62)	66 (22.74)						
Average Psychotropics	6.23	6.4 <sup>b</sup> (2.6)	6.2 <sup>b</sup> (2.28)	6.4 (2.6)	6.6 (2.3)						

ANOVA, analysis of variance; MADRS, Montgomery-Asberg Depression Scale; IDS-SR, Inventory of Depression Symptoms–Self-Report; CGI, Clinical Global Impression; Q-LES, Quality of Life, Enjoyment and Satisfaction Questionnaire; MOS\_SF36, Medical Outcomes Study Short Form-36.

<sup>a</sup> Patient 4 self-rating was 25.

<sup>b</sup> Postoperative pain medications.

**Table 6**  
 Mean (SD) Neuropsychological Testing Scores Before and During EpCS (Testing Performed 2–3 Weeks After Implantation)

Condition	Mean and (SD)									
	<u>Cognitive Estimation</u> Number Correct	<u>Stroop Color–Word</u> Time (s)	<u>Sentence Repetition</u> Percentile	<u>Oral Trails B</u> Secs Converted	<u>Digit Span</u> Scaled Score	<u>Logical Memory I</u> Scaled Score	<u>Logical Memory II</u> Scaled Score			
Before EpCS Activation	8.40 (1.517)	8.20 (2.05)	6.00 (2.236)	86.85 (66.48)	9.40 (2.41)	10.40 (2.96)	10.80 (1.92)			
During EpCS	9.00 (.71)	11.00 (3.67)	11.00 (4.183)	71.8 (46.04)	10.00 (3.94)	10.40 (2.88)	12.00 (2.24)			

EpCS, epidural prefrontal cortical electrical stimulation.

Mean (SD) Neuropsychological Testing Scores Before and After 20 ( $\pm$  9) Weeks of Epidural Prefrontal Cortical Electrical Stimulation Therapy

**Table 7**

	Baseline Mean Score (SD)	Follow-up Mean Score (SD)	t	df	p
Choice Reaction Test (No. Correct)	58.80 (1.30)	50.80 (20.02)	.86	4	.437
Choice Reaction Test (msec)	836.08 (432.68)	508.72 (322.89)	1.22	4	.288
Choice Reaction Test (No. Incorrect)	1.20 (1.30)	9.20 (20.02)	-.86	4	.437
Simple Reaction Time (msec)	402.40 (138.80)	361.82 (96.53)	1.50	4	.208
Continuous Performance Task (No. False Alarms)	3.00 (2.45)	3.75 (.96)	-.57	3	.608
Continuous Performance Task (False Alarm Time—msec)	602 (90.39)	625.37 (183.61)	-.23	2	.839
Continuous Performance Task (No. Hits)	18.75 (7.09)	21.50 (6.03)	-2.48	3	.089
Continuous Performance Task (Hit Time—msec)	536.21 (30.23)	519.59 (45.65)	.52	3	.640
Cognitive Failures Test	51.25 (10.50)	37.75 (18.37)	1.61	3	.206
Modified Mini-Mental Status Examination (Total Score)	60.25 (6.95)	63.50 (.58)	-.89	3	.437