Epidural Cortical Stimulation of the Left Dorsolateral Prefrontal Cortex for Refractory Major Depressive Disorder

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BACKGROUND: A significant number of patients with major depressive disorder are unresponsive to conventional therapies. For these patients, neuromodulation approaches are being investigated.

OBJECTIVE: To determine whether epidural cortical stimulation at the left dorsolateral prefrontal cortex is safe and efficacious for major depressive disorder through a safety and feasibility study.

METHODS: Twelve patients were recruited in this randomized, single-blind, sham-controlled study with a 104-week follow-up period. The main outcome measures were Hamilton Depression Rating Scale-28 (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Global Assessment of Function (GAF), and Quality of Life Enjoyment and Satisfaction (QLES) questionnaire. An electrode was implanted over Brodmann area 9/46 in the left hemisphere. The electrode provided long-term stimulation to this target via its connections to an implanted neurostimulator in the chest.

RESULTS: During the sham-controlled phase, there was no statistical difference between sham and active stimulation, although a trend toward efficacy was seen with the active stimulation group. In the open-label phase, we observed a significant improvement in outcome scores for the HDRS, MADRS, and GAF but not the QLES (HDRS: $df = 7$, $F = 7.72$, $P < .001$; MADRS: $df = 7$, $F = 8.2$, $P < .001$; GAF: $df = 5$, $F = 16.87$, $P < .001$; QLES: $df = 5$, $F = 1.32$, $P > .2$; repeated measures ANOVA). With regard to the HDRS, 6 patients had $\geq$ 40% improvement, 5 patients had $\geq$ 50% improvement, and 4 subjects achieved remission (HDRS < 10) at some point during the study.

CONCLUSION: Epidural cortical stimulation of the left dorsolateral prefrontal cortex appears to be a safe and potentially efficacious neuromodulation approach for treatment-refractory major depressive disorder.

KEY WORDS: Cortical stimulation, DLPFC, Major depressive disorder, Neuromodulation, PET

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ABBREVIATIONS: DBS, deep brain stimulation; **DLPFC,** dorsolateral prefrontal cortex; **ECT,** electroconvulsive therapy; **EPCS,** epidural cortical stimulation; **FDA,** Food and Drug Administration; **FDG,** fluorodeoxyglucose; **GAF,** Global Assessment of Functioning; **HDRS,** Hamilton Depression Rating Scale-28; **MADRS,** Montgomery-Asberg Depression Rating Scale; **MDD,** major depressive disorder; **QLES,** Quality of Life Enjoyment and Satisfaction questionnaire; **rCMRG,** regional cerebral metabolic rate of glucose; **TMS,** transcranial magnetic stimulation; **VNS,** vagus nerve stimulation

According to the World Health Organization, major depressive disorder (MDD) is the leading cause of disability worldwide and the third-leading contributor to global burden of disease (World Health Organization Global Burden of Disease, 2004 Update). At its worst, untreated or unsuccessfully treated depression can be a fatal illness, leading to the loss of life by suicide. Currently available therapies for MDD include various classes of antidepressant drugs, several depression-focused psychotherapies, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagus nerve stimulation (VNS), although antidepressant

medications are used most commonly in clinical practice. The goal of antidepressant drug therapy should be the absence of significant depressive symptoms, along with a complete recovery of social and vocational function, referred to as full remission.[1] Data from the Sequenced Treatment Alternatives to Relieve Depression study of depression found remission rates of 36.8%, 30.6%, 13.7%, and 13.0% for first, second, third, and fourth treatment steps, respectively.[2] Therefore, the overall cumulative remission rate was 67%. Hence, a significant proportion of depressed patients are left with residual or persistent symptoms despite apparently adequate antidepressant therapy, whereas others have little or no response at all. Treatment-resistant depression is therefore defined as the failure to achieve a meaningful response or full remission with an antidepressant drug used at an adequate dose for an adequate duration of time.[3] Compared with MDD, chronic treatment-resistant depression is associated with persistent social and vocational disability, an increased risk of suicide, greater medical morbidity and mortality, and higher healthcare use and costs.[4-6]

The use of "neuromodulation" for depressive disorders can be traced back to late 1938 with the advent of the use of ECT, which involves the electrical induction of a generalized seizure. Electroconvulsive therapy continues to be used in patients who do not respond to treatment with standard antidepressants and psychotherapies and is still considered the gold standard for patients who have failed treatment with medication or psychotherapy. It is estimated that $>$ 100 000 people undergo ECT annually in the United States.[7] ECT has a long history of short-term efficacy, with studies showing 60% to 80% response rates.[8-10] However, its use is often constrained by concerns about stigma, amnesia, tolerability, and high relapse rates.[11]

The modern use of neuromodulation for psychiatric disorders comes from the continuing elucidation of these neurophysiological underpinnings of MDD. The first use of surgical neuromodulation for psychiatric disease was a direct evolution of the experience with stereotactic neurosurgery for psychiatric disorders. In 1999, Nuttin et al[12] used the classic anterior capsulotomy site as a deep brain stimulation (DBS) target for the treatment of refractory obsessive-compulsive disorder with promising results.

In addition, there have been several other novel neuromodulation approaches for refractory MDD introduced and evaluated for efficacy over the past decade, including VNS,[13-16] TMS,[17,18] and DBS.[19-21]

For mood disorders, TMS is usually directed at the prefrontal cortex because neuropsychological studies, neuroimaging studies, and postmortem investigations have implicated disturbances in the function of this brain region. Typically, 5 TMS sessions are administered weekly for 4 to 6 weeks for the treatment of depression. Many short-term placebo-controlled studies (using sham TMS) have used high-frequency TMS focused on the left dorsolateral prefrontal cortex (DLPFC) because this area is "hypofunctional" in depression.[22,23] Controlled studies of TMS have found it effective in major depression,[24] including treatment-resistant depression.[25] Low-frequency TMS focused on the right prefrontal cortex also is effective,[26] although this approach is less well studied than high-frequency left DLPFC stimulation. The interesting differential effects of high-frequency vs low-frequency and right vs left TMS are consistent with the known imbalance between right and left DLPFC in mood disorders.[27] On the basis of the results of a large multicenter study,[17,18] the use of TMS has been cleared by the Food and Drug Administration (FDA) for the treatment of depressed patients who have not responded to 1 antidepressant drug. The effectiveness of TMS for more refractory forms of depression may be relatively less compared with ECT.[25,28,29] The long-term efficacy, tolerability, and safety of TMS for mood disorders are still to be refined by future studies,[30] although a recently published study has been much more comprehensive in addressing these issues.[31] Furthermore, it can be a logistically difficult treatment to deliver effectively because it can require daily treatments for $\geq$ 4 weeks for optimal efficacy.[18]

Epidural cortical stimulation (EpCS) is a means of neuromodulation in which a surgically implanted neurostimulator delivers an electrical stimulus directly to a targeted area of the cortex. It has been used experimentally in the treatment of several neurological conditions, including central neuropathic pain, movement disorders, poststroke motor recovery, and tinnitus and now, in this trial, MDD.[32-35]

Our present study looked at the safety and feasibility of using an implantable system that delivers epidural electrical stimulation directly to the left DLPFC (Brodmann area 9/46) of patients with chronic, refractory MDD as a treatment option. This target is similar to that used in many TMS studies in MDD.[36]

Several converging data support the direct targeting of the DLPFC for MDD. The specific target area called for in this protocol corresponds roughly to the Brodmann transitional zone of 9 to 46.[37] Besides its thalamic projections to the ventral anterior nucleus, this cortical region has strong connections to the anterior cingulate and Brodmann area 24, areas that are potential access points to limbic-related circuitry.[38-40] Studies with TMS have indicated that successful stimulation of this site (left DLPFC) can increase the local metabolism of this site and the anterior cingulate.[41]

The primary objective of this study was to evaluate the safety and effectiveness of targeted cortical stimulation delivered to the left DLPFC in subjects suffering from chronic, treatment-refractory MDD. Furthermore, functional imaging in the form of positron emission tomography (PET) was obtained in both the baseline and treated states to examine changes in brain metabolism after treatment and to assess whether baseline patterns of brain metabolism correlate with subsequent treatment response. We hypothesize that EpCS, despite being more invasive than TMS, may hold several distinct advantages. Surgical implantation of the stimulating electrodes may lead to a more potent, consistent, and accurate stimulus delivery to the target cortex, one of the chief concerns associated with the variability seen in TMS studies.[42] Furthermore, having an implanted system may also overcome another disadvantage of TMS therapy, the need for

repetitive treatment encounters over the period of several weeks. Given the nature of the patient population, this absolute need for adherence to achieve long-term optimal efficacy is obviated by the implanted system.

METHODS

Recruitment and Consent

This was a multisite study with enrollment at 3 centers: the Medical College of Wisconsin, the Massachusetts General Hospital, and the University of Pittsburgh. Each site obtained Institutional Review Board approval, and informed consent was obtained from each subject at the time of enrollment. Subjects were recruited through ongoing clinical care at each site. This study was sponsored by Northstar Neuroscience (Seattle, Washington).

Participants

Inclusion in this study required that subjects meet criteria for *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision, diagnosis of recurrent MDD without psychotic features. Subjects either were in a current depressive episode lasting for at least 2 years or had had at least 4 lifetime major depressive episodes with the current episode lasting for at least 1 year. All subjects were adults; women were required to use contraception, and pregnancy was an exclusion criterion.

Specific exclusion criteria included strong left-handed dominance (defined as at least 75% left-handed dominance on the Edinburgh Handedness Inventory); preexisting neurological disease including epilepsy; active comorbid axis I psychiatric disorders, including substance disorders/anxiety disorders/psychotic disorders; comorbid axis 2 disorders of borderline or histrionic personality disorders; a Mini-Mental Status Examination score < 24 or other evidence of cognitive disorder; having undergone ECT within 6 months of implantation; having current and active suicidal ideation; or having a medical condition that, in the opinion of the investigator, might interfere with completion of the study.

At the time of randomization, all subjects were required to score at least 20 on the Hamilton Depression Rating Scale-28 (HDRS) and a Global Assessment of Functioning (GAF) score of < 60. To be enrolled in this study, subjects had to have a failed response to at least 4 different antidepressant treatments, which may have included medications of various psychotherapeutic classes prescribed at therapeutic doses for adequate periods of time (as determined by investigators judgment), ECT, VNS, or psychotherapy. Their current treatment regimen needed to be unchanged for at least 8 weeks before implantation.

Twelve subjects were enrolled and randomized into treatment conditions; however, 1 subject was excluded from the study analyses because of a protocol violation (inadvertent TMS treatment during the baseline period). This subject did, however, receive open-label EpCS treatment throughout the study. Data from the 11 subjects (6 men, 5 women) who completed the study are presented in Table 1.

Study Design

This was a prospective, longitudinal, single-blind feasibility study. Because this was a safety and feasibility study and not a pivotal trial supporting a premarket approval application, the sponsor, investigators, and FDA felt it was in the best interest of patient safety to keep all investigators aware of patient status. Figure 1 depicts the study design and time course.

Baseline

After informed consent was obtained, subjects underwent a series of baseline evaluations, including a neurological examination, PET and magnetic resonance imaging (MRI), electroencephalogram, and neuropsychological testing. The primary outcome measure of depression severity was the HDRS. Secondary outcome measures of depression severity and quality of life included the Montgomery-Asberg Depression Rating Scale (MADRS), GAF, and Quality of Life Enjoyment and Satisfaction questionnaire (QLES). All axis I diagnoses were confirmed by structured clinical interview. In addition, study psychiatrists assessed subjects, and their history was established through interview and review of records of previous antidepressant treatment trials and adequacy of those trials. During the baseline period, the study psychiatrist observed each subject for a minimum of 8 weeks, with subjects seen by a study investigator at least every 2 weeks; at each visit, subjects were assessed with an HDRS and MADRS and examined for regimen changes.

Study Phase

After completing their baseline assessments, eligible subjects were implanted with an investigational device system that consisted of an implanted neurostimulator and an electrode over the left DLPFC. After implantation, subjects were randomized in a single-blind manner to receive active 50-Hz continuous stimulation (n= 6) or sham stimulation (n= 5; Figure 1). One patient, after undergoing implantation, was discovered to have had TMS during the baseline period and was excluded from the data analysis. After 8 weeks, subjects randomized to sham stimulation received active 50-Hz continuous stimulation for 8 weeks. At no time were patients informed of their active or sham stimulation status. After completion of 8 weeks of 50-Hz continuous stimulation (at week 8 for subjects randomized to active stimulation and at week 16 for subjects

TABLE 1. Subject Characteristics[a]

	n	Mean	SD	Minimum	Maximum
Age, y	11	49.18	5.95	39.74	56.94
Duration of major depressive episodes at the start of study, y	11	6.99	8.14	1.25	30.00
Time since major depressive episode onset, y	11	26.72	9.97	11.23	42.68
Failed treatments, n	11	10.00	1.73	7.00	13.00
ECT treatments, n	11	16.27	N/A	0.00	84.00

[a]ECT, electroconvulsive therapy.

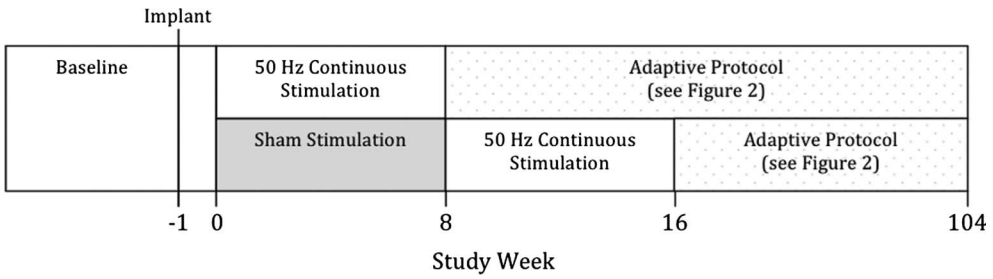

FIGURE 1. *Timeline for sham and active treatment groups. The sham-controlled stimulation session started 1 week after implantation surgery (time point 0) and continued for 8 weeks (time point 8). Patients who previously were in the sham stimulation group were then stimulated continuously with standard settings per the protocol. After this 8-week period (time point 16), all patients were programmed in an open-label manner (adaptive protocol) dictated by clinical picture and investigator judgment.*

randomized to sham stimulation), subjects entered an adaptive protocol during which device settings were based on subject response (Figure 2) and effectiveness was defined a priori as a ≥ 50% reduction relative to the average HDRS scores during the baseline period. The patients were then followed up for the remainder of the 2-year study.

Medication/Treatments

Cortical stimulation was used as an adjunctive treatment, added to a treatment regimen that was stable for at least 8 weeks before implantation. After this baseline observational period of 8 weeks, subjects were continued on their stabilized regimen of antidepressant, mood stabilizer, or other psychotropic medications (eg, atypical antipsychotics). After baseline studies were completed, any changes in medication type and dosage were to be discouraged (particularly during the first 16 weeks) and noted. Adjustment of stimulation parameters was to be the first line used to address depression severity. Psychotherapy was kept consistent throughout the baseline period and initial 16 weeks of the study. Concomitant investigational drugs or treatment of depressive symptoms with another medical device was not permitted during the study. Because the safety of the use of this device concomitantly with ECT is unknown, ECT was not permitted during the trial.

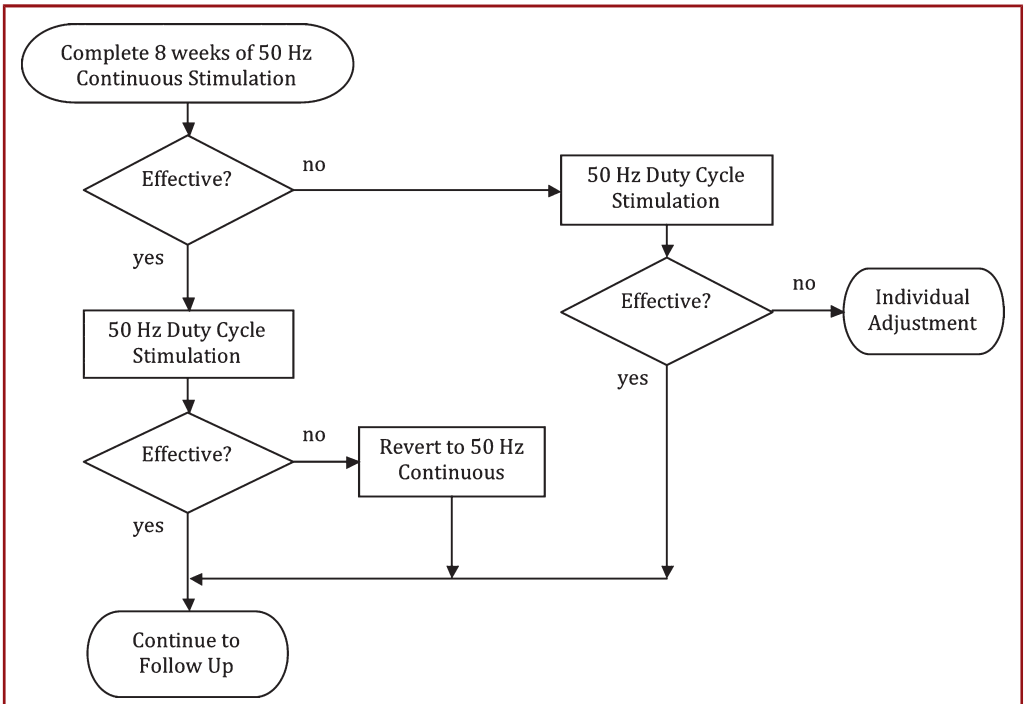

FIGURE 2. *Flow diagram of stimulation parameters used during the adaptive protocol phase.*

Brain Imaging Protocol

An MRI was performed for the purpose of surgical planning with a commercially available, whole-body, high-speed scanner with a 1.5- or 3.0-T magnet. Subjects also underwent fluorodeoxyglucose (FDG) PET at baseline. Approximately 5 to 10 mCi[18] FDG was injected intravenously into the patient, who remained in a quiet room with his or her eyes open. After a 45-minute uptake period, the patient's head was immobilized with a custom fabricated head holder and positioned so that the imaging plane was parallel to the orbitomeatal line. Emission data were acquired in a single bed position for 30 minutes. The primary imaging parameters of the HR+ PET scanner are in-plane and axial resolutions of 4.5-mm full width at half-maximum and 63 contiguous slices of 2.5-mm separation. The HR+ images were reconstructed with a conventional filtered back-projection algorithm to an in-plane resolution of 4.5-mm full width at half-maximum. Projection data were corrected for nonuniformity of detector response, dead time, random coincidences, and scattered radiation. An analytic attenuation correction was applied to the data on the basis of an estimate of slice contour and the assumption of a uniform attenuation coefficient equal to that of water. A repeat FDG PET scan was done after the subject met response criteria or reached study week 28, whichever occurred first. This repeat scan was obtained 2 hours after the neurostimulator was temporarily inactivated.[42]

Identification of the Stimulation Site

From the MRI images, the investigators identified the target as the DLPFC for placement of the stimulation electrode. The electrode grid was to be placed on the midportion of the middle frontal gyrus by placing the posterior edge of the electrode grid 2 cm anterior to the precentral sulcus, inferior to the sulcus frontalis superior, and superior to the sulcus frontalis inferior (Figure 3). Data from the imaging studies were transferred to a frameless stereotactic neuronavigation system, whereupon the surgical and the cortical sites for electrode placement were projected for use by the neurosurgeon.

Surgical Procedure

While the patient was under general anesthesia, the surgical site was prepared for an approximate 4-cm-diameter craniotomy centered directly over the predetermined area of the left dorsal lateral prefrontal cortex as guided by stereotactic neuronavigation.

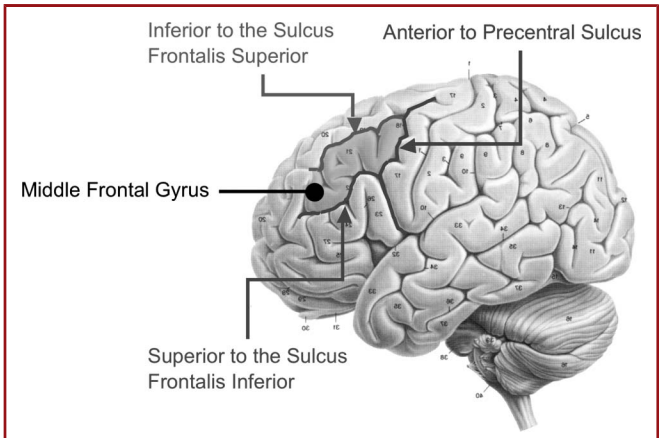

FIGURE 3. *Surface location of intended target site of the stimulation electrode, the middle frontal gyrus. Specifically, the a priori intent was to place the posterior edge of the electrode grid 2 cm anterior to the precentral sulcus, inferior to the sulcus frontalis superior, and superior to the sulcus frontalis inferior. This corresponds to the transcranial magnetic stimulation target most often reported to have an antidepressant effect.*

The electrode was placed epidurally (outside and lying on the dura) over the posterior half of the middle frontal gyrus as described above. The electrode was anchored by suturing it to the dura (Figure 4). After electrode placement, the craniotomy bone flap was secured in place. With the use of standard tunneling procedures, the electrode lead was tunneled beneath the scalp and the skin of the neck and connected to a subclavicularly implanted neurostimulator.

Subjects remained in the hospital overnight after neurostimulator and electrode placement surgery. Before discharge from the hospital, a postoperative head computed tomography scan (without contrast) was acquired. This scan was coregistered with the preoperative MRI scan to verify that electrode placement was in the desired location.

Stimulation Procedure

The implanted stimulation system was designed and manufactured by Northstar Neuroscience. The system was a current-controlled

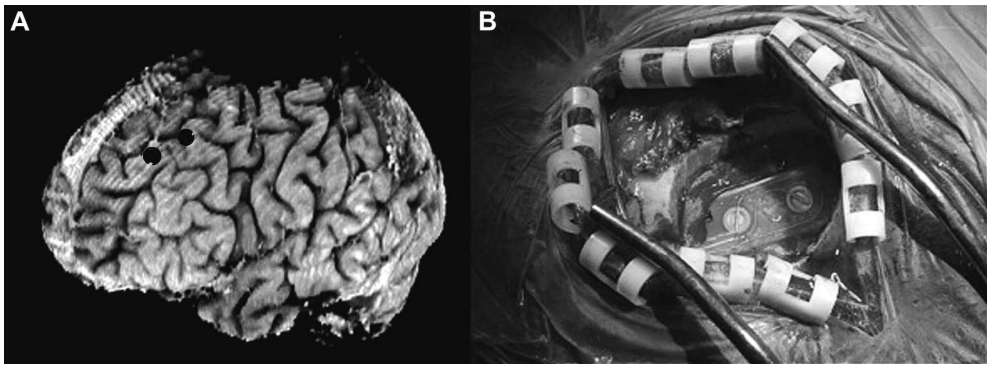

FIGURE 4. **A**, *surface anatomical rendering of the brain. The black dots represent the position of the contacts of the electrode over the anatomic target region.* **B**, *example of actual electrode during surgical implantation procedure.*

neurostimulator with a Silastic electrode. The electrode consisted of 2 platinum-iridium contacts (3.75-mm diameter, 15 mm apart on center). As noted, after implantation, subjects were randomized in a single-blind manner to receive active 50-Hz continuous stimulation (n = 6) or sham stimulation (n = 5). After 8 weeks, subjects randomized to sham stimulation received active 50-Hz continuous stimulation for 8 weeks. On completion of 8 weeks of 50-Hz continuous stimulation (at week 8 for subjects randomized to active stimulation and at week 16 for subjects randomized to sham stimulation), subjects entered an adaptive protocol wherein device settings were based on subject response. The stimulation delivered during the 8 weeks for the test group and 16 weeks for the sham group was as follows: pulse width, 150 microseconds; polarity, anodal; and current, 6.5 mA. The goal of the adaptive protocol was to optimize outcomes and battery life.

Outcome Measurement

From after implantation to week 14 in 2-week intervals, subjects were assessed for adverse events and had their stimulator checked. They were also assessed with the HDRS and MADRS. At week 16, the above measurements were taken, along with neurological exam, the Mini-Mental Status Examination, the Clinical Global Impressions scale, the GAF, and the QLES. The subjects were then assessed every 4 weeks (weeks 20 and 24) in a fashion similar to that at weeks 2 to 14. At week 28, an evaluation similar to that at week 16 was performed with repetition of the baseline neuropsychological battery. Subjects were followed up until week 104. At weeks 24, 34, 46, 65, and 91, they were assessed in a manner similar to that at weeks 2 to 14. Subjects were seen at weeks 40 and 78, at which time they were assessed in a manner similar to that at week 16. Finally, subjects were seen at weeks 52 and 104 and were evaluated in a manner similar to that at week 28.

At 52 weeks, interim analysis revealed that there was an interaction between electrode placement location and efficacy of the implant (see Results). At that time, certain subjects were offered a revision surgery.

Adverse Event Recording

Adverse events were recorded and tracked in all patients in this study, including the patient excluded because of protocol violation in the baseline period. Epoch 1 covered any adverse events from study inception to the study dissolution at 104 weeks. Epoch 2 covered any adverse events from study dissolution to explantation of the device.

Statistical Analyses

Statistical analysis was performed with SPSS version 17 (SPSS Inc, Chicago, Illinois). The QLES and GAF were measured at baseline (before surgery), followed by periodic reevaluation until week 78. The HDRS and MADRS were measured at least 5 times during baseline (before surgery), followed by periodic reevaluation until week 104. For each outcome, the active (n = 6) vs sham (n = 5) groups were evaluated during the blinded period with a *t* test that compared differences from baseline average to 8-week values. Longitudinal effects were evaluated by first adjusting each patient to treatment duration and then averaging each outcome over 3-month epochs through the course of the study. The effects of stimulation as a function of time were evaluated with a repeated measures ANOVA.

For the PET data, after reconstruction, movement-corrected, whole-brain normalized images reflecting regional cerebral metabolic rate of glucose (rCMRG) were transformed to Montreal Neurological Institute space (http://www.bic.mni.mcgill.ca). After spatial normalization, scans were filtered with a 12-mm full width at half-maximum 2-dimensional gaussian filter. Analysis of whole-brain, voxel-wise PET data followed the theory of statistical parametric mapping and was performed with SPM2 software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, United Kingdom).

For the predictors or response analyses, a statistical parametric map was generated reflecting the relationship between rCMRG and percentage improvement in the HDRS score. The ''covariates only'' option was selected, so that a regression analysis was performed to test the linear relationship between rCMRG and HDRS change, yielding a z score at each voxel in space. For ease of discussion, we refer to the findings in terms of significant correlations, although the analysis used formally involved linear regression rather than assessment of correlation per se. Both direct and inverse relationships were assessed. For analyses of within-group changes in rCMRG after treatment, voxelwise analyses were performed using the theory of statistical parametric mapping in which, at each voxel, PET data were normalized to the global mean and fit to a linear statistical model by the method of least squares.

Our a priori regions of interest for the predictors of response analyses were the DLPFC and pregenual anterior cingulate cortex; we hypothesized that within-group changes would occur in the DLPFC. The statistical parametric maps were inspected to identify all foci of significant correlations. Because this represents the first study of its kind, we chose to use relatively liberal statistical thresholds in the hope of generating more refined hypotheses for future studies; more stringent thresholds together with more circumscribed hypotheses are recommended for follow-up experiments. Although $z > 2.58$ ($P < .005$, uncorrected for multiple comparisons) was selected a priori as our threshold for statistical significance, such findings should not be taken as strong evidence of reliable effects before corroboration, ideally by independent replication.

RESULTS

We evaluated 11 patients over a 104-week period. During the first 8 weeks after surgery, patients were blinded and divided into active (n = 6) and sham (n = 5) groups. Baseline statistics for the patient sample are summarized in Table 1. Descriptive statistics about the patients are provided in Table 2. The ranges of stimulation parameters used for each patient are summarized in Table 3.

Blinded Period

During the 8-week single-blind period after surgery, we observed a trend toward improvement for all major outcome measures for the active group vs the sham group (Figure 5), although none of these differences was statistically significant (HDRS, $P > .1$; MADRS, $P > .2$; GAF, $P > .4$; QLES, $P > .3$; *t* test). Debriefing of the subjects revealed no indication that the patients ever knew their active or sham stimulation status.

Over the first 16 weeks of the study, we observed that clinical improvement in the primary outcome measure (HDRS) was significantly correlated with electrode distance from the precentral sulcus with a roughly bimodal distribution in which electrodes placed posterior to the aforementioned target site appeared to be less efficacious than those placed at or anterior to the target site (Figure 6).

TABLE 2. Baseline Statistics for Subjects[a]

Initial Treatment Arm	n	Mean	SD	Minimum	Maximum
Active					
Baseline HDRS	6	34.43	6.54	27.80	46.40
Baseline MADRS	6	31.97	5.07	26.40	40.60
Baseline GAF	6	42.00	7.69	35.00	50.00
Baseline QLES	6	34.50	8.04	25.00	46.00
Sham					
Baseline HDRS	5	34.04	2.96	29.40	37.00
Baseline MADRS	5	32.16	2.08	29.60	34.40
Baseline GAF	5	42.60	3.36	38.00	45.00
Baseline QLES	5	34.60	3.29	31.00	39.00
All/ active					
Baseline HDRS	11	34.25	4.99	27.80	46.40
Baseline MADRS	11	32.05	3.82	26.40	40.60
Baseline GAF	11	42.27	5.85	35.00	50.00
Baseline QLES	11	34.55	6.06	25.00	46.00

[a]GAF, Global Assessment of Functioning; HDRS, Hamilton Depression Rating Scale-28; MADRS, Montgomery-Asberg Depression Rating Scale; QLES, Quality of Life Enjoyment and Satisfaction questionnaire.

Long-term Outcomes

Patients with electrodes located < 2 cm in front of the precentral sulcus were offered revision surgery at week 52. Of the 6 patients in this group, 3 underwent lead revision.

During the first 21 months of treatment, we observed a significant improvement in outcome scores for the HDRS, MADRS, and GAF but not for the QLES (HDRS, $df = 7$; $F = 7.72$; $P < .001$; MADRS: $df = 7$; $F = 8.2$; $P < .001$; GAF: $df = 5$, $F = 16.87$, $P < .001$; QLES: $df = 5$, $F = 1.32$, $P > .2$; repeated measures ANOVA; Figure 7). With regard to the HDRS, which was the primary outcome measure for the study, 6 patients had a $\geq 40\%$ improvement and 5 patients had a $\geq 50\%$ improvement at some point during the study. Overall, 4 subjects achieved remission at some point during the study (HDRS < 10; Figure 8). Decreases in scores for HDRS and MADRS and increases in scores for QLES and GAF indicate improvement. During this study, there were no recorded changes in medications except for the single patient excluded from data analysis.

Revision Surgery Outcomes

Six patients were noted to have electrodes more posteriorly than the a prior target region, defined as 2 cm in front of the precentral sulcus. After consultation with the FDA and the local Institutional Review Board, these patients were offered revision surgery. Three patients gave consent to undergo revision. One patient's electrode was moved from 9 to 26 cm; another patient's electrode was moved from 11 to 23 cm; and the third patient's electrode was moved from 16 to 32 cm in front of the precentral sulcus. After 4 months of stimulation after the revision, the average change in HDRS was -4.0 and the average change in MADRS was -0.1 (Table 4).

PET Outcomes

The predictors analyses found a positive correlation between baseline rCMRG in 1 a priori region, the DLPFC ($z = 3.12$, $k = 83$, $x = 38$, $y = 22$, $z = 32$), and subsequent clinical response as measured by percentage change in the HDRS. Interestingly, this correlation was with baseline rCMRG in the right dorsolateral prefrontal cortex (see Figure 9 and Table 5), whereas the electrode was placed over the left DLPFC. Post hoc findings included positive correlations between subsequent clinical response and baseline rCMRG in bilateral superior frontal gyri ($z = 3.94$, $k = 161$, $x = 48$, $y = 22$, $z = 52$; $z = 3.56$, $k = 629$, $x = -44$, $y = 2$, $z = 58$), right cuneus/precuneus ($z = 3.22$, $k = 42$, $x = 16$, $y = -48$, $z = 30$), and right posterior cingulate cortex ($z = 3.15$, $k = 169$, $x = 16$, $y = -26$, $z = 36$). There were no significant negative correlations between baseline rCMRG and subsequent clinical response.

Analysis of changes in rCMRG after long-term stimulation revealed an increase in rCMRG in 1 a priori region, the left DLPFC ($z = 2.76$, $k = 7$, $x = -28$, $y = 12$, $z = 36$). Note that this region within the left DLPFC (see Figure 10 and Table 6) is below the electrode location but not on the cortical surface. Post

TABLE 3. Stimulation Protocol

Subject	Pulse Width, μs	Frequency, Hz	Amplitude, mA	Polarity
103	150	50	6.5	Bipolar, monopolar (1 or 2 anodes)
105	150-250	50	6.5	Bipolar, monopolar (1 or 2 anodes)
106	150-250	50	6.5	Monopolar (2 anodes)
108	150-250	50	6.5	Monopolar (2 anodes)
201	150	50	6.5	Monopolar (1 or 2 anodes)
202	150	50	6.5	Monopolar (1 or 2 anodes)
203	150	50	6.5	Monopolar (1 or 2 anodes)
204	150-250	50	6-6.5	Monopolar (1 or 2 anodes)
303	150-250	50	6-6.5	Monopolar (1 or 2 anodes)
304	150-250	50	5.5-6.5	Monopolar (1 or 2 anodes)
306	150-250	50	6.5	Monopolar (1 or 2 anodes)

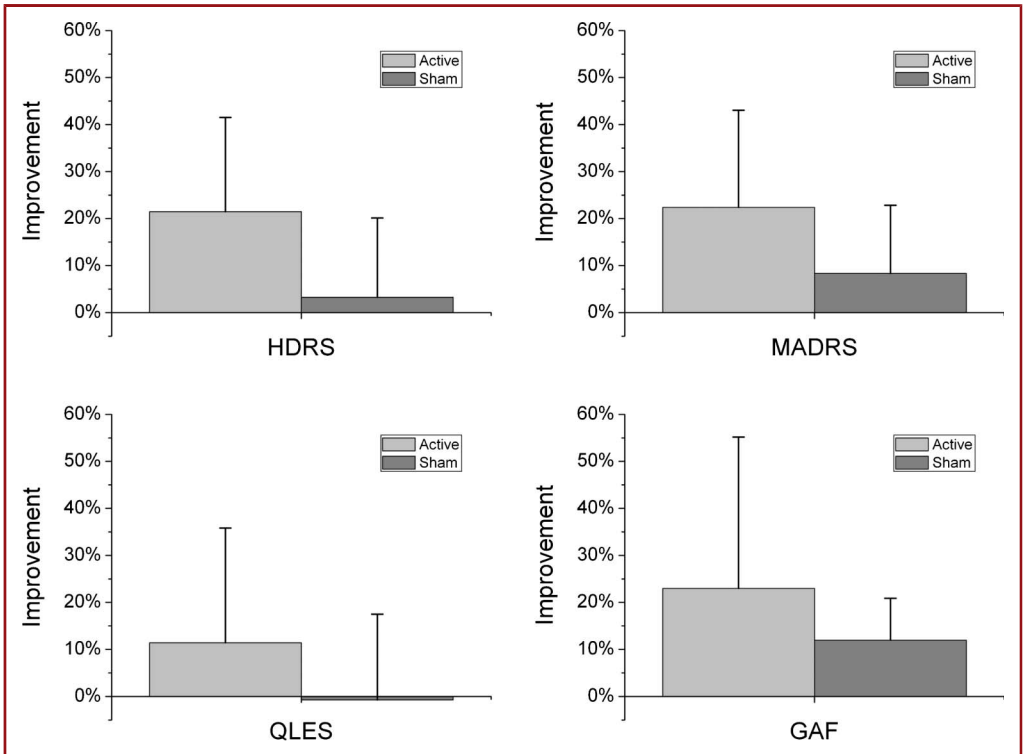

FIGURE 5. *Efficacy during the 8-week sham-controlled stimulation period. Mean ± SD for improvement of 4 outcome measures at 8 weeks vs baseline. All outcomes displayed a trend toward higher improvement levels for active group vs sham group. GAF, Global Assessment of Functioning; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; QLES, Quality of Life Enjoyment and Satisfaction questionnaire.*

hoc findings included increases in rCMRG in the left orbitofrontal cortex ($z = 2.91$, $k = 11$, $x = -22$, $y = 24$, $z = -10$) and left precentral gyrus ($z = 2.87$, $k = 16$, $x = -46$, $y = -4$, $z = 22$). There were no significant decreases in rCMRG after long-term stimulation.

Adverse Events

Epoch 1 (Study Period)

There were no surgery-related adverse events such as intracranial hemorrhage, infection, or hardware complications. We also did not observe any serious stimulation-related side effects (eg, seizures), significant adverse neuropsychiatric phenomena (eg, hypomania, mania, or psychosis), or adverse cognitive effects (eg, working-memory deficits) among the 11 patients in the study.

The patient who was excluded from the study because of protocol violation in the baseline period attempted suicide during this period via a medication overdose. The patient required intubation and acute medical management in an intensive care setting.

Epoch 2 (From Study Dissolution to Explantation)

Two adverse events were noted in this period. One patient developed a bone flap infection after the explantation surgery. The bone flap was removed, and the infection was resolved with intravenous antibiotics. An artificial prosthetic flap was eventually reimplanted without incident.

One patient completed suicide despite regularly scheduled appointments with the study team, her outpatient psychiatrist, her outpatient psychotherapist, and her TMS team during which she repeatedly denied suicidality. It appears that the suicide was planned rather than spontaneous in that the patient acted while her husband was away and left a note. This was the patient initially excluded from efficacy follow-up owing to protocol violation in the baseline period who attempted suicide in epoch 1.

DISCUSSION

This feasibility study indicates that EpCS appears to be a potentially safe approach in the treatment of refractory MDD. There were no major complications in terms of the surgical implantation procedure, neuropsychological functioning, or hardware-related issues. This underscores the potential advantage of EpCS over DBS as a means of surgical neuromodulation for MDD; the less invasive approach of EpCS obviates the need to penetrate brain parenchyma. In addition, PET FDG studies

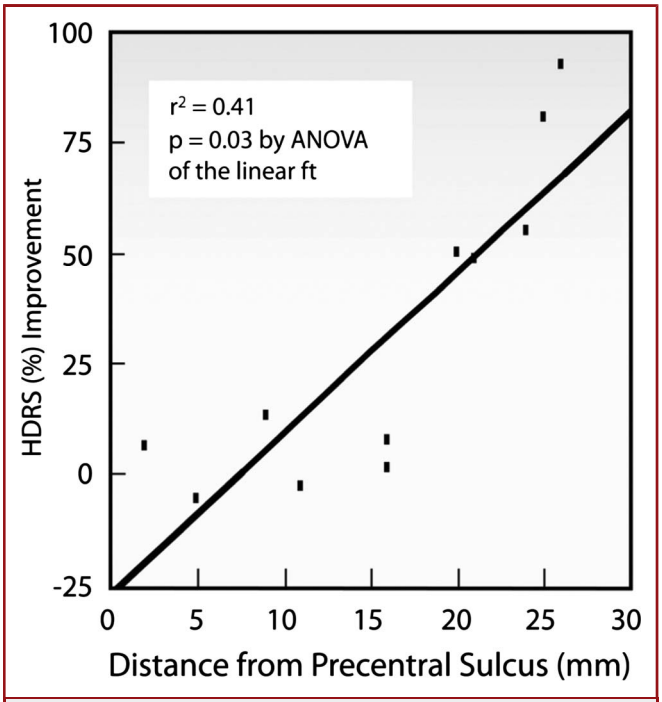

FIGURE 6. *Relationship of the position of the electrode with respect to percent improvement in Hamilton Depression Rating Scale (HDRS) scores for each of the 11 patients. ANOVA, analysis of variance.*

demonstrated that higher baseline rCMRG in the DLPFC correlated with subsequent clinical response to EpCS and that long-term treatment with EpCS resulted in increased rCMRG in the DLPFC. These supplementary preliminary PET studies suggest that baseline neuroimaging may ultimately prove useful for patient selection and may provide clues as to the mechanism of action of EpCS.

The single wound infection occurred during the explantation procedure. Although bone flap infection is a well-known adverse event from craniotomy,[43] MDD patients are known to have concomitant immune system dysfunction that may make them more susceptible to postsurgical wound infections.[44]

With regard to the decision to explant all patients after study dissolution, because the company was being dissolved, all devices had to be accounted for and destroyed per FDA mandate. Although responders could have been implanted with similar commercially available stimulation technology, that would have required a company sponsor and a funded clinical trial, which the investigators were unable to procure by the time all batteries had become depleted.

Although the sole serious adverse event in this series occurred in the patient who was excluded from the formal study, it underscores the very fragile nature of the typical patient enrolled in surgical neuromodulation studies in the psychiatric arena. Several antecedent factors may have contributed to the patient's ultimate decision to end her life. Most notably, this patient had a nearly lethal suicide attempt earlier during the study period. Other contributing stressors include dissolution of the patient's marriage the preceding month and several significant losses in the preceding year (eg, death of mother and death/severe illness of other close family members). We cannot exclude the possibility that news of required EpCS device explantation (owing to liquidation of the study sponsor) may have served as an additional antecedent. Several factors suggest that the suicide may have been planned (rather than the result of impulsive act): A suicide note was left addressed to the spouse; household bills were reported to be neatly organized and left in plain view; and the anniversary of the death of the patient's father was on or about the same date as her suicide. In summary, a large number of conspiring factors played a role in her suicide; therefore, the pending withdrawal of EpCS cannot be solely implicated.

One contributing factor that could have increased morbidity in this study was related to battery life. Patients generally required stimulation amplitudes that resulted in only a 9-month battery life. There were 21 neurostimulator replacements in the 11 patients followed up to week 104. Future sponsors of these types of studies must ensure that if a primary cell neurostimulator is used, the battery life must be projected to last the entire study or a rechargeable system should be considered.

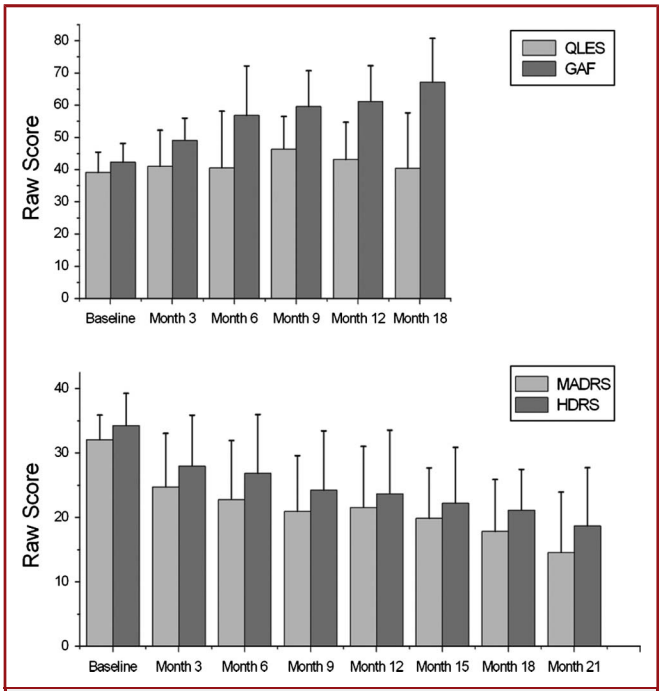

FIGURE 7. *Long-term follow up of changes in efficacy measures. Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), and Global Assessment of Functioning (GAF) significantly improved over the duration of the study period for all patients (sham and active groups were normalized to treatment duration after the 8-week sham period). QLES, Quality of Life Enjoyment and Satisfaction questionnaire.*

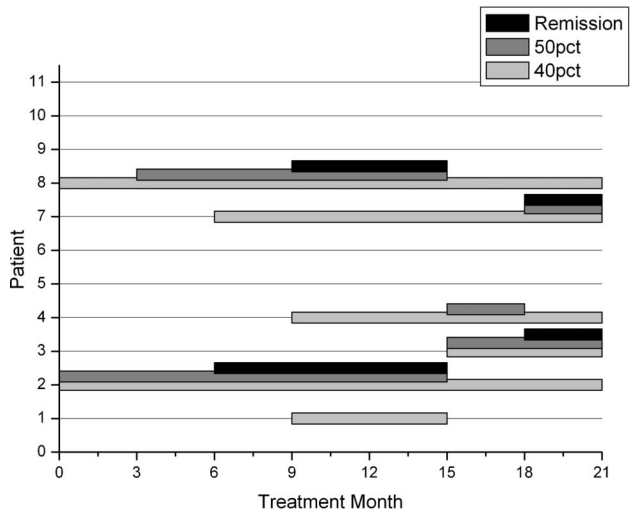

FIGURE 8. *Study timeline depicting effectiveness for each patient. Thresholds for improvement were 40% and 50% reduction in Hamilton Depression Rating Scale scores and remission.*

In patients refractory to most other forms of treatment, EpCS at the left DLPFC appears to have a durable antidepressant effect. In several patients in this study, the antidepressant effect was profound. This was the first neuromodulation study to include an a priori sham-controlled period. During this period, several findings were noted. The mean improvement for the active group was higher for each of the 4 outcome measures during this period compared with the sham group, although it did not rise to the level of statistical significance. Furthermore, the sham group did not appear to have a significant placebo effect, underscoring the current understanding that refractory MDD patients are somewhat resistant to the placebo effect. Because this was a single-blind study, it is possible that rater bias and/or placebo response may have had an effect on the results. However, the effects of placebo response are likely minimal because the patients in this study, to be eligible for the study, had already exhibited non-response to a vast array of conventional treatments, including ECT. It is likely that patients with this level of refractoriness would have markedly low response rates. Although there are few data in the literature regarding response rates in patients with this degree of treatment-resistant depression, data on placebo response in VNS studies revealed that only 10% of patients responded to sham stimulation over a 10-week period.[14] In addition, the patients in the VNS study had far fewer medication trials than our patients and were not required to have had ECT. Therefore, it is reasonable to assume that the patients in our study would have comparable or lower response rates than those in the VNS study.

The fact that the treatment difference did not reach statistical significance may reflect the small numbers of patients in this study, the length of the study period, and the lead placement with respect to precentral gyrus. Future study designs may need to make this period much longer to reflect the time it takes for EpCS to show efficacy.

Long-term follow-up demonstrated that at some point over a period of 21 months, 6 of 11 patients had at least a 40% reduction in their depression symptoms. Four of the 11 patients were able to achieve remission. It was also noted that the GAF was significantly improved at 18 months. The only measure that did not show significant improvement by EpCS was the QLES. The underlying reasons may be multifactorial but also may reflect the persistent social effects of chronic symptomatic depression on the patient even after the depressive symptoms themselves have been improved.

Overall, however, the approach used in this study appears to be more variable in response compared with other studies of surgical brain stimulation. In 2008, Lozano et al[20] reported their 1-year follow-up of 20 patients with refractory MDD undergoing bilateral implantation of DBS electrodes in the white matter of the subgenual cingulate region. In that study, 60% of patients were responders and 35% met the criteria for remission. In 2009, a Medtronic-sponsored study of bilateral DBS of the ventral anterior internal capsule/ventral striatum for treatment-resistant depression demonstrated 15 implanted patients with a 40% response and 20% remission rate at the 6-month follow-up. A small subcohort was followed up to 12 months, with an increase in effect size.[21] Nahas et al[45] reported their experience with EpCS for treatment-resistant MDD in a smaller open-label study in 2010. Their study differed from ours in several respects. Most important, they targeted a cortical region that is considerably anterior to the one used in this study. In addition, electrodes were implanted bilaterally. Furthermore, their stimulation was more

TABLE 4. Revision Data[a]

Subject	Prerevision Electrode Position, cm	Postrevision Electrode Position, cm	Prerevision HDRS/MADRS	Postrevision HDRS/MADRS (4 mo of stimulation)
203	9	26	31.8/23.8	22.8/24.5
303	11	23	31.0/27.3	27.0/25.8
304	16	32	28.5/29.0	29.5/29.5

[a]HDRS, Hamilton Depression Rating Scale-28; MADRS, Montgomery-Asberg Depression Rating Scale. Position data are given in terms of the position of the posterior edge of the electrode in front of the precentral sulcus.

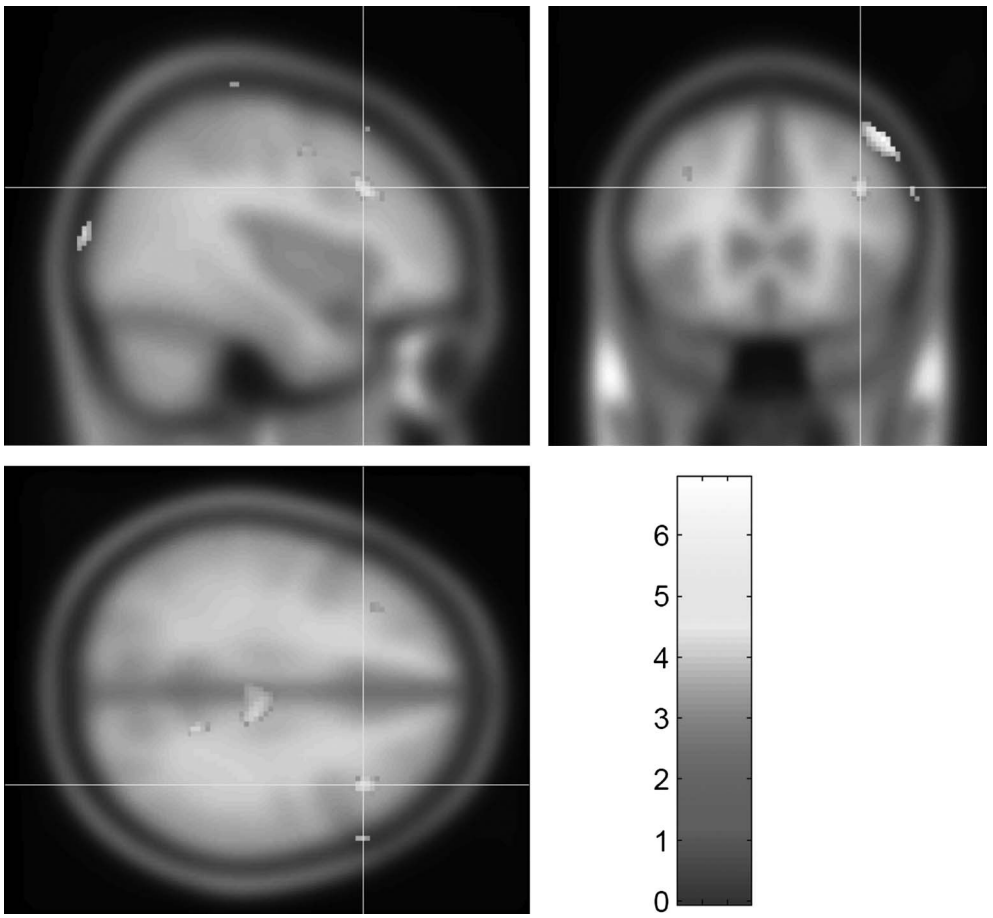

FIGURE 9. *Positron emission tomography data demonstrating a positive correlation between baseline regional cerebral metabolic rate of glucose in the contralateral (right) left dorsolateral prefrontal cortex (contralateral cortical target homolog) (z = 3.12, k = 83, x = 38, y = 22, z = 32), and subsequent clinical response as measured by percentage change in the Hamilton Depression Rating Scale.*

consistent with the approach used in TMS studies in that they stimulated only in an intermittent fashion. Finally, their study did not include a placebo-controlled design. In the 7-month follow-up, 5 patients had an 80% response and 60% remission rate. One common feature of all of these studies and the presently reported study is that patients who respond to these treatments tend to go into remission.

This application of EpCS for MDD suffers from the primary obstacle faced by other forms of investigative neuromodulation: variability of response. This variability may be due to targeting, patient selection, and device limitations.

In this cohort, we noted a significant bimodal distribution of the ultimate site of electrode implantation. The investigative protocol called for the electrodes to be placed at least 2 cm in front of the precentral sulcus along the middle frontal gyrus. This was to ensure the electrodes were stimulating the brain region that has been the traditional target of TMS studies. Furthermore, anatomic studies have demonstrated that posterior to this 2-cm distance, the middle frontal gyrus is involved in motor rather than associative/limbic circuits.[46,47] According to the postoperative imaging data, only 5 patients had electrodes implanted at or anterior to this 2-cm boundary. A technical explanation for this result is that current neuronavigational surgical suites are not designed to measure distances accurately along a curved surface. Distances reported often represent the secant of the curved surface, underestimating the true distance from a cortical landmark. Furthermore, when EpCS is applied epidurally, there is no ability to see the sulcus, making the accuracy of placement even more difficult. Unfortunately, the revision surgery did not have a large impact on the patients' clinical responses. Although this may invalidate the anatomic relationship depicted in Figure 6, another explanation is more epistemological. Given the variability of cortical anatomy in the prefrontal region from patient to patient, perhaps defining the target based solely on sulcal

TABLE 5. Correlations Between Voxelwise Regional Cerebral Metabolic Rate of Glucose and Subsequent Clinical Response[a]

	Brain Region	Cluster Size, voxels	*z* Score	Montreal Neurologic Institute Coordinates (*x*, *y*, *z*)
Positive	DLPFC	83	3.12	38, 22, 32
	Superior frontal gyrus	161	3.94	48, 22, 52
	Superior frontal gyrus	629	3.56	−44, 2, 58
	Cuneus/precuneus	48	3.22	16, -48, 30
	Posterior cingulate cortex	169	3.15	16, -26, 36
Negative	None			

[a]DLPFC, left dorsolateral prefrontal cortex. DLPFC findings are a priori; the others are post hoc findings.

landmarks is not the best idea. Diffusion tensor imaging can resolve features of cortical anatomy just below the surface.[48] A combined target based on surface and fiber tract anatomy may reduce the aspect of anatomic patient variability. Functional imaging with blood-oxygen level–dependent sequences with a working-memory task could have helped define the target area in question with a greater degree of specificity than simply by sulcal anatomy alone. Furthermore, with the ability to localize aberrations in brain dynamics through the use of magneto-encephalography with high-density electroencephalogram,

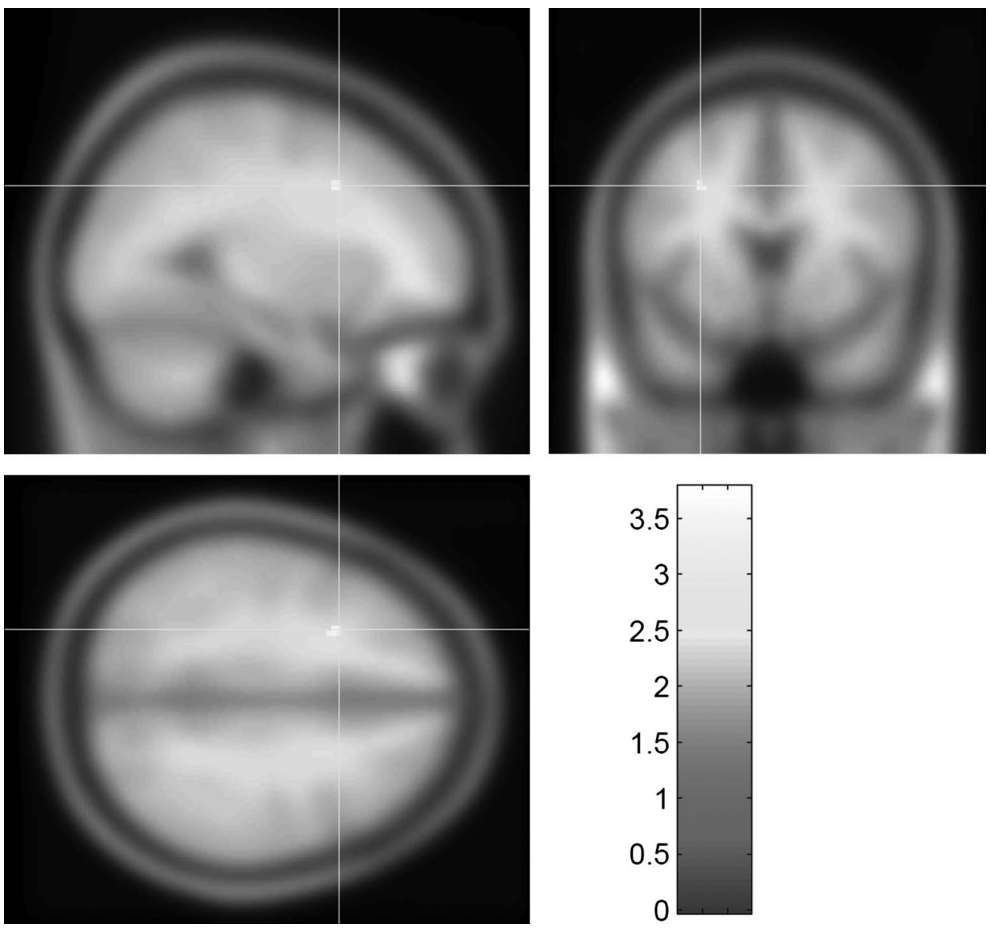

FIGURE 10. *Positron emission tomography data demonstrating increases in regional cerebral metabolic rate of glucose at the target site, the left dorsolateral prefrontal cortex (z = 2.76, k = 7, x = −28, y = 12, z = 36), after long-term stimulation.*

TABLE 6. Changes in Regional Cerebral Metabolic Rate of Glucose After Long-term Stimulation

	Brain Region	Cluster Size, Voxels	*z* Score	Montreal Neurologic Institute Coordinates (*x*, *y*, *z*)
Increases	DLPFC	7	2.76	−28, 12, 36
	Orbitofrontal cortex	11	2.91	−22, 24, −10
	Precentral gyrus	16	2.87	−46, −4, 22
Decreases	None			

[a]DLPFC, dorsolateral prefrontal cortex. DLPFC findings are a priori; the others are post hoc findings.

a much more precise cortical target could be defined than the one used in this study.

One of the chief hallmarks of the success of DBS for movement disorders has been patient selection. Screening efforts in the realm of surgical neuromodulation MDD may be even more challenging given the possibility of biological subtypes in MDD patients.[49] However, TMS offers the possibility of a noninvasive form of EpCS to screen out patients who are less likely to respond to cortical stimulation and to increase the overall yield of response rate. Although this study did not include a TMS screen, other studies of EpCS have demonstrated its usefulness for such conditions as neuropathic pain and tinnitus.[50,51]

To rationally use TMS as a screening tool for EpCS, the quantitative similarities and differences need to be addressed. There are several distinct differences. Transcranial magnetic stimulation is typically done in a high- and low-frequency mode. A high frequency ($\geq$ 10 Hz) is believed to induce local increases in cortical excitability, whereas a low frequency (typically 1 Hz) is believed to induce local decreases in cortical excitability.[52-54] Most forms of EpCS that are reported, including this study, typically stimulate in the high-beta/gamma range. The effects of this frequency of stimulation have not been well characterized. If the "goal" of EpCS is to overcome the abnormally low metabolic state of the DLPFC target zone (in undertreated or untreated MDD patients),[41,55] then this must be addressed. Furthermore, dosage between TMS and EpCS must be normalized if they are to be truly used interchangeably. Typically, dosages of TMS interventions are given in number of pulses per given time period. Furthermore, there is growing evidence that stimulation with specific burst patterns may have a greater and longer-lasting effect on cortical dynamics than regular trains of stimulation.[56] As in this study, EpCS is typically done with constant, regular stimulation patterns, although the Nahas et al[45] study used intermittent stimulation in an attempt to more fully emulate TMS. Finally, the magnitude and pattern of induced current at the cortical target from TMS compared with EpCS need to be more fully elucidated. All of these differences need to be addressed for TMS is be rationally used as a screen for future EpCS studies for MDD.

The device used in this study itself could have been a source of some response variability. The Northstar Neuroscience cortical stimulation system has several significant limitations compared with other neurostimulation systems currently available commercially. Only 2 contacts were available to the investigators for stimulation at the cortical target. This made slight variances in implantation locations difficult to overcome with programming. Furthermore, the contacts were not independent in their capacity to stimulate. The device could put forth only a maximum of 6.5 mA. With both contacts active, each contact could deliver only 3.25 mA. Furthermore, the device was not capable of emulating the burst mode of stimulation that has proved promising for TMS applications. Future studies of EpCS should endeavor to use technology that can closely emulate TMS modes to completely harness TMS as a potential screening tool. State-of-the-art, commercially available spinal cord stimulation technology, with its greater power delivery and more flexible programming features, could easily be adapted for the EpCS technique described in this study.

Although these studies are preliminary, EpCS of the left DLPFC appears to be a safe and potentially efficacious approach for patients with treatment-resistant MDD. Future investigations are needed to refine this approach to achieve a more consistent response rate in treatment-resistant major depression.

Disclosures

Dr Kopell was a consultant to Northstar Neuroscience, is on the scientific advisory board of Prism Clinical Imaging, and is a consultant and member of the clinical advisory board of Neurostream Technologies. Dr Butson is a consultant and shareholder of Intelect Medical and a consultant to NeuroPace and Advanced Bionics. Dr Harsch reports the following conflicts of interest: Forest Lab (honorarium, speaker), Pfizer (honorarium, grant, speaker, consultant, principal investigator), Lilly (honorarium, speaker, consultant), AstraZeneca (honorarium, speaker, consultant), Merck (honorarium, speaker), Takeda (educational grant, teaching), e-Medicine (honorarium, editor), Novartis (grant, principal investigator), Cyberonics (grant, principal investigator), St. Jude Medical Neuromodulation (grant, principal investigator), Sanofi-aventis (grant, principal investigator), Otsuka (grant, principal investigator), and Glaxo-SmithKline (grant, principal investigator). Dr Kondziolka is a consultant to Elekta Instruments. Dr Eskandar has received a consultant honorarium from Medtronic. Dr Evans has received research support from Cyberonics, Medtronic, and Pfizer and has received an honorarium from Medtronic. Dr Dougherty has the following conflicts of interest to report: Medtronic (research support, consultant, honorarium), Eli Lilly (research support, consultant, honorarium), Brand Ideas (consultant, honorarium), McNeil (research support, consultant, honorarium), Reed Elsevier (consultant, honorarium), and Cyberonics (research support). This study was sponsored by Northstar Neuroscience (Seattle, Washington). At the time of this publication, Northstar Neuroscience has ceased operations. This trial, Assessment of the Safety and Effectiveness of Cortical Stimulation in Subjects With Major Depressive Disorder (PROSPECT), is registered at www.ClinicalTrials.gov; unique identifier, NCT00380042. The

authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology*. 2006;31(9):1841-1853.
2. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905-1917.
3. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry*. 2003;53(8):649-659.
4. Carney RM, Freedland KE. Treatment-resistant depression and mortality after acute coronary syndrome. *Am J Psychiatry*. 2009;166(4):410-417.
5. Crown WH, Finkelstein S, Berndt ER, et al. The impact of treatment-resistant depression on health care utilization and costs. *J Clin Psychiatry*. 2002;63(11):963-971.
6. Dunner DL, Rush AJ, Russell JM, et al. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. *J Clin Psychiatry*. 2006;67(5):688-695.
7. Hermann RC, Dorwart RA, Hoover CW, Brody J. Variation in ECT use in the United States. *Am J Psychiatry*. 1995;152(6):869-875.
8. Rasmussen K. The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging (second edition). *J ECT*. 2002;18(1):58-59.
9. Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry*. 2000;57(5):425-434.
10. Husain MM, Rush AJ, Fink M, et al. Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for Research in ECT (CORE) report. *J Clin Psychiatry*. 2004;65(4):485-491.
11. Rasmussen KG, Sampson SM, Rummans TA. Electroconvulsive therapy and newer modalities for the treatment of medication-refractory mental illness. *Mayo Clin Proc*. 2002;77(6):552-556.
12. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet*. 1999;354(9189):1526.
13. Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol Psychiatry*. 2000;47(4):276-286.
14. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry*. 2005;58(5):347-354.
15. Rush AJ, Sackeim HA, Marangell LB, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biol Psychiatry*. 2005;58(5):355-363.
16. Nahas Z, Marangell LB, Husain MM, et al. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. *J Clin Psychiatry*. 2005;66(9):1097-1104.
17. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. 2007;62(11):1208-1216.
18. Lisanby SH, Husain MM, Rosenquist PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*. 2009;34(2):522-534.
19. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005;45(5):651-660.
20. Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol Psychiatry*. 2008;64(6):461-467.
21. Malone DA Jr, Dougherty DD, Rezai AR, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry*. 2009;65(4):267-275.
22. Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *J Psychiatr Pract*. 2002;8(5):270-275.
23. Rogers MA, Kasai K, Koji M, et al. Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. *Neurosci Res*. 2004;50(1):1-11.
24. Gross M, Nakamura L, Pascual-Leone A, Fregni F. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. *Acta Psychiatr Scand*. 2007;116(3):165-173.
25. Lam RW, Chan P, Wilkins-Ho M, Yatham LN. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *Can J Psychiatry*. 2008;53(9):621-631.
26. Fitzgerald PB, Hoy K, McQueen S, et al. Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol*. 2008;28(1):52-58.
27. Grimm S, Beck J, Schuepbach D, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. *Biol Psychiatry*. 2008;63(4):369-376.
28. Eranti S, Mogg A, Pluck G, et al. A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. *Am J Psychiatry*. 2007;164(1):73-81.
29. McLoughlin DM, Mogg A, Eranti S, et al. The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis. *Health Technol Assess*. 2007;11(24):1-54.
30. Demirtas-Tatlidede A, Mechanic-Hamilton D, Press DZ, et al. An open-label, prospective study of repetitive transcranial magnetic stimulation (rTMS) in the long-term treatment of refractory depression: reproducibility and duration of the antidepressant effect in medication-free patients. *J Clin Psychiatry*. 2008;69(6):930-934.
31. George MS. Transcranial magnetic stimulation for the treatment of depression. *Expert Rev Neurother*. 2010;10(11):1761-1772.
32. Velasco F, Arguelles C, Carrillo-Ruiz JD, et al. Efficacy of motor cortex stimulation in the treatment of neuropathic pain: a randomized double-blind trial. *J Neurosurg*. 2008;108(4):698-706.
33. Priori A, Lefaucheur JP. Chronic epidural motor cortical stimulation for movement disorders. *Lancet Neurol*. 2007;6(3):279-286.
34. Brown JA, Lutsep HL, Weinand M, Cramer SC. Motor cortex stimulation for the enhancement of recovery from stroke: a prospective, multicenter safety study. *Neurosurgery*. 2006;58(3):464-473.
35. Friedland DR, Gaggl W, Runge-Samuelson C, Ulmer JL, Kopell BH. Feasibility of auditory cortical stimulation for the treatment of tinnitus. *Otol Neurotol*. 2007;28(8):1005-1012.
36. Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet*. 1996;348(9022):233-237.
37. Rajkowska G, Goldman-Rakic PS. Cytoarchitectonic definition of prefrontal areas in the normal human cortex, II: variability in locations of areas 9 and 46 and relationship to the Talairach Coordinate System. *Cereb Cortex*. 1995;5(4):323-337.
38. Kopell BH, Greenberg BD. Anatomy and physiology of the basal ganglia: implications for DBS in psychiatry. *Neurosci Biobehav Rev*. 2008;32(3):408-422.
39. Johansen-Berg H, Gutman DA, Behrens TE, et al. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. *Cereb Cortex*. 2008;18(6):1374-1383.
40. Petrides M, Pandya DN. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *Eur J Neurosci*. 1999;11(3):1011-1036.
41. Kito S, Fujita K, Koga Y. Changes in regional cerebral blood flow after repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in treatment-resistant depression. *J Neuropsychiatry Clin Neurosci*. 2008;20(1):74-80.
42. Lefaucheur JP, Brugieres P, Menard-Lefaucheur I, Wendling S, Pommier M, Bellivier F. The value of navigation-guided rTMS for the treatment of depression: an illustrative case. *Neurophysiol Clin*. 2007;37(4):265-271.
43. Dashti SR, Baharvahdat H, Spetzler RF, et al. Operative intracranial infection following craniotomy. *Neurosurg Focus*. 2008;24(6):E10.
44. Anisman H, Merali Z. Cytokines, stress, and depressive illness. *Brain Behav Immun*. 2002;16(5):513-524.
45. Nahas Z, Anderson BS, Borckardt J, et al. Bilateral epidural prefrontal cortical stimulation for treatment-resistant depression. *Biol Psychiatry*. 2010;67(2):101-109.
46. Petrides M. Lateral prefrontal cortex: architectonic and functional organization. *Philos Trans R Soc Lond B Biol Sci*. 2005;360(1456):781-795.

47. Calzavara R, Mailly P, Haber SN. Relationship between the corticostriatal terminals from areas 9 and 46, and those from area 8A, dorsal and rostral premotor cortex and area 24c: an anatomical substrate for cognition to action. *Eur J Neurosci*. 2007;26(7):2005-2024.
48. Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S. Fiber tract-based atlas of human white matter anatomy. *Radiology*. 2004;230(1):77-87.
49. Heinzel A, Grimm S, Beck J, et al. Segregated neural representation of psychological and somatic-vegetative symptoms in severe major depression. *Neurosci Lett*. 2009;456(2):49-53.
50. Canavero S, Bonicalzi V, Dotta M, Vighetti S, Asteggiano G. Low-rate repetitive TMS allays central pain. *Neurol Res*. 2003;25(2):151-152.
51. De Ridder D, Vanneste S, van der Loo E, Plazier M, Menovsky T, van de Heyning P. Burst stimulation of the auditory cortex: a new form of neurostimulation for noise-like tinnitus suppression. *J Neurosurg*. 2010;112(6):1289-1294.
52. Speer AM, Willis MW, Herscovitch P, et al. Intensity-dependent regional cerebral blood flow during 1-Hz repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers studied with $H_2{}^{15}O$ positron emission tomography, II: effects of prefrontal cortex rTMS. *Biol Psychiatry*. 2003;54(8):826-832.
53. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol*. 1998;15(4):333-343.
54. George MS, Nahas Z, Kozol FA, et al. Mechanisms and the current state of transcranial magnetic stimulation. *CNS Spectr*. 2003;8(7):496-514.
55. Luborzewski A, Schubert F, Seifert F, et al. Metabolic alterations in the dorsolateral prefrontal cortex after treatment with high-frequency repetitive transcranial magnetic stimulation in patients with unipolar major depression. *J Psychiatr Res*. 2007;41(7):606-615.
56. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005;45(2):201-206.

COMMENT

The authors report the results of a prospective longitudinal study of epidural stimulation of the dorsolateral prefrontal cortex for the treatment-refractory major depressive disorder. This interesting contribution includes an explanation of the rationale for this novel approach, as well as positron emission tomography data and comparisons with noninvasive neurostimulation methods and deep brain stimulation. This investigation is important to the field because it explores an approach that is less invasive than deep brain stimulation and more practical than transcranial magnetic stimulation. Further investigation with larger samples may show whether this approach is indeed safe and measure the magnitude of any clinical effect. Of note, the company that sponsored the study has ceased operation. We applaud the authors for maintaining their academic collaboration past corporate failure to report the outcomes and the lessons learned from this clinical trial. This can be valuable for other investigators in this field and to science in general.

The authors made interesting study design and methodological choices and provide insight into those decisions. The study was conducted without double blinding, which is feasible in this type of investigation. Instead, only the patients, but not the investigators collecting outcome data, were blinded to the treatment group. Patients reported improvements only in the open phase when both investigator and patient were aware that the stimulation was active. There were no significant improvements during the single-blinded phase. Hence, one must consider the possibility that assessment bias and placebo effect influenced the outcome. On the other hand, the duration of the effects observed during the course of long-term stimulation and the refractoriness of this group of patients to multiple treatments reduce the likelihood of placebo effect contributing significantly to the results. Until larger studies are conducted with double-blinded design, it will remain uncertain whether dorsolateral prefrontal cortex stimulation has a therapeutic effect in this population.

Epidural lead placement was guided by neuronavigation to localize the planned surgical target in the posterior part of the middle frontal gyrus. However, localization turned out not to be as consistent as expected, which was detected with postoperative imaging. Patients implanted posterior to the intended target, over cortical areas more likely associated with motor planning, tended to respond less to cortical stimulation. Surgical revision for repositioning the leads was beneficial to some patients. The lessons learned from the targeting nuances are discussed and recommendations for future target localization are provided.

Surgery for implantation of the devices and long-term stimulation of the DLPFC were generally safe. However, 1 patient who was excluded from the study first attempted and then finally completed suicide. Although other life circumstances may have contributed to the patient's decision to commit suicide, it is also possible that hopelessness associated with exclusion from a "last resort" procedure may have contributed to the patient's decision. This underscores the severity of this patient population and the risks related to conducting clinical trials to test novel approaches for treatment-resistant depression. Awareness of these risks will become increasingly important. Depending on the outcome of ongoing clinical trials, neurosurgeons may become more involved in the care of this complex population.

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