



Five-Year Follow-Up of Bilateral Epidural Prefrontal Cortical Stimulation for Treatment-Resistant Depression



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ARTICLE INFO

Article history:

Received 4 April 2016

Received in revised form 22 June 2016

Accepted 25 June 2016

Available online 28 June 2016

Keywords:

Deep brain stimulation

Treatment-resistant depression

Epidural cortical stimulation

Brain stimulation

Interventional psychiatry

ABSTRACT

Background: Epidural prefrontal cortical stimulation (EpCS) represents a novel therapeutic approach with many unique benefits that can be used for treatment-resistant depression (TRD).

Objective: To examine the long-term safety and efficacy of EpCS of the frontopolar cortex (FPC) and dorsolateral prefrontal cortex (DLPFC) for treatment of TRD.

Methods: Adults ($N = 5$) who were 21–80 years old with severe TRD [failure to respond to adequate courses of at least 4 antidepressant medications, psychotherapy and ≥ 20 on the Hamilton Rating Scale for Depression (HRSD24)] were recruited. Participants were implanted with bilateral EpCS over the FPC and DLPFC and received constant, chronic stimulation throughout the five years with Medtronic IPGs. They were followed for 5 years (2/1/2008–10/14/2013). Efficacy of EpCS was assessed with the HRSD24 in an open-label design as the primary outcome measure at five years.

Results: All 5 patients continued to tolerate the therapy. The mean improvements from pre-implant baseline on the HRSD24 were [7 months] 54.9% (± 37.7), [1 year] 41.2% (± 36.6), [2 years] 53.8% (± 21.7), and [5 years] 45% (± 47). Three of 5 (60%) subjects continued to be in remission at 5 years. There were 5 serious adverse events: 1 electrode ‘paddle’ infection and 4 device malfunctions, all resulting in suicidal ideation and/or hospitalization.

Conclusion: These results suggest that chronic bilateral EpCS over the FPC and DLPFC is a promising and potentially durable new technology for treating TRD, both acutely and over 5 years.

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Introduction

Depression is a severely disabling disorder of extreme sadness or melancholia that affects a person’s activities of daily life as well as social functioning [1]. Depression is a major public health problem and is the second leading cause of disability worldwide [2]. Although pharmacotherapeutic approaches to depression treatment

are effective for some, they have demonstrated limited success in large clinical studies [3]. When depression fails to remit after adequate treatment, it is labeled treatment-resistant depression (TRD) [4]. TRD represents a spectrum that is often quantified by the number and type of failed adequate trials of treatments. This typically ranges from a minimum of a single failed trial of pharmacological monotherapy to more treatment-resistant forms of TRD that fail numerous trials of pharmacological monotherapies as well as pharmacological augmentation strategies, and to the most resistant forms of TRD that fail treatment with electroconvulsive therapy (ECT) [5].

Approximately 72% of patients will fail to remit after treatment with a single pharmacological monotherapy and thus meet criteria for some degree of TRD [6]. For these patients, an interventional

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Clinical Trials Registration: Epidural Cortical Stimulation for Depression, NCT00565617.

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psychiatric approach may be considered [7,8], with several options being available, depending in part on how many and what types of adequate trials of treatments that the patient has received. For example, transcranial magnetic stimulation (TMS) [9] is FDA-approved to treat patients who have failed treatment with a single antidepressant medication, and although no FDA recommendations currently exist for ECT, typical guidelines limit use to patients who have failed one or more antidepressant trials and/or require a rapid antidepressant response [10,11]. In contrast, the FDA recommends treatment with vagal nerve stimulation (VNS) only for patients who have failed treatment with at least 4 antidepressants or ECT [12]. Unfortunately, many patients experience a particularly resistant form of TRD with no current FDA-approved treatment options once all treatments have failed [8]. For these patients with the most treatment-resistant form of TRD, a more invasive approach using devices implanted into the encephalon is warranted. For example, deep brain stimulation (DBS) of several structures, including the ventral striatum [13] and subgenual cingulate, is currently being developed for TRD [14]. Although DBS was initially a promising treatment option for these patients [14], large, controlled clinical trials have failed thus far to demonstrate efficacy [15,16].

One promising target for the treatment of patients with highly treatment-resistant TRD using implanted devices is the prefrontal cortex [17,18]. Studies have suggested that in depression, the left dorsolateral prefrontal cortex (DLPFC) is hypoactive and the right DLPFC may be hyperactive [19]. The relationship between left DLPFC activity and depression is likely causal, as repetitive TMS (rTMS) over left DLPFC has been shown to be effective and is a US Food and Drug Administration (FDA)-approved intervention for TRD [9,20]. Furthermore, there is emerging data of utilizing transcranial direct current stimulation over DLPFC for treatment of depression [21]. Another region of the prefrontal cortex, the frontopolar cortex (FPC), specifically BA 10, is also a promising depression target. The FPC has gained attention as an important node in the mood regulatory circuitry [22], and is consistently found to have increased resting-state activity in patients with depression [23]. Thus, the FPC and DLPFC represent promising targets for neuromodulation as treatment for TRD [8].

Epidural cortical stimulation (EpCS) represents a novel therapeutic approach that can be used to stimulate the DLPFC and FPC to treat TRD [24,25]. EpCS involves placing stimulating electrodes directly on the dura mater dorsal to the cortical areas to be stimulated [26]. Chronic EpCS of sensory or motor areas has demonstrated efficacy in managing intractable pain syndromes [27–30], improving recovery from stroke [31], and addressing Parkinson's disease and other motor disorders [26].

We have previously reported outcomes up to 7 months in 5 patients with TRD that were implanted with bilateral EpCS over the DLPFC and FPC in an open-label design [24]. We continued to assess the long-term safety and efficacy of chronic intermittent EpCS for treatment of TRD and report outcomes for all 5 of these patients 5 years following initial implantation. During this time an expanded array of stimulation parameters was investigated and additional treatments were combined with EpCS during this unrestricted phase of the investigation. The efficacy and safety of EpCS endured during this follow-up period and several trends in stimulation parameters were observed and are discussed herein.

Methods and materials

This long-term follow-up study was conducted at the Medical University of South Carolina (MUSC) in compliance with the original Investigational Device Exemption issued to Z.N. and later transferred to E.B.S. under the guidance of the FDA. For the original study, the inclusion criteria limited enrollment to individuals

with definite histories of depression with substantial treatment-resistance in order to address the ethical concerns of providing an experimental and untested intervention that required surgery. The MUSC Institutional Review Board approved the research protocol. Written consents were obtained at the onset before the initial implantation and included permission for further ratings at these extended time-points. All subjects underwent comprehensive assessments including detailed neuropsychological testing at baseline, after implantation, and at the 5-year follow-up.

Participants

For the original study, all 5 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]. For the initial enrollment, all participants scored ≥ 20 on the 24-item Hamilton Rating Scale for Depression (HRSD24) [33,34] before implantation [24]. We retained all 5 of our original study patients in this 5-year follow-up study. All 5 of our patients had not benefited sufficiently from trials of at least 4 classes of antidepressant medications or other somatic treatments as defined by the Antidepressant History Treatment Form (ATHF) criteria [5] as well as a minimum of 6 weeks of prior psychotherapy during any MDE prior to surgical intervention. During the long-term follow-up study time-period, both stimulation parameters and medications could be modified in both type and dose. For 3 of the 5 patients, VNS was reactivated after the initial 1-year mark and the VNS device stayed on chronically. ECT, TMS, and DBS could not be provided to any of the patients after EpCS implantation. The majority of treatment changes during the study consisted of EpCS stimulation parameter modifications (e.g., current, frequency, duty cycle, different leads stimulated) with minimal changes in medications (primarily removal of medications in the remitters) across the entire 5 years.

Chronic stimulation parameters

For the last 2–3 years, patients received chronic, bilateral stimulation of the left and right FPC and DLPFC using a total of 4 paddle leads at 130 Hz, 4.5–6.5 V, 210 μ s (except one patient with a pulse width of 90 μ s), double bipolar (0–/1+/2–/3+) across all 4 paddles for each lead. These settings evolved over time and parameters were selected on a trial and error basis during the final 4 years of therapy. The pulse width and frequency settings were altered from the original protocol during years 2–5 and the recent pulse width and frequency settings were based on DBS obsessive-compulsive disorder (OCD) treatment trial parameters [35]. Eventually all patients' frequency settings were reprogrammed from an initial 60 Hz to 130 Hz, which represents a difference from another study utilizing a single paddle [25] and reflects a programming strategy similar to DBS [36].

Assessments

Unmasked clinical outcome measures included the HRSD24, the 10-item Montgomery-Asberg Depression Rating Scale (MADRS) [37], Inventory of Depressive Symptoms – Self-Report (IDS-SR) [38], the 11-item Young Mania Rating Scale (YMRS) [39], the Clinical Global Impression: Severity (CGI-S) and Clinical Global Impression: Improvement (CGI-I) ratings. These measurements were obtained at pretreatment (baseline), weekly for the first 3 months, biweekly for the next 2 months and monthly after that for the first year. Follow-up assessments were completed within ± 1 week of scheduled visits. Functional outcomes were assessed with the Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES) [40], Medical

Table 1
Sample demographics.

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Group
Gender	F	M	F	F	F	4 F/1 M
Diagnosis recurrent	MDD	BPAD depressed	BPAD depressed	Recurrent MDD	Recurrent MDD	3 MDD/2 BPAD
Current age	42	57	47	31	45	44.4 (± 9.7) ^b
Length of illness (years)	17	32	31	16	32	25.6 (± 8.3)
Current depressive episode (months)	N/A	N/A	84	8	N/A	46 (± 53.7)
HRSD score (24 item)	23	33	33	29	24	28.4 (± 8)
Previous brain stimulation therapies	ECT, VNS, TMS	ECT, VNS, TMS	ECT	VNS, TMS	None	4 yes/1 no
Past psychotherapy	Yes	Yes	Yes	Yes	Yes	All
Family history of depression	Yes	Yes	No	Yes	Yes	4 yes/1 no
Number of psychiatric treatments in current depressive episode ^a	12	18	6	8	5	9.8 (± 5.3)
Current ATHF	8	8	4	5	4	5.8 (± 2.05)
Number of psychotropics at baseline	9	5	6	3	7	6 (± 2.23)
Number of psychotropics at 5 years	5	2	5	5	5	4.4 (± 1.34)

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.

^a Excluding psychotherapy.

^b Mean (\pm SD).

Outcomes Study (MOS) Short Form-36 (SF-36) [41] at baseline, 4 months, 7 months, and 5 years.

Neuropsychological testing

Participants underwent a brief neuropsychological testing at baseline, at the end of acute phase (20 weeks), and at 5 years. These tests included the Choice Reaction Test, the Continuous Performance Task, the Cognitive Failures Test and the Modified Mini Mental Status.

Data analyses

Response was defined *a priori* as a 50% or greater reduction in mean HRSD24 scores relative to the mean of the baseline (pre-implantation) visits. Prior to the investigation, it was determined that 5 participants would be required to achieve a power of 0.80 to detect differences in mean HRSD24 scores from baseline under a repeated-measures analysis of variance (ANOVA). *Post hoc* power testing of our initial report found that a power of 0.879 was achieved. For secondary analyses, we defined secondary outcomes of interest to be a 50% or greater reduction in the mean of baseline MADRS score, or a 50% or greater reduction in the mean of baseline IDS-SR score. Remission was defined *a priori* as an HRSD24 score of 10 or lower. We again employed a last observation carried forward analysis for missing data. All data were quality checked and queries clarified before final analyses were conducted. For computerized cognitive tests, 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. In statistical analyses, we calculated means and standard deviations (SD) for outcomes of interest. Paired-sample *t* tests and repeated-measures ANOVAs were used for bivariate and multivariate comparisons respectively. All statistical tests were two-tailed at 0.05 alpha level.

Results

Sample characteristics

Six participants were initially enrolled, and 5 received EpCS and participated in this study. One participant withdrew consent before implantation. Table 1 summarizes the sample characteristics. The mean age (\pm SD) was 44.4 (± 9.7) years at the time of implantation. Four were women, and 3 were diagnosed with recurrent MDD; 2

others had bipolar affective disorder I, depressed type. All were unemployed, and 3 continued to receive disability. At the time of implantation, the average length of depressive illness was 25.6 (± 8.3) years, and the average length of the current depressive episode was 43 months (± 38 months). The average length of the current depressive episode was 46 months (± 58.7 months) for the 2 non-responders. It is noteworthy that participants had received a mean of 9.8 (± 5.3) unsuccessful clinical treatments during the MDE that preceded implantation. Of these psychotropic compounds, an average of 6.2 (± 2.1) were classic antidepressant treatments of which 5.8 (± 2.05) met ATHF criteria for trial adequacy [5]. Four of the patients had received prior treatments with ECT, TMS, or VNS. VNS was reactivated in all 3 patients at some point during the final 4 years prior to this study. No patients had received ECT or TMS during EpCS treatment given the risks of interactions with their implanted devices. They enrolled in the study taking a mean of 6 (± 2.3) psychotropic drugs and were on 4.4 (± 1.34) at the time of the 5-year follow-up.

Clinical outcomes

Table 2 details the individual scores at study landmarks. After 7 and 60 months of active stimulation, the group showed a mean HRSD24 improvement of 55% (± 38) and 42.9% (± 38.4) respectively. Repeated measures ANOVA revealed a significant difference in mean HRSD24 scores across time points ($F_{5,4} = 6.12$, $p < 0.01$); however, post-hoc, paired *t* tests only detected a significant difference from baseline for the 7-month time point ($p < 0.05$). All of the patients' HRSD24 scores were within 3 points of the 7-month score except for Subject 3 who had an increase in the HRSD24 score from 19 at 7 months to 38 at 60 months.

Table 2
Individual 24-item Hamilton rating scale for depression scores.

Time	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Preoperative baseline	23	33	33	29	24
Week of EpCS activation	22	32	38	29	28
2 weeks post-EpCS activation	14	36	38	24	14
4 months	2	33	23	29	10
7 months	4	3	19	30	9
5 years	7	1	38	27	8

EpCS, epidural prefrontal cortical electrical stimulation.

Secondary outcomes

Mean scores and statistical test results of the MADRS and IDS-SR are provided in Table 3. MADRS percent change from baseline significantly improved over time. The IDS-SR scores at baseline, 7 months, and 60 months were also significantly improved.

Functional measures

Participants completed the Quality of Life, Enjoyment and Satisfaction Questionnaire [40] at baseline, at 7 months, and at 60 months (Table 3). They also completed the Medical Outcomes Study Short Form-36. At 60 months after implant, no changes were noted as a group in physical functioning, pain or general health.

Neuropsychological testing

Neuropsychological testing scores at baseline, after 20 (±9) weeks, and after 5 years of EpCS are displayed in Table 4. No significant differences were observed at any time point.

Adverse events

All of the adverse events from the initial surgical implantation have been described in the first publication [24]. One infection of the left surgical site at 3 months in 1 patient was unexpected but resolved quickly. In addition to the infection, there were 4 other serious adverse events, all involving device malfunctions and resulting in suicidal ideation and/or hospitalization. Three of these events involved the battery depleting, and 1 involved the device's connectors.

Discussion

Here we report on the long-term safety, tolerability, and durability of the therapeutic benefits of bilateral anterior (FPC) and lateral (DLPFC) EpCS in patients diagnosed with TRD. At the initial 7-month acute end-point, adjunctive intermittent open-label EpCS was well tolerated and associated with marked and sustained improvement in 3 of the 5 severe TRD patients [24]. Subsequently after 5 years of ongoing clinical assessment, 3 out of the 5 (60%) continued to be in remission while 2 subjects were non-responders. Despite the invasive nature of EpCS and the level of functional impairment in these patients at the time of enrollment, patients tolerated the surgical procedure and chronic stimulation. There was no evidence of worsening in tasks associated with frontal cortex, e.g. working memory, or problem solving [24], and these findings are in line with uncontrolled reports showing enhanced cognitive functions with EpCS over various cortical areas [42,43].

Although the number of responders remained constant from 7 months to 5 years, post-hoc testing revealed that HDRS24 scores were significantly improved from baseline only at the 7-month time point. This change was driven mostly by Subject 3, who initially showed some improvement at 7 months but failed to meet response criteria. Although HRSD24 scores remained relatively constant in 4 of the 5 participants, Subject 3 had a worsening of their HRSD24 during the follow-up period. This worsening was likely due to significant prefrontal atrophy secondary to an early dementing process. The patient had several centimeters of distance between the skull and the cortical surface, and this skull-to-cortex distance has been demonstrated to affect the ability of brain stimulation interventions to modulate cortex [44,45]. Interestingly, Subject 4 (also a non-responder) later responded after the voltage for both left hemisphere leads was increased such that the current delivered was >10 mA. We did this after we noticed that the impedance in the leads for

Table 3 Changes in average group scores over time for primary (HRSD₂₄) and secondary (MADRS, IDS-SR₃₀, and CGI-C) outcome measures with corresponding statistical values, functional measures (Q-LES and MOS-SF36), and mean psychotropic drugs.^a

	Patients (n = 5) mean scores (SD)					Repeated-measures ANOVA			Paired t test p values			
	Preop	Activation	2 Weeks	4 Months	5 Years	df	F	p	Observed power	Preop vs. 4 months	Preop vs. 7 months	Preop vs. 5 years
HRSD (24 item)	28.4 (4.8)	29.8 (5.8)	25.2 (11.5)	19.4 (13)	16.2 (15.6)	4	4.867	0.009	0.879	0.092	0.037	0.130
MADRS	32.0 (7.6)	31.2 (9.6)	27 (6.2)	22.0 (6.6)	17.0 (14.6)	4	3.886	0.022	0.683	0.075	0.043	0.052
IDS-SR (30 item)	45.8 (16.2)	43.0 (12.9)	36.8 (19.1)	31.4 (25.3)	25 (18.7)	4	4.419	0.014	0.842	0.100	0.023	0.065
CGI	5.6 (1.1)	5.2 (0.8)	4.8 (1.3)	3.0 (1.2)	3.4 (1.7)	4	7.647	<0.001	0.981	0.075	0.043	0.043
Q-LES	40.0 (7.1)	-	-	52.0 (20.9)	52.8 (11.4)							
MOS-SF36												
Physical functioning	62 (22.0)	-	-	71 (25.8)	71 (32.1)							
Role limit due to physical health	0	-	-	0	48 (47.6)							
Role limit due to emotional problem	0	-	-	0	46.6 (50.6)							
Energy/fatigue	13 (10.4)	-	-	32 (19.6)	40 (22.6)							
Emotional well-being	36.8 (22.2)	-	-	56.8 (38.1)	67.2 (25.2)							
Social functioning	22.5 (18.5)	-	-	50 (47.59)	47.6 (33.6)							
Pain	67.0 (31.3)	-	-	65.5 (23.4)	69.5 (30.7)							
General health	50 (28.1)	-	-	50 (31.6)	57 (27.3)							
Mean psychotropics	6.23	6.4 ^b (2.6)	6.2 ^b (2.28)	6.4 (2.6)	4.4 (1.34)							

ANOVA, analysis of variance; MADRS, Montgomery-Asberg Depression Scale; IDS-SR, Inventory of Depression Symptom-Self-Report; CGI, Clinical Global Impression; Q-LES, Quality of Life, Enjoyment and Satisfaction Questionnaire; MOS_Sf36, Medical Outcomes Study Short Form-36.

^a Patient 4 self-rating was 25.
^b Postoperative pain medications.

Table 4Neuropsychological testing scores before, after 20 (± 9) weeks, and after 5 years of epidural prefrontal cortical electrical stimulation.

	Baseline	20 (± 9) weeks follow-up	5 year follow-up	t^b	df	p
Choice reaction test (no. correct)	58.80 (1.30) ^a	50.80 (20.02)	59.5 (0.58)	-1.41	3	0.252
Choice reaction test (msec)	836.08 (432.68)	508.72 (322.89)	605.51 (116.60)	0.75	3	0.508
Choice reaction test (no. incorrect)	1.20 (1.30)	9.20 (20.02)	0.5 (0.58)	1.41	3	0.252
Simple reaction time (msec)	402.40 (138.80)	361.82 (96.53)	393.51 (122.98)	-1.66	3	0.196
Continuous performance task (no. false alarms)	3.00 (2.45)	3.75 (0.96)	5.8 (3.77)	-0.69	3	0.539
Continuous performance task (false alarm time – msec)	602 (90.39)	625.37 (183.61)	514.27 (60.30)	1.65	2	0.241
Continuous performance task (no. hits)	18.75 (7.09)	21.50 (6.03)	22.2 (5.36)	0.37	3	0.734
Continuous performance task (hit time – msec)	536.21 (30.23)	519.59 (45.65)	526.32 (64.78)	0.37	3	0.734
Cognitive failures test	51.25 (10.50)	37.75 (18.37)	33.2 (22.30)	2.12	4	0.101
Modified mini-mental status examination (total score)	60.25 (6.95)	63.50 (0.58)	64.6 (2.3)	-1.09	4	0.336

^a Mean (SD).^b t tests compare baseline to 5-year follow up.

Subject 4 was >800 ohms and causing the current delivered to be lower than the rest of the cohort (average impedance of around 300 ohms for all other subjects' leads). After making this change, Subject 4's HRSD24 decreased to 11 and remained there for the duration of the first author's time programming the patient (about one year). However, we did not report the improvement in Subject 4's HRSD24 in the Results section, as it occurred outside of the study timeframe. These two cases suggest that for EpCS to be effective, there likely has to be >10 mA delivered, and the stimulation must be directly underlying the cortical surface of interest.

Several other studies have explored sub-convulsive brain stimulation for TRD, e.g., VNS therapy was one of the first interventions to be systematically tested and is now FDA approved for TRD [46–49]. Three of the 5 participants in the current study were implanted with VNS devices. These devices were deactivated during the first year of the study [24] and reactivated thereafter. Thus, it is possible that VNS contributed to the sustained remission experienced by 2 of these participants. Indeed, VNS may interact synergistically with EpCS through paired associative stimulation (PAS), a Hebbian type of neural potentiation elicited via a spike-timing-dependent mechanism in which pairs of contemporaneously occurring stimuli intersect in a local cortical region [50]. PAS has been shown to occur in the DLPFC when cortical stimulation is paired with stimulation of the median nerve [51]. Although VNS and EpCS devices were not synchronized, numerous paired stimuli undoubtedly occurred over time and could have produced a cumulative effect on cortical plasticity. Future studies might exploit PAS using EpCS synchronized with VNS to augment the efficacy of both approaches.

There are several notable differences between EpCS and other sub-convulsive brain stimulation for TRD, including differences in safety, configurability, and the degree of influence on cortical circuits. EpCS carries several risks inherent in implanted devices, such as intracranial bleeding and infection. However, although a burr hole is required for placement inside the skull, the leads and electrodes remain above the dura mater, so the arachnoid space provides a natural barrier between the electrodes and the underlying cortical region [24]. Thus, EpCS is potentially safer than more invasive therapies such as DBS [27], which inherently requires electrodes to penetrate brain parenchyma [52,53]. Additionally, EpCS offers a more direct approach than safer interventions such as TMS [54,55] or transcranial direct current stimulation [21], therefore potentially allowing greater modulation of cortical nodes in the mood regulation circuitry, possibly resulting in greater efficacy. Similarly to DBS, EpCS also offers flexibility in its stimulation configurations with the ability to vary the size and polarity of the induced electrical field as well as the activation of specific neuronal elements via manipulations of pulse width, intensity, and frequency settings. This contrasts with surgical techniques that produce permanent lesions.

EpCS has become increasingly well investigated since our initial manuscript's release. An EpCS study reported shortly after our initial report involved a controlled trial with 12 TRD patients who were randomized to active or sham single-blind treatment for 8 weeks with an adaptive open design follow-up [25]. During the first 21 months of treatment, the authors observed a significant improvement in the HDRS, and 4 subjects (30%) achieved remission at some point during the study (HDRS ≤ 10) compared to the 60% remission we report here. Importantly, this study had several major differences compared with our report: the study by Kopell et al. involved only stimulation of the left DLPFC with 2-paddle leads [25], not bilateral stimulation of 2 targets (FPC and DLPFC) with 4-paddle leads as we performed here [24]. Additionally, the left DLPFC was targeted suboptimally in this past study using relative distance from the central sulcus [25], whereas in our approach anatomically delineated cytoarchitecturally defined areas were utilized to determine electrode placement [24]. Further, our approach in the current report utilized evolving stimulation parameters, including an increase in stimulation frequency from an initial 60 Hz to 130 Hz in all subjects. In contrast, Kopell et al. maintained constant 50 Hz stimulation throughout the study [25]. Finally, the study by Kopell et al. was a sham-controlled trial, as opposed to the open label trial we report here. Neurosurgical treatments for TRD have shown promise in numerous open-label trials [14] that have failed when repeated in larger, controlled trials [15,16]. These differences may account for the enduring remission in depressive symptoms that we observed.

In an effort to better understand the relationship between stimulation parameters and mood outcomes, the potential effects of a variety of parameters were assessed. These included amplitude, pulse width, rate, and on/off cycling frequency. Initial stimulation settings were determined in the operating room, where participants underwent a battery of psychiatric tests. These settings were then adjusted as needed at subsequent follow-up visits. Although the small sample size of the study prevented the use of summary statistics, a number of potentially useful relationships appeared to be present. Amplitudes of 5 V or higher appeared to be positively related to patients' moods. There was no clear relationship between rate or on/off cycling frequency and mood. Additionally, no hypotheses regarding pulse width could be drawn, as this was consistent at 210 μ s throughout for all but one patient. In one case, the pulse width was modified to 90 μ s and this resulted in an improvement in the subject's mood. This is a potential factor worth investigating in future studies. Future studies should also examine the relationship between current and mood, as this parameter was not tracked until the 5-year follow-up. Since measuring current inherently accounts for differences in resistance between circuits, it is anticipated that this will have more predictive value than voltage. With a sample size adequate for predictive analysis, it is possible that rate and on/off cycling

frequency could also prove to be important factors in both treatment efficacy and long-term durability. The identification of emerging patterns between stimulation parameters and mood outcomes should provide direction and serve as a useful starting point for future studies, and the determination of optimal stimulation parameters will be crucial to understanding the mechanism of this approach.

The antidepressant mechanisms of action of EpCS continue to be unknown. It is hypothesized that EpCS does not create a functional lesion [24], but rather appears to modulate cortical function [42,56]. The antidepressant effect of EpCS we observed in the current study is likely due to the major roles that the DLPFC and FPC play in regulation of mood. In the most straightforward case, the left DLPFC is hypoactive and the right DLPFC is hyperactive in patients with depression [19]. The veracity of this association is highlighted by the efficacy of DLPFC-targeted treatments for TRD [9,21]. More specifically, EpCS over the DLPFC may alter a patient's emotional valence. A recent meta-analysis of depression imaging studies revealed that the DLPFC is essential for assigning emotional valence [57], which may at least partially explain how the DLPFC plays such a critical role in mood regulation [58] as well as the efficacy of DLPFC-targeted treatments. Similarly to the DLPFC, the FPC is consistently found to have changes in resting-state activity in patients with depression [23] and is a node in the mood regulatory circuitry [22], playing a key role in the regulation of negative affect [56]. The medial prefrontal cortex (MPFC) (including BA 10, the FPC) has been causally implicated in animal [59] and human [60] studies of depression. Furthermore, the efficacy of open label DBS of the subgenual cingulate in TRD has been associated with reduction in the metabolic activity of BA 10 [8,52,61], and the efficacy of this approach depends on the active contact interfacing with the forceps minor, the white matter tract from the subgenual cingulate to BA 10 [62]. Although a large subgenual cingulate DBS trial was negative [15], the patients utilized for the tractographic analysis above have been reported to have good clinical response to DBS of the subgenual cingulate [63], suggesting that the FPC plays a critical role in depression [62].

The role of the DLPFC and FPC in depression is also supported by studies of the neural networks underlying mood and cognition. Abnormal connectivity in the default mode network (DMN) and central executive network (CEN) has been associated with depression [64]. Although there is some variation in the precise regions associated with each of these networks, the MPFC (including BA 10, the FPC) is consistently identified as a primary node of the DMN [64–66], and the DLPFC is a primary node of the CEN [64]. There is some suggestion that the antidepressant efficacy of rTMS of the left DLPFC (CCN node) is related to increased dopaminergic signaling and reductions in activity and connectivity within the subgenual cingulate, further supporting that the effects of DLPFC stimulation modulate deep structures in the neural network [64,67,68].

By modulating cortical activity at discrete nodes, EpCS likely changes the brain functions on a circuit, i.e. network, level [69]. Considering depression and several other neuropsychiatric diseases are primarily a result of disturbances of neural circuits [70,71], EpCS may be particularly efficacious as it has the capacity to directly alter the activity of these neural circuits. One possibility is that EpCS of the FPC may enhance this structure's connectivity with the insula. A recent report found significantly reduced functional connectivity between the FPC and the right insula in depressed participants compared to non-depressed controls [22]. This group hypothesized that this loss of connectivity could hinder appropriate integration of interoceptive information with introspection, impairing the individual's ability to regulate emotions. Enhanced connectivity between the FPC and insula with EpCS may restore the capacity to regulate emotions in depressed individuals. Ultimately, an imaging approach that combines functional and tractographic

information with EpCS is likely to be helpful in elucidating the changes in brain network function that underlie the efficacy of EpCS.

This follow-up study continues to have clear limitations regarding its small sample size and open-label design. We speculate that the optimal parameters, although thoroughly explored, may have not yet been utilized. It is also not known whether a bilateral approach is always necessary to optimize treatment outcomes. It is notable that the voltage amplitude necessary for the epidural stimulation appears to be significantly more than that of motor cortex stimulation [72]. This finding suggests that a direct comparison of motor cortex epidural (or subdural) stimulation to prefrontal epidural cortical stimulation would not be appropriate because of the limitations of the amplitude in motor cortex stimulation prior to eliciting suprathreshold motor evoked potentials and therefore limiting stimulation parameters to those below the stimulation induced motor threshold. Future controlled studies that address these limitations will determine the efficacy and further inform the possible mechanism of EpCS of the FPC and DLPFC for the treatment of TRD.

Conclusion

Bilateral anterior pole (FPC) and midlateral (DLPFC) EpCS for TRD appear relatively safe and durable. EpCS has demonstrated an open-label improvement that continues to be efficacious after 5 years and is similar in effect side to other functional neurosurgical approaches in a TRD cohort. The relative ease of this approach compared to DBS, the apparent long-term safety, and the potential of marked efficacy in the treatment of TRD all warrant expanded, controlled, and blinded studies of EpCS for treatment of TRD.

Funding/support

Medtronic, Inc. (Minneapolis, MN) donated the devices but was otherwise not involved in the study, particularly data acquisition, analysis, or drafting the article. Ziad Nahas, MD, declares no conflict of interest in relation to the work described and was funded by a National Alliance of Research for Depression and Schizophrenia (NARSAD) Independent Investigator Award. Brandon Bentzley, MD, PhD, declares no conflict of interest in relation to the work described and was supported by NIH grants F30 DA035065 and T32 GM008716. Nolan Williams, MD, and Thomas Hopkins, BA, declare no conflict of interest in relation to the work described and were supported by NIH grant R25 DA020537. No other contributors declare a conflict of interest in relation to the work described.

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