Left versus right subcallosal cingulate deep brain stimulation for treatment-resistant depression

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ABSTRACT

Deep brain stimulation (DBS) of the subcallosal cingulate has emerged as a promising therapy for treatment-resistant depression (TRD). To date, all studies have employed bilateral stimulation; however, the physiology of affect and pathophysiology of depression are known to be asymmetric across hemispheres. Unilateral stimulation may provide efficacy while decreasing risk. Five patients were exposed to unilateral open-label DBS to the subcallosal cingulate for 12 weeks each to the left and then right hemispheres in a double-blind, crossover fashion. After 12 weeks of stimulation to each hemisphere, bilateral stimulation was initiated, and patients were followed for 12 additional weeks. Additionally, nine months of long-term follow up data were collected. Left, but not right, unilateral stimulation was associated with significant decrease in depression scores; with bilateral stimulation, all patients improved and one patient remitted. No serious adverse events were associated with surgery or acute or chronic stimulation. This small study suggests that unilateral DBS to the subcallosal cingulate may be an effective treatment for TRD. All patients improved with bilateral stimulation, though antidepressant effects following 12 weeks were modest. These findings contrast somewhat with prior open-label trials, though duration of bilateral stimulation was shorter in this trial. The current study continues to confirm safety of implantation and use of DBS to the subcallosal cingulate for patients with TRD and highlights the importance of personalization of therapy, for example by hemisphere, in future trials.

Keywords: deep brain stimulation; treatment-resistant depression; subcallosal cingulate

1. Introduction

Treatment-resistant depression (TRD) affects >1% of the US population [1], and evidence-based treatments are limited. Deep brain stimulation (DBS) of the subcallosal cingulate (SCC) has emerged as a promising therapy, with 29-80% response (defined as 50% decrease in symptoms) and 41-50% remission rates over two to six years of follow-up (reviewed in [2]). Recently, a sham-controlled double blind study [3] with 90 patients did not find a significant difference between stimulation and sham condition over 6 months (20% stimulation response rate vs 17% for sham). However, after 6 months, open label stimulation was initiated for all patients, and response and remission rates notably increased to 48% and 25%, respectively, over 24 months.

To date, SCC DBS studies have employed bilateral stimulation. However, the physiology of affect [4] and pathophysiology of depressive disorders[5] are structurally and functionally asymmetrical across hemispheres. Thus, some patients with TRD may benefit from unilateral stimulation on a particular side, consistent with the potentially unique contribution of laterality to the etiology and/or treatment of depression. Indeed, a single case study from Argentina reported remission from TRD with right-sided but not bilateral or left-sided SCC DBS [6]. The present double-blind, crossover study aimed to compare left- and right-sided stimulation, in addition to providing further data about the safety and antidepressant efficacy of SCC DBS in TRD.

2. Methods

2.1 Study overview

The controlled portion of this study consisted of three phases occurring over a total of 36 weeks: 24 weeks of unilateral stimulation (12 weeks of stimulation to each side), followed by 12 weeks of open-label stimulation to either the previously responsive side (if patient responded to unilateral stimulation) or bilateral stimulation. There was a 4-week evaluation period before surgery to define baseline. To allow recovery from surgery and to assess for any insertion effect, there was a 4-week period prior to stimulation initiation. Following the two phases of unilateral stimulation and after 12 weeks of open-label stimulation, patients were offered participation in a long-term follow up observational study. The Dartmouth College Committee for the Protection of Human Subjects (CPHS) approved all study procedures, and the Dartmouth-Hitchcock Department of Psychiatry Data Safety Monitoring Board monitored the study. All participants gave written informed consent. DBS devices were used under investigator-held FDA Investigational Device Exemption (G120090/SI). The study was registered at clinicaltrials.gov (NCT01898429).

2.2 Eligibility

Inclusion criteria were: 22-70 years of age; current treatment-resistant major depressive episode of at least 12 months' duration secondary to MDD or bipolar disorder (types I, II, or NOS) as assessed by the Mini International Neuropsychiatric Interview and confirmed by two independent study

psychiatrists; score of ≥20 on Hamilton Depression Rating Scale (HDRS-17) [7] at screening and at baseline (averaged over the four weeks prior to surgery); Global Assessment of Functioning (GAF) ≤50, and ability to provide informed consent. For participants with bipolar disorder, the last manic or hypomanic episode must have been at least two years prior to study entry. TRD was defined as: 1) failure to respond to a minimum of four different antidepressant medications, evidence-based psychotherapy or electroconvulsive therapy (ECT) administered at adequate dosage and duration during the current episode; and 2) failure or intolerance of an adequate course of ECT during any episode, or refusal of ECT due to a reason considered valid by a study psychiatrist.

Exclusion criteria included another clinically significant Axis I psychiatric disorders; severe Axis II disorders that would interfere with cooperation and adherence to study protocol; psychotic symptoms; substance use disorder not in full sustained remission; active suicidal ideation with intent; suicide attempt within the last six months; more than three suicide attempts within the last two years; pregnancy or planned pregnancy during study period; general contraindications for anesthesia or DBS surgery; previous stroke, head trauma, or neurodegenerative disorder.

2.3 Assessments

A battery including the Hamilton Depression Rating Scale (HDRS-17) [7] and the Beck Depression Inventory-II [8] was administered weekly for four weeks pre-

and post-operatively, as well as at weeks 1, 2, 3, 4, 6, 8, 10, and 12 of each stimulation phase. Long-term follow up included the same instruments at 1, 3, 6, and 9 months. A neuropsychological battery was also administered prior to surgery and at the end of each stimulation phase.

2.4 Concomitant treatments

Patients were permitted to remain on stable doses of psychiatric medications during the study. Psychotherapy was permitted if it was consistent throughout the study.

2.5 Pre-surgical planning and surgical procedure

Pre-surgical diffusion weighted magnetic resonance imaging was used for structural-connectivity-based target planning as previously described [9]. Stereotactic bilateral DBS lead implantation with the Brio Rechargeable DBS System (Abbott [formerly St. Jude Medical], Plano TX), intraoperative testing, and infraclavicular implantable pulse generator (IPG) placement were performed as previously described [10].

2.6 Post-operative, stimulation off phase

Patients were discharged from the hospital with stimulation off. Mood evaluations were performed weekly for 4 weeks. After surgery, high resolution CT was obtained to visualize electrode placement. CT data was combined with pre-operative MRI to select which electrode on each side was best situated in the

subcallosal cingulate region. This was the contact for chronic stimulation on each side.

2.7 Double-blind controlled phase

Four weeks post-operatively, patients were assigned to left- or right-sided unilateral monopolar SCC DBS for 12 weeks. Given the small sample size, a randomization protocol was not used. Instead, the unblinded programmer was instructed to select the initial side of stimulation and withhold this information from the rest of the study team. The unblinded programmer performed all programming adjustments during the controlled phases of the study. Thus, patients and all raters were blinded to the side of stimulation during the controlled phases of the study. Monopolar stimulation was used with the following parameters: 130 Hz, 90 microseconds pulse width, 6 mA. After 4 weeks of initial stimulation, if the patient's HDRS score was <10% lower compared to baseline and the evaluating psychiatrist concluded that the patient had not improved significantly, stimulation intensity was increased to 8 mA; otherwise, stimulation was continued at 6 mA.

After 12 weeks of stimulation, all patients received unilateral monopolar stimulation on the other side for 12 weeks, with identical initial parameters and subsequent programming protocol.

At the end of the second twelve weeks, patients who responded (≥50% decrease in HDRS score from baseline) to stimulation on the first side but not second side were assigned to the first side. Responders to stimulation on the second side but not first side were assigned to stimulation of the second side. In each case, stimulation parameters were set to those used at the end of 12 weeks on that side. Patients who did not respond to stimulation on either side, or who responded to the first side and remained responders to the second side, were assigned to bilateral stimulation at 130 Hz, 90 μseconds pulse width, 6 mA amplitude. Patients were then evaluated for an additional 12 weeks, at which point they were offered entry into a long-term follow-up study.

2.8 Outcome measures

The primary outcome measure was the Illness Density Index for Depression (IDI-D), calculated using HDRS-17 measurements during each phase [11]. A repeated measures general linear model, including IDI-D for baseline, postoperative, and left, right, and bilateral phases, was used.

Secondary outcome measures included numbers of patients with response and remission at the end of each phase; for these, response was defined as a 50% decrease from baseline HDRS or BDI-II and remission was defined as HDRS-17 < 8 or BDI-II < 10.

3. Results

3.1 Participants

Six participants were enrolled between July 2013 and January 2016. One participant died by suicide prior to baseline evaluation or surgery, so subsequent analyses are based on data from the remaining 5 participants. Postoperative imaging verified accurate electrode placement in all 5 participants. Participant characteristics are detailed in Table 1. For the last phase of the study, four out of five participants were switched to bilateral stimulation, and one participant was switched back to unilateral stimulation of the side used in the first phase of the study. All 5 patients completed the study protocol and elected to enter the long-term follow-up study.

3.2 Antidepressant efficacy

Mean illness density index (IDI) scores (SD) were 22.3 (1.9) at baseline, 21.1 (3.4) post-operatively, 18.4 (1.4) with left-sided stimulation, 21.8 (0.9) with right-sided stimulation, and 18.7 (2.5) with 12 weeks of bilateral stimulation. There was a significant within-subjects effect of treatment phase ($F(4,16) = 4.329$; $p = 0.015$). Pairwise comparisons revealed that both left-sided ($p = 0.011$) and bilateral stimulation ($p = 0.030$), but not right-sided stimulation, resulted in lower IDI compared to baseline. IDI scores were lower during left-sided treatment compared to right-sided treatment ($p = 0.013$).

HDRS and BDI-II scores for each patient are shown in table 2. Based on assessment at the end of each phase, one patient (003) remitted with bilateral

stimulation (HDRS = 6 at end of 12 weeks) and remained in remission through nine months of follow-up. No other patients responded or remitted during the controlled portion of the study, or during nine months of long-term follow up.

3.3 Safety

As stated above, one participant died by suicide prior to baseline evaluation. The investigators, the patient's primary psychiatrist and the Data Safety Monitoring Board for this study deemed this event unrelated to participation in the study. No SAEs related to surgery or study device were reported. Thirty-two adverse events occurred in five patients. One (post-operative pain) was associated with the surgery, and one (persistent pain at IPG site during charging) was potentially related to the study device. Both were rated as mild by the patients. No adverse changes were observed in any phase on neuropsychological testing, and there were no differences in neuropsychological performance following left- versus right-sided stimulation.

3.4 Parameter adjustments and medication changes

All patients were maintained on 6 mA stimulation amplitude for left-sided stimulation; three of the five patients were increased to 8 mA stimulation amplitude during right-sided stimulation due to lack of initial response. No antidepressant medication changes were made during the unilateral or 12-week initial bilateral phases.

4. Discussion

This initial study of unilateral DBS to the subcallosal cingulate for major depression in 5 participants found statistical improvement with left, but not subsequent right unilateral stimulation when delivered for 12 weeks, although no patients met criteria for response or remission during this time. Two participants (2 and 4) showed HDRS decreases of 5-7 points after left-sided treatment that returned to near pre-DBS baseline after right-sided treatment. For two participants (5 and 6), HDRS scores decreased by two points after both left and right stimulation. The other participant remained at baseline after left-sided stimulation and worsened by 5 points after right-sided stimulation. Thus, on the level of individual participants, effects were modest for stimulation on either side, though it should be noted that treatment duration was shorter than what an increasing number of studies suggest is needed to maximize benefit (e.g., up to 2 years) [3].

After an additional 12 weeks of bilateral stimulation, patients did not show as robust an antidepressant effect as seen in prior open label trials, though again treatment duration was relatively short. Also, it should be noted that one patient did remit with 12 weeks of bilateral treatment. Importantly, this study helps confirm the safety of SCC DBS implantation and long-term stimulation. Although there was one death by suicide in this cohort, this was unrelated to DBS surgery or stimulation.

It is difficult to generalize regarding left vs. right sided treatment from such a small cohort. As patients were all started on left-sided treatment, it is possible that they may have responded better to right-sided treatment had it been delivered first. Improvement with left-sided stimulation may be consistent with results from blinded intraoperative testing of left and right contacts during SCC DBS implantation in a separate cohort of nine patients. This testing consistently showed better combined interoceptive and exteroceptive acute behavioral response to left-, rather than right-sided stimulation [12]. It is well-established that the pathophysiology of depression is asymmetrical across hemispheres [5]. However, it is important to note that affective function is lateralized in an inconsistent way even among right-handed individuals [4], and so it is possible that laterality of treatment is an aspect of DBS that will need to be personalized in individual patients for best outcomes.

SCC DBS is targeted toward white matter tracts connecting the SCC to other brain regions. Individualized precision targeting of these white matter tracts is clearly important for success in SCC DBS for TRD; treatment works best when forceps minor, cingulum bundle, uncinate fasciculus, and frontrostriatal tracts are stimulated [9, 13]. Across multiple psychiatric disorders, an overlapping set of interconnected brain regions important in regulating mood, thought, and behavior, have been implicated; the dysfunctional interaction of these regions within circuits underlies the unique pathology in each disorder [14]. Targeting particular connections through different fiber tracts, even with the same anatomic

DBS target, may be key to successfully treating particular psychiatric symptoms. Indeed, a recent case study of DBS to the SCC, but focusing stimulation on the uncinate fasciculus, was shown to successfully target the symptoms of PTSD [15]. The current study suggests that in addition to precise WM tract targeting, laterality may also be an important consideration in personalizing DBS treatment for psychiatric disorders.

Limitations of this study include small sample size, limited duration, and lack of a sham control group. Additionally, all patients received left-sided stimulation first (at the discretion of the unblinded programmer) as opposed to alternating or randomizing initial side.

One potential reason for the limited antidepressant response in this study is the relatively brief duration of stimulation of each side and bilaterally. In a large sham-controlled study of SCC DBS, active treatment was not superior to sham after 6 months of treatment; however, after up to 2 years of open-label DBS, >40% of participants responded [3]. Other prior studies of SCC DBS have also shown continuing improvement from 6 months up to 2 years [2, 9, 10]. Combined, these findings suggest that longer treatment periods are needed to fully assess the benefits of SCC DBS.

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Table 1: Demographic and illness data for each participant

ID	Age	Sex	Primary diagnosis	Duration of current episode (months)	Number of treatments rated ≥ 3 on Antidepressant Treatment History form during current episode (non-medication treatments)	Mean Baseline HDRS	Mean Baseline BDI-II
2	52	Female	MDD	55	4 (ECT, TMS)	25.50	32.50
3	29	Male	Bipolar II	60	4 (ECT)	20.25	28.25
4	68	Male	MDD	18	9 (ECT, CBT)	21.25	23.25
5	40	Female	MDD	36	4 (ECT)	22.50	35.46
6	36	Male	Bipolar II	48	7 (ECT)	22.25	33.75
Mean	45			43.4	5.6	22.35	30.64
SD	5.33			16.8	2.3	1.97	4.92

MDD = Major depressive disorder; HDRS = Hamilton Depression Rating Scale; BDI-II = Beck Depression Inventory II; ECT = Electroconvulsive therapy; TMS = Transcranial magnetic stimulation

Table 2: Depression scores at the end of each treatment phase for each participant

	Baseline (mean)		Left		Right		Bilateral		Long-term follow-up 9 months	
	HDRS	BDI-II	HDRS	BDI-II	HDRS	BDI-II	HDRS	BDI-II	HDRS	BDI-II
Patient ID										
2	25.50	32.50	18	27	24	29	20	27	21	27
3	20.25	28.25	20	40	25	45	6	12	4	0
4	21.25	23.25	16	30	22	29	20	26	21	29
5	22.50	35.46	20	20	18	21	22	29	18	28
6	22.25	33.75	20	24	18	26	19	21	15	18
Mean	22.35	30.64	18.8	28.2	21.4	30.0	17.4	23.0	15.8	20.4
SD	1.97	4.92	1.8	7.6	3.3	9.0	6.5	6.8	7.0	12.2

HDRS = Hamilton Depression Rating Scale; BDI-II = Beck Depression Inventory II

References

1. Holtzheimer, P.E. and H.S. Mayberg, *Stuck in a rut: rethinking depression and its treatment.* Trends Neurosci, 2011. **34**(1): p. 1-9.
2. Cleary, D.R., et al., *Deep brain stimulation for psychiatric disorders: where we are now.* Neurosurg Focus, 2015. **38**(6): p. E2.
3. Holtzheimer, P.E., et al., *Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. LID - S2215-0366(17)30371-1 [pii] LID - 10.1016/S2215-0366(17)30371-1 [doi].* Lancet Psychiatry, 2017(2215-0374 (Electronic)).
4. Costanzo, E.Y., et al., *Hemispheric specialization in affective responses, cerebral dominance for language, and handedness: Lateralization of emotion, language, and dexterity.* Behav Brain Res, 2015. **288**: p. 11-9.
5. Bruder, G.E., J.W. Stewart, and P.J. McGrath, *Right brain, left brain in depressive disorders: Clinical and theoretical implications of behavioral, electrophysiological and neuroimaging findings.* Neurosci Biobehav Rev, 2017. **78**: p. 178-191.
6. Guinjoan, S.M., et al., *Asymmetrical contribution of brain structures to treatment-resistant depression as illustrated by effects of right subgenual cingulum stimulation.* J Neuropsychiatry Clin Neurosci, 2010. **22**(3): p. 265-77.
7. Hamilton, M., *A rating scale for depression.* J Neurol Neurosurg Psychiatry, 1960. **23**: p. 56-62.
8. Beck, A., R. Steer, and G. Brown, *Manual for Beck Depression Inventory II (BDI-II)*. 1996, San Antonio, TX: Psychological Corp. .
9. Riva-Posse, P., et al., *A connectomic approach for subcallosal cingulate deep brain stimulation surgery: prospective targeting in treatment-resistant depression.* Mol Psychiatry, 2017.
10. Holtzheimer, P.E., et al., *Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression.* Arch Gen Psychiatry, 2012. **69**(2): p. 150-8.
11. Kelley, M.E., et al., *The Illness Density Index (IDI): A longitudinal measure of treatment efficacy.* Clin Trials, 2012. **9**(5): p. 596-604.
12. Choi, K.S., et al., *Mapping the "Depression Switch" During Intraoperative Testing of Subcallosal Cingulate Deep Brain Stimulation.* JAMA Neurol, 2015. **72**(11): p. 1252-60.
13. Riva-Posse, P., et al., *Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression.* Biol Psychiatry, 2014. **76**(12): p. 963-9.
14. McTeague, L.M., et al., *Identification of Common Neural Circuit Disruptions in Emotional Processing Across Psychiatric Disorders.* Am J Psychiatry, 2020. **177**(5): p. 411-421.
15. Hamani, C., et al., *Patient With Posttraumatic Stress Disorder Successfully Treated With Deep Brain Stimulation of the Medial Prefrontal Cortex and Uncinate Fasciculus.* Biol Psychiatry, 2020.