Personalized Medicine in Psychiatry 17–18 (2019) 43–45

Contents lists available at ScienceDirect

Personalized Medicine in Psychiatry

journal homepage: www.elsevier.com/locate/pmip

# Deep brain stimulation for treatment-resistant depression: Predicting response and optimizing treatment

Susan K. Conroy[a,*], Paul E. Holtzheimer[b]

[a] Indiana University School of Medicine, Department of Psychiatry, 355 W. 16th St., Ste 2800, Indianapolis, IN 46202, United States
[b] National Center for PTSD, Executive Division; Departments of Psychiatry and Surgery, Geisel School of Medicine at Dartmouth, Dartmouth Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, United States

ARTICLE INFO

*Keywords:*
Major depressive disorder
Treatment-resistant depression
Deep brain stimulation
Tractography

ABSTRACT

Depression has been increasingly recognized as a systems-level disorder; thus, treatments that target critical brain regions in order to influence the function of brain circuits are an important area of study. Deep brain stimulation (DBS), a therapeutic modality initially used in movement disorders, was first applied to treatment-resistant depression (TRD) in 2005. Multiple groups around the world have treated several hundred TRD patients with DBS on an investigational basis. There is no current single accepted protocol for DBS in TRD; variation is possible both in anatomic site and stimulation parameters. The purpose of this article is to discuss the current state of knowledge for DBS in TRD as it relates to patient selection, anatomic target selection and optimization, and stimulation parameters.

## 1. Introduction

Depression is a common and devastating illness, and many patients do not respond to available treatments, including multiple classes of medications, psychotherapy, and electroconvulsive therapy [1]. These patients are referred to as having treatment-resistant depression (TRD). Depression has been increasingly recognized as a systems-level disorder; thus, treatments that target critical brain regions in order to influence the function of brain circuits are an important area of study. Deep brain stimulation (DBS), a therapeutic modality initially used in movement disorders, was first applied to TRD in 2005 [2]. With DBS, intracranial electrodes are implanted using imaging-guided stereotactic surgery, in order to stimulate a particular brain area continuously, often for years. A battery and pulse generator are implanted under the skin on the chest, with wires running subcutaneously up to the intracranial electrodes. Multiple groups around the world have treated several hundred TRD patients with DBS on an investigational basis, as recently reviewed elsewhere [3,4]. There is no current single accepted protocol for DBS in TRD; variation is possible both in anatomic site and stimulation parameters. The subcallosal cingulate (SCC) is the most common stimulation site [2,5–12]. Other stimulation sites include the ventral capsule/ventral striatum (VC/VS) [13,14], the anterior limb of the internal capsule (ALIC; adjacent to VC/VS) [15], and the superolateral branch of the median forebrain bundle (slMFB) [16–18]. Randomized controlled trials, with various study designs, have been conducted for DBS to the SCC (BROADEN) [11], VC/VS (RECLAIM) [14], and ALIC, [15]; plans exist for an RCT of DBS to the slMFB [18]. Overall, results are promising, despite ongoing questions about optimal study design. The purpose of this article is to discuss the current state of knowledge for DBS in TRD as it relates to patient selection, anatomic target selection and optimization, and stimulation parameters.

## 2. Patient selection

### 2.1. Degree of treatment resistance/responsiveness

To date, no upper limit of treatment resistance has been correlated with lack of response to DBS for TRD. In other therapeutic modalities for TRD, greater number of past treatment failures is associated with decreased likelihood of response to treatment. This has been shown for electroconvulsive therapy (ECT) [19], medication [20], and in some studies, repetitive transcranial magnetic stimulation (rTMS) [21]. Naturally, as DBS is an invasive and investigative therapy in TRD, patients who undergo DBS implantation are very highly treatment-resistant. Methods of reporting medication trials and adequacy of such trials vary among studies, but mean medication trials in TRD DBS studies are generally in the range of 6–9 in the current episode [7,14,18], or 8–20 lifetime medication trials [11,14,15,18]. In contrast, the mean number of medication failures in rTMS RCTs for depression generally ranges from 1 to 3 [21]. Further, the large majority of patients

* Corresponding author.
*E-mail address:* sconroy@iu.edu (S.K. Conroy).

https://doi.org/10.1016/j.pmip.2019.10.002

Available online 07 November 2019

in most DBS studies have either failed to respond to or failed to tolerate electroconvulsive therapy; many trials include patients who responded to ECT in previous, but not current, depressive episodes [7,11,14,15]. This overall very high degree of treatment resistance among enrolled patients creates a floor effect, decreasing likelihood of a statistical association between DBS responsiveness and past medication/ECT trials.

On the other hand, a history of treatment responsiveness with return to inter-episode euthymia appears to be associated with response to DBS in TRD, at least as observed at Emory, the center with the most experience in SCC DBS [22]. In one cohort treated at Emory [7], duration of longest euthymic episode since the first onset of major depression was positively associated with response to SCC DBS following six months of open-label stimulation (unpublished data). An analogous phenomenon has been demonstrated in Parkinson's disease, wherein positive response to DBS is predicted by good response to L-DOPA [23].

### 2.2. Duration of current depressive episode

Within individual DBS trials, no association has been shown between length of current episode and treatment response. Mean episode durations in published trials range from 3 to 12 years [7,12,14,15,18]. However, it is notable that in the BROADEN trial, a large industry sponsored RCT of SCC DBS, duration of current episode was around 12 years [11], nearly twice that of previous studies of SCC DBS in TRD [7,12,24]. The negative results of the 6-month placebo-controlled portion of the study may have been partly explained by the extremely chronic depression in this cohort. In the subsequent longer-term open-label portion of this study, 49% of patients responded by 24 months of stimulation, which is more in line with other studies of DBS in TRD. Thus, it is possible that patients with more chronic depression require longer treatment duration with DBS; this should be explored in future DBS studies. In other treatment modalities, including ECT [19] and rTMS [25] increased duration of episode is associated with decreased response to treatment and increased rate of relapse after treatment.

### 2.3. Other illness characteristics

Some characteristics of patients' illness are thought to be predictive of outcomes with DBS in TRD. Low emotional reactivity appears to be associated with better outcome in SCC DBS [22], whereas anxiety, including panic attacks or generalized anxiety disorder, that has occurred outside the context of a depressive episode, is associated with worse SCC DBS outcomes [26]. In BROADEN, the largest TRD DBS study to date, melancholic features were not predictive of treatment response [11]. Inadequate data exist regarding effectiveness in treating unipolar vs. bipolar depression with DBS, as most studies of DBS exclude patient with a history of bipolar disorder; exceptions include [7], which found similar efficacy in unipolar and bipolar patients, and [13,18], which each included one patient with bipolar disorder. One analysis of baseline neuropsychological factors found that executive dysfunction (more total errors in the Wisconsin Card Sort Task) and lack of psychomotor slowing (faster Finger Tap task) predict SCC DBS efficacy in a group of 20 patients [27].

### 2.4. Other patient characteristics

Of course, patients who undergo DBS for TRD must be healthy enough to undergo neurosurgery, and reliable for regular follow-up visits. All patients in DBS trials have been adults, with mean age of 40–50 in most trials. Samples have been overwhelmingly white, non-Hispanic. Minimal guidance as to demographic predictors of response is available; the largest DBS trial to date (n = 90 patients total) found no demographic factors that predicted response to DBS [11].

## 3. Stimulation targeting

As more TRD patients have had DBS devices implanted, and as imaging methods have grown increasingly sophisticated, it has become increasingly clear that targeting and activating particular white matter tracts in each individual patient is likely critical in treatment response. I.e., gross anatomic targeting alone is probably not sufficient. For the SCC, this was first suggested via a retrospective analysis, using activation volume tractography, in which DBS responders shared bilateral activation pathways from SCC to frontal regions, cingulate cortex, and subcortical regions. Non-responders did not show consistent activation pathways in all these regions [28]. A subsequent prospective study, using individualized pre-implantation deterministic tractography, showed a remarkably high response and remission rate at 1 year (9 and 6 of 11 patients, respectively) [12]. Unfortunately, the BROADEN trial did not use individualized tractography for electrode placement, which may in part account for lack of separation from placebo during the initial 6 month double-blind phase; additionally, no DTI data was collected at baseline in this study, so it is not possible to look retrospectively [11]. Ventral capsule/ventral striatum (VC/VS) is also a white matter target, studied in both TRD and obsessive-compulsive disorder (OCD). A randomized controlled trial of VC/VS in TRD (RECLAIM) that used anatomic coordinates and not tractography did not show differences from placebo during the controlled phase [14]. Individualized tractography has been utilized in a recent study of the medial forebrain bundle and is planned for an ongoing "pivotal trial" [29].

Further advances in imaging, precision targeting, and stimulation modeling can be expected to enhance predictive power, and eventually treatment efficacy to the level of an individual patient. Multiple recent studies have demonstrated new techniques. Machine learning rather than manual deterministic tractography is being employed in slMFB DBS routinely to enhance targeting precision [30]. New appreciation of factors such as role of sub-millimeter brain shift secondary to neurosurgical burr holes may be taken into account in the future [31]. Intraoperative targeting could potentially be enhanced by measuring autonomic responsivity to intraoperative stimulation [32]. Stimulation modeling using a field cable pathway activation model, based on relative activity of multiple tracts passing through SCC, recently demonstrated the ability to predict time to a stable treatment response [33]. Post-surgical target engagement assessment may be improved by using EEG and evoked potentials [34].

## 4. Stimulation parameters

In DBS, stimulation parameters that can vary include pulse width, intensity, frequency, and number of contacts activated. In movement disorders such as Parkinson's disease and tremor, stimulation parameters often require change over time to maintain efficacy. Studies of anatomically targeted (i.e., no individualized tractography) VC/VS DBS for OCD [35] have shown that overall less energy (decreased intensity, pulse width, and number of contacts) may be required for efficacy depending on anatomic location. In DBS for TRD, changes in intensity have generally proved to be more important than changes in pulse width. For example, during the open-label phase of BROADEN [11], an increase in stimulus intensity from 6 mA to 8 mA and then addition of another electrode contact, was associated with greater rate of response.

However, caution must be exercised in changing stimulation parameters, due to the risk of emergent side effects. Side effects vary by anatomic location. DBS of the VC/VS and ALIC have been associated with mania, hypomania, irritability, and suicidal ideation [14]. In the ALIC study, mania/hypomania resolved in three cases with decreasing the stimulus intensity [15]. The medial forebrain bundle, due to its proximity to the oculomotor nerve, is associated with visual disturbances. Strabismus has been shown to be current-related [16]. SCC stimulation has not been associated with specific stimulation-related

side effects to date, regardless of stimulation parameters.

## 5. Conclusion: Personalizing DBS for TRD

DBS for TRD is still an investigational therapy, but the studies discussed above give some guidance regarding personalization of therapy. The current crux of personalization in DBS for TRD lies in targeting particular white matter fiber bundles, as discussed in section 3 above. Advances in imaging technology, stimulation modeling, and target engagement assessment promise to further enhance personalization and potentially efficacy of DBS in TRD. The selection of one DBS anatomic site over another (e.g., SCC vs. VC/VS) has not been formally studied. Potential side effects may guide treatment selection: patients with a propensity for hypomanic symptoms may wish to avoid VC/VS stimulation, or patients with pre-existing visual disturbances may wish to avoid the slMFB. Little guidance exists regarding illness characteristics exists; it has been suggested that patients with low emotional reactivity might respond better to SCC DBS.

Critically, for DBS in TRD to become widespread, more studies are needed. There has been much discussion in the field of how to move forward in light of two recent large placebo-controlled, industry sponsored trials that failed to separate DBS from placebo during initial relatively short blinded phases [11,14]. There are many study design considerations to getting the most out of DBS that have been discussed extensively elsewhere, e.g., [3,18,36–38]. Important considerations include: individualized targeting of fiber tracts; longer trials in general; different time courses for different targets; different designs, such as a lead-in optimization phase for all patients, followed by the blinded placebo-controlled phase; and flexibility in initial parameter programming. DBS for TRD remains a promising therapy, and appropriately designed and executed studies have the power to advance psychiatry toward its eventual clinical adoption.

## Conflict of Interest Statement

Paul Holtzheimer: consultant for Abbott (formerly St. Jude Medical); receives royalties from Up-To-Date and Oxford University Press.

Susan Conroy: nothing to declare.

## References


[1] Holtzheimer PE, Mayberg HS. Stuck in a rut: rethinking depression and its treatment. Trends Neurosci 2011;34(1):1–9.
[2] Mayberg HS, et al. Deep brain stimulation for treatment-resistant depression. Neuron 2005;45(5):651–60.
[3] Filkowski MM, Sheth SA. Deep brain stimulation for depression: an emerging indication. Neurosurg Clin N Am 2019;30(2):243–56.
[4] Zhou C, et al. A systematic review and meta-analysis of deep brain stimulation in treatment-resistant depression. Prog Neuropsychopharmacol Biol Psychiatry 2018;82:224–32.
[5] Lozano AM, et al. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry 2008;64(6):461–7.
[6] Lozano AM, et al. A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. J Neurosurg 2012;116(2):315–22.
[7] Holtzheimer PE, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Arch Gen Psychiatry 2012;69(2):150–8.
[8] Puigdemont D, et al. Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression. Int J Neuropsychopharmacol 2012;15(1):121–33.
[9] Merkl A, et al. Antidepressant effects after short-term and chronic stimulation of the subgenual cingulate gyrus in treatment-resistant depression. Exp Neurol 2013;249:160–8.
[10] Ramasubbu R, et al. Double-blind optimization of subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study. J Psychiatry Neurosci 2013;38(5):325–32.
[11] Holtzheimer PE, 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).
[12] Riva-Posse P, et al. A connectomic approach for subcallosal cingulate deep brain stimulation surgery: prospective targeting in treatment-resistant depression. Mol Psychiatry 2018;23(4):843–9.
[13] Malone Jr DA, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. Biol Psychiatry 2009;65(4):267–75.
[14] Dougherty DD, et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. Biol Psychiatry 2015;78(4):240–8.
[15] Bergfeld IO, et al. Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry 2016;73(5):456–64.
[16] Bewernick BH, et al. Deep brain stimulation to the medial forebrain bundle for depression- long-term outcomes and a novel data analysis strategy. Brain Stimul 2017;10(3):664–71.
[17] Fenoy AJ, et al. Deep brain stimulation of the medial forebrain bundle: distinctive responses in resistant depression. J Affect Disord 2016;203:143–51.
[18] Coenen VA, et al. Superolateral medial forebrain bundle deep brain stimulation in major depression: a gateway trial. Neuropsychopharmacology 2019.
[19] Haq AU, et al. Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. J Clin Psychiatry 2015;76(10):1374–84.
[20] Rush AJ, 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):1905–17.
[21] McClintock SM, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J Clin Psychiatry 2018;79(1).
[22] Crowell AL, et al. Characterizing the therapeutic response to deep brain stimulation for treatment-resistant depression: a single center long-term perspective. Front Integr Neurosci 2015;9:41.
[23] Charles PD, et al. Predictors of effective bilateral subthalamic nucleus stimulation for PD. Neurology 2002;59(6):932–4.
[24] Mayberg HS. Targeted electrode-based modulation of neural circuits for depression. J Clin Invest 2009;119(4):717–25.
[25] Lisanby SH, 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):522–34.
[26] Riva-Posse P, et al. Practical considerations in the development and refinement of subcallosal cingulate white matter deep brain stimulation for treatment-resistant depression. World Neurosurg 2013;80(3–4). S27.e25-34.
[27] McInerney SJ, et al. Neurocognitive predictors of response in treatment resistant depression to subcallosal cingulate gyrus deep brain stimulation. Front Hum Neurosci 2017;11:74.
[28] 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):963–9.
[29] Coenen VA, et al. Tractography-assisted deep brain stimulation of the superolateral branch of the medial forebrain bundle (slMFB DBS) in major depression. Neuroimage Clin 2018;20:580–93.
[30] Coenen VA, et al. Machine learning-aided personalized DTI tractographic planning for deep brain stimulation of the superolateral medial forebrain bundle using HAMLET. Acta Neurochir (Wien) 2019;161(8):1559–69.
[31] Choi KS, et al. Impact of brain shift on subcallosal cingulate deep brain stimulation. Brain Stimul 2018;11(2):445–53.
[32] Riva-Posse P, et al. Autonomic arousal elicited by subcallosal cingulate stimulation is explained by white matter connectivity. Brain Stimul 2019;12(3):743–51.
[33] Howell B, et al. Quantifying the axonal pathways directly stimulated in therapeutic subcallosal cingulate deep brain stimulation. Hum Brain Mapp 2019;40(3):889–903.
[34] Waters AC, et al. Test-retest reliability of a stimulation-locked evoked response to deep brain stimulation in subcallosal cingulate for treatment resistant depression. Hum Brain Mapp 2018;39(12):4844–56.
[35] Greenberg BD, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry 2010;15(1):64–79.
[36] Fins JJ, et al. Being open minded about neuromodulation trials: Finding success in our “failures”. Brain Stimul 2017;10(2):181–6.
[37] Bhati MT, Halpern CH. Deciphering deep brain stimulation for depression. Lancet Psychiatry 2017;4(11):820–1.
[38] Dougherty DD. Deep brain stimulation: clinical applications. Psychiatr Clin North Am 2018;41(3):385–94.