Practical Considerations in the Development and Refinement of Subcallosal Cingulate White Matter Deep Brain Stimulation for Treatment-Resistant Depression

Patricio Riva-Posse[1], Paul E. Holtzheimer[3], Steven J. Garlow[1], Helen S. Mayberg[1,2]

Key words
- Deep brain stimulation
- Subcallosal cingulated
- Treatment-resistant depression

Abbreviations and Acronyms
BA: Brodmann area
DBS: Deep brain stimulation
ECT: Electroconvulsive therapy
MDD: Major depressive disorder
NAcc: Nucleus accumbens
SCC: Subcallosal cingulate
TRD: Treatment-resistant depression
VC/VS: Ventral capsule/ventral striatum

From the Departments of [1]Department of Psychiatry and Behavioral Sciences and [2]Neurology and Radiology, Emory University School of Medicine, Atlanta, Georgia; and [3]Departments of Psychiatry and Surgery, Dartmouth Medical School, Hanover, New Hampshire, USA

To whom correspondence should be addressed: Patricio Riva-Posse, M.D. [E-mail: privapo@emory.edu]

Citation: World Neurosurg. (2013) 80, 3/4:S27.e25-S27.e34. http://dx.doi.org/10.1016/j.wneu.2012.11.074

*Journal homepage: **www.WORLDNEUROSURGERY.org***

*Available online: **www.sciencedirect.com***

■ BACKGROUND: **Deep brain stimulation has been investigated in the past decade as a viable intervention for treatment-resistant depression.**

■ METHODS: **Several anatomic targets have been tested, with the most extensive published experience found for the subcallosal cingulate (SCC) white matter.**

■ RESULTS: **This article reviews the current state of clinical research of SCC deep brain stimulation for treatment-resistant depression, including an overview of the rationale for targeting SCC, practical considerations for subject recruitment and evaluation, surgical planning, and stimulation parameters.**

■ CONCLUSION: **Clinical management of patients in the initial and long-term naturalistic phases of treatment, including the potential role for psychotherapeutic rehabilitation, is discussed.**

INTRODUCTION

Major depressive disorder (MDD) is a common and costly condition, with lifetime prevalence in the United States estimated at 17% (49). MDD is the leading cause of years lost due to disability worldwide and the third overall contributor to the global burden of disease (and projected to be the largest contributor by 2030) (93). MDD is a chronic illness, with a majority of patients following a pattern of partial to full remission followed by multiple recurrences (67, 85).

Medications and psychotherapy can be effective treatment for MDD. However, incomplete resolution of symptoms is common, with up to 33% of patients failing to reach remission after several standard interventions, and relapse rates are high (75). Somatic nonpharmacologic treatments remain viable options for people with treatment-resistant depression (TRD). The most effective currently available intervention is electroconvulsive therapy (ECT), which has reported remission rates greater than 40% in patients with TRD (46, 90). However, relapse is common, and its cognitive side effects limit use. It is estimated that more than 10% of patients with MDD are significantly treatment resistant because they have exhausted all reasonable and available treatment modalities (41).

Ablative neurosurgical procedures for the relief of TRD have been available for decades and typically involve disruption of frontolimbic circuits (57). Four accepted procedures include: subcaudate tractotomy (11), in which white matter tracts between the prefrontal cortex are interrupted, in particular the orbitofrontal region, and subcortical structures; anterior cingulotomy (87); limbic leucotomy (14), which is a combination of the previous two procedures; and anterior capsulotomy (17), in which the frontothalamic connections in the anterior limb of the internal capsule are interrupted (76, 83). Side effects are common and the use of these procedures is limited (43, 65).

Based largely on neuroimaging data during the past two decades, depression is now widely viewed as a multidimensional, systems-level disorder affecting discrete but functionally integrated pathways (22, 58, 59). This neural network of depression provides a working platform to consider brain regions that may be involved in the pathophysiology of the disorder and linked to an antidepressant response. This framework has aided in the development of focal neuromodulation strategies that aim to treat depression by directly changing the activity of a specific brain region to modulate overall network function in a therapeutic way. These strategies include repetitive transcranial magnetic stimulation (29, 72), vagus nerve stimulation (78), transcranial direct current stimulation (28, 69), magnetic seizure therapy (50), direct cortical stimulation (68), and deep brain stimulation (DBS).

In this article, we will briefly review the rationale for and data supporting DBS as a promising treatment for severe TRD. DBS represents a unique and invasive treatment strategy for psychiatric disorders; as such, its study and use raise a number of important research, clinical, and ethical issues. With these issues in mind, and based on our collective experience with subcallosal cingulate (SCC) DBS for TRD, we will discuss a number of practical considerations in the development of clinical trials of this treat-

ment and the clinical management of these patients.

DBS FOR TRD

Compared with ablation, DBS has significant potential safety and therapeutic advantages due to its reversibility, revisability, and adjustability. DBS is a well-established treatment for medication-refractory movement disorders such as Parkinson disease (6), essential tremor (55), and dystonia (89). DBS increasingly is being explored for several psychiatric disorders, and a DBS system was recently granted approval from the Food and Drug Administration for the treatment of severe, treatment-resistant obsessive-compulsive disorder through a Humanitarian Device Exemption (27).

Surgical techniques and algorithms for stimulation delivery have largely followed directly on those developed for movement disorders, with the hypothesis that stimulation is comparable with ablation and that high-frequency stimulation induces a functional lesion via neuronal inhibition (10). However, it has become increasingly clear that the mechanisms mediating DBS effects are more complex, with evidence of both excitatory and inhibitory effects on brain regions adjacent to and remote from the site of stimulation (92).

DBS FOR TRD: POTENTIAL TARGETS

SCC White Matter

For TRD, several potential DBS targets have emerged on the basis of different rationales. The SCC white matter was selected as a target based on the prominent role of this region within a "depression" neural network and its apparent role in antidepressant response to various treatments (60, 61). Changes in metabolic activity in the SCC, more specifically Brodmann area 25, correlate with response to fluoxetine (61). These changes in the region are not exclusive to one therapeutic modality, but have been demonstrated in successful response to active and placebo pharmacotherapy, ECT, and cognitive behavioral therapy (48, 61, 63, 70). Functional hyperactivity of this region characterizes more treatment-resistant patients (21, 34, 62). Additionally, the SCC has reciprocal connections with multiple different regions in charge of modulating cognitive, homeostatic, autonomic, and circadian processes, validating its role as a critical node within a mood-regulation network. This finding was supported by studies in nonhuman primates in which authors described the area's multiple connections (12, 73).

Because it is considerably more medial than the standard subcaudate tractotomy lesion, SCC white matter has never been reported as a target for ablative surgery. Since 2005, an increasing number of studies have been published in which authors describing the antidepressant effect of SCC DBS. To date, there are published results on 67 patients from six separate centers with outcome data in some series reporting on 3–6 years of continuous stimulation (35, 40, 47, 52, 53, 62, 74). An initial response rate (24 weeks to 6 months) of 41%–66% is reported. The remission rate at this first time point varies between 18% and 50%. With longer follow-up, in which protocols allow for other treatment changes, the response and remission rates increase. With 2–6 years of follow-up, response rates are 64%–92% with remission rates of 42%–58%. In general, patients reaching remission with SCC DBS appear to stay well over time: antidepressant effects are robust as long as stimulation is maintained and a slow but predictable loss of effect is seen with stimulation discontinuation, such as with battery depletion, even after more than 5 years of sustained remission. Chronic SCC stimulation is usually well tolerated; there are no significant side effects related to increase in current settings and the neurocognitive profile remains intact, even improving on certain domains (40, 64).

Other Potential DBS Targets for TRD

Other targets for DBS investigated for TRD include the ventral capsule/ventral striatum (VC/VS) (56), nucleus accumbens (NAcc) (81), inferior thalamic peduncle (44), habenula (79), and median forebrain bundle (19). VC/VS for depression was developed from observations of antidepressant effects of DBS in patients with obsessive-compulsive disorder and comorbid depression (71). This intervention has a reported response rate of 40% with 20% remission in 15 patients at 6 months. At last follow-up, response and remission rates are 53% and 40%, respectively (6–51 months).

DBS targeting the NAcc is based on the behavioral hypotheses of modulation of pathways in the motivation and reward system (32, 81). Published response and remission rates (10 patients) are 50% and 30%, respectively, at 12 months (7) and 45% and 9% at 2 years (11 patients) (8). With both the VC/VS and NAcc targets, stimulation-related adverse effects were reported as anxiety, hypomania/mixed-bipolar state, and restlessness that were attenuated with parameter changes.

There are single case reports of DBS in inferior thalamic peduncle (44) and lateral habenula (79) with antidepressant effects suggested. The medial forebrain bundle (projecting from the ventral tegmental area to the NAcc) has been proposed as a potential target for DBS for TRD (19), and preliminary pilot testing is underway (80) (**Table 1**).

Summary

The studies of DBS for depression thus far have been primarily open-label. Overall, 6- to 12-month response and remission rates appear similar for the SCC, VC/VS, and NAcc targets. For the SCC target, response and remission rates increase up to 2 years after the onset of stimulation, and patients achieving remission tend not to relapse unless stimulation is discontinued (40). DBS at these various targets appears to have no significant long-term effects, although adverse effects of acute stimulation have differed. Multicenter, randomized, sham-controlled clinical trials are now underway recruiting patients for DBS in SCC (United States, Europe) and VC/VS (United States).

SCC DBS FOR TRD: PRACTICAL CONSIDERATIONS

Collectively, we have been involved with the management of more than 40 patients who have received SCC DBS for TRD (including a new cohort of patients now being enrolled at Emory). On the basis of this experience, we have developed a number of suggestions for further development of this treatment. In this section, we will discuss several practical considerations in the design and conduct of clinical trials of SCC DBS for TRD, including recruitment and evaluation, target selection, parameter selection and device programming, as well as long-term clinical management.