Deep Brain Stimulation for Obsessive-Compulsive Disorder

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EDUCATIONAL OBJECTIVES

1. Provide an overview of the history and origins of deep brain stimulation (DBS) for treatment-refractory obsessive-compulsive disorder (OCD).
2. Describe the various neuroanatomic targets of DBS implant for OCD as well as the neurocircuitry involved.
3. Explain the effects of DBS for OCD, both intended and unintended, as well as the promise the treatment holds for select treatment-resistant OCD patients.

Obsessive-compulsive disorder (OCD) is a chronic anxiety disorder that affects approximately 2% to 3% of the population. OCD is characterized by persistent, intrusive, and distressing thoughts (obsessions) and ritualistic behaviors (compulsions), such as counting, organizing, or cleaning, which are used to lessen anxiety caused by the obsessive thoughts. The symptoms of OCD generally manifest in childhood or adolescence and may result in significant impairment in everyday functioning. The etiology of OCD is hypothesized to involve a combination of genetic and environmental factors.

Currently, first-line treatment options for OCD include medications such as serotonergic antidepressants, including clomipramine and all of the selective serotonin reuptake inhibitors, and cognitive-behavior therapy. However, double-blind, placebo-controlled studies have shown that approximately one-third of patients receiving antidepressants and therapy may not experience a substantial benefit.
For extremely treatment-resistant OCD, neurosurgical interventions should be considered. Historically, neurosurgery as treatment for psychiatric disorders has been a subject of controversy. However, the published long-term data indicate very high response rates for lesion procedures such as cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leucotomy for treatment-resistant OCD.\textsuperscript{3} Greenberg et al\textsuperscript{4} reported outcomes of neurosurgical intervention for intractable OCD, indicating response rates of roughly 30% to 70%, with “response” defined as at least 35% reduction in symptoms. However, despite these encouraging reports of efficacy, lesion procedures are reserved in the most severe cases because they could cause permanent negative effects on cognition and personality changes.

Over the past 20 years, deep brain stimulation (DBS) has been proposed as a novel, non–lesion-based, reversible, neurosurgical procedure with significant potential as a treatment option for patients with severe, treatment-refractory OCD. DBS consists of surgically implanting electrodes at specific locations within the brain and conveying electrical charges of adjustable frequency and intensity through those electrodes. This stimulation is thought to cause modulation of the underlying circuitry that mimics the effect of a lesion at the same site.

In the early 1960s, it was found that electrical stimulation of the ventrolateral thalamus could alleviate tremor,\textsuperscript{5} and in the early 1990s, DBS was developed for the treatment of essential tremor in Parkinson’s disease.\textsuperscript{6} Since then, the safety and efficacy of DBS for movement disorders have been shown in rigorous clinical trials.\textsuperscript{7,8} Since the first application of DBS for OCD by Nuttin et al\textsuperscript{9} in 1999, a number of research studies have investigated the efficacy and safety of DBS for OCD using different anatomic targets for the implantation of the electrodes.

**ANATOMICAL TARGETS**

Clinical trials and case studies have investigated five different targets for DBS lead placement: the anterior limb of the internal capsule (ALIC); the nucleus accumbens (NAcc); the subthalamic nucleus (STN); the inferior thalamic peduncle (ITP); and the ventral capsule/ventral striatum (VC/VS). Currently, there are approximately 120 patients worldwide being treated for OCD with DBS.

**The Anterior Limb of the Internal Capsule (ALIC)**

The internal capsule encompasses white matter that separates the thalamus and caudate nucleus from the putamen and globus pallidus. The first published data on DBS for the treatment of OCD came from Nuttin et al\textsuperscript{9} This group performed bilateral stimulation of the ALIC in six patients who were followed for 21 months.\textsuperscript{10} Beneficial effects were observed in three of the six patients, with an average decrease of symptoms of 35%.

Another group of researchers recruited a sample of four patients who received bilateral stimulation of the ALIC.\textsuperscript{11} Their study design used a double-blind phase followed by an open phase, and two of the four patients experienced a decrease of symptoms of 35% or more at the end of the study.

Overall, early trials and case studies showed modest efficacy for the ALIC as a DBS target. Researchers focusing on the internal capsule as a target subsequently used a more ventral position, the VC/VS, which includes the ventral ALIC and the adjacent ventral striatum. This junction is what is referred to as the VC/VS.

**The Ventral Capsule/Ventral Striatum (VC/VS)**

The rationale for using the VC/VS as a target is derived from its specific use as the location of ablative procedures for treatment-refractory OCD and anterior capsulotomies and more recent results of neuroimaging research involving neuroanatomic models of OCD. A study by Rauch et al\textsuperscript{12} used oxygen-15 positron emission tomography imaging to show how DBS increased the perfusion of the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), striatum, pallidum, and thalamus compared with normal controls. Therefore, DBS at the target VC/VS site was believed to be associated with the modulation of circuitry specifically implicated in the pathophysiology of OCD.

Greenberg et al\textsuperscript{13} published the results of a trial using the VC/VS site. It should be noted that the VC/VS site used for stimulation in Greenberg et al’s 2006 trial was significantly more posterior than the target for capsulotomy lesions and more posterior compared with previous DBS studies.\textsuperscript{11} Greenberg et al’s study reported the outcome of DBS at the VC/VS site in 10 patients, eight of whom were followed for 3 years; four of eight patients were considered responders as defined by symptom reduction of at least 35%.

In 2010, the same investigators published the results of an expanded sample including 26 patients who were followed by four different research groups over the course of 8 years.\textsuperscript{14} The patients included in the report were broken into three different cohorts based on the time since their implant procedure;
the reason for this was that the precise target within the VC/VS evolved during this period, gradually moving to a more posterior area. It is important to note that the outcomes of the three cohorts improved progressively as more posterior targets were engaged. Their results corroborated the hypothesis that the neurocircuitry associated with OCD is more effectively modulated at a more posterior VC/VS location, where the white-matter cortico-striatal-thalamic-cortical (CSTC) tracts become more compact. Based on the results of previous studies, the group at Brown University led by Greenberg initiated a large, multicenter, sham-controlled, randomized, double-blind study of DBS for OCD with the VC/VS as the target of interest. The study is currently ongoing and intends to follow 30 patients at sites across the United States for up to 4 years.15

The Subthalamic Nucleus (STN)

The STN is located within the basolateral ganglia system and is ventral to the thalamus. The STN has been actively investigated as a target for DBS treatment in patients with Parkinson’s disease. In two case reports, three patients who were implanted with DBS for Parkinson’s also had concomitant OCD, and they showed an attenuation of their OCD symptoms.16,17 A few years later, the same investigative group published the results of a randomized, sham-controlled, double-blind, multicenter study that included 16 patients with OCD who were treated with DBS at the STN. The stimulation had significant effects for compulsive symptoms, with a mean Yale-Brown Obsessive Compulsive Scale (YBOCS) score decrease of 41% after 3 months, but no effects were observed on mood.18 The target chosen for OCD patients was in the limbic part of the STN, 2 mm anterior and 1 mm medial to the traditional target used for Parkinson’s treatment.

The Nucleus Accumbens (NAcc)

The NAcc composes the primary part of the ventral striatum. It is implicated in the circuitry of reward, pleasure, and addiction. Both bilateral and unilateral stimulation has been attempted at the NAcc target. In 2003, a study was published with four OCD patients receiving DBS.19 Of these patients, three showed marked improvement, displaying nearly full remission of anxiety and OCD symptoms. Interestingly, these three received unilateral implants, whereas the fourth, who did not show an improvement, received bilateral stimulation.

A larger (n = 10) double-blind, sham-controlled, crossover study of unilateral NAcc stimulation was conducted in 2010 by Huff et al.20 The results were unfavorable, with only 1 of 10 patients having a significant response (defined by a decrease in YBOCS score by > 35%).

Denys and colleagues21 presented their results on bilateral stimulation of the NAcc and reported greater efficacy compared with unilateral stimulation. In this study, nine of the 16 patients were considered responders, with a mean YBOCS score reduction of 47% after 1 year. Anxiety and depressive symptoms were also reduced by approximately 50%.

The Inferior Thalamic Peduncle (ITP)

The ITP was the target chosen by a research group in Mexico.22 Of five patients who received a bilateral implant, a 49% mean reduction in symptoms was observed at 12 months. The study was unique in that it included one patient with schizoid personality disorder and three with substance abuse problems, comorbidities that are routinely excluded from similar clinical research trials.

DEVICE IMPLANTATION

The device used for the current large multicenter National Institute of Mental Health–sponsored trial15 is similar to the device used in movement disorders. It is manufactured by Medtronic (Minneapolis, MN). In this trial, the neurosurgeon implants the leads bilaterally into the VC/VS, along the anterior limb of each internal capsule and extending into the ventral striatum (see Figure 1). The lead used in the study (model 3387) is 1.27 mm in diameter and has four cylindrical electrode contacts. Each contact is 1.5 mm long and is separated from the adjacent contact by 1.5 mm. The contacts are numbered from 0 to 3, distal to proximal. Stereotactic coordinates are determined based on the patient’s individual structural neuroanatomy by using the

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**Figure 1.** Coronal view (left panel) and sagittal view (right panel) from a computed tomography scan in a patient immediately after implant surgery (ie, lead placement in the ventral capsule/ventral striatum). The extension wires and neurostimulators have not yet been implanted.
resolution magnetic resonance imaging and a computed tomography scan. The leads are connected to batteries and implanted subcutaneously in the chest via extension wires.

During the implantation of the electrodes, the patient remains awake. After the electrodes are implanted and placed, stimulation is performed with a temporary, external stimulator. Intraoperative testing is conducted to identify settings and individual contacts that have an acute impact on mood and anxiety. The patient provides verbal feedback about the symptoms modified by a particular stimulation or change in parameter. Furthermore, the intraoperative testing enables the identification of settings that may cause adverse effects for the patient (such as twitching, tachycardia, flushing, or increased anxiety).

Postoperative imaging allows confirmation of adequate electrode placement. After the leads are implanted and test stimulation is completed, the neurostimulator batteries and extension wires are implanted, a procedure usually performed under general anesthesia. A 2-week period is typically required before the batteries are turned on to allow adequate time for incision wounds to heal.

**ADVERSE EFFECTS**

Complications from this procedure may fall into one of three categories: surgical/procedural, device related, or psychiatric (caused by stimulation). According to a review of large samples of patients with psychiatric and movement disorders treated with DBS, symptomatic hemorrhage, infection, and seizure each occur in about 1% to 4% of cases but usually respond to treatment or resolve without serious sequelaes.23 Among the published data on the approximate 120 OCD patients who have received DBS therapy, there have been three reported intracerebral hemorrhages. Of 26 patients published in the study by Greenberg et al, one experienced an asymptomatic hemorrhage and one experienced hemorrhage resulting in transient apathy. In the second case, the hemorrhage was resolved within 3 months without clinical sequelae. Mallet et al reported an event of intracranial hemorrhage that resulted in permanent finger palsy. Another instance of a surgical adverse event includes a single tonic-clonic seizure.14 The most common surgical adverse event was wound infection, which occurred in two patients in the Mallet et al study and in one patient in the Greenberg et al study.

Device-related complications were reported for two patients by Greenberg et al in which a break was found in a stimulating lead or extension wire, requiring replacement surgery. Overall, the incidence of those adverse events in patients with psychiatric disorders does not appear to be significantly different from the incidence reported in large, controlled studies in patients with movement disorders.

The majority of adverse events occurring during DBS treatment in OCD patients were associated with stimulation. These may be divided into acute effects or chronic effects. Different side effects were reported for the stimulation of different brain regions. Acute side effects, which could be physical or mental, generally are transitory and dissipate after acclimation to stimulation parameters or with the discontinuation of the stimulation itself. Acute changes in mood included an elevation of mood toward normal in patients with depression, an elevation above what is considered normal, a lowering of mood toward baseline in patients who have shown improvement, and a lowering of mood beyond baseline. The elevation of mood from baseline toward normal was an intended effect of the DBS and thus not considered an adverse event. A transient elevation of mood above normal (“nonserious” hypomania) was reported in eight of 26 patients by Greenberg et al. According to this report, patients would describe feeling “happy,” “giddy,” or simply “feeling a lot better” generally within only seconds or minutes after stimulation parameter adjustments. For such acute events, symptoms would peak in 5 to 30 minutes and then gradually subside.

In addition, a lowering of mood was a common effect of abruptly halting stimulation in patients who were receiving chronic stimulation, such as in battery depletion or accidental battery shutoff. However, none of the patients experienced depression or suicidality as severe as pre-DBS implant.

Sensorimotor effects were observed in some patients. Okun et al reported stimulation-related gustatory and olfactory sensations. Additionally, other sensations were observed, such as a “tingling” in the mouth or facial regions and acute muscle contractions, mainly in the orofacial location. These sensorimotor adverse events were most strongly associated with stimulation of the ventral electrode contacts, and, as in the case of acute changes in mood, these acute sensations subsided quickly.

The most common unfavorable chronic effect of the stimulation was increased anxiety. Worsening of anxiety was noticed acutely upon parameter adjustment but also continued into the chronic phase of treatment. Anxiety symptoms were reported to be associated with stimulation by the most distal electrode contact. Because OCD patients often struggle with comorbid major depression, the most common favorable
chronic effect was mood improvement. Many patients reported a greater positive effect, emotional clarity, and “blissful” feelings. At 36 months postimplant, Greenberg et al.\textsuperscript{14} reported a mean decrease of 43% in depression symptoms after stimulation of the VC/VS. An improvement in depression scores was also reported by Abelson et al.\textsuperscript{11} in one of four patients who received stimulation of the internal capsule, whereas stimulation of the STN resulted in no apparent improvement of depressive symptoms.\textsuperscript{18}

Unlike ablative interventions, DBS has not been linked to permanent cognitive changes or decline. Some patients reported adverse cognitive effects associated with particular stimulation parameters, but these changes were usually mild to moderate and decreased with a change of stimulation parameters. Some patients described diminished concentration; one patient experienced intrusive memories, or flashbacks, that ceased after parameters were changed.\textsuperscript{14} Neuropsychological assessments are usually administered during the course of treatment, and no cognitive decline has been consistently reported across studies. However, Denys et al.\textsuperscript{21} reported mild forgetfulness in five of 16 patients after bilateral stimulation of the NAcc, and the same group also reported increased libido, up to a normal level, as well as inadvertent, effortless, smoking cessation.\textsuperscript{25}

**MECHANISMS OF ACTION: NEUROBIOLOGY OF DBS IN OCD**

The mechanisms of action underlying DBS effects have yet to be elucidated.

One of the major limitations in this line of research is the lack of adequate animal models of OCD. Psychiatric disorders, as opposed to movement disorders, present symptoms of distress in subjective, emotional, and affective domains, which cannot be translated from nonhuman models. In recent years, imaging and functional data have greatly fostered the understanding of the pathophysiology of OCD. Further neuroimaging research, in addition to the review of therapeutic outcomes of clinical trials, will help elucidate the mechanisms of DBS. In fact, recent neuroimaging studies support the dysregulation of the basal ganglia and limbic striatal circuitry in conjunction with OFC and ACC connections as the primary physiopathologic mechanism of OCD.

Regarding the putative physiopathology of OCD, a positive feedback loop runs from the OFC and the prefrontal cortex to the thalamus via the ALIC. These projections are excitatory. Circuitry connects the OFC, striatum, and the thalamus, creating the CSTC loop. Overall, this pathway is inhibitory, serving as a counterweight to the positive feedback loop from the cortex to the thalamus. Furthermore, the limbic system is thought to be implicated in the neurocircuitry of OCD. The limbic system is linked to the ACC, which is connected to the frontal cortex. These limbic connections are believed to contribute to the affective and anxiety components of OCD. OCD symptoms are thought to be related to inadequate positive feedback in the orbito-fronto-thalamic circuit related to dysfunction of the inhibitory feedback via the CSTC loop. Therefore, symptoms of OCD would be expected when the CSTC loop is underactive (not enough inhibition) or when the orbito-fronto-thalamic circuit is overactive (too much excitation). Increasing the activity of the CSTC loop or decreasing the activity of the orbito-fronto-thalamic circuit should provide therapeutic benefit for the symptoms of OCD.\textsuperscript{3}

**IMAGING AND OCD**

Imaging studies have confirmed hyperactivity of the OFC in OCD patients at rest.\textsuperscript{26} Metabolic imaging of patients with OCD revealed not only abnormal hypermetabolism in the OFC but also in the caudate nucleus and basal ganglia as well.\textsuperscript{27} Moreover, there have been consistent reports of reduced activity in the OFC after successful treatment of OCD symptoms.\textsuperscript{10,28} Electrical stimulation at specific nodes of the circuitry modulates the activity within the CSTC network (see Figure 2).\textsuperscript{29} The available neuroimaging research seems to support the hy-
hypothesis that DBS produces functional changes within the CSTC network, such as alterations involving the OFC.

Following this hypothesis, the target site within the VC/VS has migrated to a more posterior position, and outcome data have been found to be more robust in posterior targets. The greater efficacy in engaging more posterior locations is hypothesized to be related to fibers within the CSTC network becoming more compact as they run posteriorly toward the thalamus, where they connect via the ITP.14

Further neuroimaging studies would be invaluable in identifying predictors of treatment response. Van Laere et al40 conducted a fluorodeoxyglucose positron emission tomography study in six patients with OCD before beginning VC/VS DBS treatment. They found in baseline fluorodeoxyglucose data that preoperative resting metabolic activity in the subgenual ACC was predictive of a subsequent clinical response. Similar studies need to be conducted in the future to identify patterns predictive of positive patient response.

CONCLUSIONS

Although to date there have been numerous small clinical trials and case studies, more data are needed to understand the possible role of DBS for OCD, with the aim of identifying the optimal targets and stimulation parameters. Stimulation of the five different potential targets showed differences in therapeutic efficacy and has led to different effects. For example, stimulation of the STN only improved compulsions, whereas stimulation at the VC/VS site affected mood, anxiety, obsessions, and compulsions. Some of the studies applying NAcc stimulation showed effects on anxiety and OCD symptoms along with inadvertent effects on reward circuitry. The VC/VS target is a modification of the initially engaged ALIC, and even targeting within the VC/VS is continuously being refined to maximize efficacy. No consensus about a choice target exists, and more clinical data are necessary to establish the ideal target for each patient.

It is difficult to determine the relative efficacy of stimulation at these anatomic targets because previous studies have followed very different methodologies in patient selection, stimulation, and length of follow-up. The studies have significant limitations including small sample sizes, different assessment measures at different intervals, different models of electrodes, and different stimulation parameters. The positive results of the initial studies on DBS led to US Food and Drug Administration humanitarian device exemption approval for DBS at the VC/VS target for treatment-resistant OCD in 2009, which allows the use of DBS in clinical practice for patients with severe treatment-refractory OCD.

As more experience is gained in the field and more data are acquired, DBS represents a promising option for patients suffering from severe treatment-refractory OCD who have failed to respond to numerous pharmacologic and behavioral therapies. The technique presents many benefits over the lesion-based procedures, including reversibility, lack of effect on cognition and personality, and adjustable parameters after surgery that appear to overcome the significant risks of a neurological procedure and device implantation. In the future, a careful characterization of patients, together with neuroimaging findings preceding DBS implant, could allow for more precise and scientifically appropriate patient selection, resulting in higher response rates.

REFERENCES