

## REVIEW ARTICLE

# Deep Brain Stimulation for the Treatment of Severe, Medically Refractory Obsessive-Compulsive Disorder

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## Abstract

Deep brain stimulation is a rapidly expanding therapy initially designed for the treatment of movement disorders and pain syndromes. The therapy includes implantation of electrodes in specific targets of the brain, delivering programmable small and safe electric impulses, like a pacemaker, that modulates both local and broad neurologic networks. The effects are thought to primarily involve a focus in the brain, probably inhibitory, which then restores a network of neural circuitry. Psychiatric diseases can be refractory and severe, leading to high medical costs, significant morbidity, and even death. Whereas surgery for psychiatric disease used to include destructive procedures, deep brain stimulation allows safe, reversible, and adjustable treatment that can be tailored for each patient. Deep brain stimulation offers new hope for these unfortunate patients, and the preliminary results are promising.

## Historic Review of Psychiatric Surgery

Surgical interventions for the treatment of psychiatric illness began in 1932, when Antonio Egas Moniz observed that an extensive bilateral frontal lobe lesioning in a monkey produced a tame, calm animal.<sup>1</sup> He then extended this result to humans in 1936 and developed the first somatic therapy of the modern era for psychiatric conditions—the frontal lobotomy. He was corecipient of the 1949 Nobel Prize for this work. James Papez formulated the so-called Papez Circuit at about the same time based on his work involving feline rabies infections. The Papez Circuit defined a core circuit of neuroanatomical connections that were thought to underlie emotional behaviors.<sup>2</sup> Many of these structures have been studied since those times, in vast detail, and found to be excellent targets for surgical therapy.

From the beginning, psychiatric surgery has been exalted and celebrated but also mired in ethical, moral, and scientific controversy. These swings reflect not only

the complex social currents of the time but also the evolving scientific milieu and the personalities of the prominent advocates of psychiatric surgery. In Moniz's time, the bilateral frontal lobotomy promised "salvation" and stood in contrast to bleak alternatives, which included lifetime institutionalization under inhumane conditions. Less attention, therefore, was focused on the obvious adverse sequelae of loss of frontal initiative and personality changes caused by these nonspecific ablative procedures. These procedures reached their pinnacle with Freeman's cavalier application of orbital frontal leucotomies in the mid-1960s.<sup>3</sup> The emergence of successful pharmacologic agents for the treatment of psychiatric illnesses was the final force driving orbital frontal leucotomies from favor.

A subsequent somatic therapy, electroconvulsive therapy, did little to increase enthusiasm for nonpharmacologic somatic therapies.<sup>4</sup> Despite the loss of interest in ablative surgical interventions for psychiatric diseases, centers in Europe and in

the US continued to refine indications, techniques, and targets for psychosurgery. Ultimately, these centers helped define criteria for surgical intervention and localize targets of ablation. The Massachusetts General Hospital group refined cingulotomy for refractory obsessive-compulsive disorder (OCD), and a group at the Catholic University of Leuven in Belgium refined capsulotomy for the same indications.<sup>5,6</sup> Remarkably, both groups independently defined similar indications for surgery. They both discovered that the interventions improved OCD. Appropriate surgical candidates were defined as those who had failed all somatic therapies, inclusive of multiple trials of pharmacologic agents and appropriate behavioral therapies.

The use of these approaches, particularly in the US, was hampered by a vigorous debate about the potential misuse of psychiatric somatic therapies as an instrument of social control, based on fears of mind control by the government amidst the prevailing social climate. These fears were reinforced with the publishing of Ervin and Marks' *Violence and the Brain*,<sup>7</sup> which proposed the use of these therapies for control of what was then perceived as sociopathic behaviors arising from aberrant neural processes.<sup>8-10</sup> These concerns led to the State of California adopting legislation to regulate somatic therapies for psychiatric diagnosis, inclusive of psychiatric surgery.<sup>11</sup>

As technology evolved, stereotactic radiosurgery, an incisionless technique, first came into significant use in the 1970s

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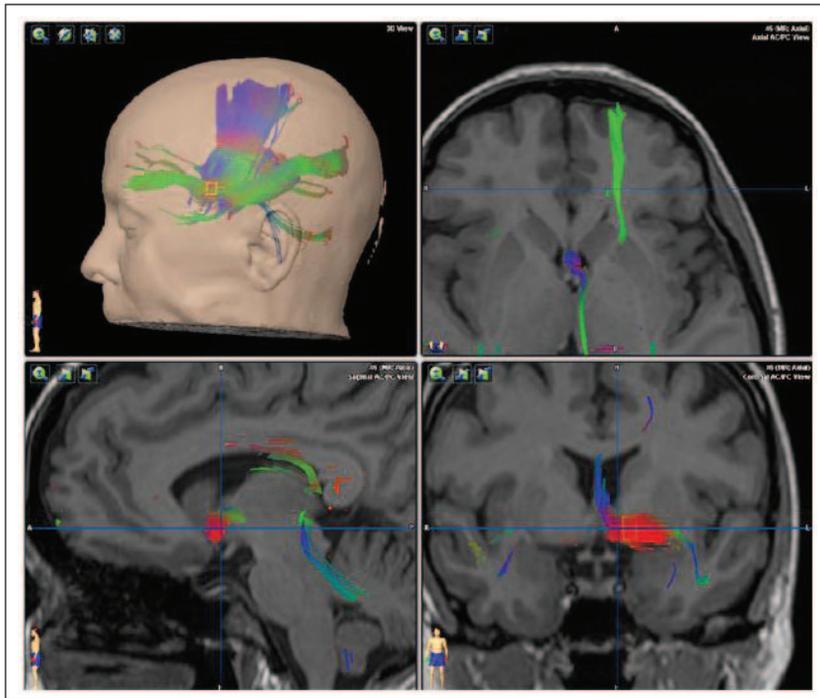


Figure 1. Diffusion tensor image demonstrating connections between prefrontal cortex regions and the ventral portion of the anterior limb of the internal capsule (ALIC) and the adjacent ventral capsule ventral striatum (VC/V5). Yellow box in upper left corner is a 3x3mm voxel seed point. Tractography was set at threshold of 0.15 and minimal fiber length of 15mm. Intense orbitofrontal connections are seen. Other fiber pathways include dorsolateral prefrontal cortex, supplementary motor, sensorimotor, uncinate fasciculus, inferior occipitofrontal fasciculus, thalamus, and various dorsal mesencephalic pathways.

and involved ablating either the anterior limb of the internal capsule (capsulotomy) or the posterodorsal cingulum bundle (cingulotomy), which connects the cingulate cortex with orbitofrontal and dorsolateral convexities (Figure 1).<sup>12,13</sup> This procedure has had a response rate of up to 64% in individuals with OCD. Enlargement of the initial ablative zone in a second procedure, however, is often required to achieve the 64% response rate and can lead to major complications including altered frontal lobe functioning (disinhibition and abulia) as well as radiation necrosis.<sup>14</sup> Although outcomes reflected an impressive long-term response in an otherwise intractable disease and desperate population, the irreversible nature of the intervention and the historic misapplication of other ablative psychiatric surgeries limited the adoption of stereotactic radiosurgery for psychiatric indications.

Psychiatric surgery, however, has taken on new vigor with the introduction of a minimally invasive, reversible somatic therapy: deep brain stimulation (DBS). DBS has evolved and gained in popularity through its safe application in the treatment of Parkinson disease, essential tremor, and dystonia.<sup>15,16</sup> Both the efficacy and complication rate for the DBS implantation procedure are now well defined, derived from outcomes of tens of thousands of DBS implantations performed worldwide for movement disorders.<sup>17</sup> Serious complications with long-lasting, severe neurologic sequelae or death occur at a rate between 0.5% and 1%. Remaining complications, such as stroke or intracranial hemorrhage without lasting symptoms, skin erosions, seizures, device failure, and infection, have been reported to occur at rates of 3% to 15%.<sup>18</sup>

The relative safety of DBS coupled with identification of potential efficacious therapeutic targets has led to trials of its effectiveness in treatment-refractory OCD.<sup>6,19,20</sup> The results of these trials led to the US Federal Drug Administration's Humanitarian Device Exemption approval of DBS for treatment-refractory OCD in 2009.<sup>21</sup>

### Obsessive-Compulsive Disorder and Deep Brain Stimulation

OCD is categorized as an anxiety disorder and is marked by recurrent obsessive thoughts and compulsive behaviors.<sup>22</sup> Affecting about 1% to 3% of the adult

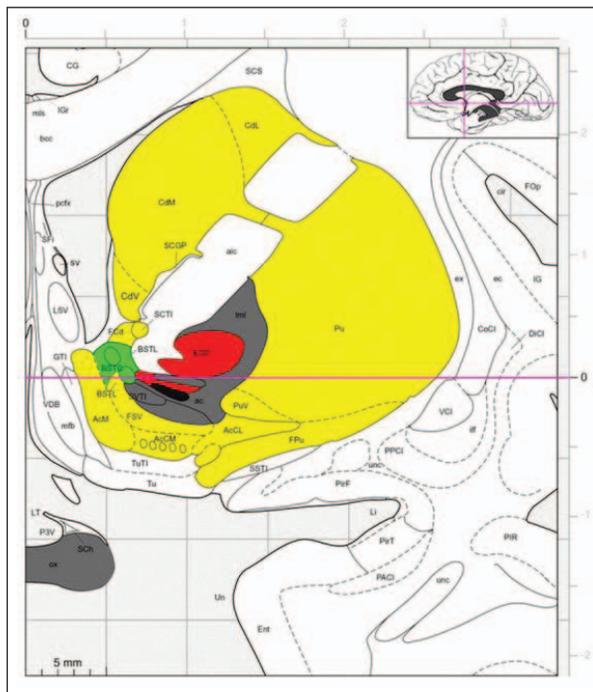


Figure 2. Frontal section through the target area, giving the topographic relations between internal capsule, nucleus accumbens, and bed nucleus of stria terminalis. Target point: 3 mm rostral CA, 7 mm right lateral of midline. 3-4 mm ventral of AC-PC line. Green: rostral edge of bed nucleus of stria terminalis. White: caudal part of anterior limb of internal capsule.<sup>1</sup>

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population, it is one of the most common anxiety disorders.<sup>23</sup> In 50.6% of these patients, OCD is classified as severe.<sup>24</sup> OCD can be extremely disabling because of the time the affected individual spends performing compulsive behaviors and the mental energy required to distract oneself from obsessive thoughts. In a 2000 World Health Organization mental health report,<sup>25</sup> OCD was estimated to be the 11th leading cause of nonfatal burden in the world, accounting for 2.5% of total global years lost to disability. Moreover, many other research reports cite OCD as the fourth-

most common mental illness, after phobias, substance abuse, and major depression.

Conventional treatments for OCD are well established.<sup>26</sup> Cognitive-behavioral therapy, including exposure and ritual prevention, and medications, particularly serotonin reuptake inhibitors, are first-line treatments. In a naturalistic clinical study, over one-third of participants receiving recommended doses of serotonin reuptake inhibitors did not perceive substantial long-term benefit from pharmacotherapy.<sup>27</sup> Treatment of OCD rarely results in complete remission.

OCD exacts a huge toll on patients and is a heavy economic burden. Between 10% and 27% of OCD patients attempt suicide at least once in their lifetime.<sup>28</sup> Total annual cost of OCD was estimated to be \$8.4 billion, constituting 5.7% of the total mental health care cost in 1990. This includes both direct and indirect costs. Direct costs are for outpatient services by physicians and other professionals, hospital care, supported housing and administrative costs, and private health insurance. These accumulate to \$2.1 billion. Indirect costs, reflecting lost

**Table 1. Outcomes of deep brain stimulation for obsessive-compulsive disorder**

Study	Jadad score	Double-blind	Started/finished, n	Final observation, mo	Cerebral blood flow	Clinical scales	DBS location	Adverse effects <sup>a</sup>	Improved, n (%)	Recovered, n (%)
Nuttin <sup>1</sup>	3	Yes	6/4	21	fMRI, PET	POMS	AL/IC		3 (75)	
Gabriëls <sup>2</sup>	0	No	3/3	33-39		BPRS, POMS, Y-BOCS	AL/IC		2 (67)	
Nuttin <sup>3</sup>	4	Yes	6/4	21	fMRI, PET	CGI, Y-BOCS	AL/IC, DMNT		3(75)	
Sturm <sup>4</sup>	0	No	4/4	30-34	fMRI, PET		Right NA		4 (100)	
Abelson <sup>5</sup>	3	No	4/4	10	PET	GAF, HDRS	AL/IC	Mild dizziness	3 (75)	1 (25)
Greenberg <sup>6</sup>	4	Yes	10/8	36		HDRS, Y-BOCS	AL/IC, VC/C	Seizure, hypomania, relapse with battery failure	2 (25)	4 (50)
Jiménez <sup>27</sup>	0	Yes	1/1			GAF	ITP		1 (100)	1 (100)
Mallet <sup>8</sup>	4	Yes	18/16	3		GAF, CGI, MADRS, MDRS, MINI, Y-BOCS	STN	15 major including a brain hemorrhage; 22 minor	10 (62)	4 (25)
Nuttin <sup>9</sup>	4	Yes	6/6	21	PET	CGI, Y-BOCS	AL/IC		3 (50)	

<sup>a</sup> other than minor surgical effects.

<sup>b</sup> In this study, one patient with obsessive-compulsive disorder and another with treatment resistant depression underwent DBS.

AL/IC = anterior limbs of internal capsule; BPRS = Brief Psychiatric Rating Scale; DBS = deep brain stimulation; CGI = Clinical Global Impressions; DMNT = dorsa-medial nucleus of the thalamus; fMRI = functional magnetic resonance imaging; GAF = Global Assessment of Scale; HDRS = Hamilton Depression Rating Scale; ITP = inferior thalamus peduncle; MADRS = Montgomery-Asberg Depression Rating Scale; MDRS = Mattis Dementia Rating Scale; MINI = Mini International Neuropsychiatric Interview; mo = month; NA = nucleus accumbens;

PET = positron-emission tomography; POMS = Profile of Mood States; STN = subthalamic nucleus; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

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... a 38.7% decrease in Y-BOCS scores at 12 months. This level of symptom reduction is equivalent to full response as defined by the Expert Consensus Panel on OCD.

productivity of individuals dying from or otherwise suffering from the disorder, were estimated at \$6.2 billion, or 73.8% of the total cost of OCD.<sup>29</sup> According to one survey, 21.8% of severe OCD patients undergo psychiatric hospitalization during a year of treatment.<sup>30</sup> Of these, more than 50% are hospitalized more than once, and more than 10% experience 5 or more hospitalizations. The average cost per hospitalization is approximately \$12,500. Approximately 28% of OCD patients receive inappropriate treatment (no serotonin reuptake inhibitors or behavior therapy), such that for each of them about \$4000 per year is spent on nonproductive outpatient provider costs and \$1500 per year is spent on ineffective medication. This amounts to approximately \$2 billion per year for ineffective treatment.<sup>31</sup> In a retrospective analysis of claims data from a large, prepaid health plan, Koran et al found that OCD patients had 63% higher mean annual costs for nonpsychiatric (ie, medical) visits, and 56% higher costs for laboratory and radiology services compared with patients with no psychiatric visits.<sup>32</sup>

Abnormalities in so-called corticostriatal-thalamic-cortical loops seem to be involved in the pathophysiology of OCD.<sup>33</sup> Recent diffusion tensor magnetic resonance imaging tractography data demonstrate rich interconnections between these systems in the anterior limb of the internal capsule target area.<sup>34,35</sup> Connections between the orbitofrontal cortex, medial prefrontal cortex (anterior and rostral cingulate gyrus), caudate, ventral striatum, anterior cingulate nucleus accumbens, bed nucleus of the stria terminalis, and thalamus are central to OCD (Figure 2). Numerous studies have demonstrated associated abnormal metabolic activity in these regions, with normalization following successful somatic therapies inclusive of DBS.<sup>20,34,36,37</sup> Acute DBS has been shown to increase perfusion to the orbitofrontal cortex, anterior cingulate, striatum, pallidum, and thalamus.<sup>19</sup> Interestingly, normalization of subsystems in this network is seen with any effective treatment for OCD, be it behavioral or pharmacologic intervention or

the aforementioned somatic intervention.<sup>36</sup>

Results of DBS for the treatment of severe OCD have been published for at least 9 studies (Table 1). Six of these studies were double-blind. In the double-blind studies, improvement rates ranged from 25% to 100%. Pooled together, 22 out of 43 (51%) study participants responded.<sup>38</sup>

More specifically, Abelson et al reported on 4 patients with medically intractable OCD who participated in a double-blind crossover stimulation paradigm in the anterior limb of the internal capsule, the site of prior ablative brain targeting and interventions.<sup>20</sup> Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score, used to measure OCD symptom severity in all active-stimulation patients, decreased from 30 to 10 (a decrease from severe to mild symptom intensity) during each of the ON-STIM testing periods; researchers and patients were blinded to ON and OFF stimulation status. Greenberg et al<sup>19</sup> reported 3-year follow-up data for 9 OCD patients with stimulating leads implanted in the anterior limb of the internal capsule. Eight patients had been followed up for at least 36 months. Mean Y-BOCS score decreased from 34 (severe) at baseline to 22 (moderate) at 36 months ( $p < 0.001$ ). Four of 8 patients had a 35% decrease in Y-BOCS at 36 months; in 2 patients, scores declined between 25% and 35%. Depression and anxiety improved, as did functioning in self-care, independent living, work, school, and social domains.

These data led to a multicenter DBS trial conducted by Medtronic.<sup>6</sup> Deep brain stimulating leads were implanted in a total of 29 patients, with a 38.7% decrease in Y-BOCS scores at 12 months. This level of symptom reduction is equivalent to full response as defined by the Expert Consensus Panel on OCD. A responder is a subject with a 25% reduction in Y-BOCS score. These data were used to obtain a Humanitarian Device Exemption from the Federal Drug Administration that was approved in 2009.<sup>39</sup> Since then, a number of small studies have been done using DBS in a variety of targets.<sup>38,40</sup> Stronger research designs using blind or crossover protocols are problematic because stimulation produces rapid and marked clinical effects.<sup>41</sup> Patients feel the dramatic effects of stimulation immediately, breaking the on and off blinding spontaneously and

making crossover studies impractical—a testament to the dramatic effects of DBS.

## Conclusion

DBS is established as a safe, reversible, adjustable, efficacious, evidence-based treatment for severe, refractory OCD. Patients with severe, refractory OCD suffer from high morbidity, and the illness exacts an enormous toll on their well-being. Considerable resources are devoted to reducing their suffering. The emergence of DBS as a highly effective treatment for this population offers them hope of a much higher quality of life as well as more effective and efficient use of their financial resources. The Permanente Medical Group is uniquely situated to define and develop the appropriate scope of application of this promising intervention. ❖

## Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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### Inherently Mysterious

One of the reasons that [the brain] remains so mysterious is that it is governed by both mechanical and quantum principles. As a result, the brain is inherently indeterminate, unpredictable, and uncertain.

— Richard Restak, b 1942, American neurologist, neuropsychiatrist, author, and professor