Deep Brain Stimulation for Intractable Obsessive Compulsive Disorder: Pilot Study Using a Blinded, Staggered-Onset Design

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Background: Prior promising results have been reported with deep brain stimulation (DBS) of the anterior limb of the internal capsule in cases with severe obsessive compulsive disorder (OCD) who had exhausted conventional therapies.

Methods: In this pilot study, six adult patients (2 male; 4 female) meeting stringent criteria for severe (minimum Yale-Brown Obsessive Compulsive Scale [Y-BOCS] of 28) and treatment-refractory OCD had DBS electrode arrays placed bilaterally in an area spanning the ventral anterior limb of the internal capsule and adjacent ventral striatum referred to as the ventral capsule/ventral striatum. Using a randomized, staggered-onset design, patients were stimulated at either 30 or 60 days following surgery under blinded conditions.

Results: After 12 months of stimulation, four (66.7%) of six patients met a stringent criterion as "responders" ($\geq$35% improvement in the Y-BOCS and end point Y-BOCS severity $\leq$16). Patients did not improve during sham stimulation. Depressive symptoms improved significantly in the group as a whole; global functioning improved in the four responders. Adverse events associated with chronic DBS were generally mild and modifiable with setting changes. Stimulation interruption led to rapid but reversible induction of depressive symptoms in two cases.

Conclusions: This pilot study suggests that DBS of the ventral capsule/ventral striatum region is a promising therapy of last resort for carefully selected cases of severe and intractable OCD. Future research should attend to subject selection, lead location, DBS programming, and mechanisms underpinning therapeutic benefits.

Key Words: Arousal, deep brain stimulation, major depression, obsessive compulsive disorder, ventral capsule, ventral striatum

Despite advances in pharmacological and behavioral therapies for obsessive compulsive disorder (OCD), a number of patients fail to improve sufficiently following years of conventional, as well as experimental interventions (1). An option of last resort has been the use of stereotactic neurosurgery (either cingulotomy or anterior capsulotomy) for seriously ill patients with OCD who have exhausted most existing treatments. The available, albeit limited, evidence suggests that ablative procedures may lead to long-term benefits with acceptable levels of risk (2). Although deep brain stimulation (DBS) is also an invasive procedure with potentially serious adverse events, in contrast to ablative approaches, it is an adjustable and partially reversible therapy (3).

Deep brain stimulation has been successfully employed for the treatment of a variety of movement disorders (4). Deep brain stimulation was first reported to be a promising intervention for OCD in a study by Nuttin *et al.* (5). The specific target in this study, referred to as the ventral capsule/ventral striatum (VC/VS), was chosen in part on positive experiences with gamma knife capsulotomy by the Brown University group (6). These studies, which were staged lesions over two operative sessions over time, demonstrated that adding a more ventral region lesion of the anterior limb of the internal capsule, impinging inferiorly on the ventral striatum, improved outcome (S.A. Rasmussen, unpublished data, 2009). This experience was important to refining and choosing an appropriate target for DBS.

Following the Nuttin *et al.* (5) publication, a team from the University of Florida was funded by the National Institute of Mental Health to conduct an independent pilot study of DBS in six patients with treatment-refractory OCD who might otherwise have been candidates for ablative neurosurgery. In consultation with National Institute of Mental Health staff, a blinded, staggered-onset design was adopted to enhance objectivity of the behavioral ratings while minimizing withholding of active DBS treatment to a maximum of 2 months following surgery.

Methods and Materials

Patients

This study was conducted at the University of Florida as a collaboration of the departments of Psychiatry, Neurology, and Neurosurgery in consultation with Dr. Benjamin Greenberg of Brown University. Prior to recommending surgery, an independent internal multidisciplinary team (psychiatrist, neurologist, neurosurgeon, and medical ethicist) reviewed all past treatments, evaluations, and procedures to ensure appropriateness of the candidate. Psychiatric diagnoses were based upon administration of the Structured Clinical Interview for DSM-IV (7), review of medical records, and expert clinical interview.

All subjects were adults who met DSM-IV criteria for OCD with a minimum score of 28 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (8,9). Subjects must have had at least a 5-year history of treatment-refractory OCD symptoms since age 18, and the disorder must have caused substantial

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suffering as well as a reduction in the subject's functioning. Additional inclusion/exclusion criteria are available in Supplement 1.

Six subjects signed informed consents and were apprised of the risks, possible benefits of, and alternatives to DBS surgery. Partial outcome data from these subjects were included in a recently published report on a worldwide experience with DBS in OCD (10). The first subject was implanted in October 2003; the sixth subject completed 12 months of DBS in January 2008. The two men and four women had a mean age of 36.2 years (range: 27–52) (Table S1 in Supplement 1). Five of the six subjects had childhood onset (i.e., before age 18 years) OCD and the mean duration of illness was 24 years for the cohort (range: 11–35 years). Presurgical mean severity on the Y-BOCS at screening and at baseline was 32.7 and 33.7, respectively. All six subjects had lifetime diagnoses of major depression that were deemed secondary to OCD. One met criteria for a current diagnosis of secondary major depression but most reported depressive symptoms. One subject met criteria for Tourette syndrome. Although tics were present, his obsessive compulsive symptoms caused more subjective distress and dysfunction.

The medications prescribed at baseline were held constant and continued at the same doses as much as possible during chronic DBS. In some cases, the dosages were reduced. Patients were encouraged to apply the cognitive and behavioral skills they had previously learned during Exposure and Response Prevention.

Stimulation and Optimization

At 30 days postsurgery, subjects were randomized to either true DBS stimulation or sham stimulation. Half of the patients had DBS turn on at that point. At 60 days postsurgery, the three subjects previously assigned to sham underwent true DBS stimulation. Patients, raters, and the study psychiatrists were kept blind to the manipulations made (true stimulation, sham stimulation, or no change) at the postsurgery 30-day and 60-day visits and assignment was not disclosed until 120 days postimplantation after ratings were obtained. The standardized sham-controlled programming procedure was performed by the study neurologist (M.S.O.) as previously described (11). Patients were informed that they would have the device activated at some point during the first 90 days following the 1-month postoperative visit. Active settings were kept stable for the first 6 months and for at least 30 days before assessments whenever possible.

Details of device implantation and intraoperative testing are provided in Supplement 1.

Outcome Measures

Yale-Brown Obsessive Compulsive Scale severity was assessed categorically at each rating point according to percentage change from baseline. In this study, a responder was defined as both a 35% percentage change and an actual score of 16 or less at the time of assessment. The score of 16 was selected because it corresponded to mild-to-moderate symptoms at the diagnostic threshold for OCD and generally would not qualify a patient for entry into a clinical drug trial. Yale-Brown Obsessive Compulsive Scale scores were also analyzed as a continuous outcome with repeated-measures analysis of variance (ANOVA; two-tailed). The Y-BOCS was administered by expert clinicians, either the principal investigator (W.K.G.), one of the study psychiatrists, or a psychiatric research nurse (N.R.). For the most part, these assessments were conducted face-to-face, but some were completed on the telephone because of long travel distances.

Secondary outcome measures included the Hamilton Rating Scale for Depression (12), the Clinical Global Impressions Severity Scale (13), the Profile of Mood States (POMS) (14), and the SF-36 (15) as a measure of quality of life. Cognitive performance was assessed before implantation and after chronic DBS with a neuropsychological battery that included the Wisconsin Card Sorting Test (WCST) (16), the Karolinska Scales of Personality (17), Controlled Oral Word Association Test (18), Hopkins Verbal Learning Task (19), Grooved Pegboard (20), Tower of London Task (21), and a measurement of working memory capacity (Wechsler Adult Intelligence Scale-Third Edition Digit Span) (22). With respect to the WCST, the computerized version was used (WCST-Computerized Version Three, for Windows) to allow more computation of expected test-retest changes and to compare treatment-associated alterations in performance. In evaluating the degree to which treatment-associated neuropsychological change exceeded that expected by chance, a reliable change score was calculated to reflect the amount of test-retest change expected by chance.

Patients were closely monitored for deterioration in psychiatric status or stimulation-related adverse effects throughout the study. Deep brain stimulation continued until it was interrupted by stimulator battery depletion, at which time the implantable neurostimulators were replaced in outpatient surgery. In one case that required higher voltage settings, the two Soletra models (Medtronic, Minneapolis, Minnesota) were replaced by two larger Kinetra models (Medtronic) to reduce the frequency of replacement surgeries.

Results

DBS Lead Locations and Programming

A summary of the active DBS contacts used for chronic stimulation is provided in Table 1 along with lead locations. Three patients (patients 2, 3, and 5) had sham DBS programming for 1 month and then were subsequently activated at the next study visit under double-blind conditions. All patients were activated in a single contact monopolar setting for the first 6

Table 1. DBS Programming and Lead Locations at 12 Months of Chronic Stimulation

Patient	DBS Setting	Lateral	AP	Axial
1[a]	Rt 1-C+, 5 V, 210 μs, 135 Hz	10.4	16.2	1.7
	Lt 0-C+, 4 V, 210 μs, 135 Hz	6.3	13.7	−3.8
2	Rt 2-C+, 3.5 V, 210 μs, 135 Hz	10.5	17.3	8.4
	Lt 2-C+, 3.5 V, 210 μs, 135 Hz	12.8	18.1	9.4
3[a]	Rt 0-1-C+, 8.5 V, 150 μs, 130 Hz	4.8 (0 contact)	18.0	−3.8
	Lt 0-1-C+, 7.5 V, 150 μs, 130 Hz	10.4 (0 contact)	18.8	−3.8
4	Rt 1-C+, 6.5 V, 180 μv, 135 Hz	8.9	12.4	−2.6
	Lt 1-C+, 6.5 V, 180 μv, 135 Hz	13.4	16.0	−2.3
5[a]	Rt 0-1-C+, 2.5 V, 210 μv, 135 Hz	9.2 (0 contact)	12.2	−1.7
	Lt 1-C+, 2.5 V, 210 μv, 135 Hz	12.2 (1 contact)	14.8	4.8
6[a]	Rt 1-O+, 3.5 V, 90 μs, 135 Hz	9.4	15.9	1.5
	Lt 1-O+, 3.3 V, 90 μs, 135 Hz	11.2	15.2	.9

Table shows patients 1 through 6 with chronic DBS settings at the active contact at 12 months of DBS. The DBS settings show right side, left side, volts, pulse width, and rate. The lateral, anteroposterior, and axial coordinates of the center of the active contact relative to the mid-commissural point are provided.

AP, anteroposterior; DBS, deep brain stimulation; Hz, rate; Lt, left side; μ, pulse width; Rt, right side; V, volts; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a]Patients who had a clinical response based on Y-BOCS criteria.