A Trial of Scheduled Deep Brain Stimulation for Tourette Syndrome

Moving Away From Continuous Deep Brain Stimulation Paradigms

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Objective: To collect the information necessary to design the methods and outcome variables for a larger trial of scheduled deep brain stimulation (DBS) for Tourette syndrome.

Design: We performed a small National Institutes of Health–sponsored clinical trials planning study of the safety and preliminary efficacy of implanted DBS in the bilateral centromedian thalamic region. The study used a cranially contained constant-current device and a scheduled, rather than the classic continuous, DBS paradigm. Baseline vs 6-month outcomes were collected and analyzed. In addition, we compared acute scheduled vs acute continuous vs off DBS.

Setting: A university movement disorders center.

Patients: Five patients with implanted DBS.

Main Outcome Measure: A 50% improvement in the Yale Global Tic Severity Scale (YGTSS) total score.

Results: Participating subjects had a mean age of 34.4 (range, 28-39) years and a mean disease duration of 28.8 years. No significant adverse events or hardware-related issues occurred. Baseline vs 6-month data revealed that reductions in the YGTSS total score did not achieve the prestudy criterion of a 50% improvement in the YGTSS total score on scheduled stimulation settings. However, statistically significant improvements were observed in the YGTSS total score (mean [SD] change, −17.8 [9.4]; P=.01), impairment score (−11.3 [5.0]; P=.007), and motor score (−2.8 [2.2]; P=.045); the Modified Rush Tic Rating Scale score total score (−5.8 [2.9]; P=.01); and the phonic tic severity score (−2.2 [2.6]; P=.04). Continuous, off, and scheduled stimulation conditions were assessed blindly in an acute experiment at 6 months after implantation. The scores in all 3 conditions showed a trend for improvement. Trends for improvement also occurred with continuous and scheduled conditions performing better than the off condition. Tic suppression was commonly seen at ventral (deep) contacts, and programming settings resulting in tic suppression were commonly associated with a subjective feeling of calmness.

Conclusions: This study provides safety and proof of concept that a scheduled DBS approach could improve motor and vocal tics in Tourette syndrome. Refinements in neurostimulator battery life, outcome measure selection, and flexibility in programming settings can be used to enhance outcomes in a future larger study. Scheduled stimulation holds promise as a potential first step for shifting movement and neuropsychiatric disorders toward more responsive neuromodulation approaches.

Trial Registration: clinicaltrials.gov Identifier: NCT01329198

is characterized by intermittent tics. The nonpersistent nature of tics in TS may offer a window of opportunity for development of a scheduled stimulation approach, instead of the classic continuous approach. In the present study, we aimed to investigate how scheduled DBS would affect the 6-month outcomes in TS. The goal of the scheduled paradigm was to tailor the stimulation pulse trains so that there would be an interval when stimulation was on and an interval when stimulation was off (eg, 2 seconds on and 10 seconds off).

Scheduled therapy delivery systems can be personalized to the frequency and duration of the behavioral manifestation of a particular disorder.18,19 We endeavored in this project to study electricity delivery through a scheduled paradigm in 5 subjects treated with bilateral centromedian thalamic region DBS. The human centromedian brain region was selected because of its importance to basal ganglia motor, associative, and limbic circuitry and because it has been implicated in tic generation.20-22 In this study, we introduced the use of a cranially contained constant-current neurostimulator for TS that was capable of scheduled and responsive stimulation. Although the device was capable of delivering responsive pulses,23 the present study only addressed the outcomes of a scheduled paradigm.

METHODS

We performed a clinical trials planning study (National Institutes of Health R34 Clinical Trials Planning Project) of the safety and preliminary efficacy of bilateral simultaneous implantation of centromedian region DBS. The study was prospective, with randomization to treatment timing and blinding of the patients and the rating clinicians. The study was approved by the institutional review board at the University of Florida. All subjects provided informed consent. Five subjects with medication-refractory and severely disabling TS were enrolled (Figure). All potential candidates had to meet the criteria set by the Tourette Syndrome Association for DBS candidacy34 and had to be examined by an experienced interdisciplinary team (from the Departments of Neurology, Psychiatry, Neurosurgery, and Neuropsychology). The team then met as a group to discuss the risks, benefits, and alternatives to participation. Agreement had to be reached on candidacy, and a separate ethics panel remained blinded. A CONSORT diagram of the study design is provided in the Figure. Further details of the screening procedures are available in the eMethods (http://www.jamaneuro.com).

The inclusion criteria were diagnosis of TS made by a fellowship-trained movement disorders neurologist and a psychiatrist, based on Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)35 criteria for diagnosis of TS; a YGTSS total severity (motor and phonic) score greater than 35 and motor severity score greater than 15; TS-caused incapacitation with severe distress; self-injurious behavior and/or quality-of-life disruption; and being older than 23 years. In addition, TS symptoms must have been medication refractory, with failed medication trials by a psychiatrist or neurologist experienced in TS. Specifically, tics had to be persistent despite appropriate doses of at least 3 dopamine-blocking drugs37 and a single α2-adrenergic agonist. In addition, clinically relevant depression must have been pharmacologically treated and deemed stable by the study psychiatrist. Medication therapy for TS must have been stabilized for 1 month without a dose change before any surgical intervention. Subjects had to be willing to try to keep TS-related medication regimens unchanged throughout the trial. All subjects were required to have been offered habit-reversal/comprehensive behavioral therapy for tics (all declined). Finally, all subjects had to pass urine toxicology screening to exclude illicit drug use. Potential subjects were excluded for any previous neurosurgical brain intervention, including DBS or ablative brain lesions. Subjects were excluded for untreated or unstable psychosis, anxiety, depression, bipolar disorder, or any other Axis I psychiatric disorder. Also excluded were subjects with severe medical comorbidities, including a cardiovascular or lung disorder, kidney disease, chronic neurological disease, hematological disease, or frailty that would potentially affect tolerability of the surgery.

Magnetic resonance imaging (MRI) of the brain must not have revealed evidence of hydrocephalus, stroke, structural le-
sions, demyelinating lesions, or infectious causes of tics. Subjects had to be judged by a formal neuropsychological screening not to have dementia or cognitive dysfunction that would place them at risk for worsening cognition or affect their ability to cooperate with tasks involved in the study. Subjects had to be deemed by the study psychiatrist not to have had suicidal ideation or suicide attempts within the past 6 months.

ACUTE CONTINUOUS STIMULATION VS OFF STIMULATION VS ACUTE SCHEDULED STIMULATION

An experiment was performed at 6 postoperative months that used baseline data compared with acute changes in settings at 6 months (continuous, off, and scheduled). The experiment was performed in the General Clinical Research Center at the University of Florida and Shands Hospital, Gainesville, and each subject underwent a videotaped MRTRS in 3 conditions (continuous stimulation, off stimulation, scheduled on stimulation) during 3 days; in each case, the findings were compared with the pretreatment baseline results. Three raters, including a movement disorders expert at the University of Florida (R.L.R.) and one external to the University of Florida site (J.W.M.) and an internal study coordinator, reviewed the videotapes blinded to condition. All subjects were in the off-stimulation condition the night before testing; on the morning of the actual testing, their stimulators were placed in 1 of the 3 conditions (off, continuous, and scheduled) and held steady for 1 hour before evaluation. Each condition was tested on a separate day. Treatment order was randomized and counterbalanced, with blinding of participants and raters.

SURGICAL PROCEDURE

A high-resolution, volumetric, 3-T MRI scan with gadolinium-enhanced T1-weighted fast gray matter acquisition T1-weighted inversion recovery sequences was obtained 1 day before the surgical procedure. On the morning of the procedure, a head ring (CRW; Radionics) was applied with the participant under local anesthesia, and a high-resolution stereotactic computed tomographic (CT) scan of the head was obtained. The CT images and MRIs were fused, and direct stereotactic targeting was performed using the 3-T MRI and a deformable 3-dimensional atlas modified from that of Schaltenbrand and Bailey. Stereotactic microelectrode recording confirmed the centromedian location. Bilateral leads were implanted, and cranially based neurostimulators (NeuroPace) were placed in a single operating room session.

STATISTICAL ANALYSIS

Means and standard deviations were provided for the baseline scores and 6-month changes. The primary null hypothesis regarding the proportion of successful responders was tested with the exact binomial test. We used a paired t test to distinguish significant change from baseline to 6 months in numerical measures. All statistical tests were 2-sided and considered significant if P values were less than .05.

RESULTS

Three women and 2 men were included in the study. Their disease characteristics, including history of medication intake and pre- and post-DBS medications, are summarized in Table 1. Medication changes were allowed only after consultation with the study psychiatrist, who had to deem it best medical therapy for a particular participant; otherwise, every attempt was made to keep dosages and medications unchanged. Study subjects had a mean age of 34.4 (range, 28-39) years and a mean disease duration of 28.8 years.

PRE- AND POST-DBS OUTCOMES

After 6 months, no significant adverse events occurred, and the YGTSS total score was reduced by 5%, 16%, 16%, 26%, and 30% for the 5 study participants. None of the subjects achieved the prestudy success criterion of a 50% reduction in YGTSS; hence, we could not reject the primary null hypothesis that the proportion of successful responders was at most 0.10.

Baseline and 6-month study outcome measures are summarized in Table 2. These measures were collected before the DBS implant procedure and after 6 months of scheduled stimulation. Statistically significant improvements were observed in the YGTSS total score (mean [SD] change, −17.8 [9.4]; P = .01), impairment score (−11.3 [5.0]; P = .007), and motor score (−2.8 [2.2]; P = .045); the MRTRS total score (−5.8 [2.9]; P = .01); and the phonic tic severity score (−2.2 [2.6]; P = .04). The Hamilton Depression Rating Scale, Young Mania Rating Scale, Yale-Brown Obsessive Compulsive Scale, Quality of Life Assessment Schedule, and 36-Item Short Form Health Survey scores did not improve, although we found a trend toward improved physical functioning on both quality of life measures. The results of the delayed-start design comparing the 2 participants who were randomized to on stimulation at day 30 vs the 3 participants who were randomized to on stimulation at day 60 were not statistically different. However, the MRTRS mean change from baseline was −5.40 (direction of improvement) for the immediate-activation group and 0.83 (direction of worsening) for the delayed-activation group, indicating a trend in the expected directions.

Table 3 summarizes the means and standard deviations from an experiment that used baseline data compared with acute changes in settings at 6 months (continuous, off, and scheduled). There was strong agreement in MRTRS scores among 3 raters, with interclass correlation coefficients of 0.78 (95% CI, 0.37-0.97) at baseline, 0.97 (0.92-0.99) at 6 months during the continuous condition, 0.92 (0.77-0.99) at 6 months during the off condition, and 0.98 (0.93-0.99) at 6 months during the scheduled condition. The mean MRTRS total scores at baseline were 15.2, 16.2, and 17.2 for 3 raters. The mean MRTRS improvements at 6 months were 6.2, 6.6, and 6.8 during the continuous condition; 3.6, 3.6, and 5.2 during the off condition; and 5.4, 5.6, and 7.6 during the scheduled condition. Table 3 provides summary statistics for the averaged blinded MRTRS scores of the 3 raters who reviewed the videotapes. The scores during all 3 conditions showed a trend for improvement, with trends for improvements during the chronic and scheduled conditions performing better than the off condition.
Table 1. General Characteristics of the TS DBS Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subject No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2345</td>
</tr>
<tr>
<td></td>
<td>2 35/M/37</td>
</tr>
<tr>
<td></td>
<td>3 27/M/28</td>
</tr>
<tr>
<td></td>
<td>4 38/F/39</td>
</tr>
<tr>
<td></td>
<td>5 35/F/36</td>
</tr>
<tr>
<td>Age at enrollment, y/sex/current age, y</td>
<td>32/F/34</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>26</td>
</tr>
<tr>
<td>Most common tic symptoms</td>
<td>Head jerks, limb jerking, slapping/hitting self and hitting nearby objects, abdominal tensing, coprolalia</td>
</tr>
<tr>
<td></td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Eye rolling, rotating wrists and shoulders, cracking joints, hitting nearby objects, vomiting</td>
</tr>
<tr>
<td></td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Face scrunching, arm jerks, head twists, bending at the waist, copropraxia, squawking, grunting, sniffing</td>
</tr>
<tr>
<td></td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Eye rolling, jaw cracking, head twists, finger tip tapping, hitting with elbow, copropraxia, growling, coprolalia</td>
</tr>
<tr>
<td></td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Fingertip waving, grimming, eye rolling, echolalia, yelling, growling</td>
</tr>
<tr>
<td>Self-injury</td>
<td>Yes</td>
</tr>
<tr>
<td>Associated behavioral disorders</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>ADHD, hyperactive and impulsive, stable and secondary substance dependency, OCD traits</td>
</tr>
<tr>
<td></td>
<td>Moderate and chronic OCD</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Current moderate and chronic OCD; mild and chronic PTSD (resolved at time of DBS)</td>
</tr>
<tr>
<td>Family history</td>
<td>Father and cousin</td>
</tr>
<tr>
<td></td>
<td>Son</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Father, mother, sister, brother</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Social/professional</td>
<td>Unmarried, 1 child/unemployed</td>
</tr>
<tr>
<td></td>
<td>Married, 2 children/unemployed</td>
</tr>
<tr>
<td></td>
<td>Unmarried/unemployed</td>
</tr>
<tr>
<td></td>
<td>Married/unemployed</td>
</tr>
<tr>
<td>Medication use</td>
<td>Pimozide; haloperidol lactate; alprazolam; diazepam; zolpidem tartrate; trazodone hydrochloride; clonidine hydrochloride; fluphenazine hydrochloride; imipramine hydrochloride; cyclobenzaprine hydrochloride; olanzapine; clonazepam; temazepam; quetiapine fumarate; amitriptyline hydrochloride; aripiprazole</td>
</tr>
<tr>
<td>Trials before enrollment</td>
<td>Haloperidol lactate; benztopine mesylate; lorazezapam; clonidine hydrochloride patch; clonazepam; hydroxyzine hydrochloride; clonidine; fluoxetine hydrochloride; reserpine; venlafaxine hydrochloride (Effexor XR); alprazolam; quetiapine fumarate (Seroquel); pimozide; diazepam; tizanidine hydrochloride; ropinirole hydrochloride</td>
</tr>
<tr>
<td></td>
<td>Haloperidol lactate; fluphenazine decanoate; risperidone; pimozide; pergolide mesylate; clonazepam; citalopram hydrobromide; clonidine hydrochloride; aripiprazole; tetrabenazine; divalproex sodium ER; trifluoperazine hydrochloride; topiramate; ziprasidone hydrochloride</td>
</tr>
<tr>
<td></td>
<td>Diazepam; lorazezapam; clonidine hydrochloride; tizanidine hydrochloride; risperidone; pimozide; carbamazepine; pimozide; haloperidol lactate; divalproex sodium (Depakote); fluvoxamine maleate; olanzapine; paroxetine hydrochloride; quetiapine fumarate; lithium carbonate; acetaminophen + hydrocodone bitartrate (Vicodin); aripiprazole; quetiapine fumarate; estazolam; fluoxetine hydrochloride; benztopine mesylate; ziprasidone hydrochloride; clarithromycin (Biaxin XL); alprazolam; tramadol hydrochloride</td>
</tr>
</tbody>
</table>

(continued)
POSTOPERATIVE LEAD LOCATIONS AND DBS SETTINGS

Postoperative lead locations as derived by CT-MRI fusion are summarized in Table 4. A preoperative 3-T MRI performed 1 day before surgery was fused to a high-resolution CT scan obtained 30 days after the operation. The DBS threshold testing of each contact and each electrode often elicited a subjective response of calmness, and the calmness was accompanied by visible tic suppression.

The specific programming settings are summarized in eTable 2. The settings revealed wide differences be-
between subjects. Thresholds for benefits and adverse effects (eTable 1) were documented, followed by monthly programming sessions that occurred until month 5, when all settings had to be maintained as stable for 30 days before collecting 6-month overall study outcomes. Wide variations in currents of 1.0 to 4.5 mA were used, and the amount of current used could vary from one side of a subject’s brain to the other. This variation in brain hemisphere programming precipitated an early change in study protocol so that all subjects could be offered indepen-

table 2. Baseline and 6-Month DBS Scheduled TS Stimulation Outcome Scores

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean (SD) Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 6-mo</td>
</tr>
<tr>
<td>MRTRS precondition score</td>
<td></td>
</tr>
<tr>
<td>No. of body areas</td>
<td>3.8 (0.4)</td>
</tr>
<tr>
<td>Motor tics/min</td>
<td>2.2 (1.1)</td>
</tr>
<tr>
<td>Phonic tics/min</td>
<td>2.4 (1.1)</td>
</tr>
<tr>
<td>Motor tic severity</td>
<td>4.0 (0.0)</td>
</tr>
<tr>
<td>Phonic tic severity</td>
<td>3.8 (0.4)</td>
</tr>
<tr>
<td>Total</td>
<td>16.2 (2.3)</td>
</tr>
<tr>
<td>YGTSS score</td>
<td></td>
</tr>
<tr>
<td>Motor severity</td>
<td>23.6 (2.1)</td>
</tr>
<tr>
<td>Phonic severity</td>
<td>22.0 (2.7)</td>
</tr>
<tr>
<td>Severity</td>
<td>45.6 (4.6)</td>
</tr>
<tr>
<td>Impairment</td>
<td>46.0 (5.5)</td>
</tr>
<tr>
<td>Total</td>
<td>91.6 (8.8)</td>
</tr>
<tr>
<td>17-item HAM-D total score</td>
<td>8.6 (4.6)</td>
</tr>
<tr>
<td>YMRS total score</td>
<td>2.8 (2.7)</td>
</tr>
<tr>
<td>YBOCS score</td>
<td></td>
</tr>
<tr>
<td>Obsessions</td>
<td>7.8 (3.9)</td>
</tr>
<tr>
<td>Compulsions</td>
<td>9.6 (3.1)</td>
</tr>
<tr>
<td>Total</td>
<td>17.6 (6.7)</td>
</tr>
<tr>
<td>QOLAS score</td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>8.0 (1.4)</td>
</tr>
<tr>
<td>Psychological</td>
<td>7.4 (1.9)</td>
</tr>
<tr>
<td>Social and family</td>
<td>8.8 (0.8)</td>
</tr>
<tr>
<td>Work</td>
<td>6.8 (2.3)</td>
</tr>
<tr>
<td>Cognitive</td>
<td>6.6 (1.9)</td>
</tr>
<tr>
<td>Total</td>
<td>37.6 (5.9)</td>
</tr>
<tr>
<td>SF-36, %</td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>41.4 (22.6)</td>
</tr>
<tr>
<td>Role limitations physical</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>32.0 (24.5)</td>
</tr>
<tr>
<td>General health</td>
<td>61.8 (26.1)</td>
</tr>
<tr>
<td>Verbal</td>
<td>31.0 (25.1)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>35.1 (10.3)</td>
</tr>
<tr>
<td>Role limitations emotional</td>
<td>59.9 (36.6)</td>
</tr>
<tr>
<td>Mental health</td>
<td>64.0 (11.7)</td>
</tr>
</tbody>
</table>

Abbreviations: DBS, deep brain stimulation; HAM-D, Hamilton Depression Rating Scale; MRTRS, Modified Rush Tic Rating Scale; QOLAS, Quality of Life Assessment Schedule; TS, Tourette syndrome; YBOCS, Yale-Brown Obsessive Compulsive Scale; YGTSS, Yale Global Tic Severity Scale; YMRS, Young Mania Rating Scale.

a Outcomes significant at the .05 level are highlighted in bold.

Table 3. Acute Changes in Stimulation Settings and Rush Tic Ratings

<table>
<thead>
<tr>
<th>MRTRS Score</th>
<th>Continuous Stimulation</th>
<th>Off Stimulation</th>
<th>Scheduled Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Score</td>
<td>6-mo Change</td>
<td>P Value</td>
</tr>
<tr>
<td>No. of body areas</td>
<td>3.7 (0.4)</td>
<td>2.3 (1.2)</td>
<td>−1.5 (1.2)</td>
</tr>
<tr>
<td>Motor tics/min</td>
<td>2.6 (0.9)</td>
<td>1.7 (1.1)</td>
<td>−0.8 (0.6)</td>
</tr>
<tr>
<td>Phonic tics/min</td>
<td>2.5 (1.4)</td>
<td>1.5 (1.9)</td>
<td>−1.0 (1.8)</td>
</tr>
<tr>
<td>Motor tic severity</td>
<td>4.0 (0)</td>
<td>2.5 (1.3)</td>
<td>−1.5 (1.3)</td>
</tr>
<tr>
<td>Phonic tic severity</td>
<td>3.3 (1.3)</td>
<td>1.6 (2.0)</td>
<td>−1.7 (1.8)</td>
</tr>
<tr>
<td>Total</td>
<td>16.2 (2.5)</td>
<td>9.7 (7.1)</td>
<td>−6.5 (5.6)</td>
</tr>
</tbody>
</table>

MRTRS, Modified Rush Tic Rating Scale.

a Outcome items significant at the .05 level are highlighted in bold.
Among the 5 participants included, no significant adverse events, including hemorrhages, deaths, and suicidal ideations or suicide attempts, were encountered. All participants tolerated the procedure and the device programming. Subjects 2 and 4 noted that they continually felt they could sense the stimulation on and off periods (ie, the schedule) and that subjectively and occasionally the stimulation was “too much.” In these circumstances, subjects could use a cranial handheld magnet swipe to turn off the DBS for 1 hour. Both subjects were offered alternative stimulation settings but decided to keep their current setting, citing that their tic suppression was “too good” to change programming. eTable 1 summarizes the reversible stimulation-induced adverse effects during threshold testing of each DBS contact (eg, paresthesia, dizziness, and subjective eye movement abnormalities). eTable 1 also summarizes transient and reversible programming-related adverse effects, including headache, slurred speech, paresthesias, nausea, dizziness, gait problems, balance problems, and subjective eye movement abnormalities. The cranial implant was well tolerated by all study participants, and no device infections or device fractures occurred. A prestudy concern that the self-injurious behavior commonly present in TS would lead to damage of the implantable hardware was not reported in any subject.

SAFETY

This study provides important proof of concept that scheduled DBS could visibly suppress motor and vocal tics in a group of individuals with medication-refractory TS. Although in the present paradigm no subject achieved greater than 50% tic reduction on the YGTSS, the study provided important planning information for how the approach to therapy and the outcomes could be improved. The most robust changes observed across these 5 subjects were visible improvements in motor and vocal tics. The subjective and historical YGTSS statistically improved; however, the percentage of change was much less than expected. The MRTRS was a more objective scale that focused exclusively on motor and vocal tics and better captured the benefits that were subjectively reported. The MRTRS also facilitated a blinded video-taped review.

The results of this planning study are important because they open the door for scientists and clinicians to begin to think about and to design scheduled and responsive approaches for the treatment of TS. Deep brain implantation of neurostimulators for each of their brain hemispheres. Subject 1 converted at month 4 to a second neurostimulator. Subject 2 experienced good control with a single neurostimulator and a single set of programming settings that were identical for both brain hemispheres. Subjects 3 to 5 opted for 2 neurostimulators to be placed during the initial procedure. Each subject in the study underwent empirical programming to an optimal scheduled stimulation setting that was based on bedside observations of visible tic suppression. Stimulation frequencies across subjects were all 125 Hz. Pulse widths varied from 80 to 200 microseconds. The active cathodic electrodes of stimulation in general across the group were the ventral R1 or R2 (deepest) electrodes. Scheduled stimulation settings at 6 months were variable across participants (programming in 2 subjects was set at 2 seconds on/2 seconds off; in 2 subjects at 16 seconds on/120 seconds off; and in 1 subject at 10 seconds on/10 seconds off). The number of hours on per 24-hour period also varied at 10, 24, 8, 24, and 5 across the cohort.

<table>
<thead>
<tr>
<th>Subject No., Side</th>
<th>Electrode 1</th>
<th>Electrode 2</th>
<th>Electrode 3</th>
<th>Electrode 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td>X</td>
</tr>
<tr>
<td>1 Right</td>
<td>5.25</td>
<td>(-1.50)</td>
<td>0.17</td>
<td>5.73</td>
</tr>
<tr>
<td></td>
<td>(-5.39)</td>
<td>(-2.59)</td>
<td>0.70</td>
<td>(-6.48)</td>
</tr>
<tr>
<td>Left</td>
<td>6.21</td>
<td>(-5.25)</td>
<td>0.12</td>
<td>7.44</td>
</tr>
<tr>
<td></td>
<td>(-3.74)</td>
<td>(-3.52)</td>
<td>1.34</td>
<td>(-6.09)</td>
</tr>
<tr>
<td>3 Right</td>
<td>3.08</td>
<td>(-5.36)</td>
<td>0.26</td>
<td>4.07</td>
</tr>
<tr>
<td></td>
<td>(-7.72)</td>
<td>(-5.51)</td>
<td>0.14</td>
<td>(-8.17)</td>
</tr>
<tr>
<td>Left</td>
<td>3.59</td>
<td>(-4.45)</td>
<td>0.13</td>
<td>4.87</td>
</tr>
<tr>
<td></td>
<td>(-2.62)</td>
<td>(-5.73)</td>
<td>0.21</td>
<td>(-3.90)</td>
</tr>
<tr>
<td>4 Right</td>
<td>3.87</td>
<td>(-3.51)</td>
<td>(-1.60)</td>
<td>5.11</td>
</tr>
<tr>
<td></td>
<td>(-6.53)</td>
<td>(-4.44)</td>
<td>(-0.86)</td>
<td>(-8.03)</td>
</tr>
</tbody>
</table>

Abbreviations: DBS, deep brain stimulation; X, lateral to midline; Y, relative to the mid-commissural point; Z, axial relative to the anterior commissure–posterior commissure line.

For each subject on each side, the target was the centromedian region. The site of stimulation on each DBS lead location was measured from computed tomography and magnetic resonance imaging fusion. Lead 1 represents the deepest (ventral) electrode, and all subjects underwent long-term stimulation on electrode 1, with the exception of subject 2, who underwent stimulation on electrode 2. The parenthetical minus signs denote the laterality of left-sided leads.
stimulation of several brain targets has been highly efficacious in cases that undergo appropriate screening; however, in all major studies the paradigm used has always been continuous stimulation.11-13 The device used in this study is capable of use in a closed-loop system (eg, sensing TS physiology and delivering stimulation).14 Although a closed-loop system was not used for the present trial, information gleaned from the study will help to provide a foundation for more advanced neuromodulatory approaches. Several unique design features may offer advantages over the other currently used DBS systems in movement and neuropsychiatric disorders. The cranial contained implant has a potential to lessen infection risk and to curb lead and connector fractures (eg, due to neck and shoulder tics). In addition, the ability of the neurostimulator to be programmed to provide scheduled stimulation, instead of the standard 24-hour continuous stimulation, may offer battery life improvements, possibly less stimulation-induced tolerance, and a more scientific and physiological approach to address the paroxysmal symptoms of TS.

The present study was designed to provide proof of principle, safety data, and the critical information necessary for determining the design of a future clinical trial. The data on these first 5 subjects demonstrated an excellent safety record and reasonable feasibility for the scheduled approach. The adverse event profile was excellent because no hemorrhages, infections, device breakages, or device malfunctions were reported. The adverse effects of stimulation were all reversible through changes in programming variables. The consistent deep (ventral) adverse effects of paresthesias, nausea/dizziness, and subjective eye movement abnormalities were similar to other published studies.11,14,42 The DBS electrodes discovered to induce these adverse effects were in many cases associated with a sense of calmness and tic reduction. Changes in the stimulation settings by the clinician led to resolution of the eye issues for affected patients. One other major limitation, however, was that the neurostimulator used in the 5 subjects was designed for closed-loop stimulation in epilepsy, where stimulation is much more intermittent, but in this study was only capable of providing stimulation for intervals ranging from 5 to 24 hours a day without quickly depleting the battery. Physiologically, specific bands in the local field potentials related to tic expression have been identified and associated with improvement in clinical measurements.23

The experience from this trial revealed that independent programming of the neurostimulators for each brain hemisphere was necessary for optimization in all but subject 2. The bilateral implantation of neurostimulators required connecting each battery to a single DBS lead and thus required more operations per subject. Another issue that surfaced was that the neurostimulator used in the study allowed only 0.5-mA changes to programming settings, and this interval proved too broad for clinical use and for the refinement of settings. Changes of 0.5 mA were too large to improve tic symptoms optimally and to alleviate concurrently the subjective sense that the device was cycling on and off (in subjects 2 and 4). The follow-up study will use a rechargeable system capable of 0.1-mA changes, which will also allow more fine-tuning of the stimulation settings, and therefore more fine-tuning of the clinical response with independent control of each lead. Finally, another important observation was that the intervals set by the programmers between the pulses were variable, and these intervals could affect the overall clinical response to tic suppression. The neurostimulator in the follow-up study will be more flexible and allow programmers to set patients on scheduled stimulation intervals as close as 0.1 seconds on/0.1 seconds off, which may be necessary to control severe motor and vocal tics, such as in subject 1, who after 6 months of therapy preferred a continuous stimulation setting.

An important aspect of the study was the acute blinded trial of continuous and scheduled stimulation paradigms. The data from this experiment revealed that short-term continuous stimulation and scheduled stimulation had the potential to improve tic symptoms. The findings should be interpreted with caution because settings were active for only 1 hour after an overnight washout. Large differences in the neurophysiology are likely to result from acute perturbations in activity compared with longer-term continuous or scheduled stimulation. The mechanisms of these differences and how they affect behavioral expression in cortical, basal ganglia, and limbic circuits will require additional investigation. The off stimulation improvements seen during this experiment raise interesting questions, and we would speculate that these improvements could be explained by implantation effects, stimulation carryover effects (ie, washout effects), or a placebo response. Although continuous stimulation outperformed scheduled stimulation, the experiment was performed acutely (only 1 hour in each condition) and was designed to examine possible improvement in the scheduled group and not the superiority of one approach vs another. Larger and longer studies could address the potential long-term benefits favoring a scheduled approach and whether these benefits can prove equal to or better than a standard continuous paradigm. The limitations in pulse intervals, charge density, and neurostimulator battery life also likely added to the better overall outcome in the continuous stimulation group; these factors will all be addressed in the follow-up study. Versions of scheduled stimulation are available on other DBS devices offered from other companies; however, scheduled stimulation has been infrequently used in movement disorders populations.

All 5 study subjects reported experiencing improvements in motor and vocal tics; however, despite this subjective improvement, mood, measures of obsessive-compulsive disorder severity, and quality-of-life measures did not change. We suspect that the small sample size and the inability to stimulate for 24 hours a day with scheduled stimulation in all subjects affected the outcomes. In addition, all patients had adapted to severe TS symptoms for years, and thus a 6-month period may have been too short to assess meaningful change in their quality of life, employment status, and social relationships. Depression, mania, and obsessive-compulsive issues did not statistically change from baseline to postoperative test-
ing, but these domains will be important for monitoring safety and will be important to track in future studies. We would anticipate with a larger sample size and with 24-hour scheduled stimulation that these features would have a better chance to improve. Subject 3 had medication-refractory obsessive-compulsive disorder, with very severe obsessions and compulsions, including ripping clothes, breaking furniture, and breaking objects with handles. He reported that these behavioral features improved after DBS.

In summary, this study provided safety data and proof of concept that scheduled stimulation had the potential to improve motor and vocal tics in TS. Refinements in neurostimulator battery life and better flexibility in programming settings will bring the potential for further enhancements of outcomes in DBS for TS. Scheduled stimulation may provide the first step as the field moves toward more responsive DBS technologies.

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REFERENCES