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Scheduled, intermittent stimulation of the thalamus reduces tics in Tourette syndrome

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ABSTRACT

Introduction: Personalized, scheduled deep brain stimulation in Tourette syndrome (TS) may permit clinically meaningful tic reduction while reducing side effects and increasing battery life. Here, we evaluate scheduled DBS applied to TS at two-year follow-up.
Methods: Five patients underwent bilateral centromedian thalamic (CM) region DBS. A cranially contained constant-current device delivering stimulation on a scheduled duty cycle, as opposed to the standard continuous DBS paradigm was utilized. Baseline vs. 24-month outcomes were collected and analyzed, and a responder analysis was performed. A 40% improvement in the Modified Rush Tic Rating Scale (MRTRS) total score or Yale Global Tic Severity Scale (YGTSS) total score defined a full responder.
Results: Three of the 4 patients followed to 24 months reached full responder criteria and had a mean stimulation time of 1.85 h per day. One patient lost to follow-up evaluated at the last time point (month 18) was a non-responder. Patients exhibited improvements in MRTRS score beyond the improvements previously reported for the 6 month endpoint; on average, MRTRS total score was 15.6% better at 24 months than at 6 months and YGTSS total score was 14.8% better. Combining the patients into a single cohort revealed significant improvements in the MRTRS total score (−7.6 [5.64]; $p = 0.02$).
Conclusion: Electrical stimulation of the centromedian thalamic region in a scheduled paradigm was effective in suppressing tics, particularly phonic tics. Full responders were able to achieve the positive DBS effect with a mean of 2.3 ± 0.9 (SEM) hours of DBS per day.

1. Introduction

Tourette syndrome (TS) is a childhood-onset disorder characterized by motor and vocal tics [1]. TS is a lifelong syndrome; however, in most cases, tics wane by the late teenage years [2]. Some patients with TS have symptoms resistant to medication and to behavioral intervention [3]. These individuals may develop severe complications, including strokes and cervical myelopathies [4–6]. Deep brain stimulation (DBS) has emerged as a highly efficacious treatment option for addressing tics in at least some of these cases; however, this technique should only be applied following appropriate multidisciplinary screening [7]. Several studies of thalamic DBS have previously demonstrated significant improvement in tic behavior [8]. A recent open-label study with a two-year follow-up which used continuous centromedian thalamic stimulation reported 52% and 54.2% mean tic reductions as measured by the Yale Global Tic Severity Scale (YGTSS) [9]. In addition, an open-label study of one-year outcomes following continuous centromedian thalamic stimulation in 6 patients by Ackermans and colleagues demonstrated a 49% improvement in YGTSS total score and a 35% improvement in the Modified Rush Tic Rating Scale (MRTRS) total score [10]. Though the results of the two studies were similar, the former group used a slightly more anterior target.

Based on the paroxysmal nature of tics in TS, we recently hypothesized that treatment via a scheduled as opposed to a continuous DBS approach [11] might be better suited for TS.

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Scheduled stimulation is a form of open loop DBS whereby stimulation is delivered in an a priori determined manner rather than from a responsive, or closed-loop approach. Still, it may be viewed on the continuum as moving closer to a responsive approach in that 1) it delivers less cumulative stimulation than continuous DBS and 2) it temporally limits the stimulation provided to more pathological states (i.e. periods of greater tic activity) and reduces duty cycles (e.g. turning off the device at night). One advantage to scheduled therapy is that the duty cycle can be personalized to an individual patient's needs [12]. Other advantages include a potential decrease in stimulation-related side effects and an increased battery life [13,14].

We previously reported the six-month outcomes of 5 TS patients treated with bilateral centromedian thalamic region DBS in a scheduled stimulation paradigm [11]. In brief, there were significant improvements in several clinical measures of tic severity using this scheduled stimulation during the first six months of therapy. The goal of the scheduled stimulation paradigm was two-fold: 1) to tailor stimulation pulse trains to a stimulation ON period followed by a post-stimulation OFF interval (e.g., 2 s ON and 10 s OFF) and 2) to establish a 24-h duty cycle for delivery of these pulse trains that targeted time periods when tic behavior posed the greatest burden to patient quality of life and interfered with daily activities important to the patient. The present study expanded the follow-up of scheduled stimulation to 24-month outcomes and presents a responder analysis.

2. Methods

2.1. Overview

The present study is a long-term continuation of a clinical trials planning grant (National Institutes of Health R34 Clinical Trials Planning Project), which explored the safety and preliminary effectiveness of bilateral simultaneous implantation of centromedian thalamic region deep brain stimulation (DBS). Details of this study, including surgical candidate selection, inclusion and exclusion criteria, and outcomes at 6-month follow-up, have been previously published [11]. In brief, the parent study included a cohort of 5 individuals with medication-refractory and severely disabling TS who underwent an approved DBS surgery protocol as part of the NIH study. Ethical approval to conduct the study was obtained by the institutional review board and all patients provided written informed consent to enroll in the study. Pre-surgical mean YGTSS total score and MRTRS total scores at baseline were 92.2 ± 9.34 and 16.6 ± 1.95, respectively. At baseline, information pertaining to general disease characteristics (age, disease duration, medication, tic subtypes) [11] was obtained along with the following scales: the 36-Item Short Form Health Survey Quality of Life Assessment [15], the modified Structured Clinical Interview for TS diagnosis [16], the Yale Global Tic Severity Scale (YGTSS) [17,18], the videotaped Modified Rush Tic Rating Scale (MRTRS) [18,19], the 17-item Hamilton Depression Rating Scale [20], the Yale-Brown Obsessive Compulsive Scale [20,21], and the Young Mania Rating Scale [22]. The scales were repeated at each six-month interval. Initial scheduled stimulation settings and revisions to these settings at 6-month follow-up appointments were also obtained.

For the present follow-up study, the outcomes were examined at the 24-month endpoint. During the outcome assessments, all subjects were tested in the ON stimulation state at the parameters implemented during the prior programming session (i.e. no acute changes). While both subjects and raters were blinded to stimulation pulse train settings, patients were aware of the 24-h duty cycle, i.e. the timing of stimulation ON hours during the 24-h period, since this parameter was based on patient preference. Thus, the long-term evaluations were single-blinded.

2.2. Primary outcome measures

The two primary outcome measures were the Modified Rush Tic Rating Scale (MRTRS) [18,19] and the Yale Global Tic Severity Scale (YGTSS) [17,18]. The MRTRS assesses tic behavior using a structured short-term videotape protocol. This method can yield objective data on tic counts and anatomical distribution, but it remains vulnerable to sampling bias and bias due to TS patients' ability to (unconsciously) suppress tics while being videotaped [23]. Thus, an MRTRS assessment performed at a random time in clinic may not validly approximate the usual degree of tic activity in the patient's regular environment. In contrast, the YGTSS employs a clinician-rated scale based on information elicited during a semi-structured interview. This method affords a window into a longer time duration (the 1-week interval prior to clinical assessment) and the more subjective dimensions of tic symptoms such as interference and impairment; however, this method is vulnerable to recall and interviewer biases. Due to its relative simplicity, the YGTSS has been more widely used in research and clinical practice compared to the MRTRS. Given the relative advantages and disadvantages of the two scales described above, we elected to utilize both scales in our study to determine the merits of each scale in this population.

2.3. Stimulation settings

Key terms are defined as follows: The pulse train was defined as the duration and spacing of stimulation delivery; it is given in a ratio of seconds of stimulation ON to seconds of stimulation OFF. The duty cycle was defined by one or more blocks of time of variable duration in which pulse trains were delivered. These blocks lasted between 0.5 and 24 h, and occurred between 1 and 4 times per day. Total cycling time refers to the total number of scheduled hours within a 24-h period that fixed pulse trains of stimulation were delivered. Total cycling time varied from 2 to 24 h. Finally, total daily stimulation time was calculated as the amount of time within a 24-h period that electrical current was actually emitted from the implanted electrode. For example, a pulse train of 4 s on, 30 s off in a duty cycle of 08:00–20:00 (12 h total cycling time) would result in a total daily stimulation time of 1.6 h. A schematic showing scheduled stimulation settings for a sample patient is shown in Fig. 1.

DBS programming sessions were performed at each 6-month follow-up interval. The stimulation settings were chosen empirically and were based on bedside observations of visible motor and phonic tic suppression. At follow-up visits, settings were revised empirically based on clinical observation of tic suppression, patient feedback about changes in symptoms, and the reported quality of life on the prior settings. Pulse train settings were initially approximated based on the frequency and duration of a patient's tics, based on the hypothesis that patients with higher tic frequencies could benefit from more frequent pulses of stimulation and those with tics with longer duration could benefit from longer pulses. Ultimately, pulse train settings were refined empirically based on apparent bedside tic suppression as well as a desire to reduce side effects (e.g. for some patients, certain pulse train settings made them "feel the stimulator turn on/off," which was described as uncomfortable). Settings were also chosen for battery life preservation since the cranially based neurostimulator (RNS300, Neuropace, Mountain View CA) had a limited battery capacity compared to conventional continuous neurostimulators. One patient (Subject 1) was lost to long-term follow-up as the patient declined to return for evaluation at 24 months.

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