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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 hours 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=.02).

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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 ± .9 (SEM) hours of DBS per day.

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. 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 seconds ON and 10 seconds OFF) and 2) to establish a 24-hour 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.

Methods

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-hour duty cycle, i.e. the timing of stimulation ON hours during the 24-hour period, since this parameter was based on patient preference. Thus, the long-term evaluations were single-blinded.

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.

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 .5 and 24 hours, and occurred between 1 and 4 times per day. Total cycling time refers to the total number of scheduled hours within a 24-hour period that fixed pulse trains of stimulation were delivered. Total cycling time varied from 2 to 24 hours. Finally, total daily stimulation time was calculated as the amount of time within a 24-hour period that electrical current was actually emitted from the implanted electrode. For example, a pulse train of 4 seconds on, 30 seconds off in a duty cycle of 08:00–20:00 (12 hours total cycling time) would result in a total daily stimulation time of 1.6 hours. A schematic showing scheduled stimulation settings for a sample patient is shown in Figure 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.

Statistical Analysis

Means and standard deviations were calculated for all pre-surgical baseline scores and all scores up to month 24. Considering the small dataset, a Shapiro-Wilk normality test was performed for all outcomes data [24]. A paired *t-test* was used to distinguish significant change between baseline and subsequent months, provided that the data were normally distributed as defined by the Shapiro-Wilk test. The statistical test was two-sided and considered significant if p-values were less than 0.05.

Responder Analysis

A *post hoc* responder analysis was performed on the 5 subjects with 24-month follow-up. The subjects were categorized as responders, partial responders, or non-responders. Analyses were conducted separately for the two main outcomes, YGTSS total score and

MRTRS total score. Since a 25% decrease on the YGTSS total score had been previously shown to predict clinically meaningful change in tic severity in TS (as correlated to the Clinical Global Impression-Improvement scale), we used this threshold [25]. We defined a 25% decrease in YGTSS total as the cutoff to distinguish responders from non-responders.

We further subdivided the responder classification into two categories to identify responders above a placebo threshold. Placebo response rate in TS DBS has not been directly measured, but in other treatments for tic disorders has been as high as 32.6% [26]. Full responders beyond a potential placebo threshold were therefore defined as having a >40% reduction in YGTSS total tic severity score, and partial responders were defined as having a 25–40% reduction in YGTSS total tic severity score (partial responders may have been biased by a placebo effect). It should be noted that the primary outcome measure in the parent 6-month outcomes study was a >50% improvement in the YGTSS. In the present study, the 40% cut-off was adopted to reflect a threshold for minimum meaningful clinical improvement above the estimated placebo effect. We implemented identical thresholds for the MRTRS total score based on the demonstrated correlations between MRTRS and YGTSS total scores previously reported in the literature [19].

Results

The five study subjects had a mean age of 34.4 (range, 28–39) years and a mean disease duration of 28.8 (range, 20–37) years. Three women and 2 men were included in the study. The specific disease characteristics, including the history of medication intake and pre- and post-DBS medications, were previously reported.

Due to variability in life circumstances, therapeutic goals, and the nature and thresholds for side effects, it was not possible to perform a well-controlled, cross-cohort investigation of the effects of stimulation parameters in this study. Therefore, we report summaries of each patient's stimulation settings throughout the study (Figure 2).

For all patients, the parameters for the left and right hemispheres were commonly the same with differences occurring only in the programming of the pulse width for Subject 3 at months 6, 12, and 18. Wide variations in the employed currents were observed with a range of 1.0 to 4.5 mA. Stimulation frequencies across subjects were 125 Hz with two exceptions: a frequency of 83.3 Hz at month 6 for subject 2, and 143 Hz at months 6 and 12 for Subject 4. The pulse widths were variable across subjects and ranged from 80 to 320 microseconds. Mean daily stimulation times and clinical outcomes for all patients are shown in Figure 2.

Primary Outcomes

Baseline vs. 24-month data revealed the YGTSS total score was improved by 10%, 46%, 58%, and 17% for the 4 active study subjects. The mean YGTSS total score improvement across the cohort was 30% (range, 10–58%). The subject lost to follow-up exhibited an 18% improvement in YGTSS score at month 18 (final measure). The MRTRS total score was improved by 21%, 79%, 81%, and 44% respectively at 24 months. The mean MRTRS total score improvement across the cohort was 56% (range, 21–81%). The subject lost to follow-up exhibited a 19% improvement in MRTRS score at month 18 (final measure). In addition,

patients followed to 24 months exhibited improvements in MRTRS score beyond the improvements previously reported for the 6 month endpoint; on average, MRTRS score was 15.6% better at 24 months than at 6 months and YGTSS total score was 14.8% better. MRTRS and YGTSS total scores for all patients at 6 month intervals are shown in Figure 3.

Change from baseline at each 6-month interval is shown in Table 1. When final outcome measure data (month 18 for subject 1 and month 24 for all others) were analyzed, there were statistically significant improvements in the YGTSS total score, MRTRS total score, and MRTRS phonic tic severity score.

Other Scales

There were no statistically significant changes in the Short Form 36, The Hamilton Depression Rating Scale (HAM-D), Young Mania Rating Scale (YMRS), and Yale-Brown Obsessive Compulsive Scale (YBOCS), and there were only trends toward improvement in the HAM-D-17 and YMRS.

Responder Analysis

A responder analysis was conducted using baseline versus 24-month values in the YGTSS and MRTRS total scores.

Full responder criterion (>40% reduction in symptoms) was attained with respect to the YGTSS total score for 2 out of 4 patients (50%, Subjects 3 and 4) (Table 2, esupp), and in 3 out of 4 patients (75%, Subjects 3, 4, and 5) with respect to the MRTRS total score (Table 3, esupp).

Ultimately, 3 out of 4 patients (Subjects 3, 4, and 5) fulfilled the full responder criterion of >40% reduction in either YGTSS or MRTRS total scores. It should be noted that with regard to the patient lost to follow-up, applying responder analysis criteria to the last available time point (month 18) revealed that the subject was a non-responder for both the YGTSS and MRTRS.

Discussion

In this study, the long-term effects of scheduled stimulation of the centromedian thalamus were analyzed in five patients suffering from severe refractory Tourette syndrome.

A key finding of this study was that TS patients on a scheduled regimen of thalamic stimulation continue to improve beyond 6 months of therapy. It should be noted that this improvement was not uniform across each 6-month follow up; in fact, an increase in tics as measured by the MRTRS was observed in most (4 of 5) patients at 12 months. However, at the 24-month mark patients experienced, on average, a 15.6% improvement in MRTRS score and a 14.8% improvement in YGTSS score compared to 6-month outcomes. Changes in stimulation parameters could explain this unexpected increase in tics at the 12-month follow-up for subjects 1, 2, 4, and 5 (Figure 2). For example, stimulation current was decreased for subjects 2 and 4; interestingly, these patients continued to improve in the YGTSS score, despite poorer MRTRS outcomes. For subject 1, the pulse train interval was

lengthened, and total duty cycle time was decreased for subject 5; for both subjects 1 and 5 the total daily stimulation time was decreased. These changes in scheduling parameters were undertaken to reduce side effects and/or improve battery longevity. In light of this unusual reversal of response, it is also worth considering that scheduled stimulation may function differently than continuous stimulation and that responses to scheduled stimulation may not match the pattern observed in continuous paradigms. Variability at 6 months intervals in this cohort suggests the importance of long-term follow-up and that more research is needed to confirm this trend in a larger cohort and, if confirmed, to investigate potential underlying causes.

We observed a significant beneficial effect of the scheduled stimulation paradigm when the 24-month follow-up assessment was compared to the preoperative baseline assessment (30% mean improvement in YGTSS total score and 56% mean improvement in MRTRS total score). Three of four patients followed to 24 months met the stringent full responder criterion (>40% improvement in either MRTRS or YGTSS total score). Two patients achieved >40% improvement in total score for both primary outcome measures, while one patient achieved >40% improvement for the MRTRS only. We thus observed a relative inconsistency between YGTSS and MRTRS outcomes in this cohort. Discrepancies between these outcomes have been observed in other similarly-sized studies of TS DBS, but almost all point to larger improvements in YGTSS total scores than in MRTRS [10] [27]. Here we present the first study where the relative improvement in MRTRS exceeded that of the YGTSS. These findings make sense in light of the variability in duty cycle scheduling across the cohort. For example, subject 5, who met responder criteria for the MRTRS but not for the YGTSS, received the fewest hours of total cycling time throughout the study [1.6 ± .5 (SEM) hours/day]. During months 12–24, Subject 5 was programmed for 4 intervals of 30 minutes per day—a total of 2 hours of total cycling time compared to a mean of 14.6±2.4 (SEM) hours of total cycling time during months 12–24 for the rest of the cohort.

The YGTSS utilizes patient reporting to measure tic behavior during the week prior to the assessment, while the MRTRS utilizes video recording to measure tic behavior in short durations (10 minutes). Since the MRTRS evaluation occurred during the stimulation ON state (when pulse trains were delivered), the MRTRS examined patients only in the treated state whereas the YGTSS combined patient feedback about the treated (i.e. stimulation ON) state with the non-treated state (stimulation OFF, no pulse trains delivered). In addition, since all MRTRS assessments were performed in the ON state, patients and raters were not blinded to the stimulation state during these assessments. These factors may have contributed to the observed discrepancy in MRTRS and YGTSS scores.

Our findings suggest that scheduled stimulation can reduce tic behavior on a level comparable to continuous stimulation paradigms reported by other studies [9,10,27–29]. However, scheduled stimulation may not be as effective for certain patients as continuous stimulation, particularly in settings where patients opt for duty cycles that may result in sub-optimal total stimulation time. We hypothesize that Subject 5’s classification as a responder by the MRTRS criterion and a non-responder by the YGTSS criterion may be explained by the delivery of clinically effective stimulation parameters for sub-optimal durations (at the

patient's request) and it is possible that tic behavior was inadequately controlled across the 24–hour period.

The main limitation of this study was the statistical power for the small number of enrolled patients. In addition, given this small sample size it was not feasible to conduct a randomized, prospective comparison of scheduled and continuous stimulation. Furthermore, the non-standardized nature of the scheduled settings in each patient—necessitated by battery constraints—in some sense limits the ability to compare across patients. However, this assessment of a personalized stimulation schedule remains valuable, given the heterogeneity of tic presentation and the hypothesis that intermittent stimulation during hours of greatest tic severity (which varied across patients) more closely resembles a responsive approach. Another limitation of this study was the use of a neurostimulator designed for the treatment of epilepsy. Since stimulation for epilepsy can be achieved via a responsive approach that does not entail continuous stimulation, battery life for these stimulators in practice can be quite short [30]. Therefore, the duty cycle had to be programmed based on both patient preferences (benefits, side effects, and most useful time for activation) and clinical judgment of optimal settings based on the confines of projected battery life.

Conclusion

Electrical stimulation of the centromedian thalamic region with scheduled pulse trains and duty cycles was effective in suppressing tics at the 24-month follow-up. Full responders (patients with >40% improvement in YGTSS or MRTRS) were able to achieve the positive effect of scheduled DBS with a mean of 2.3 ± .9 (SEM) hours of total daily stimulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We tested personalized, scheduled DBS in Tourette at 24 month time point.
- 75% of patients followed to 24 months had >40% reduction in MRTRS (responders).
- Responders improved with only 1.85 hours of DBS per day on average.
- MRTRS score at 24 months improved beyond the 6 month endpoint.
- On average, MRTRS was 15.6% better at 24 mo. than at 6 mo.

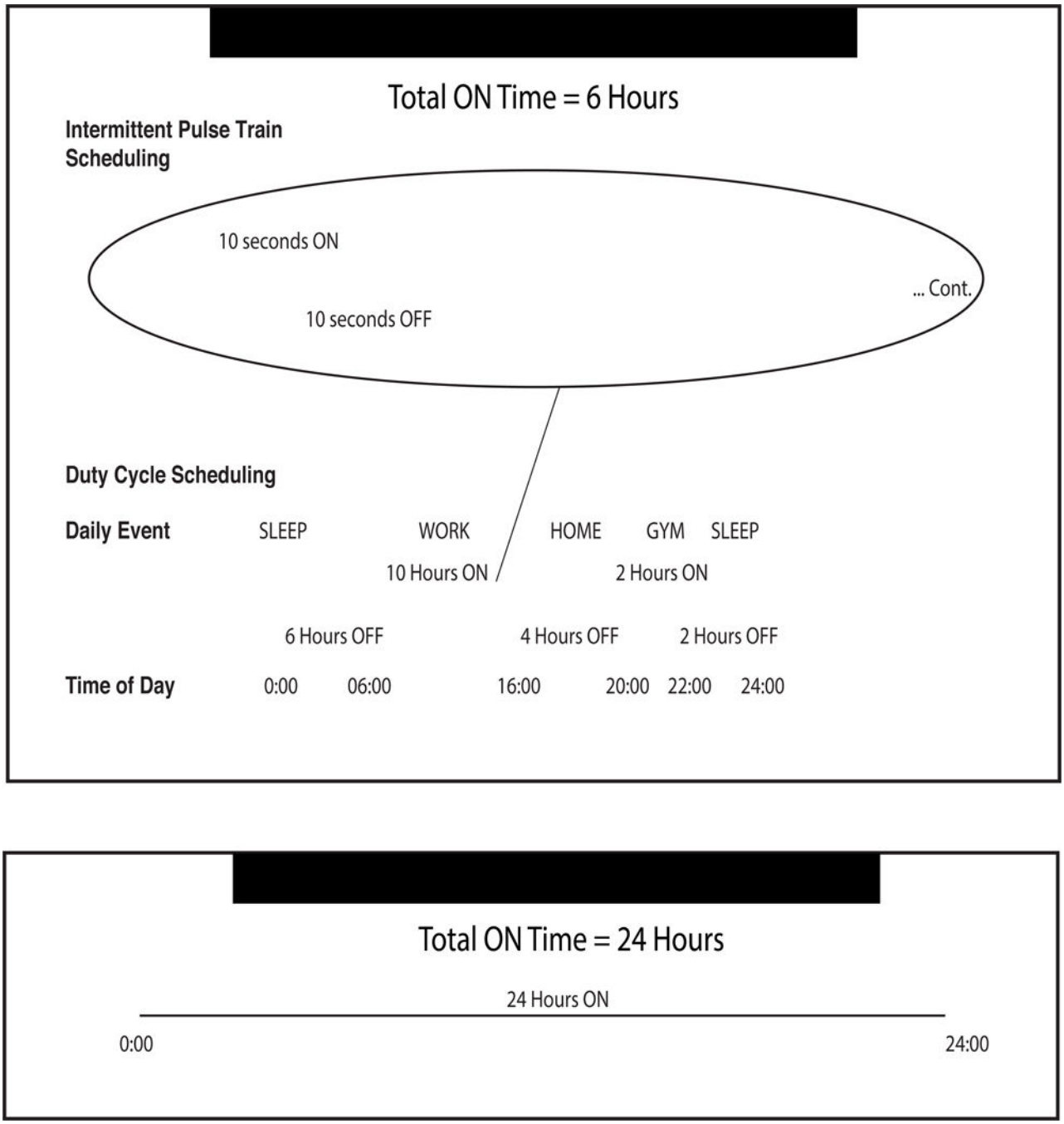


Figure 1. Scheduled vs. Continuous Stimulation

Sample scheduled stimulation settings (showing both pulse train scheduling and duty cycle scheduling) for a patient with a 10 seconds ON, 10 seconds OFF pulse train and 12 hours of total cycling time. This patient receives 6 hours of total daily stimulation (Top), as compared to the classic chronic stimulation paradigm delivering 24 hours of total daily stimulation (Bottom).

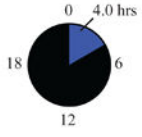
Demographic Data					Scheduled Stimulation Settings							Long Term Results			
Subject	Age	Sex	Tic Symptoms	Therapeutic Goal		Current	Frequency	Pulse Width	Pulse Train	Duty Cycle	Total Cycling Time	Total Daily Stimulation Time	Mean Daily Stimulation Time (Months 0-24)	MRTRS Improvement	YGTSS Improvement	Responder?
1	38	F	Eye-rolling, head twisting, copropraxia, coprolalia	Reduce tics to facilitate child care (throughout the day)	Month 0-6†	3 mA	125 Hz	200 μs	10.4 sec ON: 45 sec OFF	N/A	11.4 hours	2.6 hours		18%*	19%*	NO*
					Month 6	2.5 mA	125 Hz	200 μs	16 sec ON: 80 sec OFF	09:00-12:00, 13:00-1600, 18:00-22:00	10 hours	2.0 hours				
					Month 12	2.5 mA	125 Hz	200 μs	16 sec ON: 80 sec OFF	09:00-12:00, 14:00-16:00, 18:00-22:00	9 hours	1.8 hours				
					Month 18	2.5 mA	125 Hz	200 μs	16 sec ON: 80 sec OFF	09:00-12:00, 14:00-16:00, 18:00-22:00	9 hours	1.8 hours				
2	32	F	Head and limb jerking, self-injurious hitting, coprolalia	Reduce tics during critical child care hours	Month 0-6†	1.5 mA	168.3 Hz	224 μs	15.2 sec ON: 68 sec OFF	N/A	22.4 hours	5.0 hours		33%	4%	NO
					Month 6	1 mA	100 Hz	200 μs	2 sec ON: 10 sec OFF	00:00-24:00	24 hours	4.8 hours				
					Month 12	4.0 mA	125 Hz	400 μs	continuous	16:00-17:00	24 hours	1.0 hours				
					Month 18	1 mA	100 Hz	200 μs	4 sec ON: 20 sec OFF	00:00-24:00	24 hours	4.8 hours				
3	27	M	Face scrunching, arm jerking, head twisting, vocal tics	Reduce tics during work hours to maintain employment	Month 0-6†	3.7 mA	125 Hz	176 μs	8.8 sec ON: 64 sec OFF	N/A	12 hours	1.7 hours		79%	17%	YES
					Month 6	4.5 mA	125 Hz	200 μs R 120 μs L	16 sec ON: 120 sec OFF	10:00-18:00	8 hours	1.1 hours				
					Month 12	4 mA	125 Hz	200 μs R 120 μs L	16 sec ON: 120 sec OFF	10:00-12:00, 14:00-16:00	4 hours	0.5 hours				
					Month 18	4.5 mA	125 Hz	200 μs R 120 μs L	16 sec ON: 120 sec OFF	10:00- 18:00	8 hours	1.1 hours				
4	35	M	Eye rolling, shoulder rotation, hitting nearby objects	Reduce tics during hours of important daily activities	Month 0-6†	1.3 mA	132.2 Hz	160 μs	2 sec ON: 10 sec OFF	0:00-24:00	24 hours	4.8 hours		81%	58%	YES
					Month 6	0.5 mA	143 Hz	160 μs	2 sec ON: 10 sec OFF	0:00-24:00	24 hours	4.8 hours				
					Month 12	1 mA	143 Hz	160 μs	2 sec ON: 10 sec OFF	0:00-24:00	24 hours	4.8 hours				
					Month 18	1 mA	125 Hz	160 μs	8 sec ON: 40 sec OFF	15:00-23:00	8 hours	1.6 hours				
5	35	F	Grimacing, eye rolling, echolalia, vocal tics	Reduce tics during important activity times (exercising, walking dog, etc.)	Month 0-6†	0.9 mA	125 Hz	160 μs	9 sec ON: 25 sec OFF	N/A	8.3 hours	3.0 hours		45%	46%	YES
					Month 6	1 mA	125 Hz	160 μs	10 sec ON: 10 sec OFF	11:00-13:00, 16:00-19:00	5 hours	2.5 hours				
					Month 12	1.5 mA	125 Hz	160 μs	10 sec ON: 10 sec OFF	06:30-07:00, 10:30-11:00, 14:30-15:00, 17:30-18:00	1.5 hours	.75 hours				
					Month 18	1.5 mA	125 Hz	160 μs	10 sec ON: 10 sec OFF	06:30-07:00, 10:30-11:00, 14:30-15:00, 17:30-18:00	1.5 hours	.75 hours				

Figure 2. Scheduled Stimulation Parameters and Clinical Outcomes

Demographic information, scheduled stimulation parameters, and long term outcomes. The duty cycle is based on times of the day when patients reported the greatest interference of tics with activities of daily living. Stimulation parameters reflect settings for leads in both left and right hemispheres, unless otherwise specified (L= Left, R=Right). Percent improvements in YGTSS and MRTRS total scores reflect change from pre-surgical baseline at 24-month follow-up. Responders achieved >40% improvement in either YGTSS or MRTRS total scores at month 24. *Subject 1 was lost to follow-up; long term results presented here reflect the final evaluation (month 18).

†Stimulation parameters were modified on a monthly basis for the first 6 months of the study. Here we present means for stimulation parameters in months 0–6. Parameters from individual months (including duty cycles) are available in Okun, et al, 2013. YGTSS= Yale Global Tic Severity Scale; MRTRS= Modified Rush Tic Rating Scale.

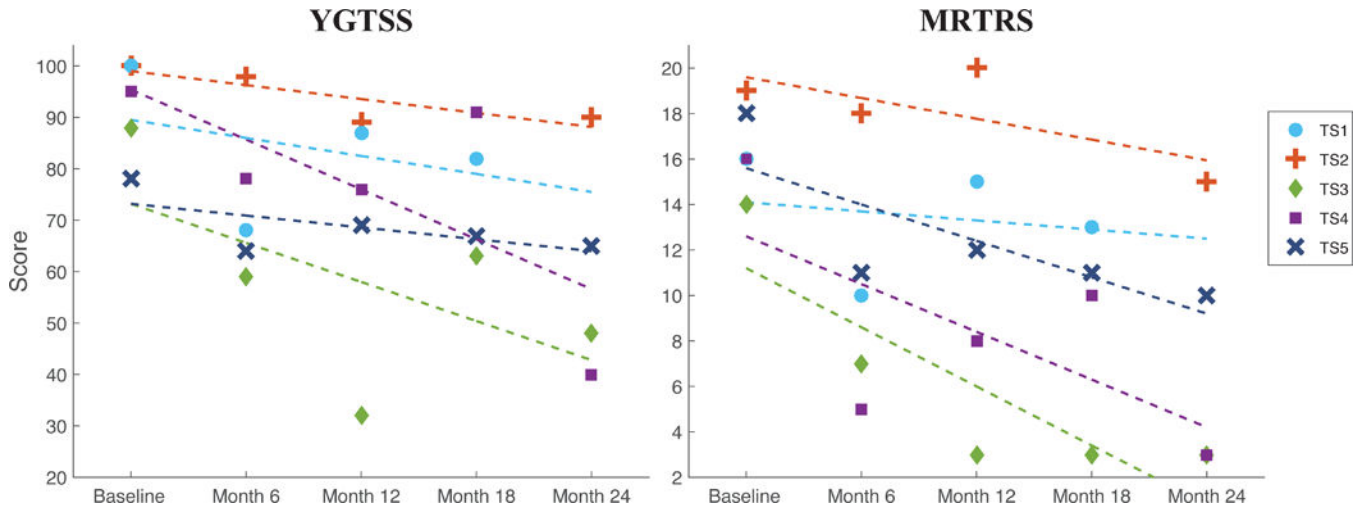


Figure 3. Change in YGTSS and MRTRS Total Scores

Changes in YGTSS and MRTRS total scores for all subjects at 6 month intervals. The dotted lines signify trends of improvement via linear regression. Responders achieved >40% improvement in YGTSS or MRTRS total scores at month 24 compared to pre-surgical baseline; partial responders achieved 25%–40% improvement; non-responders exhibited <25% improvement.

Table 1

Baseline and 6 Month Interval Outcome Scores

Scale	Domain	Month 6	Month 12	Month 18	Month 24	Final Outcome
YGTSS	Motor severity	−16	X	−19	−32	−29
	Phonic severity	−22	−20	−23	−44	−38
	Total severity	−19	−16	−21	−38	−33
	Impairment	−22	X	X	X	X
	Total	−20	X	−16	−33	−29.5*
HAM-D 17	Total	5.26	28.95	19.35	−70.83	−48.39
MRTRS	No. of body areas	−36.84	−21.05	X	−40	−31.58
	Motor tics/min	−38.46	X	−33.33	−63.64	−53.85
	Phonic tics/min	−33.33	−33.33	X	X	X
	Motor tic severity	−25	−25	−31.25	−50	−40
	Phonic tic severity	−57.89	−52.63	−73.33**	−60	−57.89*
	Total	−38.55*	−30.12	−42.19*	−53.73*	−46.99*
YMRS	Total	−7.14	0	−8.33	X	−25
YBOCS	Obsessions	−4.44	−4.44	18.18	X	−12.12
	Compulsions	−12.28	−15.79	14.29	3.33	4.76
	Total	−8.82	−10.78	16	−13.21	−2.67

Abbreviations: DBS, deep brain simulation; HAM-D, Hamilton Depression Rating Scale; MRTRS, Modified Rush Tic Rating Scale; SD, Standard Deviation; TS, Tourette syndrome, YBOCS, Yale-Brown Obsessive Compulsive Scale; YGTSS, Tale Global Tic Severity Scale; YMRS, Young Mania Rating Scale.

X: No value computed; data not normally distributed (Shapiro-Wilk test)

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

Table 2

Responder Analysis for Yale Global Tic Severity Scale (YGTSS)

Responder Category	Patient	YGTSS Domain	Baseline	24 Months	Change (%)	
	Subject					
Non-Responder‡	*5*	Motor severity	20	16	−20.00	‡
		Phonic severity	18	19	5.56	‡
		Total severity	38	35	−7.90	‡
		Impairment	40	30	−25.00	†
		Total	78	65	−16.67	‡
	Subject					
Full Responder*	*4*	Motor severity	25	10	−60.00	★
		Phonic severity	20	0	−100.0	★
		Total severity	45	10	−77.78	★
		Impairment	50	30	−40.00	★
		Total	95	40	−57.90	★
	Subject					
Full Responder*	*3*	Motor severity	24	13	−45.84	★
		Phonic severity	24	5	−79.17	★
		Total severity	48	18	−62.50	★
		Impairment	40	30	−25.00	†
		Total	88	48	−45.46	★
	Subject					
Non-Responder‡	*2*	Motor severity	25	25	0.00	‡
		Phonic severity	25	25	0.00	‡
		Total severity	50	50	0.00	‡
		Impairment	50	40	−20.00	‡
		Total	100	90	−10.00	‡
				18 Month		

Responder Category	Patient	YGTSS Domain	Baseline	24 Months	Change (%)	
	Subject					
Non-Responder[‡]	*1*	Motor severity	25	21	−16.00	‡
		Phonic severity	25	21	−16.00	‡
		Total severity	50	42	−16.00	‡
		Impairment	50	40	−20.00	‡
		Total	100	82	−18.00	‡
Mean Responder Outcomes		Motor severity	23	13	−41.95	★
		Phonic severity	20.67	8	−57.87	★
		Total severity	43.67	21	−49.40	★
		Impairment	43.34	30	−30.00	†
		Total	87	51	−40.01	★

★Full Responder:≥40% improvement in YGTSS total score

†Partial Responder=40%–25% improvement in YGTSS total score

‡Non-Responder: < 25%improvement in YGTSS total score

Table 3

Responder Analysis for Modified Rush Tic Rating Scale (MRTRS)

Category	Patient	MRTRS Domain	Baseline	24 Months	Change (%)	
Full Responder*	*Subject 5*	No. of body areas	4	3	−25.00	†
		Motor tics/min	2	1	−50.00	★
		Phonic tics/min	4	2	−50.00	★
		Motor tic severity	4	2	−50.00	★
		Phonic tic severity	4	2	−50.00	★
		Total	18	10	−44.45	★
Full Responder*	*Subject 4*	No. of body areas	4	1	−75.00	★
		Motor tics/min	4	1	−75.00	★
		Phonic tics/min	1	0	−100.0	★
		Motor tic severity	4	1	−75.00	★
		Phonic tic severity	3	0	−100.0	★
		Total	16	3	−81.25	★
Full Responder*	*Subject 3*	No. of body areas	3	1	−66.67	★
		Motor tics/min	1	1	0.00	≠
		Phonic tics/min	2	0	−100.0	★
		Motor tic severity	4	1	−75.00	★
		Phonic tic severity	4	0	−100.0	★
		Total	14	3	−78.58	★
Non-Responder≠	*Subject 2*	No. of body areas	4	4	0.00	≠
		Motor tics/min	4	1	−75.00	★
		Phonic tics/min	3	2	−33.34	†
		Motor tic severity	4	4	0.00	≠
		Phonic tic severity	4	4	0.00	≠
		Total	19	15	−21.06	≠
				18 Month		
Non-Responder≠	*Subject 1*	No. of body areas	4	4	0.00	≠

Category	Patient	MRTRS Domain	Baseline	24 Months	Change (%)	
		Motor tics/min	2	2	0.00	≠
		Phonic tics/min	2	1	−50.00	★
		Motor tic severity	4	4	0.00	≠
		Phonic tic severity	4	2	−50.00	★
		Total	16	13	−18.75	≠
Mean Responder Outcomes		No. of body areas	3.67	1.67	−55.56	★
		Motor tics/min	2.34	1	−41.67	★
		Phonic tics/min	2.34	0.67	−83.34	★
		Motor tic severity	4	1.34	−66.67	★
		Phonic tic severity	3.67	0.67	−83.34	★
		Total	16	5.34	−68.10	★

★Full Responder: ≥40% improvement in MRTRS total score

†Partial Responder=40%–25% improvement in MRTRS total score

≠Non-Responder: < 25%improvement in MRTRS total score