

Articles

Lessons Learned from Open-label Deep Brain Stimulation for Tourette Syndrome: Eight Cases over 7 Years

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Abstract

Background: Deep brain stimulation (DBS) remains an experimental but promising treatment for patients with severe refractory Gilles de la Tourette syndrome (TS). Controversial issues include the selection of patients (age and clinical presentation), the choice of brain targets to obtain optimal patient-specific outcomes, and the risk of surgery- and stimulation-related serious adverse events.

Methods: This report describes our open-label experience with eight patients with severe refractory malignant TS treated with DBS. The electrodes were placed in the midline thalamic nuclei or globus pallidus, pars internus, or both. Tics were clinically assessed in all patients pre- and postoperatively using the Modified Rush Video Protocol and the Yale Global Tic Severity Scale (YGTSS).

Results: Although three patients had marked postoperative improvement in their tics (>50% improvement on the YGTSS), the majority did not reach this level of clinical improvement. Two patients had to have their DBS leads removed (one because of postoperative infection and another because of lack of benefit).

Discussion: Our clinical experience supports the urgent need for more data and refinements in interventions and outcome measurements for severe, malignant, and medication-refractory TS. Because TS is not an etiologically homogenous clinical entity, the inclusion criteria for DBS patients and the choice of brain targets will require more refinement.

Keywords: Gilles de la Tourette syndrome, deep brain stimulation, globus pallidus internus, midline thalamic nuclei

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Introduction

Tourette syndrome (TS) is a childhood-onset neuropsychiatric disorder characterized by multiple motor and vocal tics lasting a minimum of 1 year. Tic disorders are frequently chronic, if not lifelong conditions. Usual clinical practice focuses initially on educational and supportive interventions. In addition, a recent multisite randomized clinical trial demonstrated the efficacy of comprehensive behavioral intervention for tics in a subset of pediatric and adult patients.^{1,2}

Nevertheless, most controlled treatments have focused on pharmacologic interventions. Although valuable in the management of individuals with TS, pharmacotherapy rarely eradicates tics completely, and many individuals have residual and clinically impairing symptoms.^{3,4} Furthermore, some of the most effective medications for reducing tics can be associated with a range of adverse effects, and there is a small subset of patients who will not respond to either behavioral or pharmacologic approaches.³

Deep brain stimulation (DBS) has been introduced as an investigational approach for addressing some of the intractable symptoms of malignant TS. The stimulation targets that have been used in TS include: 1) the midline thalamic nuclei, with electrodes positioned at various points along the anterior–posterior axis (centromedian nucleus, parafascicular nucleus, and nucleus ventro-oralis internus); 2) the globus pallidus pars internus (GPi), either in the posteroventrolateral (somatosensory) region or the anteromedial (limbic) region; 3) the globus pallidus pars externus; 4) the nucleus accumbens/anterior limb of the internal capsule; and 5) the subthalamic nucleus (Table 1).^{5–42}

While many of the TS patients reported in the literature have had beneficial short-term outcomes following DBS, randomized controlled studies of larger cohorts have not been performed. Although some surgeries are free of complications, a number of surgery-related serious adverse events (e.g. bleeding, infection, hardware malfunction) have been reported, as well as stimulation-related serious adverse events (e.g. nausea, eye movement abnormalities, sedation, anxiety, altered mood, changes in sexual function).^{5–42} In general, the degree of tic improvement appears to be more robust for the thalamic and GPi targets. However, there is at least one case in which targeting the nucleus accumbens resulted in a marked improvement in self-injurious tics.¹⁹

This paper details the outcomes of eight additional patients with intractable, treatment-refractory TS who were treated with DBS. These patients had their DBS electrodes inserted at various times during a 7-year period (2004–2011), employing various targets and approaches based on the available knowledge at the time of implantation. Two distinct GPi sites (somatosensory [posteroventral] vs. limbic [anteromesial]) and midline thalamic sites were targeted. The initial outcome of the first patient discussed here has been previously reported.¹²

Methods

Patient selection

Each of the patients presented had severe malignant tics that impaired their quality of life and activities of daily living. Five of the patients exhibited self-injurious tics that either resulted in or threatened permanent neurologic injury. The decision to treat was taken on a case-by-case basis based on clinical necessity. Although we did not have *a priori* inclusion and exclusion criteria, all patients were required to have exhausted at least three known treatment options, including adequate trials with both a typical and atypical neuroleptic. The treatments had to be administered in adequate dosages and for at least 6 months.⁴³ Candidates could not have medical, neurologic, or psychiatric conditions that may have increased the risk of the procedure, precluded full participation (during the procedure or follow-up), or compromised the accuracy of the outcome assessment measures.^{43,44} Four of the patients were ≥ 25 years of age at the time of the surgery and in only three patients was there a documented failed treatment trial with an α -adrenergic agonist. The decision to not require a failed trial with an α -adrenergic agonist was based on a clinical judgment that the length of time needed to complete an

adequate trial (≥ 12 weeks) placed the individual at undue risk of permanent injury, and also the consideration that the degree of improvement, even if the trial was successful, would not be sufficient to reduce the risk of self-injury. Patient inclusion was based on the consensus of clinicians and the patient that the symptoms and their associated impairment were severe enough to justify surgery as a medical necessity.

Prior to surgery, the patients were evaluated by the team at Yale (M.G.M., R.A.K., A.L.-W.) as well as by the surgeons and other knowledgeable professionals (A.C.J.L. at Yale and New York College of Medicine; R.L.A. at Mt. Sinai and Beth Israel Deaconess Medical Center; and A.Y.M. and M.H.P. at North Shore-Long Island Jewish Health System). Comorbid conditions and other psychopathology and psychosocial factors were also assessed. Efforts were made to address any psychosocial issues that could affect patient participation and assessment prior to the surgical intervention, but no formal protocol was followed.

Surgical technique

Frame-based stereotactic targeting employing MRI (Magnetic Resonance Imaging) with or without CT (Computed Tomography) was used in each case. The stereotactic coordinates for the targeted anatomic structure were based on the best available data.^{45–50} Typically, the initial coordinates, derived relative to the intercommissural plane, were then adjusted by direct visualization on the MRI, with or without the assistance of digital overlays of the *Schaltenbrand and Wahren Atlas*. Implantation trajectories were planned to avoid sulci and cortical vessels.

Intraoperative macrostimulation was performed to assess for adverse events with the exception of one patient (subject 7), who was consciously sedated throughout his second and third surgeries. During test stimulation the patients were asked to report any unwanted side effects, including but not limited to muscle spasms, persistent spontaneous sensations, pain, dizziness, and double vision. The implanted electrodes were secured to the skull employing accepted techniques and were connected to implantable pulse generators on the same day or shortly thereafter.

Postoperative management

Postoperative adjustments were performed by a DBS-trained clinician. The first session occurred 10–14 days following electrode implantation. A range of pulse widths (60–210 microseconds), stimulation rates (60–200 Hz), and electrode combinations were tested. Both monopolar and bipolar arrays were programmed empirically with the goal of achieving the greatest possible tic reduction with minimal side effects. Stimulation amplitudes varied from 0.1 to 5 V. Programming sessions were performed as needed, typically on a monthly basis for the first year and every 3–6 months thereafter. A summary of the active DBS contacts and lead locations is provided in Table 2.

Table 1. Published Studies on Deep Brain Stimulation in Tourette Syndrome

Target	Study	No. Patients	Follow-up, Months	Tic Improvement (YGTSS or MRVRS), %
Midline thalamus (CM-Pf/Voi, CM-Pf)	Visser-Vandewalle (2003) ⁵	3	12, 8, 60	90, 72, 83
	Ackermans et al. (2006) ¹⁰	1 (CM-PF/Voi)	12, 12	Tic 20 3 min,
	Ackermans et al. (2007) ¹¹	1 (CM-PF and postroventrolateral GPI)		Tic 28 2 min
	Bajwa et al. (2007) ¹²	1	24	66
	Maciunas et al. (2007) ¹⁴	5	3	40 (Mean)
	Servello et al. (2008) ¹⁷	18	3–18	65 (Mean)
	Shields et al. (2008) ²⁰	1	3	46
	Vernaleken et al. (2009) ²¹	1	Not reported	36
	Porta et al. (2009) ²⁵	15–18	24, 60–72 long-term follow-up	52 (Mean)
	Porta et al. (2012) ³⁴		(same cases)	41, 33, 32, 18, 1
	Servello et al. (2009) ²⁶	4	10–26	Slight to modest improvement
	Idris et al. (2010) ²⁸	1	2	Not reported
	Marceglia et al. (2010) ²⁹	7	6–24	33 (Mean)
	Ackermans et al. (2011) ³⁰	6	12	49 (Mean)
	Lee et al. (2011) ³²	1	18	58
	Kuhn et al. (2012) ³⁵	2	12	75 and 100
Savica et al. (2012) ³⁶	3	12	70 (Mean)	
Maling et al. (2012) ³⁷	5	4–6	41, 33, 32, 18, 1	
Okun et al. (2013) ⁴¹	5	6	19 (Mean)	
GPi	Deidreirich et al. (2005) ⁶	1	14	47–76
	Gallagher et al. (2006) ⁹	1	Several	Disappearance of tics
	Ackermans et al. (2006) ¹⁰	1 (CM-Pf and posteroventral GPi)	12	Tics 28 2/min
	Shahed et al. (2007) ¹⁵	1	6	84
	Dehning et al. (2008) ¹⁶	1	12	88
	Dueck et al. (2009) ²²	1	12	No improvement
	Martínez-Fernández et al. (2011) ³¹	5 (one subject had both), 3 (posteroventral), 3 (anteromedial)	3–24	32, 19, 14, 63, 32, 19
	Cannon et al. (2012) ³³	11 (anteromedial)	4–30	51

Table 1. Continued

Target	Study	No. Patients	Follow-up, Months	Tic Improvement (YGTSS or MRVRS), %
	Dong et al. (2012) ³⁹	2 right GPi only (posteroventral)	12	59 and 53
	Massano et al. (2013) ⁴²	1 (anteromedial)	3, 12, 24	61
CM-Pf and/or GPi (anteromedial)	Houeto et al. (2005) ⁷	1	24	82
	Welter et al. (2008) ¹⁸	3	20, 27, 60	65–96
GPe	Piedimonte et al. (2013) ⁴⁰	1	3, 6, 24	39
A/C – NA	Flaherty et al. (2005) ⁸	1	18	25
	Kuhn et al. (2007) ¹³	1	30	41
	Zabek et al. (2008) ¹⁹	1	28	80
	Neuner et al. (2009) ²⁴	1	36	44
	Burdick et al. (2010) ²⁷	1	39	15% worse
	Sachdev et al. (2012) ³⁸	1	8	57
STN	Martinez-Torres et al. (2009) ²³	1	12	76

Abbreviations: A/C, Anterior Limb of Internal Capsule; CM-Pf, Centromedial-Parafascicular Complex; GPe, Globus Pallidus, Pars Externus; GPi, Globus Pallidus, Pars Internus; MRVRS, Modified Rush Videotape Rating Scale; NA, Nucleus Accumbens; STN, Subthalamic Nucleus; Voi, Ventralis Oralis; YGTSS, Yale Global Tic Severity Scale.

Assessments

The *Diagnostic and Statistical Manual, 4th edition, Text Revised* (DSM-IV-TR) criteria for TS and comorbid diagnosis were used in this study to establish an official diagnosis.⁵¹ We administered additional rating scales at baseline, including the Yale Global Tic Severity Scale (YGTSS),⁵² the Yale-Brown Obsessive-Compulsive Scale,⁵³ the Hamilton Depression Rating Scale,⁵⁴ and the Hamilton Anxiety Rating Scale.⁵⁵ These assessments were also conducted at various intervals from 1 month to 6 years after surgery. Marked improvements were defined as more than 50% improvement in the Total Tic Score on the YGTSS (range 0–50). These evaluations were not performed in a scripted fashion as the DBS therapy was not provided as part of a prospective trial, but rather on a humanitarian basis.

Results

The clinical characteristics of the eight patients with TS at baseline are summarized in Table 3. As detailed in Table 3, three of the patients under the age of 25 years had severe malignant self-injurious tics. Baseline characteristics of tics and associated symptoms, together with follow-up evaluations for the eight subjects, are detailed in Table 4. We observed significant reduction in tic severity in three TS patients (subjects 1, 6 and 8; see Supplementary Materials). The range of improvement in the YGTSS Total Tic Score for the entire group was

0–85%. The mean percent improvement was 45%, and the median value was between 20% and 44%.

Two of eight subjects have had their electrodes removed. In one this was because of postoperative infection (subject 2), and in the other because of lack of therapeutic benefit after 3 years of stimulation (subject 3) (see Supplementary Materials for presentations of each case). At present, one individual has turned off his electrodes but continues to show a clear benefit (tic reduction) despite a gradual worsening of his overall neurologic status (subject 1, see below and Supplementary Materials).

Discussion

There are many unknowns when considering DBS for TS. These include the optimal target, the best indications for surgery, the optimal stimulation parameters, the optimal approach to assess social status, and the potential for social reintegration postsurgery.^{41,43,44,56–58}

Patient selection

In this series, the two youngest patients (subjects 6 and 8) benefited the most from surgery and, thus far, these two patients have also been most successful in resuming a reasonably ‘normal’ life, with good to excellent reintegration into society. These individuals have also been successfully withdrawn from psychoactive medications, thus freeing them from potential side effects. The third individual (subject 1) who

Table 2. Stimulation Parameters and Lead Location at Follow-up Evaluation for all Subjects

Patient	Location	Identification of the Anatomic Target	DBS Settings
1 ^a	Thalamus	Leksell frame, MRI intraoperative guidance, general anesthesia (propofol), macrostimulation used, no microelectrode recording	*R 5-7+, 2.5 V, 210 μ s, 185 Hz
	X (mm lateral AC-PC)=5		*L 1-3+, 2.35 V, 180 μ s, 185 Hz
	Y (mm posterior AC-PC)=4		
	Z (mm beneath AC-PC)=0		
	GPI (posteroventral/sensorimotor)		*R 5-C+, 1.0 V, 120 μ s, 130 Hz
	X (mm lateral to intercommissural)=17		*L 1-2+, 1.0 V, 120 μ s, 130 Hz
	Y (mm anterior to mid-commissural)=4 Z (mm deep to mid-commissural)=5		
2 ^b	Thalamus	Leksell frame, MRI intraoperative guidance, deep sedation, macrostimulation used, no microelectrode recording	NA
	X (mm lateral AC-PC)=5		
	Y (mm posterior AC-PC)=4		
	Z (mm beneath AC-PC)=0		
3 ^c	Thalamus	Leksell frame, MRI intraoperative guidance, deep sedation, macrostimulation used, no microelectrode recording	NA
	X (mm lateral AC-PC)=5		
	Y (mm posterior AC-PC)=4		
	Z (mm beneath AC-PC)=0		
4	GPI (posteroventral/sensorimotor)	Leksell frame, MRI intraoperative guidance, deep sedation, macrostimulation used, no microelectrode recording	R 2-C+, 2.5 V, 90 μ s, 185 Hz
	X (mm lateral to intercommissural)=17		L 2-C+, 2.0 V, 90 μ s, 185 Hz
	Y (mm anterior to mid-commissural)=4		
	Z (mm deep to mid-commissural)=5		
5	GPI (posteroventral/sensorimotor)	Leksell frame, MRI intraoperative guidance, deep sedation, macrostimulation used, no microelectrode recording	R 4+6-5-7+, 2.1 V, 180 μ s, 185 Hz
	X (mm lateral to intercommissural)=17		L 2-1-0-C+, 2.1 V, 180 μ s, 185 Hz
	Y (mm anterior to mid-commissural)=4		
	Z (mm deep to mid-commissural)=5		

Table 2. Continued

Patient	Location	Identification of the Anatomic Target	DBS Settings
6	Thalamus	Leksell frame, MRI/CT fusion, procedure performed under local anesthesia with dexmedetomidine used for sedation	R I-C+, 3.0 V, 90 μs, 130 Hz
	X (mm lateral AC-PC) = 5		L I-C+, 3.2 V, 90 μs, 130 Hz
	Y (mm posterior AC-PC) = 4		
	Z (mm beneath AC-PC) = 0		
		Physiologic confirmation with microelectrode recording and macrostimulation	
7	GPi, anterior mesial (limbic)	Leksell frame, MRI intraoperative guidance, sedation with dexmedetomidine/propofol, physiologic confirmation with microelectrodes recording only	*R I-C+, 3.0 V, 150 μs, 90 Hz
	X (mm lateral to intercommissural)= 14		*L I-C+, 2.5 V, 180 μs, 120 Hz
	Y (mm anterior to mid-commissural)= 18		
	Z (mm deep to mid-commissural)=5		
	Thalamus		*R 11-C+, 2.0 V, 60 μs, 120 Hz
	X (mm lateral AC-PC)=6		*L 9-10-C+, 3.0 V, 60 μs, 120 Hz
	Y (mm posterior AC-PC)=3		
	Z (mm beneath AC-PC)=0		
	GPi (posteroventral/sensorimotor)		R 8-C+, 2.5 V, 90 μs, 185 Hz
	X (mm lateral to intercommissural)= 17		*L 8-C+, 2.5 V, 90 μs, 180 Hz
Y (mm anterior to mid-commissural)=4			
Z (mm deep to mid-commissural)=5			
8	Thalamus	Leksell frame, MRI/CT fusion, procedure performed under general anesthesia with propofol and remifentanyl	R C+1-, 2.1 V, 90 μs, 130 Hz
	X (mm lateral AC-PC)=5		L C+1-, 1.9 V, 90 μs, 130 Hz
	Y (mm posterior AC-PC)=4		
	Z (mm beneath AC-PC)=0		

Table 2. Continued

Patient	Location	Identification of the Anatomic Target	DBS Settings
		Physiologic confirmation with microelectrode recording and macrostimulation	

Abbreviations: AC, Anterior Commissural; DBS, Deep Brain Stimulation; GPi, Globus Pallidus Pars Internus; PC, Posterior Commissural; NA: Not Applicable.
 The DBS settings show right side (R), left side (L), voltage (V), pulse width (μ s), and rate (Hz).
^aGPi electrodes are not currently functional secondary to forceful head-snapping tics that led to electrode dysfunction.
^bElectrodes were removed because of infection.
^cElectrodes were removed because of lack of therapeutic benefit.
^dElectrodes are currently turned OFF.

also had a ‘marked improvement’ remains disabled, despite being virtually tic free for significant periods of time. His disability is a consequence of permanent and progressive spinal injury secondary to an extremely forceful whole-body and head-snapping tic.¹² The forcefulness of this malignant tic has not been lessened by DBS, but its frequency has been markedly reduced despite the fact that his electrodes have been turned off for more than 8 months (see Supplementary Materials, subject 1). While these results may argue for earlier surgical intervention, it is also worth noting that subject 1 has more recently experienced a failure of his GPi leads because of wire fractures resulting from the forceful head snapping. These observations, albeit in a small number of patients, mirror the published experiences with DBS at the globus pallidus for primary generalized dystonia.^{59,60} Here, too, younger patients and those who had not yet developed secondary skeletal changes responded more quickly and more robustly to DBS.

In typical TS, tics usually improve by 20 years of age, an observation that is often cited to support the view that surgery should not be considered prior to 25 years of age.^{43,61} However, it is important to note that TS is a heterogeneous clinical entity and that the prevalence and severity of tics and the behavioral and emotional comorbidities observed in TS are both higher in younger patients.^{62,63} In addition, tics and comorbidities in young people with severe refractory TS often have a strong association with difficulties encountered in remaining in school and maintaining normal peer relationships. It is also the case that younger patients are less likely to have sustained significant physical injury because of their tics. These observations suggest that surgical intervention prior to 25 years of age may be indicated in highly selected patients. Our current view is that a strict cut-off for eligibility based on age alone may exclude reasonable candidates, and that as in Parkinson’s disease, age should be just one of many factors considered when determining an individual patient’s surgical candidacy.

Target

In four patients, the tics virtually disappeared for 10–14 days immediately after surgery. In one patient (subject 1) the midline thalamic site was the target and in three patients (subjects 4, 5, and 7)

the GPi (two sensorimotor and one limbic) was the target. This disappearance of tics might be attributable to the immediate trauma of the electrode placement (the so-called microlesion effect). Alternatively, it might represent a placebo response. Regardless of the underlying cause, in our experience this immediate response is *not* indicative of a long-term improvement in tic symptoms.

In the current case series, we report significant reductions in tic severity in three TS patients (subjects 1, 6, and 8) with electrode placement in the midline thalamic nuclei. Servello et al. reported a similar response to DBS (although to differing degrees) in 18 similarly treated patients with severe TS.¹⁷ Subject 1 showed a further significant benefit with the placement of a second set of electrodes in the sensorimotor GPi. Indeed, this patient experienced periods during which he reported being virtually tic free for the first time in more than 40 years. The other patients had disappointing outcomes from their surgeries. However, a longer follow-up interval is needed in at least one patient (subject 7, who had DBS electrodes placed in both GPi sites as well as in the midline thalamic nuclei) before we can make this statement with certainty.

A ‘definitive neuroanatomic target’ for TS DBS has not yet emerged. The reasons for this are many. First, the specific neuronal circuitry underlying TS is only partially known.^{64–71} In fact, it is not known if the pathophysiology of TS is the same for all patients, or if different types of TS patients have similar or dissimilar pathophysiologies requiring distinct neuromodulatory strategies. This is especially true for many of the patients in this series, given their severe, refractory tics, which often failed to show the typical bouts during the course of a day, or alternatively the waxing and waning course of weeks to months. Compounding these gaps in our knowledge is a lack of representative animal models for TS.⁷² Finally, the best location for stimulation within each target (i.e. thalamus or GPi) may be very specific, and to date we are unable to refine the target physiologically as is the case for Parkinson’s disease.^{50,73}

A prevailing model of TS and other hyperkinetic movement disorders (including dystonia and chorea) implicates a low firing rate in output neurons of the GPi as a pathophysiologic hallmark.^{74,75} However, recent observations suggest that the GPi activity seen in dystonia and tic disorders may be similar to that encountered in

Table 3. Baseline Clinical Characteristics of the Eight Patients with Tourette Syndrome

Subject	Sex	Age (Years)	Disease Duration (Years)	Tic Symptoms	Typical Waxing and Waning Course	Self-Injury	Comorbid Disorders	Family History	Living and Work Situation	Medication Before Surgery	Current Medication
I	M	48	45	Eye blinking, violent head jerks, throwing elbow against ribs, abdominal tensing, snapping, grunting, screeching, coprolalia	No	Yes, slamming forearm against forehead	OCD (mild to moderate), depression	No	Separated, employed part time	Haloperidol, pimozide, risperidone, clonidine, fluoxetine, clonazepam, pergolide	Haloperidol, fluoxetine, gabapentin, tizanidine, diazepam, temazepam, aspirin
2 ^a	M	44	41	Eye movements, facial tics, head jerking and snapping, shoulder shrugs, grunting, throat clearing	Yes	Yes, skin picking	OCD (severe)	Yes	Unmarried, self-employed	Pimozide, risperidone, olanzapine, quetiapine, fluoxetine, fluvoxamine, sertraline, clomipramine, clonazepam	Sertraline, clonazepam

Table 3. Continued

Subject	Sex	Age (Years)	Disease Duration (Years)	Tic Symptoms	Typical Waxing and Waning Course	Self-Injury	Comorbid Disorders	Family History	Living and Work Situation	Medication Before Surgery	Current Medication
3 ^b	M	37	27	Head and neck movements, body jerking, shifting body position, tongue movements, hand and arm tensing, bumping objects into teeth, toe curling, diaphragmatic dystonic tics limiting ability to breathe	No	No	OCD, attention-deficit disorder, anxiety symptoms	No	Unmarried, employed	Haloperidol, pimozide, clonidine, fluoxetine, sertraline, clonazepam	Clonidine, clonazepam,
4	M	42	38	Facial grimacing, flopping hands in front of face, pointing finger back and front, chest rubbing, grunting, yelling, whistling, curse words	No	No	OCD, history of ADHD	No	Unmarried, unemployed	Haloperidol, pimozide, clonazepam, methylphenidate	Clonazepam

Table 3. Continued

Subject	Sex	Age (Years)	Disease Duration (Years)	Tic Symptoms	Typical Waxing and Waning Course	Self-Injury	Comorbid Disorders	Family History	Living and Work Situation	Medication Before Surgery	Current Medication
5	M	24	15	Head jerks, snapping arm against side, kicking, licking items, head grabbing, copropraxia, loud screaming, sniffing	Yes	Yes, punching, hitting himself	OCD	Yes	Married, one child, unemployed	Haloperidol, pimozide, risperidone, fluphenazine, clonidine, fluvoxamine, imipramine, nortriptyline, clonazepam, pergolide	Clonazepam, quetiapine, zolpidem, topiramate, nicotine patches, ketamine, opiates
6	M	16	13	Eye blinking, head and shoulder jerking, head bobbing, flexion and extension of arms and fingers, spinning in place, throat clearing, coprolalia	Yes	No	ADHD	No	Unmarried, high-school student	Risperidone, aripiprazole, ziprasidone, sertraline, tetrabenazine, methylphenidate, topiramate	None

Table 3. Continued

Subject	Sex	Age (Years)	Disease Duration (Years)	Tic Symptoms	Typical Waxing and Waning Course	Self-Injury	Comorbid Disorders	Family History	Living and Work Situation	Medication Before Surgery	Current Medication
7	M	19	11	Dystonic posturing, exclusively left-sided tics and self-injurious behaviors such as poking left cornea and pulling on left eye lid, repeating single words or syllables	No	Yes poking left eye and pulling on left eye lid, left cheek biting	OCD, some symptoms of ADHD	No	Unmarried, unemployed	Haloperidol, risperidone, aripiprazole, fluphenazine, sertraline, clonazepam, tetrabenazine, guanfacine, topiramate, etanercept, N-acetyl cysteine	Haloperidol, clonazepam, clonidine, sertraline, carbamazepine

Table 3. Continued

Subject	Sex	Age (Years)	Disease Duration (Years)	Tic Symptoms	Typical Waxing and Waning Course	Self-Injury	Comorbid Disorders	Family History	Living and Work Situation	Medication Before Surgery	Current Medication
8	M	17	13	Atypical long bouts of severe tics (20 minutes to 1 hour) interspaced with long tic-free periods, tics include opening mouth wide, arm and shoulder movements, head and neck jerks, rapidly shaking head from side to side, gyrating head, arching back, flexion and extension of arms one side at a time	No	Yes, pounding of chest, punching forehead	OCD, mild depression, some symptoms of general anxiety disorder	Yes for OCD	Unmarried, student	Pimozide, risperidone, ziprasidone, aripiprazole, fluphenazine, clonidine, guanfacine, fluoxetine, clonazepam, topiramate	None

Abbreviations: ADHD, Attention-Deficit Hyperactivity Disorder; M, Male; OCD, Obsessive-Compulsive Disorder.

Positive family history: a first-degree (parent, sibling, child) or second-degree (grandparent, aunt, uncle, nephew, niece, half-sibling or a grandchild) relative with a chronic tic disorder. For additional clinical details, see Supplementary Materials.

^aThe electrodes removed due to side effect of infection.

^bThe electrodes removed due to a lack of therapeutic benefit.

Table 4. Individual Changes in Severity of Tics and Associated Behaviors in Eight Patients with Tourette Syndrome

Patients	Duration of Follow-up (Months)	YGTSS*		YBOCS***		HDRS		HARS	
		Before Surgery	At Last Follow-up**	Before Surgery	At Last Follow-up	Before Surgery	At Last Follow-up	Before Surgery	At Last Follow-up
1	107	36	10 (72%)	29	8	10	15	0	0
2 ^a	95	41	32 (20%)	15	0	0	0	5	1
3 ^b	84	43	40 (7%)	20	27	5	4	20	15
4	51	50	40 (20%)	12	10	3	3	4	3
5	8	38	22 (44%)	0	0	4	1	5	3
6	16	46	7 (85%)	5	5	0	0	2	1
7 ^c	37	25	25 (0%)	0	0	3	15	3	3
8	6	43	14 (67%)	20	22	2	0	3	3

Abbreviations: HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; YBOCS, Yale–Brown Obsessive–Compulsive Scale; YGTSS, Yale Global Tic Severity Scale.

*Total tic severity does not include impairment score and is based on the worst-ever tic severity measured at the time of interview.

**Percent improvement in the YGTSS Total Tic Score.

***Obsessive–compulsive symptom severity is based on the total obsessive–compulsive severity measured at the time of interview.

^aElectrodes were removed because of infection.

^bElectrodes were removed because of lack of therapeutic benefit.

^cThis patient does not have any vocal tics.

Parkinson's disease^{75–79} and, if true, this could challenge existing physiologic models. More data regarding TS physiology are needed before definitive conclusions can be drawn.

Because of the wide interpatient variability in specific tic symptoms and comorbidities, it still seems appropriate to consider multiple potential targets for DBS and to select targets based on the specific clinical characteristics of each patient. Another important factor that may complicate the interpretation of surgical results is that the amount of electrical energy delivered to a target can be very different from one patient to another, and even between hemispheres for the same patient. In some studies, the current intensity and spread have been so high that it is doubtful whether the effects of DBS are restricted to the specific target area.

Postoperative complications

In our case series, one patient (subject 2) developed an infection secondary to picking at the incision sites. Interestingly, in one recent study patients with TS were found to have a higher incidence of infectious complications following DBS than patients with Parkinson's disease or dystonia.⁸⁰ The basis of this increase is unknown, but conceivably could be related to host-specific immune factors as there is a growing body of evidence implicating immune dysregulation in TS patients.⁸¹

Programming

In addition to careful intraoperative targeting, thoughtful and labor-intensive programming of the stimulators is very important to achieving optimal clinical outcomes (see case material for subject 4). The potential need for frequent programming should be considered when choosing candidates for surgery, and families need to be fully apprised of this reality preoperatively. Although a monthly checkup for optimization and programming following DBS (for the first 6 months) is a reasonable standard in movement disorders, in our experience a more flexible schedule can be necessary for TS patients. Reasons for this include natural symptom fluctuations and variability in patients' responses to treatment and expectations. We had similar programming experiences to Porta et al.²⁵

Confounding factors of the present report include multiple surgeons (three surgeons in five different centers) employing varied techniques, as well as the use of unblinded assessments. At the present time there is no consensus regarding the use of DBS in TS, although most experts believe it should be used as a last resort in a small subset of individuals who have severe, self-injurious tics or tics that are both refractory to treatment and severely impair quality of life. Randomized trials employing blinded ratings of patients treated by experienced DBS teams are sorely needed.⁴¹ Finally, a deeper understanding of the circuitry involved in TS may lead to more successful tailored targeting for patients with refractory and malignant TS. Presently, however,

clinicians should be aware that outcomes are mixed and that ‘one size does not fit all.’

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