The use of deep brain stimulation in Tourette's syndrome

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Tourette's syndrome (TS) is a childhood neuropsychiatric disorder characterized by multiple involuntary motor and vocal tics. It is commonly associated with other behavioral disorders including attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, anxiety, depression, and self-injurious behaviors. Tourette's syndrome can be effectively managed with psychobehavioral and pharmacological treatments, and many patients experience an improvement in tics in adulthood. However, symptoms may persist and cause severe impairment in a small subset of patients despite available therapies. In recent years, deep brain stimulation (DBS) has been shown to be a promising treatment option for such patients. Since the advent of its use in 1999, multiple targets have been identified in DBS for TS, including the medial thalamus, globus pallidus internus, globus pallidus externus, anterior limb of the internal capsule/nucleus accumbens, and subthalamic nucleus. While the medial thalamus is the most commonly reported trajectory, the optimal surgical target for TS is still a topic of much debate. This paper provides a review of the available literature regarding the use of DBS for TS.

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KEY WORDS • Tourette's syndrome • tics • deep brain stimulation •
medial thalamus • globus pallidus

IN 1885, Georges Gilles de la Tourette described 9 patients who suffered from “a neurological condition characterized by motor incoordination accompanied by echolalia and coprolalia.”³⁰ Charcot later named the condition Tourette's syndrome (TS).³⁰ Tourette's syndrome is a complex childhood neuropsychiatric disorder characterized chiefly by the presence of tics. Tics are sudden, involuntary, repetitive muscle contractions (motor tics) or phonic productions (vocal tics). Tics are usually preceded by premonitory sensory urges with feelings of relief after execution of the tic.³¹ Once thought to be rare, recent studies suggest that TS is more common than previously believed. The prevalence of TS differs among studies due to variations in age, sex, diagnostic criteria, and assessment methods, but is estimated at 0.77% in children and is considered to be 4 times more common in males than in females.²⁸

Symptoms of TS typically develop during the 1st de-

cade of life, with a mean age of onset of 7 years. Initial symptoms commonly manifest as simple motor tics of the head and face, with vocal tics appearing 1–2 years later.³¹ Motor tics can be characterized as abrupt in onset, fast, and brief (clonic) or slow and sustained (dystonic or tonic). Simple tics involve only a single muscle or group of muscles, such as eye blinking, grimacing, sniffing, or throat clearing, while complex tics involve the coordinated action of multiple muscles to produce seemingly voluntary motor movements; examples include throwing, hitting, head shaking, or uttering phrases.²⁵ Symptoms wax and wane throughout its course, with tics changing in character, frequency, and location over time. Tics typically become more frequent and severe during periods of excitement, stress, or fatigue or when the patient is alone. On the other hand, tics may improve during times of relaxation and selective attention.¹⁰ It has been reported that tics can be voluntarily suppressed for brief periods of time, but results in increased inner tension and a rebound period.¹⁸ Patients with TS typically experience worsening symptoms during prepubescent years, peaking around age 10, with improvement during adolescence. An estimated 59%–85% of patients with TS experience a decline in the severity and number of tics in adulthood.²¹ Complete remission of tics in adulthood has also been documented in several studies.^{8,43}

A diagnosis of TS is based on clinical evaluation. Diagnostic criteria for TS, as outlined in the *Diagnostic and*

Abbreviations used in this paper: ADHD = attention-deficit/hyperactivity disorder; ALIC = anterior limb of the internal capsule; BDI = Beck Depression Inventory; CM = centromedian; DBS = deep brain stimulation; GPe = globus pallidus externus; GPi = globus pallidus internus; NA = nucleus accumbens; OCD = obsessive-compulsive disorder; PD = Parkinson's disease; Pf = parafascicular; Spv = substantia periventricularis; STAI = State-Trait Anxiety Inventory; TS = Tourette's syndrome; Voi = ventral oral internal; YBOCS = Yale-Brown Obsessive Compulsive Scale; YGTSS = Yale Global Tic Severity Scale.

Statistical Manual of Mental Disorders-IV,³ require the presence of both multiple motor tics and 1 or more vocal tics, not necessarily simultaneously. Symptoms must develop before the age of 18 years and tics must occur multiple times per day nearly every day or intermittently for at least 1 year, with no more than 3 consecutive tic-free months. The tics must not be due to the direct physiological effects of a substance or general medical condition.³ Other than the presence of tics, the neurological examination is typically normal. Currently, there are no laboratory tests or imaging studies that can definitively diagnose TS, but these may be useful in ruling out other diseases.⁵⁷

Tourette's syndrome is frequently associated with other psychiatric disorders. Attention-deficit/hyperactivity disorder (ADHD) is the most common comorbidity, found in 21%–90% of TS patients. Obsessive-compulsive disorder has been reported in 11%–80% of TS patients, and self-injurious behavior is found in approximately 33% of TS patients. Other psychiatric comorbidities include anxiety, depression, and personality disorders.⁴⁷ The severity of tics and psychiatric disorders, and their impact on the life of patients with TS, ranges from mild to severe. Higher tic severity is generally associated with greater functional impairment.¹² However, psychiatric and behavioral symptoms may be more problematic and have a greater impact on quality of life than tics.¹⁶

Much of the pathophysiology of TS still remains unclear, but dysfunction of the basal ganglia and parallel striatal-thalamic-cortical circuits are believed to play a major role in the disorder.¹⁹ The striatum and subthalamic nucleus receive excitatory input from the cortex and serve as the major inputs to the basal ganglia. The globus pallidus internus (GPi) and the substantia nigra pars reticulata serve as the major output, with inhibitory projections to the thalamus and midbrain that modulate motor patterns of the cerebral cortex and brainstem.⁴⁰ Inappropriate activation of striatal neurons with inhibitory projections to the GPi and substantia nigra pars reticulata have been suggested in TS. Abnormal inhibition of the GPi and substantia nigra pars reticulata can lead to increased thalamocortical drive, resulting in unwanted motor patterns and the execution of tics.³⁹ Aberrant action of dopamine has also been implicated in the pathophysiology of TS. Dopamine-mediated long-term potentiation of striatal neurons can cause excessive activity modulating cortical-striatal transmission.⁴⁰ This theory is supported, in part, by the relative efficacy of neuroleptics in treating TS.²⁵ Dysfunction in excitatory thalamostriatal loops are also believed to play a role. These loops involve the centromedian-parafascicular (CM-Pf) complex of the thalamus and project to the motor striatum and midline thalamic nuclei (substantia periventricularis [Spv]), toward the limbic part of the striatum.⁵⁰

Due to its complex and variable clinical presentation, a multifactorial approach is often taken in the treatment of TS. It is important to assess the individual needs of the patient and treat the most debilitating symptoms. In patients with milder forms of TS, psychobehavioral therapy is often an effective form of treatment and aims to teach patients how to control environmental factors that affect their tics. These therapies include relaxation training, cognitive behavioral therapy, habit reversal training, and com-

prehensive behavioral intervention for tics.⁵⁶ For patients with moderate to severe TS, pharmacological treatment may be necessary. Standard tic-suppressing medications include α_2 -adrenergic agonists, typical and atypical neuroleptics, benzodiazepines, and botulinum toxin injections into muscle groups responsible for debilitating tics.^{38,56} In some cases, symptoms of associated behavioral disorders can be more debilitating than tics and must be treated.¹⁶ Despite previous conceptions that stimulant medications for ADHD can worsen tics, recent evidence suggests that methylphenidate, α_2 agonists, desipramine, and atomoxetine can effectively treat patients with TS and ADHD without worsening tics.⁷ Comorbid obsessive-compulsive disorder (OCD) can be treated with cognitive behavioral therapy, selective serotonin reuptake inhibitors (SSRIs), and typical and atypical neuroleptics.³⁸ Despite available behavioral and pharmacological treatments, there is a small subset of patients with TS who fail to show clinical improvement or experience potentially life-threatening tics or self-injurious behavior ("malignant TS").¹¹ If symptoms remain severe and cause marked impairment in functioning, surgical intervention may be warranted.

An Overview of Surgery for TS

Baker⁵ described what is believed to be the first neurosurgical procedure for TS, in a 22-year-old patient suffering from somatomotor and vocal tics since the age of 9. Other clinical symptoms included severe panic attacks with depersonalization and feelings of hopelessness. Pharmacological treatment showed no efficacy in improving tics or behavioral symptoms. In 1960, a bimedial leucotomy was performed, which resulted in significant reduction in tic severity and panic attacks following the procedure and at 1-year follow-up. Since then, there have been more than 24 reports of ablative surgery for treatment-refractory TS in more than 60 patients. These cases have been described in detail and include: prefrontal lobotomy; bimedial frontal leucotomy; limbic leucotomy; anterior cingulotomy; lesions of the medial, intralaminar and ventrolateral thalamic nuclei; lesions of the zona incerta; lesions of the red nucleus; and dentatotomy. Unfortunately, most of these procedures yielded disappointing results or produced adverse side effects, such as hemiplegia and dystonia.⁵⁸

In 1999, deep brain stimulation (DBS) for intractable TS was introduced by Vandewalle et al.⁶⁰ Bilateral stimulation of the medial thalamus at the cross-point of the CM and ventral oral internal (Voi) thalamic nuclei and the Spv was performed in a single patient. This target mimicked the trajectory of Hassler and Dieckmann,²² who performed bilateral ablation of the intralaminar and medial thalamic nuclei in 9 patients. Three of the 9 patients reported 70%–100% reduction in their tics. Vandewalle et al.⁶⁰ revealed similar results at 1-year follow-up, with almost complete abolition of tics.

Deep Brain Stimulation Targets

Since 1999, reports of DBS for refractory TS have continued to surface, but are sparse, and the procedure is still considered experimental. Based on the developing pathophysiology of TS, 5 DBS targets have been identi-

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fied: the medial thalamus,^{1,2,4,26,33,45,46,51–53,55,60,61} GPi,^{9,13–15,23,36,54,59,62} globus pallidus externus (GPe),⁴⁴ anterior limb of the internal capsule (ALIC)/nucleus accumbens (NA),^{17,29,41,49,63} and the subthalamic nucleus.³⁷ While the medial thalamus has been the most widely reported DBS target, there is still much debate over which target provides optimal results. This paper provides a review of available literature regarding the use of DBS to treat TS.

Medial Thalamus

Visser-Vandewalle et al.⁶¹ published a second report on 3 patients who received bilateral stimulation of the CM and Voi thalamic nuclei and the Spv (Table 1). All of the patients had experienced severe and impairing tics since childhood, with minimal relief from pharmacological or alternative treatments. The authors reported a 90.1% tic reduction after 5 years in Patient 1, a 72.2% tic reduction after 1 year in Patient 2, and an 82.6% tic reduction after 8 months in Patient 3. The authors conducted a follow-up study to assess the long-term effects of DBS in these patients.¹ At the 10-year follow-up, Patient 1 continued to experience a significant reduction in tics (92.6%). At the 6-year follow-up, a 78% reduction in tics was reported for Patient 3. Patient 2 was lost to follow-up. Patients 1 and 3 reported side effects of decreased energy and changes in sexual functioning.

In 2007, Bajwa et al.⁴ published a case report on a single patient who underwent DBS for chronic, severe TS. Trajectory included the CM and Voi thalamic nuclei and

the Spv. At 24 months' follow-up, a 66% reduction in tics was reported.

Later in 2007, Maciunas et al.³⁵ published a prospective, randomized, double-blind trial of bilateral thalamic stimulation in 5 patients with TS. Electrodes were implanted at the anterior extent of the CM-Pf complex. Patients were randomized and evaluated in 1 of 4 states of unilateral or bilateral stimulation (both stimulators on, left on/right off, right on/left off, both off) for 1 week each. A subsequent open-label evaluation with 3 months' follow-up was conducted. There was a mean 53% reduction in motor tics with both stimulators on, but no reported benefit from unilateral stimulation. Three of the 5 patients showed a statistically significant reduction in motor and vocal tics at all points of evaluation. At final follow-up, a mean 44% reduction in tics was observed.

Servello et al.⁵² published a case series of 18 patients treated with DBS for treatment-refractory TS in 2008. Bilateral stimulation of the CM-Pf and Voi thalamic nuclei was chosen for all patients and patient follow-up ranged from 3 to 18 months. All patients responded well to DBS and reported a reduction in the number of tics, but 12 patients continued to experience tics and required multiple adjustments to the stimulation parameters. Furthermore, 4 patients reported unsatisfactory results after 3–6 months of follow-up. Nine months after the initial procedure, a blinded "on-off" evaluation was performed in 9 patients. Eight patients experienced worsening symptoms in the "off" condition.

TABLE 1: Thalamic targets of DBS for TS*

Authors & Year	No. of Patients	Target	Follow-Up	Outcome
Visser-Vandewalle et al., 2003	3	CM-Voi-Spv	patient 1: 5 yrs patient 2: 1 yr patient 3: 8 mos	reduction in tic scores: 90.1% (patient 1), 72.2% (patient 2), 82.6% (patient 3)
Bajwa et al., 2007	1	CM-Voi-Spv	2 yrs	66% reduction in tic score
Maciunas et al., 2007	5	CM-Pf	3 mos	mean 44% tic reduction
Servello et al., 2008	18	CM-Pf-Voi	3–18 mos	mean 28.6% tic reduction
Shields et al., 2008	1	CM-Pf-Voi	3 mos	41% reduction in tic score, 50% reduction in overall impairment
Porta et al., 2009	15	CM-Pf-Voa	2 yrs	score reductions: 76.5 to 36.6 (YGTSS) 20.9 to 14.4 (YBOCS) 30.7 to 22.7 (BDI) 44.2 to 29.5 (STAI)
Servello et al., 2010	19	CM-Pf-Voi	2 yrs	score reductions: 75.5 to 40 (YGTSS) 19.6 to 16.3 (YBOCS) 26.2 to 17.7 (BDI) 45.8 to 31.3 (STAI)
Ackermans et al., 2010	2	CM-Voi-Spv	patient 1: 10 yrs patient 2: 6 yrs	reduction in tic scores: 92.6% (patient 1), 78% (patient 2)
Ackermans et al., 2011	6	CM-Voi-Spv	1 yr	mean 49% improvement in tic severity
Kaido et al., 2011	3	CM-Pf-Voi	1 yr	55%–70% decrease in YGTSS score
Pullen et al., 2011	1	CM-Pf	18 mos	reduction in YGTSS score from 77 to 14
Lee et al., 2011	1	CM-Pf	6 mos	62% decrease in tic severity
Savica et al., 2012	3	CM-Pf	1 yr	70% reduction in tics, 78% improvement in overall impairment

* Voa = ventral oral anterior.

Shields et al.⁵⁵ performed a within-subject comparison of DBS for treatment-refractory TS. Electrodes were originally placed at the ALIC-NA, and at the 18-month follow-up there was a 21% reduction in total tic score and 25% reduction in overall impairment. Mild side effects included apathy, depressed mood, and hypomania. Due to device complications, the electrodes needed to be reimplanted and the patient opted for placement at the CM-Pf-Voi thalamic nuclei. When compared with baseline scores, the authors now reported a 41% reduction in total tic score and 50% reduction in overall impairment, 3 months after the second surgery.

Porta et al.⁴⁵ reported on the long-term follow-up of 18 patients who received bilateral thalamic stimulation of the CM-Pf and ventral oral anterior thalamic nuclei. Two patients withdrew from the study and 1 needed further DBS surgery targeting the GPi. Therefore, only 15 patients were evaluated during a 2-year follow-up period. At 24 months, there was a reduction in global tic severity in all patients and a reduction in social impairment in 14 patients. Furthermore, there was a statistically significant decrease in reported depression, anxiety, and obsessive-compulsive symptoms.

One of the largest studies on DBS for TS was conducted by Servello et al.⁵³ The goal was to find a “common target” for both tics and behavioral comorbidities. Beginning in 2004, 36 patients were selected and underwent a collective 76 procedures. The specific target for each surgery was chosen based on clinical presentation of the individual patient: 67 procedures targeted the CM-Pf-Voi complex of the thalamus; 2 procedures targeted the posterior GPi. This trajectory was chosen to address dystonic tics in the patient. Ten procedures, in a total of 5 patients, targeted the ALIC-NA. This procedure was performed as a second “rescue surgery” for severe comorbidity in 4 of the 5 patients, despite a decrease in tic severity and frequency after the initial DBS surgery. A single patient received stimulation of the ALIC-NA alone. Electrodes were implanted bilaterally in all but 1 patient, who received unilateral stimulation of the right CM-Pf-Voi. Two-year follow-up was reached for 22 patients, 3 of whom turned off their devices and were excluded from analysis. The remaining 19 patients received stimulation of the CM-Pf-Voi and showed significant improvement in the Yale Global Tic Severity Scale (YGTSS),³² Yale-Brown Obsessive Compulsive Scale (YBOCS),⁴⁸ Beck Depression Inventory (BDI),⁶ and the State-Trait Anxiety Inventory (STAI).²⁷

More recently, Ackermans et al.² conducted a randomized, double-blind cross-over trial of 6 patients who received bilateral stimulation targeting the CM-Voi-Spv. Patients were randomly assigned to either have a stimulation-on period after surgery for 3 months, followed by stimulation-off period for 3 months (Group A) or vice versa (Group B). Following the crossover period, stimulators were switched on for 6 months. Primary outcome was tic severity, measured using the total YGTSS score, and secondary outcome was change in associated behavioral disorders and mood. Tic severity at the end of the stimulation-on period was significantly (37%) lower than at the end of the stimulation-off period. Significant im-

provement in tic severity from baseline (49%) was sustained at 1-year follow-up. No significant changes in behavioral disorders and mood were observed between on and off conditions or at 1-year follow-up.

Case reports continue to be published and provide further evidence for the effectiveness of DBS in treating TS. Kaido et al.²⁶ reported on an open-label case series study describing 3 patients who received DBS for severe, self-injuring TS. Electrodes were implanted at the CM-Pf-Voi of the thalamus and patients were evaluated at 1, 3, 6, and 12 months after surgery. In all patients, there was a significant decrease in YGTSS scores, total tic scores, and social impairment at all points of follow-up. The severity of OCD symptoms decreased in 2 patients, but increased in the other patient. The only reported side effect was blurred vision, which resolved when stimulation amplitude was lowered.

Pullen et al.⁴⁶ described a 17-year-old patient with worsening intractable TS, OCD, and ADHD, who received bilateral stimulation of CM-Pf complex. The surgery resulted in a significant improvement in tic severity and psychosocial functioning at the 18-month follow-up. Additionally, Lee et al.³³ reported on a patient with chronic, intractable TS with worsening tics at the age of 30. Electrodes were implanted at the CM-Pf complex and a reduction in tics was observed immediately following surgery. Tics reappeared 1 week later and persisted even after the stimulator was switched on. Voltage was gradually increased until the patient reported significant improvement in his tics after 6 weeks. At 6-months follow-up, there was a 62% improvement in tics, which remained stable 18 months after surgery.

In 2012, Savica et al.⁵¹ reported on the 1-year follow-up of 3 patients who underwent DBS for debilitating, treatment-refractory TS and comorbid OCD and ADHD. The CM-Pf complex was targeted, bilaterally. A mean 70% reduction in tic severity and 78% improvement in overall impairment was reported.

Globus Pallidus

The posteroventral GPi, anteromedial GPi, and globus pallidus externus (GPe) have all been targeted in DBS for TS. However, the number of studies regarding these targets and the sample sizes used remain small. The effects of bilateral stimulation of the posteroventral GPi were first described by Van der Linden et al.⁵⁹ in 2002 (Table 2). A 95% reduction in tics was observed at the 6-month follow-up in a single patient.

In 2005, Diederich et al.¹⁵ reported on the 14-month follow-up of a 27-year-old patient suffering from treatment-refractory TS and compulsive tendencies that caused profound social impairment and secondary depression. The posteroventral GPi was targeted during DBS and an improvement in tics was observed progressively in the months following surgery. There was a reported 73% reduction in tic frequency. The patient also reported a decrease in the internal urge to produce tics. When the stimulator was switched off for 48 hours during follow-up, a 66% increase in tic frequency was observed. There was no change in compulsions, but a reduction in depression and anxiety were reported.

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TABLE 2: Pallidal targets of DBS for TS

Authors & Year	No. of Patients	Target	Follow-Up	Outcome
Van der Linden et al., 2002	1	posteroventral GPi	6 mos	95% tic reduction
Diederich et al., 2005	1	posteroventral GPi	14 mos	73% decrease in tic frequency; score reductions: 8 to 2 (BDI), 66 to 40 (STAI)
Houeto et al., 2005	1	anteromedial GPi/ thalamus (CM-Pf)	2 mos for each condition, 2 yrs total	65% tic reduction (CM-Pf), 65% decrease in tics (Gpi); final evaluation: remained improved, 70% tic reduction
Shahed et al., 2007	1	posteroventral GPi	6 mos	84% tic reduction, 69% improvement in OCD symptoms
Welter et al., 2008	3	anteromedial GPi/ thalamus (CM-Pf)	patient 1: 60 mos patient 2: 27 mos patient 3: 20 mos	82% reduction in tics w/ combined stimulation, stable reduction in tics w/ pallidal stimulation, 74% reduction in tics w/ combined stimulation
Dehning et al., 2008	1	posteroventral GPi	1 yr	reduction in YGTSS score from 83 to 10
Martínez-Fernández et al., 2011	5	posteroventral GPi; anteromedial GPi	3–24 mos	29% improvement in tics, 26% improvement in YBOCS score, 54.4% improvement in reported quality of life
Dehning et al., 2011	3	posteroventral GPi	1 yr	patient 1: 17% tic reduction patient 2: no benefit patient 3: 64% decrease in tic severity
Cannon et al., 2012	11	anteromedial GPi	4–30 mos	49.6% decrease in total tic severity, 59% decrease in OCD symptoms
Piedimonte et al., 2013	1	GPe	6 mos	70.5% tic reduction, improvement in anxiety, depression, & global functioning

In the same year, Houeto et al.²³ conducted a prospective, randomized, double-blind study using a single patient with intractable TS and self-injurious behaviors. The goal was to determine if there was an observed difference in benefits from using different targets or with multiple targets used in combination. Deep brain stimulation electrodes were implanted bilaterally at the CM-Pf complex of the thalamus and the anteromedial GPi. The patient was randomized into 1 of 5 conditions (no stimulation, thalamic stimulation alone, pallidal stimulation alone, sham stimulation, and combined thalamic and pallidal stimulation). Two months after thalamic stimulation was started, there was a 65% decrease in tic severity, disappearance of self-injurious behaviors, and an improvement in mood, anxiety, and impulsivity. Pallidal stimulation also resulted in a 65% decrease in tic severity, but coprolalia persisted. Self-injurious behaviors were absent, but mood and impulsivity were not as improved as in thalamic stimulation. One month after stimulation was stopped (sham stimulation), tics progressively returned and became as severe as before surgery. Within 12 hours of combined thalamic and pallidal stimulation, the patient ceased self-injurious behaviors; final assessment revealed a 70% reduction in tics. Two years following the end of blinded conditions, tics and self-injurious behaviors remained significantly improved.

A similar randomized, controlled, double-blind crossover study was published by Welter et al.⁶² in 2008. Three patients with TS received DBS with trajectory mimicking that of Houeto et al.²³ Patients were then randomized into 1 of 4 conditions (thalamic stimulation, pallidal stimulation, thalamic and pallidal stimulation, and no [sham] stimulation) for 2 months each. Bilateral pallidal stimulation resulted in a 65%, 96%, and 74% reduc-

tion in tic severity in Patients 1, 2, and 3, respectively. Bilateral thalamic stimulation resulted in a 64%, 30%, and 40% reduction in tic severity in Patients 1, 2, and 3, respectively. Combined stimulation showed no added benefit, with a reported 60%, 43%, and 76% reduction in tic severity in Patients 1, 2, and 3, respectively. In the sham condition, patients experienced an increase in tic severity compared with when stimulation was on. Long-term benefits continued in Patients 1 and 3 with combined thalamic and pallidal stimulation and in Patient 2 with solely pallidal stimulation.

Shahed et al.⁵⁴ published a case report of a 16-year-old male with severe, intractable TS, ADHD, OCD, self-injurious behaviors, anxiety, and depression. Due to marked functional and academic impairment, severe comorbidity, and lack of response to conventional treatment, the patient received bilateral DBS of the posteroventral GPi, despite his young age. At the 6-month follow-up, an 84% tic reduction was reported, with improvement in comorbidities and quality of life.

In 2008, Dehning et al.¹⁴ described the effects of bilateral stimulation of the posteroventral GPi in a 44-year-old woman with worsening treatment-refractory TS, self-mutilating behaviors, and compulsions. During a 12-month follow-up period, the patient experienced full remission of tics. Reported side effects included depression, vertigo, and stomach aches. The authors later reported on 3 other patients who received bilateral DBS of the posteroventral GPi.¹³ At 12 months after surgery, 1 patient experienced a 64% reduction in tics. However, the other 2 patients experienced no benefit from DBS and stimulation was eventually stopped.

A larger cohort of 5 patients was evaluated by Martínez-Fernández et al.³⁶ Three patients underwent bilat-

eral DBS of the posteroventral GPi and 2 patients received bilateral stimulation of the anteromedial GPi. One of the patients in the posteroventral GPi group experienced worsening tics after 18 months of stimulation, so electrodes were repositioned to the anteromedial GPi. One year following the second surgery, this patient had a marked decrease in motor and vocal tics. Follow-up in the other patients ranged from 3 to 24 months. A mean 29% reduction in tic severity was observed, along with a 26% decrease in obsessive-compulsive symptoms and 54.4% improvement in reported quality of life.

More recently, Cannon et al.⁹ reported on bilateral DBS of the anteromedial GPi in 11 patients with disabling, treatment-refractory TS. The authors assessed the effect of DBS on tic severity, obsessive-compulsive behaviors, depression, quality of life, and global functioning. One patient reported an increase in tics and adverse side effects, so the stimulator was switched off after 3 months. The other 10 patients reported a decrease in the number, severity, frequency, and intensity of tics. Final follow-up ranged from 4 to 30 months (mean 14 months) among patients. Motor and vocal tics were reduced by a mean 53% and 62%, respectively. Total tic severity decreased by 49.6%. The 9 patients who experienced obsessive-compulsive symptoms prior to surgery reported a mean 59% decrease in symptoms at final follow-up. There was a significant improvement in quality of life and global functioning, as well as a significant (74%) reduction in depressive symptoms. Besides the 1 patient, no adverse side effects were reported. Three patients experienced hardware malfunctions, with worsening tics when stimulation was not present. One patient developed an infection and 2 patients reported feelings of anxiety.

There have also been reports of DBS targeting the GPe. In 2013, Piedimonte et al.⁴⁴ implanted electrodes bilaterally at the GPe in a 47-year-old patient with disabling, intractable TS. At the 3-month follow-up, the patient showed a 57.5% improvement in tic severity, 50% improvement in anxiety symptoms, 58.8% improvement in depressive symptoms, and 36.4% improvement in global functioning. At the 6-month follow-up, tic severity, anxiety, and depression were improved by 70.5%, 75%, and 82.3%, respectively. Global functioning remained stable. Two years following surgery, the battery life was exhausted and could not be replaced due to financial reasons. Without stimulation, symptoms returned and a reduction in therapeutic effect was observed.

Anterior Limb of the Internal Capsule/Nucleus Accumbens

In 2005, Flaherty et al.¹⁷ published a case report of a 37-year-old patient with severe treatment-refractory TS, OCD, ADHD, and depression who received bilateral DBS of the ALIC-NA (Table 3). This trajectory was chosen based on the relative success in using DBS at this location to treat OCD.⁴² After 18 months, global tic severity had decreased by 20%.

In 2007, Kuhn et al.²⁹ described a patient with treatment-refractory TS and severe OCD who underwent bilateral stimulation of the ALIC-NA. A 40%–50% reduction in tic severity was observed at 2.5 years after surgery. Self-injurious behaviors and OCD symptoms were also

significantly reduced. In the following year, Zabek et al.⁶³ reported on the 28-month follow-up of unilateral DBS of the right NA in a single patient with severe intractable TS, self-injurious behaviors, and compulsions. At follow-up, there was a significant reduction in tics, self-injurious behavior, and compulsions. The total number of tics decreased from 236 to 48.

Long-term follow-up in a patient who received bilateral DBS of the ALIC-NA was reported by Neuner et al.⁴¹ At 36 months after surgery, there was a 44% reduction in tic severity. Self-injurious behavior had ceased and OCD symptoms were markedly decreased. More recently, Sachdev et al.⁴⁹ described a 42-year-old patient with TS and “incapacitating” OCD who failed to respond to standard pharmacological and psychobehavioral therapies. The authors opted for DBS of the NA because OCD symptoms were the most debilitating. At the 1-month follow-up, a 57% improvement in tic severity and 90% improvement in OCD symptoms were reported. These benefits were sustained at the 7-month follow-up, with further improvement in tic severity.

Subthalamic Nucleus

In 2009, Martinez-Torres et al.³⁷ performed bilateral DBS of the subthalamic nucleus in a 38-year-old patient with TS and Parkinson’s disease (PD) (Table 3). Tics began at the age of 7 and improved by the age of 12. However, tics increased during adulthood, prior to the diagnosis of PD. No medication for tics was ever prescribed. The subthalamic nucleus was chosen because it is commonly targeted in DBS for PD.²⁴ One year after surgery, there was a 57% improvement in motor symptoms of PD and 97% decrease in tic frequency. While DBS was performed mainly to treat symptoms of PD, the significant reduction in tic frequency observed suggests that the subthalamic nucleus could be a potential target for DBS in treating TS in the future.

Discussion

Tourette’s syndrome is characterized by variable clinical phenotypes and the level of severity and impairment differs among patients. In most cases, TS is self-limiting, but for a small percentage of patients tics persist in adulthood and conventional treatments prove ineffective. For these patients, DBS has been shown to be an effective and promising treatment option.

Most of the literature available regarding DBS for TS is case reports or small case series focusing on the use of a single target. The study by Servello et al.⁵³ allows for examination of a much larger cohort of patients, as well as comparison between multiple target sites. The primary target used by the authors was the medial thalamus (CM-Pf-Voi). Evidence suggests that a dysfunction of striatal-thalamic-cortical circuits plays an underlying role in the generation of tics.¹⁹ Inputs of the CM-Pf complex to the striatum modulate sensorimotor and limbic circuitry and DBS of this target may suppress excitatory feedback to motor and limbic parts of the striatum involved in the production of tics.⁵⁰ In the same study,⁵³ DBS of the posteroventral GPi was performed to address dystonic tics

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TABLE 3: Other DBS targets for TS

Authors & Year	No. of Patients	Target	Follow-Up	Outcomes
Flaherty et al., 2005	1	ALIC-NA	18 mos	20% decrease in global tic severity
Kuhn et al., 2007	1	ALIC-NA	2.5 yrs	40%–50% tic reduction
Zabek et al., 2008	1	unilateral right NA	28 mos	total no. of tics reduced from 236 to 48
Shields et al., 2008	1	ALIC-NA (later revised to thalamus)	18 mos	21% reduction in tics, 25% improvement in overall impairment
Neuner et al., 2009	1	ALIC-NA	36 mos	44% tic reduction
Martinez-Torres et al., 2009	1	subthalamic nucleus	1 yr	97% decrease in tic frequency
Sachdev et al., 2012	1	NA	7 mos	score reductions: 63 to 13 (YGTS) 39 to 6 (YBOCS)

in 1 patient based on reported benefits of DBS for dystonia.³⁴ The execution of tics in TS is believed to be caused by overactivity of striatal neurons that cause altered output to the GPi and substantia nigra pars reticulata.³⁹ Thus, targeting the GPi in DBS may counteract overactive striatal output in patients with TS.

Interestingly, Servello et al.⁵³ also performed a second “rescue surgery” targeting the ALIC-NA in a number of patients who continued to experience impairment from other comorbidities. This was performed on the basis that DBS of the ALIC-NA has been shown to successfully treat patients with OCD.²⁰ As behavioral comorbidities may have a greater impact on functioning and quality of life than tics, this target may be a better choice in such TS patients. Furthermore, the ALIC contains extensive frontothalamic and frontostriatal projections and stimulation of this area may provide a beneficial effect in TS patients by influencing striatal-thalamic-cortical circuitry.¹⁷

Studies comparing the use of 1 target over another remain sparse and have produced contradictory results. A within-subject comparison⁵⁵ revealed greater tic reduction and fewer side effects with stimulation at the medial thalamus versus the ALIC-NA, suggesting the medial thalamus as the preferable target for DBS in treating TS. Houeto et al.²³ found similar improvements in tic severity following stimulation of the GPi, thalamus, or both. However, thalamic stimulation was shown to have a greater effect on the improvement of mood symptoms. On the other hand, Welter et al.⁶² reported the greatest tic reduction upon stimulation of the GPi compared with the medial thalamus, with no added benefit from combined stimulation. Clearly, more research is needed to replicate these results and sort out contradictory findings.

Further controversy in the treatment of TS with DBS arises when determining stimulation parameters following surgery. No definitive guidelines for programming exist and are largely based on trial and error. Optimal settings vary largely from patient to patient. In the available literature, optimal stimulation parameters for DBS of the medial thalamus revealed amplitudes ranging from 1.5 to 8.5 V, pulse widths between 60 and 210 μ s, and frequencies of 60–185 Hz.^{1,2,4,26,33,51–53,55} Parameters for pallidal stimulation that afforded the best results ranged from 1 to 5 V, 60 to 300 μ s, and 20 to 185 Hz.^{9,13–15,36,54,59} For stimulation of the ALIC-NA, optimal parameters ranged

from 3 to 7 V, 60 to 210 μ s, and 130 to 185 Hz.^{17,29,41,49,63} Alterations to stimulation parameters are made at the discretion of the surgeon and are largely based upon how the individual patient responds clinically.

Deep brain stimulation holds promise for the treatment of TS. The medial thalamus is the most widely used target, but increasing evidence supports the use of the GPi and ALIC-NA as well. The lack of randomized, controlled trials makes definitive conclusions about the relative efficacy of one target over another impossible. While future research is warranted, the small number of patients with intractable TS limits the ability to conduct such studies. Future research should aim to include larger sample sizes and employ standardized methods of evaluation, surgical techniques, outcome measurements, and follow-up periods.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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