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

Maria G. Motlagh1*, Megan E. Smith1, Angeli Landeros-Weisenberger1, Andrew J. Kobets2, Robert A. King1, Joan Miravite3, Alain C. J. de Lotbinie`re4, Ron L. Alterman5, Alon Y. Mogilner6, Michael H. Pourfar6, Michael S. Okun7 & James F. Leckman1

1 Child Study Center, Yale University, New Haven, Connecticut, United States of America, 2 Department of Neurosurgery, Montefiore Medical Center, Bronx, New York, United States of America, 3 Department of Neurology, Beth Israel, New York, New York, United States of America, 4 Department of Neurosurgery, New York College of Medicine, Valhalla, New York, United States of America, 5 Division of Neurosurgery, Beth Israel Deaconess Medical Center, Harvard University, Boston, Massachusetts, United States of America, 6 Departments of Neurosurgery and Neurology, New York University, Langone Medical Center, New York, New York, United States of America, 7 Departments of Neurology and Neurosurgery, Center for Movement Disorders & Neurorestoration, University of Florida, Gainesville, Florida, United States of America

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

Citation: Motlagh MG, Smith ME, Landeros-Weisenberger A, et al. Lessons learned from open-label deep brain stimulation for Tourette syndrome: eight cases over 7 years. Tremor Other Hyperkinet Mov 2013; 3: http://tremorjournal.org/article/view/170

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).5–12

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 impai 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            | 12, 12            | Tic 20 3 min, Tic 28 2 min          |
|                            | Ackermans et al. (2007)¹¹  | 1            | 3–18              | 65 (Mean)                           |
|                            | 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              | 52 (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 (same cases) | 52 (Mean) 41, 33, 32, 18, 1 |
|                            | Porta et al. (2012)³⁴       | 4            | 10–26             | Slight to modest improvement        |
|                            | Idris et al. (2010)²⁸       | 1            | 2                 | Not reported                        |
|                            | Marcegla 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)¹⁷      | 5            | 4–6               | 41, 33, 32, 18, 1                   |
|                            | Okun et al. (2013)⁴¹        | 5            | 6                 | 19 (Mean)                           |
| GPi                        | Deiderich et al. (2005)⁶    | 1            | 14                | 47–76                               |
|                            | Gallagher et al. (2006)⁹    | 1            | Several           | Disappearance of tics               |
|                            | Ackermans et al. (2006)¹⁰  | 1            | 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                      |
|                            | Martinez-Fernández et al. (2011)³¹ | 5 (one subject had both), 3 (anteromedial) | 3–24 | 32, 19, 14, 63, 32, 19 |
|                            | Cannon et al. (2012)³³      | 11 (anteromedial) | 4–30             | 51                                  |
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. We administered additional rating scales at baseline, including the Yale Global Tic Severity Scale (YGTSS), the Yale–Brown Obsessive–Compulsive Scale, the Hamilton Depression Rating Scale, and the Hamilton Anxiety Rating Scale. 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. 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
| 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 μs, 185 Hz |
|         |          |                                      | *L 1-3+, 2.35 V, 180 μs, 185 Hz |
|         | X (mm lateral AC-PC)=5 |                                      |              |
|         | Y (mm posterior AC-PC)=4 |                                      |              |
|         | Z (mm beneath AC-PC)=0 |                                      |              |
|         | GPi (posteroventral/sensorimotor) |                                      |              |
|         | X (mm lateral to intercommissural)=17 |                                      |              |
|         | Y (mm anterior to mid-comissural)=4 |                                      |              |
|         | Z (mm deep to mid-comissural)=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 μs, 185 Hz |
|         | X (mm lateral to intercommissural)=17 |                                      | L 2-C+, 2.0 V, 90 μs, 185 Hz |
|         | Y (mm anterior to mid-comissural)=4 |                                      |              |
|         | Z (mm deep to mid-comissural)=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 μs, 185 Hz |
|         | X (mm lateral to intercommissural)=17 |                                      | L 2-1-0-C+, 2.1 V, 180 μs, 185 Hz |
|         | Y (mm anterior to mid-comissural)=4 |                                      |              |
|         | Z (mm deep to mid-comissural)=5 |                                      |              |
| 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 1-C+, 3.0 V, 90 μs, 130 Hz |
|         |          |                                      | L 1-C+, 3.2 V, 90 μs, 130 Hz |
|         | X (mm lateral AC-PC) = 5 |                                      |              |
|         | 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 1-C+, 3.0 V, 150 μs, 90 Hz |
|         |          |                                      | L 1-C+, 2.5 V, 180 μs, 120 Hz |
|         | X (mm lateral to intercommissural) = 14 |                                      |              |
|         | Y (mm anterior to mid-commissural) = 18 |                                      |              |
|         | Z (mm deep to mid-commissural) = 5 |                                      |              |
|         | Thalamus |                                      |              |
|         | X (mm lateral AC-PC) = 6 |                                      |              |
|         | Y (mm posterior AC-PC) = 3 |                                      |              |
|         | Z (mm beneath AC-PC) = 0 |                                      |              |
|         | GPi (posteroventral/sensorimotor) |                                      |              |
|         | X (mm lateral to intercommissural) = 17 |                                      |              |
|         | 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 remifentanil | R C+1-, 2.1 V, 90 μs, 130 Hz |
|         |          |                                      | L C+1-, 1.9 V, 90 μs, 130 Hz |
|         | X (mm lateral AC-PC) = 5 |                                      |              |
|         | Y (mm posterior AC-PC) = 4 |                                      |              |
|         | Z (mm beneath AC-PC) = 0 |                                      |              |
Deep Brain Stimulation for Tourette Syndrome

Motlagh MG, Smith ME, Landeros-Weisenberger A, et al

Dystonia. Here, too, younger patients and those who had not yet 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 observations suggesting 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.

**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 (µs), and rate (Hz).

*GPi electrodes are not currently functional secondary to forceful head-snapping tics that led to electrode dysfunction.  
*Electrodes were removed because of lack of therapeutic benefit.  
*Electrodes 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 progressive and aggressive spinal injury secondary to an extremely forceful whole-body and head-snapping tic. 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. 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. 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.

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. 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. 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 pathophysiology 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. 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.

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. 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 |
|---------|-----|-------------|--------------------------|--------------|---------------------------------|------------|-------------------|----------------|--------------------------|--------------------------|---------------------|
| 1       | 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       | 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 |

* Motlagh MG, Smith ME, Landeros-Weisenberger A, et al. Deep Brain Stimulation for Tourette Syndrome. Tremor and Other Hyperkinetic Movements. 2009;3:389-394.
| 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        |
| 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, coprolalia, loud screaming, sniffing | Yes | 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 | ADHD | No | Unmarried, high-school student | Risperidone, aripiprazole, ziprasidone, sertraline, tetrabenazine, methylphenidate, topiramate | None |
| 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 | No | OCD, some symptoms of ADHD | No | Unmarried, unemployed | Haloperidol, risperidone, aripiprazole, fluphenazine, sertraline, clonazepam, topiramate, etanercept, N-acetyl cysteine | Haloperidol, clonazepam, clonidine, clonazepam, sertraline, carbamazepine |

Deep Brain Stimulation for Tourette Syndrome

Motlagh MG, Smith ME, Landers-Weisenberger A, et al

http://www.tremorjournal.org

The Center for Digital Research and Scholarship
Columbia University Libraries/Information Services
| 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 | 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.

---

1 The electrodes removed due to side effect of infection.
2 The electrodes removed due to a lack of therapeutic benefit.
Parkinson’s disease 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. 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.

### 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.

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. 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.’

Acknowledgment

The authors thank the study families and participants for taking part in this study. The authors also wish to thank Nancy Thompson for her invaluable assistance in completing this study.

References

1. Centini J, Woods DW, Scahill I, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA 2010;303:1929–1937.
2. Helm S, Peterson AL, Piacentini J, et al. Randomized trial of behavior therapy for adults with Tourette syndrome. Arch Gen Psychiatry 2012;69:795–803.
3. Ger HS. Treatment of tics and Tourette syndrome. Curr Treat Options Neurol 2010;12:539–561.
4. Weisman H, Qureshi IA, Leckman JF, Scahill L, Bloch MH. Systematic review: pharmacological treatment of tic disorders—efficacy of antipsychotic and alpha-2 adrenergic agonist agents. Neuropsychopharmacology 2013;37:1162–1171.
5. Visser-Vandewalle V, Temel Y, Boon P, et al. Chronic bilateral thalamic stimulation: a new therapeutic approach in intractable Tourette syndrome. J Neuropsychiatr Clin Neurosci 2008;20:1496–1499.
6. Diederich NJ, Kalteis K, Stamenkovic M, Pieri V, Alesch F. Efficient internal pallidal stimulation in Gilles de la Tourette syndrome: a case report. Mov Disord 2005;20:1496–1499.
7. Houeto JL, Karachi C, Mallet L, et al. Tourette’s syndrome and deep brain stimulation. J Neurol Neurosurg Psychiatry 2005;76:992–995.
8. Flaherty AW, Williams ZM, Amirnovin R, et al. Deep brain stimulation of the anterior internal capsule for the treatment of Tourette syndrome: technical case report. Neurosurgery 2005;57:E403.
9. Gallagher CL, Garel PC, Montgomery EB. Hemi tics and deep brain stimulation. Neurology 2006;66:E12.
10. Ackermans I, Temel Y, Cath D, et al. Deep brain stimulation in Tourette’s syndrome: two targets? Mov Disord 2006;21:709–713.
11. Ackermans I, Temel Y, Bauer NJ, Visser-Vandewalle V; Dutch-Flemish Tourette Surgery Study Group. Vertical gaze palsy after thalamic stimulation for Tourette syndrome: case report. Neurosurgery 2007;61:E1100.
12. Bajwa RJ, de Lotbiniere AJ, King RA, et al. Deep brain stimulation in Tourette’s syndrome. Mov Disord 2007;22:1346–1350.
13. Kuhn J, Lenartz D, Mai JK, et al. Deep brain stimulation of the nucleus accumbens and the internal capsule in therapeutically refractory Tourette-syndrome. J Neurol 2007;254:963–965.
14. Maciunas RJ, Maddux BN, Riley DE, et al. Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome. J Neuropsychiatry Clin Neurosci 2007;19:1004–1014.
15. Shahed J, Ponsky J, Kemey C, Simpson R, Jankovic J. GPi deep brain stimulation for Tourette syndrome improves tics and psychiatric comorbidities. Neurology 2007;68:159–160.
16. Dehning S, Mehrkens JH, Müller N, Bütz K. Therapy-refractory Tourette syndrome: beneficial outcome with globus pallidus internus deep brain stimulation. Mov Disord 2008;23:1300–1302.
17. Servello D, Porta M, Sassi M, Brambilla A, Robertson MM. Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation. J Neurol Neurosurg Psychiatry 2008;79:136–142.
18. Weiler M, Mallet L, Houeto J, et al. Internal pallidal and thalamic stimulation in patients with Tourette syndrome. Arch Neurol 2008;65:952–957.
19. Zabek M, Sobstyl M, Koziara H, Dzierzecki S. Deep brain stimulation of the right nucleus accumbens in a patient with Tourette syndrome. Case report. Neurologia 2008;14:554–559.
20. Shields DC, Cheng ML, Flaherty AW, Gale JT, Eskandar EN. Microelectrode-guided deep brain stimulation for Tourette syndrome: withinsubject comparison of different stimulation sites. Stereotact Funct Neurosurg 2008;86:87–91.
21. Vernaleken I, Kuhn J, Lenartz D, et al. Bithalamic deep brain stimulation in Tourette syndrome is associated with reduction in dopaminergic transmission. Biol Psychiatry 2009;66:e15–e17.
22. Dueck A, Wolters A, Wunsch K, et al. Deep brain stimulation of globus pallidus internus in a 16-year-old boy with severe Tourette syndrome and mental retardation. Neuropediatrics 2010;40:259–242.
23. Martinez-Torres I, Hariz MI, Zrinzo L, Foltynie T, Limousin P. Improvement of tics after subthalamic nucleus deep brain stimulation. Neurology 2009;72:1787–1789.
24. Neumer I, Podoll K, Janoušek H, Michel TM, Sheldrck AJ, Schneider F. From psychosurgery to neuromodulation: deep brain stimulation for intractable Tourette syndrome. World J Biol Psychiatry 2009;10:366–376.
25. Porta M, Brambilla A, Cavanna AE, et al. Thalamic deep brain stimulation for treatment-refractory Tourette syndrome: two-year outcome. Neurology 2009;73:1375–1380.
26. Servello D, Sassi M, Brambilla A, et al. De novo and rescue DBS leads for refractory Tourette syndrome patients with severe comorbid OCD: a multiple case report. J Neurol 2009;256:1533–1539.
27. Burdick A, Foote KD, Goodman W, et al. Lack of benefit of accumbens/capsular deep brain stimulation in a patient with both tics and obsessive-compulsive disorder. Neurocase 2010;16:321–330.
28. Idris Z, Ghani AR, Mar W, et al. Intracerebral haematomas after deep brain stimulation surgery in a patient with Tourette syndrome and low factor XIIIa activity. J Clin Neurosci 2010;17:1343–1344.
29. Marceglia S, Servello D, Foffani G, et al. Thalamic single-unit and local field potential activity in Tourette syndrome. Mov Disord 2010;25:300–308.
30. Ackermans I, Duits A, van der Linden C, et al. Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. Mov Disord 2010;25:300–308.
31. Martínez-Fernández R, Zrinzo L, Aviles-Olmos I, et al. Deep brain stimulation for Gilles de la Tourette syndrome: a case series targeting subregions of the globus pallidus internus. Mov Disord 2011;26:1002.
32. Lee MW, Au-Yeung MM, Hung KN, Wong CK. Deep brain stimulation in a Chinese Tourette’s syndrome patient. Hong Kong Med J 2011;17:147–150.
33. Cannon E, Silburn P, Coyne T, O’Maley K, Crawford JD, Sachdev PS. Deep brain stimulation of anteromedial globus pallidus interna for severe Tourette’s syndrome. Am J Psychiatry 2012;169:860–866.
34. Porta M, Servello D, Zanaboni C, et al. Deep brain stimulation for treatment of refractory Tourette syndrome: long-term follow-up. Acta Neurochir (Wien) 2012;154:2029–2041.

35. Kuhn J, Janouschek H, Raptis M, et al. In vivo evidence of deep brain stimulation-induced dopaminergic modulation in Tourette’s syndrome. Biol Psychiatry 2012;71:e1–e13.

36. Savica R, Stead M, Mack KJ, Lee KH, Klassen BT. Deep brain stimulation in Tourette syndrome. Mayo Clin Proc 2012;87:59–62.

37. Malini N, Hashemiyouoon R, Foote KD, Okun MS, Sanchez JC. Increased thalamic gamma band activity correlates with symptom relief following deep brain stimulation in humans with Tourette’s syndrome. PLoS One 2012;7:e44215.

38. Sachdev PS, Cannon E, Coyne TJ, Silburn P. Bilateral deep brain stimulation of the nucleus accumbens for comorbid obsessive compulsive disorder and Tourette’s syndrome. BMJ Case Rep 2012;2012.

39. Dong S, Zhuang P, Zhang XH, Li JY, Li YJ. Unilateral deep brain stimulation of the right globus pallidus internus in patients with Tourette’s syndrome: two cases with outcomes after 1 year and a brief review of the literature. J Int Med Res 2012;40:2021–2028.

40. Pecidimonte F, Andreanti JC, Pecidimonte I, et al. Behavioral and motor improvement after deep brain stimulation of the globus pallidus externus in a case of Tourette’s syndrome. Neuromodulation 2013;16:53–58.

41. Okun MS, Foote KD, Wu SS, et al. A trial of scheduled deep brain stimulation for Tourette syndrome: moving away from continuous deep brain stimulation paradigms. JAMA Neurol 2013;70:85–94.

42. Massano J, Sousa C, Faltynek TR, Zrinzo I, Hariz M, Vaz R. Successful pallidal deep brain stimulation in 15-year-old with Tourette syndrome: 2-year follow-up. J Neurol 2013;260:2417–9.

43. Mink JW, Walkup J, Frey KA, et al. Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome. Mov Disord 2006;21:1831–1838.

44. Muller-Vahl KR, Cath DC, Cavanna AE, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part IV: deep brain stimulation. Eur Child Adolesc Psychiatry 2011;20:209–217.

45. Lozano AM. Globus pallidus internus pallidotomoy for generalized dystonia. Mov Disord 1997;12:863–870.

46. Ondo W, Jankovic J, Schwartz K, Almaguer M, Simpson RK. Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson’s disease. Neurology 1998;51:1063–1063.

47. Porta M, Sassi M, Ali F, Cavanna AE, Servello D. Neurosurgical treatment for Gilles de la Tourette syndrome: the Italian perspective. J Psychosom Res 2009;67:585–590.

48. Hariz MI, Robertson MM. Gilles de la Tourette syndrome and deep brain stimulation. Eur Neurol 2010;32:1128–1134.

49. Sassi M, Porta M, Servello D. Deep brain stimulation therapy for treatment-refractory Tourette’s syndrome: a review. Acta Neurochir (Wien) 2011;153:639–645.

50. Bronstein JM, Tagliati M, Alterman RL, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. Arch Neurol 2011;68:165.

51. American Psychiatric Association. American Psychiatric Association. Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders, 4th ed., text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.

52. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry 1989;28:566–573.

53. Goodman WK, Price LH, Rasmussen SA, et al. (1989). The Yale-Brown Obsessive Compulsive Scale. Arch Gen Psychiatry 1989;46:1006–1011.

54. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296.

55. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychology 32:50–56.

56. Porta M, Servello D, Sassi M, et al. Issues related to deep brain stimulation for treatment-refractory Tourette’s syndrome. Eur Neurol 2009;62:264.

57. Porta M, Sassi M, Menghetti C, Servello D. The need for a proper definition of “treatment refractoriness” in Tourette syndrome. Front Integr Neurosci 2011;5:22.

58. Porta M, Sassi M, Servello D. Surgical treatment of Tourette syndrome. In: Martino D, Leckman JF (eds). Tourette syndrome. Oxford, UK: Oxford University Press; 2015; pp. 383–604.

59. Bressman S. Treatment of generalized dystonia. Curet Treat Options Neurol 2011;13:274–289.

60. Labarr N, Bressman S. Treatment of generalized dystonia. Curet Treat Options Neurol 2011;13:274–289.

61. Bloch MH, Peterson BS, Scabhill L, et al. Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. Arch Pediatr Adolesc Med 2006;160:65–69.

62. Chang HL, Liang HY, Wang HS, Li CS, Ko NC, Hsu YP. Behavioral and emotional problems in adolescents with Tourette syndrome. Chang Gung Med J 2008;31:145–152.

63. Leckman JF, Bloch MH, Scabhill I, King RA. Tourette syndrome: the self under siege. J Child Neurol 2006;21:642–649.

64. Mink JW. Basal ganglia dysfunction in Tourette’s syndrome: a new hypothesis. Pediatr Neurol 2001;25:190–198.

65. Bohilhalter S, Goldfine A, Matteson S, et al. Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study. Brain 2006;129:2029–2037.

66. Lerner A, Bagic A, Boudreau EA, et al. Neuroimaging of neuronal circuits involved in tic generation in patients with Tourette syndrome. Neurology 2007;68:1979–1987.

67. Hampson M, Tokoglu F, King RA, Constable RT, Leckman JF. Brain areas coactivating with motor cortex during chronic motor tics and intentional movements. Biol Psychiatry 2009;65:594–599.

68. Church JA, Fair DA, Dosenbach NU, et al. Control networks in paediatric Tourette syndrome show immature and anomalous patterns of functional connectivity. Brain 2009;132:225–38.

69. Pourfar M, Feigin A, Tang CC, et al. Abnormal metabolic brain networks in Tourette syndrome. Neurology 2011;76:944–952.

70. Zebardast N, Crowley MJ, Bloch MH, Mayes LC, Leckman JF, Pelphrey KA, Swain. Brain mechanisms for prepulse inhibition in adults with Tourette syndrome: initial findings. Psychiatry Res 214:33–41.

71. Katoaka Y, Kalanithi PS, Grantz H, et al. Decreased number of parvalbumin and cholinergic interneurons in the striatum of individuals with Tourette syndrome. J Comp Neurol 2010;518:277–291.
72. McCaig K, Imamura Y, Isoda M. Animal models of tics. In: Martino D, Leckman JF (eds). Tourette syndrome. Oxford, UK: Oxford University Press; 2013; pp. 329–358.

73. Jankovic J. Tourette’s syndrome. N Engl J Med 2001;345:1184–1192.

74. Vitek JL, Chockkan V, Zhang JY, et al. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. Ann Neurol 1999;46:22–35.

75. Marsden CD, Obeso JA. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson’s disease. Brain 1994;117:877.

76. Hutchison WD, Lang AE, Dostrovsky JO, Lozano AM. Pallidal neuronal activity: implications for models of dystonia. Ann Neurol 2003;53:480–488.

77. Zhuang P, Li Y, Hallett M. Neuronal activity in the basal ganglia and thalamus in patients with dystonia. Clin Neurophysiol 2004;115:2542–2557.

78. Zhuang P, Hallett M, Zhang X, Li J, Zhang Y, Li Y. Neuronal activity in the globus pallidus internus in patients with tics. J Neurol Neurosurg Psychiatry 2009;80:1075–1081.

79. Marceglia S, Servello D, Foffani G, et al. Thalamic single-unit and local field potential activity in Tourette syndrome. Mov Disord 2010;15:300–308.

80. Servello D, Sassi M, Gaeta M, Ricci C, Porta M. Tourette syndrome bears a higher rate of inflammatory complications at the implanted hardware in deep brain stimulation. Acta Neurochir (Wien) 2011;153:629–632.

81. Murphy TK, Kurlan R, Leckman J. The immunobiology of Tourette’s disorder, pediatric autoimmune neuropsychiatric disorders associated with Streptococcus, and related disorders: a way forward. J Child Adolesc Psychopharmacol 2010;20:317–331.