Deep Brain Stimulation in Tourette's Syndrome

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Summary: Tourette's Syndrome (TS) is a neuropsychiatric disorder characterized by motor and vocal tics, often associated with behavioral disorders. Symptoms often disappear before or during adulthood. The pathophysiology of TS is still a matter of considerable debate. Current knowledge of cortico-basal ganglia-thalamocortical circuits provide explanations for the beneficial effects of deep brain stimulation (DBS) on tics. When conservative treatment fails in patients

with severe TS, DBS may be a therapeutic option. In 1999, thalamic DBS was introduced for intractable TS. Since then, multiple targets have been used in a small number of patients, including the globus pallidus pars interna and the nucleus accumbens. Inclusion and exclusion criteria have been formulated to identify good candidates for DBS. **Key Words:** DBS, Tourette's syndrome, tics, stimulation, thalamus.

INTRODUCTION

Georges Gilles de la Tourette first described TS in 1885 as "a nervous affection characterized by lack of motor coordination accompanied by echolalia and coprolalia," and Charcot later named the condition Tourette's syndrome (TS).¹ TS is a chronic complex neuropsychiatric disorder characterized by tics. Tics are sudden, repetitive, stereotyped muscle contractions (motor tics) or sounds (vocal tics) produced by moving air through the nose, mouth, or throat.² Tics can be seen as fragments of normal motor action or vocal productions that are misplaced in context and that can be easily mimicked and at times confused with goal-directed behavior.³ Tics may be abrupt in onset, fast and brief (clonic tics), or may be slow and sustained (dystonic or tonic tics).⁴ The motor patterns of tics may involve individual muscles or small groups of muscles with discrete contractions (simple tics) such as eye blinking, facial grimacing, sniffing, or throat clearing. With complex tics, more muscles are acting in a coordinated pattern to produce more complicated movements that may resemble purposeful voluntary movements.² Complex tics include head shaking, scratching, throwing, touching, and uttering phrases. Coprolalia, or uttering obscene

words, one of the most distressing and recognizable symptoms, occurs in only 10% of patients.

The frequency and intensity of tics are typically worse during periods of excitement and fatigue. Tics are often more frequent and forceful when the individual is alone.⁵ On the other hand, tics are routinely less frequent and forceful during periods when selective attention and fine motor control are required. Tics may in some cases be temporarily suppressed by an effort of will or concentration, but then may rebound afterwards.⁶

Tics usually begin in the first decade of life, with a mean age of 7 years.³ The first tics are usually motor tics, with brief bouts of transient tics involving the face or head. The severity of tics typically increases during the prepubescent years, but then the majority of patients improve spontaneously as they reach adulthood.

An important feature of TS is its association with a wide range of comorbid behavioral abnormalities. More than half of all children and adolescents with TS show evidence of psychiatric comorbidity, exhibiting symptoms of attention-deficit hyperactivity disorder, obsessive-compulsive behavior, and other anxiety and mood disorders.³ When present, these coexisting conditions can add greatly to the morbidity associated with TS and have a negative impact on the overall quality of life.⁷

The occurrence of attention-deficit hyperactivity disorder in TS patients ranges from 21% to 90% of clinical populations.³ Symptoms consist of inattention and distractibility, with or without behavioral hyperactivity. Ob-

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sessive–compulsive behavior may occur in up to 50% of TS patients. The more severe obsessions in TS may involve sexual, violent, religious, aggressive, and symmetrical themes; the compulsions may manifest with symptoms such as checking, counting, forced touching, and self-damage. As with tics, symptoms of obsessive–compulsive behavior often wax and wane during the course of the illness. Robertson³ reported that more than one-third of clinical TS patients exhibited self-injurious behavior. The most frequent type of self-injurious behavior was head-banging.

Although once thought to be rare, TS is now recognized as a relatively common disorder with an estimated worldwide prevalence of 4 to 5 in 10,000. It occurs three to four times more commonly in males.⁸ There is considerable variation among studies reporting on the prevalence of TS, which is most likely due to variations in sex, age, diagnostic criteria, and assessment methods.⁹

TREATMENT

Conservative treatment

For many patients, especially those with mild symptomatology, psychobehavioral strategies are sufficient. Pharmacological treatment may be considered when symptoms begin to interfere with social interactions, academic or job performance, or activities of daily living. At present, pharmacotherapy is the mainstay of treatment for tics, mainly involving neuroleptic medications, α_2 -adrenergic agonists, and dopamine agonists, as well as local injections of botulinum toxin.³ Selective serotonin reuptake inhibitors are recommended for the treatment of obsessive–compulsive behavior. Psychostimulants, such as methylphenidate, are the treatment of choice for attention deficit hyperactivity disorder.³

Surgical treatment: a historical note

For patients refractory to any medical treatment, surgery may be the treatment of last resort.¹⁰ Several attempts have been made to treat patients with TS through neurosurgical ablative procedures.¹¹ Diverse target sites have included the frontal lobe (prefrontal lobotomy and bimedial frontal leucotomy), the limbic system (limbic leucotomy and anterior cingulotomy), the thalamus, and the cerebellum. Combined approaches have also been tried, such as both anterior cingulotomy and infrathalamic lesions. In most of these studies, patient selection was not standardized, assessments typically were not blinded, and outcome was not quantified. The results were often unsatisfactory, or major side effects, such as hemiplegia or dystonia, occurred.

Deep brain stimulation (DBS) was first introduced as a surgical technique for the treatment of intractable TS in 1999. Vandewalle et al.¹² selected a trajectory that included the centromedian and ventral oral internal tha-

lamic nuclei and the substantia periventricularis (based on the thalamotomies described by Hassler and Dieckmann¹³ in 1970).

In 2003, the same group described the promising effects of bilateral thalamic DBS in three patients in greater detail.¹⁴ Over a follow-up period of 5 years, 1 year, and 8 months, respectively, in the three patients, there was an improvement in both tic reduction (72%–90%) and in associated behavioral disorders. Stimulation-induced side effects consisted of a sensation of reduced energy and changes in sexual functioning.^{14,15}

NEUROANATOMICAL BASIS FOR DBS IN TS

The pathophysiology of TS is still a matter of considerable debate. A growing body of evidence indicates that an abnormality in corticostriothalamocortical circuits and their neurotransmitter systems is likely to underlie tics and coexisting problems in TS. Evidence supporting a dopaminergic abnormality in TS comes from therapeutic responses to neuroleptics, preliminary data from post-mortem studies, and a variety of nuclear imaging protocols.¹⁶

Within the brain, there are anatomically segregated, parallel circuits representing different functions: motor, oculomotor, cognitive, and limbic. These basal ganglia circuits traverse the cortex, striatum, globus pallidus, and thalamus. Each circuit includes a direct and an indirect pathway. It is hypothesized that disinhibition of excitatory neurons in the thalamus results in hyperexcitability of cortical motor areas in the release of tics. If TS is associated with excessive dopaminergic activity, whether via supersensitive dopamine receptors, dopamine hyperinnervation, or abnormal presynaptic terminal function, it inhibits the indirect pathway, leading to an overactivity of thalamocortical drive.¹⁷

In addition to short-term effects, dopamine can modulate corticostriatal transmission by the mechanism of long-term depression or potentiation. Dopamine-inducing fluctuating abnormalities in the resting potential of striatal neurons have been hypothesized to influence the waxing and waning of tics. This could be an explanation for the lack of identifiable abnormalities in dopamine transmission. Alterations in striatal function have also been demonstrated in TS patients on functional MRI during active tic suppression, with a decreased activity in putamen, ventral globus pallidus, and thalamus bilaterally, and an increased activity of the head of the right caudate nucleus, and frontal and temporal cortices.¹⁸

Other cortical–subcortical loops may also be implicated in TS pathophysiology. The excitatory feedback loops from the thalamus toward the striatum, originating from the centromedian–parafascicular complex (CM–Pf), toward the motor part of the striatum, and the midline thalamic nuclei (substantia periventricularis or SPv), to-

ward the limbic part of the striatum, are considered to be circuits that may be affected in TS and explain the action of DBS in this location. Several studies have suggested that both the sensorimotor and the limbic-innervated parts of the basal ganglia, including the dorsal and ventral striatum, are involved in the pathophysiology of TS.^{19–22} This may also explain both motor and nonmotor symptoms.

TARGETS

Since the introduction in 1999 of thalamic DBS as a potential treatment for patients with refractory TS,¹² several other targets have been used. Published reports are sparse, however, and the low number of cases may reflect the very small group of potential candidates for surgery.^{13,14,23} To date, five targets have been used for DBS for TS in 34 patients (Table 1):

- 1) the medial portion of the thalamus, at the cross point of CM–SPv–Voi^{13,14,23–26};
- 2) the medial portion of thalamus, CM–Pf²⁷;
- 3) the globus pallidus pars interna (GPi), posteroventrolateral part^{28–30};
- 4) the GPi, anteromedial part²⁷; and
- 5) the nucleus accumbens (NAc) and anterior limb of internal capsule (IC).^{31,32}

Servello et al.²⁴ reported on the beneficial effects of bilateral stimulation of the centromedian parafascicular (CM–Pf) and ventralis oralis (Vo) complex of the thalamus, targets identified by Vandewalle et al.¹², in 18 patients with TS, with duration of the follow-up assessments ranging from 3 months to 18 months. They reported greater improved response for motor tics than for phonic tics after thalamic DBS. They also reported positive effects on behavioral disorders, with no serious permanent adverse effects. Bajwa et al.²⁶ described the beneficial effects of the same thalamic target in a 48-year-old patient whose relentless, violent head jerks were resulting in progressive neurological impairment. DBS resulted in 66% tic reduction on the Yale Global Tic Severity Scale at 24 months follow-up. The patient's self assessment indicated 95% improvement. A positive effect on mood and obsessive–compulsive symptoms was also reported. Maciunas et al.³³ reported results from a randomized, double-blind trial of thalamic DBS in five adults patients with Tourette Syndrome.

To date, 28 patients have been reported who have undergone bilateral thalamic stimulation with promising results on tics and associated behavioral disorders.

The effects of bilateral DBS of the posteroventral (motor) part of the internal segment of the globus pallidus (GPi) in a single patient were first described by Van der Linden et al.²⁸ in 2002. At 6 months follow-up, a tic

TABLE 1. Selected Studies of Targets for Deep Brain Stimulation in Tourette's Syndrome

Study	Target	N	Follow-up	Tic Reduction, %	Effect on Behavioral Disorders	Side Effects	Complications
Vandewalle et al. ¹² (1999)	Thalamus (med.)	1	4 mo	90–100	NA	NA	none
van der Linden et al. ²⁸ (2002)	Thalamus (med.)/GPi vpl	1	immed. postop/6 mo	80/95	NA	none/none	none/none
Visser-Vandewalle et al. ¹⁴ (2003)	Thalamus (med.)	3	5 yr, 1 yr, 8 mo	90, 72, 83	very good	none/none	none
Diederich et al. ²⁹ (2004)	GPi vpl	1	14 mo	66	no effect on compulsions	behavior (2 pt)	small hematoma around right electrode tip
Houeto et al. ²⁷ (2005)	Thalamus (Cm–Pf)/GPi am	1	24 mo/24 mo	70/70	very good/very good	impairment of left rapidly alternating movements (with GPi DBS)	none/none
Egidi et al. ²⁵ (2005)	Thalamus (med.)	1	6 mo	78	NA	more depressed	none
Servello et al. ²⁴ (2008)	Thalamus (med.)	18	3–17 mo	good	good	mild dysarthria reduced energy	wound dehiscence; abdominal subcutaneous hematoma
Flaherty et al. ³¹ (2005)	Internal capsule	1	18 mo	25	NA	hypomania; depression	none
Bajwa et al. ²⁶ (2007)	Thalamus (med.)	1	24 mo	66	good	none	none
Kühn et al. ³² (2007)	NAc	1	30 mo	40–50	very good	none	NA
Shahed et al. ³⁰ (2007)	GPi	1	6 mo	84	No effect on automatization	none	NA
Maciunas et al. ³³ (2007)	Thalamus (med.)	5	4 mo	40 ↓ motor; 21 ↑ vocal tics	good	Acute psychosis; spontaneous recurrence of tics	none

am = anteromedial part; Cm = centromedian nucleus; GPi = globus pallidus pars interna; immed. postop = immediately after surgery; med. = medial part (Cm–SPv–Voi); NA = not available; NAc = nucleus accumbens; Pf = parafascicular nucleus; pt = patient; SPv = substantia periventricularis; Voi = nucleus ventro-oralis internus; vpl = ventroposterolateral part; ↓ = % decrease; ↑ = % increase.

reduction of 95% was noted. In 2004, Diederich et al.²⁹ described the beneficial effects of chronic stimulation of the same target in a 27-year-old Tourette patient, with a follow-up of 14 months. Tic frequency per minute decreased by 73% in the postoperative phase and, in particular, the vocal tics became less intense, and the patient noticed a decrease of the internal urge to produce tics; however, there was no change in the patient's "very mild compulsive tendencies." The effects of GPi DBS in a 16-year-old boy were described by Shahed et al.,³⁰ who reported a significant effect on tics (84%) and behavior at 6 months follow-up; however, a body shield was needed for 4 weeks because the patient compulsively pushed on the implanted pulse generators.

Houeto et al.²⁷ described the effects of bilateral pallidal and thalamic stimulation in a 38-year-old female patient. The thalamic target was located in the centro-median-parafascicular complex and the pallidal target in the anteromedial (limbic) part of the GPi. Both thalamic and pallidal stimulation yielded 65% reduction in tics, but thalamic stimulation was superior for treatment of the associated behavior disturbance, after 24 months.

Flaherty et al.³¹ described the effects of bilateral stimulation of the anterior portion of the internal capsule in a 37-year-old Tourette patient who experienced severe tics without associated behavioral disorder. After 18 months, there was a 25% reduction in tics. In this patient, the lowest electrode contacts produced mild depression and the highest contacts caused hypomania. Kuhn et al.³² described the effects of DBS of the nucleus accumbens, with two poles of the electrode at the level of the anterior capsule, in a 26-year-old male patient diagnosed with severe TS, obsessive-compulsive behavior, and self-injurious behavior. The best effect on tics, with a 40% to 50% tic reduction on the Yale Global Tic Severity Scale after 2.5 years, were obtained by monopolar stimulation of all poles of the quadripolar electrode. A clear amelioration of obsessive and compulsive symptoms was also noticed.

Stimulation-dependent changes in the execution of movements reported in one case,²⁹ and a vertical, gaze palsy reported in another case,³⁴ were both due to a small hematoma around the tip of the electrode. Unexpected stimulation-induced side effects, such as drowsiness, reduced energy, changes in sexual behavior, and mild dysarthria, seem to be emerging in the majority of reported cases.^{10,13,15,24} One patient with bilateral thalamic and bilateral anteromedial GPi DBS appeared to be more depressed with the pallidal stimulation.²⁷ Stimulation-dependent changes in the execution of movements in one case with posteroventrolateral pallidal stimulation probably had to do with a small hematoma.²⁹

CLINICAL AND SURGICAL EVALUATION

Patient selection

As already noted, in most cases TS symptoms wane before, or at the onset of, adolescence. Not all patients require therapy and, of those who do, only a minority fail to respond to any medical treatment. Suitable candidates for DBS will be adults who have received careful trials of standard therapies without adequate benefit. Candidates for DBS in TS should be evaluated by a multidisciplinary team including, at minimum, a neurologist, a psychiatrist, and a doctoral-level psychologist or neuropsychologist with expertise in TS and comorbid conditions. The Dutch-Flemish Tourette Surgery Study Group has established guidelines for DBS in TS,³⁵ and the Movement Disorders Society has published the recommendations of the Tourette Syndrome Association.³⁶ The following have emerged as selection criteria for inclusion.

- 1) The patient has definite TS as established by two independent clinicians, preferably a psychiatrist and a neurologist. The diagnosis is established according to DSM-IV-TR criteria³⁷ and with the aid of the Diagnostic Confidence Index (DCI).³⁸
- 2) The patient has severe and incapacitating tics as the primary problem.
- 3) The patient is treatment refractory. This means that the patient either has not responded or has only very partially responded to three different medication regimens, each tried for at least 12 weeks, and in adequate doses, or has been proven not to tolerate medications due to side effects. Three different groups of neuroleptics should have been tried:
 - i) classic dopamine-2 antagonists (haloperidol, pimozide, or clonidine);
 - ii) modern antipsychotic medications (e.g., risperidone, olanzapine, clozapine, sulpiride, aripiprazole); and
 - iii) experimental drugs (e.g., pergolide).
- 4) Finally, a trial of at least 10 sessions of behavioral therapy for tics, such as habit reversal or exposure *in vivo*, may be attempted.
- 5) The patient should be over 25 years of age.

In terms of exclusion criteria, patients should be excluded from neurosurgical treatment if they have a tic disorder other than TS, severe psychiatric comorbid conditions (other than associated behavioral disorders), or mental deficiency. Contraindications for surgical treatment for DBS in TS are severe cardiovascular, pulmonary, or hematological disorders; structural abnormalities revealed on MRI; and active suicidal ideation.

Surgical procedure

The technique of DBS applied to TS is similar to that used for more classic indications, such as Parkinson's

disease (PD). Targets for TS, such as the nuclei of the medial portion of the thalamus, are not visible with current imaging techniques. Moreover, TS patients may pull themselves out of the stereotactic frame because of the frequent motor tics that occur in the head region. One solution would be to operate with the patient under general anesthesia.^{27,29} Because of the uncertainty of the ideal target and the importance of intraoperative findings, however, it is preferable to have the patient awake and cooperative during surgery. To avoid general anesthesia, patients may be sedated with a combination of lorazepam and clonidine,¹⁴ or with a Propofol target controlled infusion,²⁸ which reduces tics sufficiently to improve the safety and efficacy of a stereotactic procedure. With the patient awake, symptoms can be assessed so that acute, negative, stimulation-induced side effects can be detected and the position of the electrode adjusted as needed.

Perioperative evaluation

It is of paramount importance that in TS patients treated with DBS the exact location of the electrode and position of the stimulating contact is precisely determined and that all effects are meticulously described. A more comprehensive survey of guidelines for the perioperative assessment of the effects of DBS in TS is available elsewhere.³⁶

Post-operative evaluation

For the assessment of clinical effects, a careful and detailed description of the effect of DBS on tics and associated behavioral disorders and stimulation-induced side effects is mandatory. The most commonly used scale for tic rating is the Yale Global Tic Severity Scale (YGTSS).³⁹ The Rush Videotape scale is also commonly used.^{40,41} For a more objective evaluation, the patient should also be recorded on video with and without stimulation. The tics should be rated on video by two independent investigators. Ideally, the patient and investigator should be blinded to the status of the stimulation. A careful psychiatric and neuropsychological evaluation should be performed at regular intervals (e.g., at 3, 6, and 12 months).

It is essential that any investigation of the clinical effects of DBS for TS include accurate postoperative imaging to identify the exact electrode placement. In a region such as the medial thalamus that encompasses many small vessels, the localization is especially important. The most prudent approach may be to perform a postoperative computed tomography scan and fuse these images with preoperative MRI images—although many centers successfully apply other imaging approaches. Only if these prerequisites are fulfilled and a maximum amount of data is exchanged between centers can the optimal target be established.

Programming

According to our experience with DBS in the medial portion of the thalamus, the best effect in the majority of patients is obtained with a frequency between 75 Hz and 100 Hz and a pulse width of 210 μ s. From postoperative day 1, bipolar stimulation is started (to obtain the most selective effect), with each pole made active during four consecutive days (e.g., day 1: pole 0 negative, pole 1 positive; day 2: pole 1 negative, pole 2 positive, and so on). During programming, the voltage is progressively increased until unwanted side effects occur. Thereafter, the combination of electrodes may be altered (for example, two electrodes negative), or monopolar stimulation may be chosen, as suggested by clinical effects. As for other DBS indications, programming is a matter of trial and error, as directed by the best clinical effects and fewest adverse effects.

CONCLUSION

There is increasing interest in DBS as a potential therapy for patients with intractable TS. Several reports have described the beneficial effects of DBS in TS, with varying targets; the major drawback with the literature to date is the small number of patients included. The most optimal target has not yet been defined, and therefore continuous exchange and ongoing assessment of clinical experience will be important.

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