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Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome

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Deep brain stimulation of the thalamus has been proposed as a therapeutic option in patients with Tourette syndrome who are refractory to pharmacological and psychotherapeutic treatment. Patients with intractable Tourette syndrome were invited to take part in a double-blind randomized cross-over trial assessing the efficacy and safety of stimulation of the centromedian nucleus - substantia periventricularis - nucleus ventro-oralis internus crosspoint in the thalamus. After surgery, the patients were randomly assigned to 3 months stimulation followed by 3 months OFF stimulation (Group A) or vice versa (Group B). The cross-over period was followed by 6 months ON stimulation. Assessments were performed prior to surgery and at 3, 6 months and 1 year after surgery. The primary outcome was a change in tic severity as measured by the Yale Global Tic Severity Scale and the secondary outcome was a change in associated behavioural disorders and mood. Possible cognitive side effects were studied during stimulation ON at 1 year postoperatively. Interim analysis was performed on a sample of six male patients with only one patient randomized to Group B. Tic severity during ON stimulation was significantly lower than during OFF stimulation, with substantial improvement (37%) on the Yale Global Tic Severity Scale (mean 41.1 ± 5.4 versus 25.6 ± 12.8, $P = 0.046$). The effect of stimulation 1 year after surgery was sustained with significant improvement (49%) on the Yale

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Global Tic Severity Scale (mean 42.2 ± 3.1 versus 21.5 ± 11.1, $P = 0.028$) when compared with preoperative assessments. Secondary outcome measures did not show any effect at a group level, either between ON and OFF stimulation or between preoperative assessment and that at 1 year postoperatively. Cognitive re-assessment at 1 year after surgery showed that patients needed more time to complete the Stroop Colour Word Card test. This test measures selective attention and response inhibition. Serious adverse events included one small haemorrhage ventral to the tip of the electrode, one infection of the pulse generator, subjective gaze disturbances and reduction of energy levels in all patients. The present preliminary findings suggest that stimulation of the centromedian nucleus - substantia periventricularis - nucleus ventro-oralis internus crosspoint may reduce tic severity in refractory Tourette syndrome, but there is the risk of adverse effects related to oculomotor function and energy levels. Further randomized controlled trials on other targets are urgently needed since the search for the optimal one is still ongoing.

Keywords: Tourette syndrome; deep brain stimulation; trial; thalamus

Abbreviations: ADHD = attention deficit hyperactivity disorder; YGTSS = Yale Global Tic Severity Scale

Introduction

Tourette syndrome is a neuropsychiatric disorder characterized by sudden, brief, intermittent, involuntary or semi-voluntary movements (motor tics) or sounds (phonic or vocal tics) (Mink, 2001; Leckman *et al*., 2006). Tics are often preceded by a premonitory urge or sensation. Onset is in early childhood and tic frequency and intensity usually wax and wane during the natural course of the disease (Mink, 2001; Leckman *et al*., 2006). Patients may also suffer from sleep disturbances, learning disorders, anxiety and depression (Robertson, 2000). Moreover, Tourette syndrome is often accompanied by behavioural disorders such as attention deficit hyperactivity disorder (ADHD), obsessive–compulsive disorder and behaviour, as well as self-injurious behaviour (Leckman *et al*., 2006). Tics and associated disorders can have a serious impact on the overall quality of life. The occurrence of ADHD in patients with Tourette syndrome ranges from 21–90% (Leckman *et al*., 2006). Obsessive–compulsive behaviour may be present in up to 75% of patients with Tourette syndrome (Robertson, 2000). Obsessive behaviour in Tourette syndrome frequently involves sexual, violent, religious, aggressive and symmetrical themes, while compulsive behaviour is often related to checking, counting, forced touching and self-damage (Robertson, 2000). Over one-third of clinical patients with Tourette syndrome may suffer from self-injurious behaviour, with head banging being the most frequently reported type (Robertson *et al*., 1989).

Tourette syndrome is frequently a self-limiting disorder with remission or significant improvement around 20 years of age. However, in about 20% of patients, tics continue into adult life and require long-term treatment (Bloch and Leckman, 2009). Behavioural therapy and medication may provide temporary relief from symptoms but some patients remain refractory to medical therapy or experience unbearable side-effects. In 1999, deep brain stimulation was introduced as a new approach to treat intractable Tourette syndrome (Vandewalle *et al*., 1999). The target was located in the medial part of the thalamus at the centromedian nucleus-substantia periventricularis-nucleus ventro-oralis internus crosspoint of the thalamus. This was based on thalamotomies performed in patients with Tourette syndrome by Hassler and Dieckman (1970) and ideas about the role of this specific part of the thalamus within cortico-basal ganglia-thalamocortical circuits.

In a small case series ($n = 3$) (Visser-Vandewalle *et al*., 2003) a positive effect on both tics and associated disorders was observed and patients reported a better quality of life, postoperatively. Stimulation-induced side-effects included erectile dysfunction and reduced energy levels (Visser-Vandewalle *et al*., 2003; Temel *et al*., 2004). Long-term evaluation was performed in two patients at 6 and 10 years postoperatively. They demonstrated continued benefit of tic control, 78 and 92%, respectively (Ackermans *et al*., 2010). Clinical observations and neuroimaging suggest that dysfunction of the basal ganglia and related thalamocortical circuits form part of the pathophysiological basis of Tourette syndrome (Mink and Thach, 1993; Albin and Mink, 2006). The basal ganglia are thought to play a major role in the timing and sequencing of movement and behaviour by selecting desired programmes and suppressing unwanted ones (Singer, 1997). The basal ganglia thereby influence the (pre)frontal cortex, via the thalamus and modulate behavioural and/or motor responses. Uncontrolled movements and behavioural disorders in Tourette syndrome may therefore be the result of defective inhibitory mechanisms at the level of the basal ganglia circuits. Deep brain stimulation may act by modulating the relay functions of the thalamus between the basal ganglia and the cortex. Although Tourette syndrome is characterized by difficulty in suppressing involuntary behaviour, the ability to inhibit highly prepotent voluntary responses suggests impairment in response control mechanisms at the striatal rather than the cortical level (Watkins *et al*., 2005).

Since 1999, 10 different brain areas have been described as a target for deep brain stimulation in Tourette syndrome, including the centromedian nucleus - substantia periventricularis - nucleus ventro-oralis internus crosspoint of the thalamus (Bawja *et al*., 2007; Maciunas *et al*., 2007; Shield *et al*., 2008). The Milan group (Servello *et al*., 2008) targeted a similar area 2 mm more anterior. The Paris group (Houeto *et al*., 2005; Welter *et al*., 2008) targeted the centromedian nucleus, and the dorsomedial thalamus was targeted in a single patient (Vernaleken *et al*., 2009). Other targets outside the thalamus include the globus pallidus externus (Vilela Filho *et al*., 2007) and internus with both the ventroposterolateral motor and the anteromedial limbic part targeted in refractory Tourette syndrome (van der Linden *et al*., 2002; Diederich *et al*., 2005; Gallagher *et al*., 2006; Shahed *et al*., 2007; Dehning *et al*, 2008; Welter *et al*., 2008;

Dueck *et al*., 2009). The nucleus accumbens (Kuhn *et al*., 2007; Zabek *et al*., 2008; Neuner *et al*., 2009; Servello *et al*., 2009; Burdick *et al*., 2010) and the anterior limb of the internal capsule (Kuhn *et al*., 2007; Shields *et al*., 2008; Servello *et al*., 2009; Burdick *et al*., 2010) have also been targeted in patients with Tourette syndrome, particularly in those suffering from obsessive–compulsive behaviour. Finally, an improvement of tics after deep brain stimulation of the subthalamic nucleus was noted in a patient suffering from Parkinson's disease and tics (Martinez-Torres *et al*., 2009).

The effect of centromedian nucleus - substantia periventricularis - nucleus ventro-oralis internus stimulation on tics and associated disorders was examined in a randomized double-blind cross-over trial comparing the effect of stimulation ON with that of stimulation OFF. Evaluation at 1 year follow-up with stimulation ON was also conducted. The primary outcome was a change in tic severity and the secondary outcome a change in associated behavioural disorders and mood. Cognition was tested during stimulation ON at 1 year postoperatively, in order to evaluate the safety of this procedure with regard to possible side-effects.

Materials and methods

Patients

All enrolled patients had a primary diagnosis of Tourette syndrome as defined by the Diagnostic and Statistical Manual of mental disorders (1994) and a minimum score of 80 on the Diagnostic Confidence Index (Robertson *et al*., 1999). Only severe refractory patients >25 years and with a minimum score of 25 on the Yale Global Tic Severity Scale (YGTSS) (Leckman *et al*., 1989) were included. These patients had either failed to respond, or could not tolerate, 3-month trials of classical (e.g. haloperidol, clonidine), modern (e.g. risperidone, olanzapine) and experimental (e.g. quetiapine) antipsychotic medication at adequate doses. All patients had completed at least 10 sessions of behavioural therapy including habit reversal or exposure *in vivo*. Exclusion criteria included tics not related to Tourette syndrome, severe cognitive impairment, major psychiatric disorder (e.g. schizophrenia, bipolar disorder) and current substance abuse or dependence (except for nicotine), structural abnormalities on brain MRI and general contraindications for surgery or anaesthesia. All patients were evaluated by members of the Dutch–Flemish Tourette Surgery Study Group, a collaboration of health professionals with a special interest in Tourette syndrome, in order to ensure appropriate inclusion in the trial.

Randomization and masking

The trial followed a prospective, randomized, double-blind controlled cross-over design. Pre- and post-operative assessments were conducted at the Maastricht University Medical Centre in The Netherlands. Four patients underwent surgery at Maastricht University Medical Centre and two at St Lucas Hospital, Ghent in Belgium. The ethics committee of the Maastricht University Medical Centre approved the study and all patients provided written informed consent. Eligible patients were randomly assigned to one of two groups by sealed envelope selection. In Group A, stimulation was switched ON after surgery for 3 months and was followed by an OFF-stimulation period of 3 months (ON–OFF group). In Group B, stimulation was switched OFF during the first 3 months, followed by 3 months of ON stimulation (OFF–ON group). As requested by the ethics committee, the patients were given the possibility to ask for preliminary, blinded switching to the other stimulation condition if they wanted this. After the blinded cross-over period, the stimulator was switched ON for 6 months.

Evaluations were performed at the end of each condition, at 3 and 6 months after surgery, and at 1 year post-surgery by a clinician (L.A.) who was unaware of the stimulation status during the cross-over period. The patients were instructed to contact the hospital at any time during the year if they felt that there was insufficient clinical benefit or if they experienced adverse effects. Adjustments to stimulation, if necessary, were only made after completing the cross-over period. New symptoms or worsening of a pre-existing symptom during follow-up was classified as an adverse event. These adverse events were classified as serious if the patient required hospitalization or if the clinician considered the event to be serious. Medication was not changed during the cross-over period and was only adjusted, if necessary, in the 6 months of open stimulation.

Target, surgery and stimulation

Target

The hypothesis was that stimulation of the centromedian nucleus and substantia periventricularis would suppress excitatory feedback projection to motor and limbic parts of the striatum (Vandewalle *et al*., 1999), decrease tics and improve behavioural disorders. Stimulation of the nucleus ventro-oralis internus was supposed to include a projection to the facial part of the premotor cortex allowing modulation of orofacial tics. Stereotactic placement of bilateral quadripolar electrodes was thought to be effective to stimulate all three thalamic subnuclei (Neuner *et al*., 2008).

Surgery

The stereotactic procedure was performed under local anaesthesia and sedation (lorazepam, remifentanil and clonidine). The target was the centromedian nucleus - substantia periventricularis - nucleus ventro-oralis internus crosspoint of the thalamus located on fused CT/MRI images with the following coordinates: 5 mm lateral to the anterior commissure–posterior commissure, 4 mm posterior to the mid-commissural point at the level of the anterior commissure–posterior commissure plane. Target coordinates were adapted according to the width of the third ventricle and anterior commissure–posterior commissure length. MRI images were acquired after administration of a double dose of gadolinium. During planning, visible vessels were avoided in the planned trajectory. After placement of a burr hole, in line with the planned trajectory, extracellular single-unit microelectrode recordings were performed along five trajectories (central, anterior, posterior, medial and lateral). Fewer tracks were made if vessels could not be avoided. Recording started 10 mm above target and continued until 4 mm beneath target (LeadPoint, Medtronic, Minneapolis, MN, USA) in 0.5 mm steps. Subsequently, test stimulation was performed in 2 mm steps from 6 mm above to 4 mm beneath target (frequency 130 Hz, pulse width 60 μs) to assess stimulation-induced side effects. The stimulus intensity was gradually increased in steps of 1.0 mA, until unwanted side effects occurred or until a maximum stimulus intensity of 6.0 mA. Finally, the test-electrode was replaced by a final, quadripolar electrode (model 3387; Medtronic) with the second deepest contact (contact 1) at the level of the

thalamic target that gave no side-effects at all or only at the highest stimulus intensity. This definite electrode was fixed in the burr hole with acrylic cement, and connected to an externalized extension cable. Deep brain stimulation was always performed bilaterally. CT-scan was performed on the second post-operative day to evaluate electrode position and detect asymptomatic haemorrhage. Once agreement between the neurologist, the neurosurgeon and the psychiatrist was reached about the beneficial effect, the pulse generator was implanted as a separate procedure, under general anaesthesia, within 1 week (Kinetra model 7428, Medtronic).

Stimulation

After the second procedure, stimulation parameters were adjusted during a 3-week unblinded period to determine the most effective parameters on tics with the lowest amplitude. Sequential monopolar stimulation through each contact was delivered on four consecutive days with a pulse width of 60 μs and a frequency of 100 Hz. During this period the voltage was progressively increased until unwanted side effects occurred. Once the final electrode active contacts were chosen (monopolar or bipolar), the frequency, pulse width and voltage were adapted to obtain the best clinical effect on tic-reduction and side effects. These parameters were used in the ON condition during the cross-over period. After the cross-over period patients received a patient-programmer, which allowed them to change the stimulation voltage themselves between individually assigned ranges.

Outcome measures

Primary efficacy outcome

Tic assessment was performed before surgery, at the end of the blinded ON and OFF conditions (3 and 6 months after surgery) and at 1 year after surgery (L.A.). The primary outcome was the total YGTSS score (Leckman *et al*., 1989). This score provides an evaluation of the number, frequency, intensity, complexity and interference of motor and phonic tics. Total scores range from 0 to 50 with higher scores indicating higher severity. The modified Rush video-based rating scale was used to evaluate tics based on video recordings with 10 min of video recordings in the blinded conditions and at follow-up after 1 year (Goetz *et al*., 1999). Each of the six 30 min epochs was divided into five 2 min segments and intermixed into a random sequence by an independent technician for presentation and scoring.

Video recordings were performed uniformly and video segments were shuffled so that the blinded rater could not detect the stimulation.

Secondary efficacy outcome

Associated behavioural disorders and mood were assessed before surgery, at the end of each blinded condition and at 1 year postoperatively.

ADHD was measured by the Conners Adult ADHD Rating Scale (Conners *et al*., 1997) and obsessive–compulsive behaviour by the Yale–Brown Obsessive Compulsive Scale (Goodman *et al*., 1989). Anxiety was assessed by the Beck Anxiety Inventory (Beck *et al*., 1988) and the Dutch version of the Beck Depression Inventory (2nd edition) (Beck *et al*., 1996) was used to assess the existence and severity of depressive symptoms. Because there was no valid scale for self-injurious behaviour available, the patients were asked to fill in a Visual Analogue Scale, a 100 mm bar, beginning with 'no symptoms' on the left hand side.

Cognition

Given the known frontostriatal neuropathology of Tourette syndrome, we focused on attention and executive functions (Watkins *et al*., 2005). The cognitive test battery was administered before surgery and at 1 year follow-up. This included a number of subtests (i.e. similarities, digit symbol-coding, digit span and matrix reasoning) of the Wechsler Adult Intelligence Scale (3rd edition) (Wechsler, 1997), the Wisconsin Card Sorting Test (Heaton *et al*., 1993), the Stroop Colour Word Test (Stroop, 1935), the Trail Making Test (Reitan, 1992), Category (Rosen, 1980) and Letter fluency (Benton and Hamsler, 1989) and the Tower of London test with the procedure proposed by Krikorian *et al*. (1994). Post-surgical testing was conducted whilst the patient was ON stimulation with deep brain stimulation parameters that were individually optimized. All patients were tested by the same person at baseline and at follow-up. The cognitive test battery and self-report questionnaires were administered during a single session that lasted 4 h, including breaks.

Statistical analysis

The primary outcome was the difference in the total YGTSS score between blinded OFF and ON conditions and between preoperative assessment and that at 1 year after surgery. Based on previous experience (Visser-Vandewalle *et al*., 2003), the standard deviation of this difference was estimated to be 10 points on the YGTSS. A substantial improvement was deemed necessary to justify the potential risk of complications with deep brain stimulation. This was considered to be a minimum improvement of 33% compared with baseline or an absolute value of 10 points. To detect this difference with a power of 90%, 15 patients were required. An interim analysis was to be performed halfway through the trial.

For pair-wise comparisons of the respective outcome variables exact Wilcoxon signed-rank tests were used. Type I error was fixed at 5%. Besides group analyses, reliable change indices were calculated for the secondary outcome variables and cognition, in order to ensure a methodology that assessed true changes (Woods *et al*., 2002). For the YGTSS, true change corresponded with a difference of 10 points, as mentioned above. The reliable change indices statistical analysis determines whether the test performance of an individual has changed significantly between two time points (e.g. pre- to post-surgery) by taking into account the reliability of the measure. Reliable change indices therefore measure whether the change in a test score falls beyond the range that could be attributed to measurement variability of the test itself (Jacobson and Truax, 1991). Based on reliable change indices, the percentages of those patients showing either an increase or a decrease could be calculated. Standard deviations of preoperative assessments and test-retest reliability coefficients from the test manuals were used to calculate the respective reliable change indices (York *et al*., 2008). In accordance with the hypothesis that secondary outcome variables improve and cognition might decrease, a one-sided $P < 0.05$ was considered significant. All data were analysed using Statistical Package for the Social Sciences version 16.0 software (SPSS, Chicago, IL, USA).

Results

Study population

Patient inclusion started in February 2005. In April 2008 eight patients were enrolled and in 2009 interim analysis was

performed, which led to the end of the trial. Patient 7 was a 21-year-old institutionalized female with very serious self-injurious behaviour and life-threatening tics. Although she was younger than 25 years, she was included in the trial and underwent surgery for clinical urgency. Postoperatively, this patient developed neurological symptoms including hypertonia, mutism and repeated fainting, which needed extensive diagnostic evaluation and multidisciplinary treatment. Given this complex postoperative outcome, she could not be randomized within the period of follow-up and therefore was considered as lost to follow-up. Patient 8, a 43-year-old female with no associated disorders, was also lost to follow-up. During the first 3 months of the cross-over period, this patient insisted that her treatment be unblinded and that her peripheral neurologist switch ON the stimulator. This was done before we could perform the first blinded assessment in the Maastricht University Medical Centre. It appeared later that she was randomized for Group B.

In total, six patients completed the full trial, including both blinded assessments in the cross-over period and the 1 year assessment, with five patients in Group A and one (Patient 4) in Group B. Only two patients (Patients 3 and 5) completed the full 3 months OFF and 3 months ON. Four patients (Patients 1, 2, 4 and 6) asked for rescheduling after a few weeks in the ON or OFF condition and were not able to complete the required period of 3 months. Table 1 summarizes the clinical characteristics of the final sample ($n = 6$).

The mean age of the final sample ($n = 6$) at time of surgery was 40.33 years (range 35–48 years) and the mean duration of the disease was 33 years (range 28–42 years). All patients, except Patient 2, were on medication preoperatively. This medication was reduced by 50% at 1 year postoperatively in four patients and completely stopped in Patient 1 (Table 1).

Electrode localization and stimulation settings

All patients received bilateral stimulation. Due to a longer anterior-posterior commissure in Patient 1, electrodes were placed more posteriorly. In Patient 6, electrodes were placed 2 mm more laterally because of a relatively large third ventricle. Details of final electrode position are presented in Table 2. Four patients received stimulation at contacts above the aforementioned target, one patient just beneath the target and one patient on target. Unblinded adjustment of the stimulation parameters immediately after surgery took 3 weeks for five patients, as planned. A complex psychiatric situation prolonged this period to 5 months in one case (Patient 6).

Current was delivered through bipolar stimulation in three patients and monopolar stimulation in the other three patients. Voltages varied between 1.0–7.3 V (Table 3). After the cross-over period, all patients except for Patient 2 preferred continuous stimulation.

Effect on primary outcome

The total score on the YGTSS at the end of the blinded ON stimulation period was significantly lower (37%) than that at the end of

Table 1 Clinical characteristics of six patients with Tourette syndrome

Patient	Sex	Age (years)	Disease duration (years)	Tic symptoms	Associated behavioural disorders	Family history	Familial	Socio-professional	Medication before surgery	Medication 1 year after surgery
1	m	48	42	Eye blinking, coughing, head banging, shoulder shrugs	None	No	Married, two children	Employed	Risperidone 2 mg 2 ×/day	None
2	m	39	33	Neck extension, spitting, grimassing, coprolalia	Compulsion, automutilation	Yes	Married, two children	Employed	None	None
3	m	40	33	Elevation shoulder, neck extension, coprolalia	History of substance abuses	No	Divorced, two children	Unemployed	Pimozide 4 mg/day, citalopram 20 mg/day	Pimozide 1 mg/day, citalopram 20 mg/day, temazepam 10 mg/day
4	m	35	28	Jumping, flexion arm, shouting, coprolalia, echolalia	History of depression	Yes	Married, one child	Employed	Haloperidol 4 mg 2 ×/day, oxazepam 10 mg/day a.n.	Haloperidol 3 mg 2 ×/day, oxazepam 10 mg/day a.n.
5	m	40	28	Grunting, jerks of legs/arms/neck, facial grimaces, jumping	None	No	Unmarried	Employed	Clonidine 10 mg 4 ×/day	Clonidine 10 mg/4 ×/day
6	m	40	34	Head shaking, coprolalia, uttering sounds, pallilalia, echolalia	History of substance abuses	Yes	Divorced, one child	Unemployed	Clonazepam 2 mg 4 ×/day, dipiperon 40 mg 3 ×/day, disulfiram 250 mg/day, citalopram 40 mg/day, mirtazapine 45 mg 2 ×/day	Clonazepam 2 mg 2 ×/day, dipiperon 40 mg 2 ×/day, disulfiram 250 mg/day

m = male.

Table 2 Final electrode position in six Tourette patients

Patient	Left					Right				
	X (mm lateral AC-PC)	Y (mm posterior mid AC-PC)	Z (mm beneath AC-PC)	Electrode	Number of MER	X (mm lateral AC-PC)	Y (mm posterior mid AC-PC)	Z (mm beneath AC-PC)	Electrode	Number of MER
1	3	4.8	Contact 1 on target - 4.0	Medial	2 (anterior/lateral)	3	4.8	Contact 1 on target - 2.0	Medial	5
2	5	4	Contact 1 on target	Central	5	5	6	Contact 1 on target +1.0	Posterior	4 (except medial)
3	5	4	Contact 1 on target - 3.0	Central	3 (except medial/ posterior)	5	6	Contact 1 on target - 2.0	Posterior	3 (except anterior/ medial)
4	7	4	Contact 1 on target - 1.0	Lateral	5	7	4	Contact 1 on target - 1.0	Lateral	4 (except medial)
5	5	4	Contact 1 on target	Central	1	5	4	Contact 1 on target	Central	1
6	9	4	Contact 1 on target - 3.0	Lateral	3 (except medial/ posterior)	9	4	Contact 1 on target - 3.0	Lateral	3 (except anterior/ posterior)

AC = anterior commissure; PC = posterior commissure; MER = microelectrode recordings.

the OFF stimulation period ($P = 0.046$) (Table 4). There was also a reduction in the total video-tic counts after ON stimulation in comparison to OFF stimulation ($P = 0.046$). Although the modified Rush video-based rating scale was partially based on the video-tic counts, no significant difference was found between ON and OFF scores (Table 4). At 1 year follow-up, there was a significant effect on both YGTSS (49%) and modified Rush video-based rating scale (35%) scores as compared with preoperative assessments ($P = 0.028$ and 0.046, respectively).

Based on individual scores, five patients (except Patient 2) showed a substantial reduction of the total YGTSS score (10 points or more) after 3 months ON stimulation compared with the OFF condition. All patients, including Patient 2, demonstrated a substantial reduction in the total score on the YGTSS, 1 year postoperatively as compared with preoperative assessment. Individual total scores on the YGTSS are shown in Fig. 1 and individual motor and vocal tics are shown in Table 5. Three patients (Patients 1, 3 and 5) demonstrated substantial reduction of vocal tics in the ON versus the OFF condition. Only one patient (Patient 1) showed a substantial reduction in the amount of motor tics.

Effect on secondary outcome

No significant group differences ($P < 0.05$) were found between the associated behavioural disorders and mood in the stimulation ON and OFF conditions or when comparing assessment prior to surgery to that at 1 year follow-up (Table 6). There was no indication of a stimulation effect, at an individual level, between ON and OFF conditions or preoperative assessment versus that at 1 year postoperatively. Based on the reliable change indices, Patient 6 experienced the most changes between ON and OFF stimulation, with an increase in obsessive–compulsive behaviour and a decrease in depression and ADHD scores during ON stimulation (Table 7). At 1 year after surgery this patient showed an overall improvement.

Effect on cognition

Neuropsychological test scores before surgery and 1 year after surgery are shown in Table 8. Scores for the group revealed no significant change from baseline to 1 year after surgery except for the colour-word card of the Stroop test. The time needed to complete the colour-word card of the Stroop increased at 1 year after surgery. Based on calculated reliable change indices (Table 9), only one patient (Patient 6) showed a substantial increase in time on the colour-word card of the Stroop, whereas two patients (Patients 4 and 6) made more errors and as such showed a decline in accuracy on this specific test. Given the total cognitive test battery, Patient 6 showed most decline, in particular on mental speed.

Adverse events

Three patients had adverse events related to surgery. The most serious event, was a small parenchymal haemorrhage in Patient 2, deep at the tip of the left electrode, resulting in vertical gaze

Table 3 Stimulation parameters of six patients with Tourette syndrome

Patient	Left electrode					Right electrode					Voltage (mV, left/right)	Pulse (μs, left/right)	Rate (Hz)
	0	1	2	3	Case	4	5	6	7	Case			
1	–	–	+	+		–	–	+	+		6.4	60	110
2	+	–	–	+		–	–	+	+		1.0/2.1	60	70
3		–	–		+		–	–		+	2.8	210	100
4			–		+		–			+	7.3	180/150	90
5		–	–		+		–	–		+	2.6	90	130
6		–			+		–			+	2	60	110

Table 4 Results on primary outcomes in six patients with Tourette syndrome

	Before surgery	OFF	ON	1 year	*P* (ON versus OFF)	*P* (before surgery versus 1 year)
YGTSS total	42.3 (3.1)	41.1 (5.4)	25.6 (12.8)	21.5 (11.1)	0.046*	0.028*
Video-tics	233.3 (82.1)	195.3 (98.6)	85.3 (72.3)	65.3 (81.6)	0.046*	0.028*
mRVRS	12.1 (1.1)	10.8 (1.5)	6.3 (3.6)	7.8 (3.2)	0.580	0.046*

Mean (SD).
*$P < 0.05$. mRVRS = modified Rush Video-Based Rating Scale.

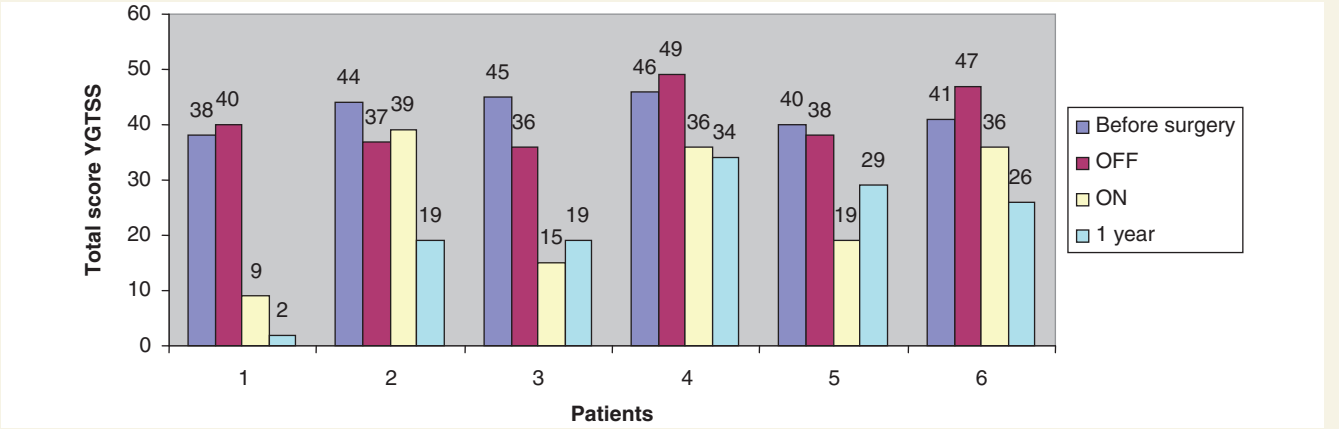

Figure 1 Individual changes in total YGTSS scores in six patients with Tourette syndrome.

palsy. This resolved after 6 months as seen on objective ophthalmological measurements (Ackermans *et al*., 2007). However, persistent subjective slowing of vertical fixation and pursuit on stimulation led the patient to switch off the stimulator after completing the cross-over period. Stimulation once a month for a few hours did not adversely affect the subjective complaint of slowing but seemed to prolong the beneficial effect on tics. Patient 3 developed a *Staphylococcus aureus* infection in the infraclavicular region, which was successfully treated with 6 weeks of intravenous antibiotic therapy (flucloxacillin and clindamycin). Patient 6 experienced varying motor and psychiatric symptoms up to 1 year after operation including lethargy, binge eating, dysarthria, apathy, gait disturbances and frequent falls. Adjustment of parameter settings and switching OFF the stimulator did not affect these symptoms. A CT-scan performed 6 months after surgery in order to exclude an electrode misposition revealed cerebral atrophy that was absent on the immediate postoperative CT-scan and preoperative imaging.

One year after surgery, all the patients reported a substantial restriction in their daily activities due to lack of energy. Patients 3 and 4 needed adjustment of their stimulation parameters in order to perform specific tasks like working or household tasks, whereas the other patients accepted this side-effect of the treatment. None of the patients in the present sample reported any sexual problems.

After the 1-year period of evaluation and 3 years after surgery, Patient 1 developed severe multidirectional nystagmus when stimulation was switched OFF. There were no reported oculomotor effects when the stimulation was switched OFF prior to this event. Subsequently, all included patients were interviewed

Table 5 Individual changes in tics (YGTSS) in six patients with Tourette syndrome

Test	Patient																							
	1				2				3				4				5				6			
	Before surgery	ON	OFF	1 year	Before surgery	ON	OFF	1 year	Before surgery	ON	OFF	1 year	Before surgery	ON	OFF	1 year	Before surgery	ON	OFF	1 year	Before surgery	ON	OFF	1 year
YGTSS																								
Vocal	19	3	19	2	19	15	13	0	25	5	18	6	25	18	25	19	18	9	19	15	25	18	25	16
Motor	19	6	21	0	25	24	24	19	20	10	18	13	21	18	24	15	22	10	19	14	16	18	22	10
Total	38	9	40	2	44	39	37	19	45	15	36	19	46	36	49	34	40	19	38	29	41	36	47	26

Table 6 Results on secondary outomes in six patients with Tourette syndrome

	Before surgery	OFF	ON	1 year	*P* (ON versus OFF)	*P* (before surgery versus 1 year)
Y-BOCS	8.3 (5.6)	7.8 (6.3)	9.1 (11.0)	2.5 (3.5)	0.686	0.249
CAARS	75.0 (27.0)	66.1 (26.1)	55.0 (33.6)	67.5 (34.8)	0.116	0.249
BAI	34.1 (11.0)	30.6 (5.0)	30.6 (9.2)	29.6 (6.3)	0.893	0.349
BDI	13.3 (8.5)	9.6 (7.3)	9.0 (11.9)	9.6 (5.8)	0.586	0.115
SIB (mm)	7.7 (18.2)	12.3 (21.1)	3.6 (5.6)	1.6 (3.9)	0.285	0.593

Mean (SD).
Y-BOCS = Yale–Brown Obsessive Compulsive Scale; CAARS = Conners Adult ADHD Rating Scale; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; SIB = self-injurious behaviour.

to detect subtle changes in oculomotor function. On direct questioning, all patients reported visual disturbances varying from blurred vision to fixation problems. These patients were examined by an optometrist and a neuro-ophthalmologist. No objective abnormalities could be detected. All patients underwent extensive electro- and video-nystagmography in a vestibular research laboratory (Wiertz *et al*., 2008), with specific investigation of gaze, smooth pursuit, saccades, anti-saccades, memory guided saccades, optokinetic nystagmus and vestibular ocular reflexes in both horizontal and vertical directions. Complementary vestibular tests, including torsion swing, torsion swing fixation and caloric tests were also performed. Because many artefacts may occur due to head movements associated with tics in the stimulation OFF condition, vestibular and oculomotor examination could only be performed with the stimulation being switched ON. In all but one (Patient 2), all tests confirmed normal vestibular and oculomotor function and no signs of central pathology. Patient 2 showed impaired vertical gaze with normal vertical vestibular ocular reflexes, indicating a supranuclear deficit (Ackermans *et al*., 2007).

Discussion

In this double-blind, cross-over trial, the effects of stimulation of the centromedian nucleus - substantia periventricularis - nucleus ventro-oralis internus crosspoint of the thalamus were analysed in six patients suffering from severe refractory Tourette syndrome. Although the sample size was small, there was a significant beneficial effect when comparing tic severity in the stimulation ON and the stimulation OFF condition with substantial improvement of the total YGTSS score (37%) when stimulation was ON. The effect of stimulation was sustained at 1 year after surgery, with a significant improvement when compared with preoperative baseline assessment (49% on the YGTSS). Individual changes in five out of six patients showed a substantial reduction in the severity of the tics (10 or more points on the YGTSS) in the stimulation ON versus the OFF condition, with more effect on vocal tics rather than on motor tics. Although Patient 2 showed no effect when comparing stimulation ON with OFF, a substantial beneficial effect of stimulation was observed in the unblinded assessment at 1 year after surgery when compared with preoperative assessment. There were no significant group effects for associated behavioural disorders and mood, either between ON and OFF stimulation or between baseline and 1 year follow-up assessments. At an individual level, there was no obvious change in associated behavioural disorders or mood except in Patient 6 who showed both positive and negative changes between ON and OFF stimulation and substantial improvement of all associated disorders from baseline to 1 year after surgery.

Group differences in cognition at baseline and at 1 year after surgery revealed no significant changes except for an increase in the time needed to complete the Stroop Colour Word Card, suggesting a decrease in selective attention and response inhibition. Since reliable change indices showed a decline in only one of the six patients, this group effect may not be clinically relevant. Again, Patient 6 showed most individual changes and in particular a decrease in mental speed. Serious adverse events included a small intracranial haemorrhage in one (Patient 2) resulting in vertical gaze palsy that resolved after 6 months and subjective changes in the velocity of upward gaze thereafter (Ackermans *et al*., 2007), one skin infection (Patient 3) successfully treated with

Table 7 Reliable change indices of associated behavioural disorders and mood in six patients with Tourette syndrome

Test	Patient																									
	1				2				3				4				5				6					
	Before surgery	ON	OFF	1 year	Before surgery	ON	OFF	1 year	Before surgery	ON	OFF	1 year	Before surgery	ON	OFF	1 year	Before surgery	ON	OFF	1 year	Before surgery	ON	OFF	1 year	95% RCI	
Associated behaviour																										
Y-BOCS	13	10	1	0	15	0	0	0	4	9	13	6	2	0	6	1	4	6	13	8	12	30	14	0	5.6	
CAARS	51	34	51	45	104	113	102	106	92	75	90	111	59	50	53	39	43	23	32	31	101	35	69	73	18.9	
BAI	22	25	25	23	34	46	39	40	39	30	32	29	25	23	31	25	32	23	26	27	53	37	31	34	11	
Mood																										
BDI	4	5	3	3	22	33	18	19	14	8	11	8	4	4	7	8	12	1	1	6	24	3	18	14	5.95	

RCI = reliable change indices; Y-BOCS; Yale–Brown Obsessive Compulsive Scale; CAARS = Conners Adult ADHD Rating Scale; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory.

antibiotics and subjective stimulation-induced gaze disturbances and reduced energy in all patients.

Although the effect of stimulation on YGTSS and video-tic ratings was significant in the present trial, the modified Rush video-Based rating scale score based on the video-tics ratings did not change significantly. The modified Rush video-based rating scale is divided into five subscores: the number of body areas involved, frequency (tics/min) and severity of both motor and vocal tics. Given the significant effect on the video-tics (the frequency of both motor and vocal tics), the absence of significance is most probably due to small changes in the severity of motor and vocal tics and the body areas involved between stimulation ON and OFF. Although significance was found for the YGTSS, the stimulation effect on tics was less pronounced than was expected on the basis of the results of our case series (Visser-Vandewalle *et al*., 2003; Ackermans *et al*., 2006). However, the percentage of improvement at 1 year was in line with our expectations and those of other studies involving stimulation of the medial part of the thalamus. Tic improvement in two single case studies was 32% (Shields *et al*., 2008) and 66% (Bawja *et al*., 2007), respectively, with the first case initially undergoing anterior inferior internal capsule stimulation with minimal results and side effects but later complicated by hardware failure (Shields *et al*., 2008). In an open label study, involving 18 patients with a minimum follow-up of 3 months, the percentage of improvement was 63% (Servello *et al*., 2008). In another study (Maciunas *et al*., 2007), using double-blind activation of the right and left stimulator in random order, three out of five patients responded with an average tic reduction of 50%, 3 months after surgery. The relatively high percentages found in the open-label phases, including the present report of 49% improvement at 1 year follow-up, versus the 37% based on our blinded ON and OFF conditions may be due to placebo effects. This difference emphasizes the need to perform double-blind randomized trials especially since patients with Tourette syndrome are known to be suggestible (Jankovic, 2001).

In this study, a better individual response was observed on vocal rather than on motor tics, whereas a previous study, stimulating the same target, reported an individual advantage for motor tics (Servello *et al*., 2008). However, no difference between vocal and motor tics was found at a group level. The heterogeneity and complexity of the pathophysiological mechanisms underlying the expression of the disease may account for the variability in therapeutic effect within and between study samples.

There was no stimulation effect on associated behavioural disorders and mood for the total group. The absence of this effect could be due to the fact that respective symptoms were subclinical or mild for all patients prior to surgery. Those with elevated obsessive–compulsive behaviour (Patients 1 and 2) showed improvement, except for Patient 6, who showed deterioration when in the stimulation ON condition. At 1 year after surgery most symptoms were decreased when compared with preoperative assessment but this effect was not significant on a group level.

In our previous studies (Visser-Vandewalle *et al*., 2003; Ackermans *et al*., 2006), obsessive–compulsive behaviour and self-injurious behaviour completely disappeared in all three patients, even when the stimulator was switched off. The Milan

group (Servello *et al*., 2008) also reported a decrease in obsessive–compulsive behaviour and self-injurious behaviour in their series but a detailed description of the associated disorders and response after thalamic deep brain stimulation was not provided.

Table 8 Cognition before and 1 year after surgery in six patients with Tourette syndrome

Test	Before surgery	1 year	*P*-value
Cognition			
WAIS digit symbol-coding	55.0 (21.4)	50.8 (14.5)	0.599
WAIS similarities	18.1 (6.3)	18.1 (4.0)	1.000
WAIS matrix reasoning	16.5 (4.7)	18.6 (3.9)	0.131
WAIS digit span	13.1 (2.8)	13.0 (3.7)	0.832
WCST total error	20.0 (12.5)	15.5 (7.0)	0.249
WCST perserverative error	9.8 (6.3)	7.0 (2.6)	0.207
WCST category	5.8 (0.4)	6.0 (0)	0.317
TMT A (sec)	34.8 (7.0)	38.1 (16.9)	0.750
TMT B (sec)	107.8 (56.2)	96.0 (38.4)	0.249
Stroop colour word (sec)	106.3 (34.1)	131.1 (70.0)	0.046*
Stroop colour word (error)	2.6 (2.0)	3.8 (4.9)	0.496
TOL total	31.5 (2.8)	30.6 (4.3)	0.269
TOL (sec)	351.5 (259.7)	347.5 (193.6)	0.916
Category fluency	32.0 (13.4)	32.3 (13.5)	0.916
Letter fluency	30.6 (8.4)	28.6 (13.0)	0.463

Mean (SD).
*$P < 0.05$.
WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test; TMT = Trail Making Test; ToL = Tower of London test; Sec = seconds.

Thalamic stimulation resulted in an improvement of 76% on the Yale–Brown Obsessive Compulsive Scale at 2 years after surgery compared with preoperative assessment in one patient with Tourette syndrome in a further report (Bawja *et al*., 2007). Measures of anxiety, depression and obsessive–compulsive behaviour showed no significant change in another series of five patients; although the noted trend was towards improvement, baseline scores were at best moderate (Maciunas *et al*., 2007).

One year postoperatively, cognitive reassessments showed a decline in a few of the executive tests with only the Stroop Colour Word Test showing a group effect. In our previous study (Visser-Vandewalle *et al*., 2003) visual reaction time and fluency, both tests within the domain of executive function, also showed a decline after thalamic deep brain stimulation. These findings are comparable with the decline in frontostriatal cognitive function found after subthalamic nucleus deep brain stimulation in Parkinson's disease (Smeding *et al*., 2006). In line with subthalamic nucleus deep brain stimulation, it is not clear whether the present findings are related to stimulation *per se* or due to other factors such as associated disorders, medication changes, surgical characteristics or to changes in energy level or lack of initiative. In addition, little is known yet about the impact on quality of life. So far, subthalamic nucleus deep brain stimulation seems to be relatively safe from a cognitive point of view (Gironell *et al*., 2003; Parsons *et al*., 2006). Based on both group and individual information, the decline in our sample was relatively mild; however, one should be aware that the small sample size and high risk of Type 2 errors might result in underestimation of negative cognitive effects. Further follow-up is required to assess whether further

Table 9 Reliable change indices of cognition in six patients with Tourette syndrome

Test	Patient												
	1		2		3		4		5		6		
	Before surgery	1 year	Before surgery	1 year	Before surgery	1 year	Before surgery	1 year	Before surgery	1 year	Before surgery	1 year	95% RCI
Cognition													
WAIS digit symbol-coding	65	53	90	68	49	50	59	60	34	49	33	25	21.4
WAIS similarities	21	24	27	21	15	17	19	17	8	18	19	12	6.3
WAIS matrix reasoning	23	25	18	18	17	20	19	17	4	13	11	19	4.7
WAIS digit span	15	18	16	13	10	9	12	11	15	17	11	10	2.4
WCST total error	9	14	11	21	17	11	18	11	44	27	21	9	16.3
WCST pers error	5	7	5	9	11	6	8	5	22	11	8	4	8.2
WCST cat	6	6	6	6	6	6	6	6	5	6	6	6	0.5
TMT A (sec)	40	45	24	17	31	36	32	23	39	44	43	64	9.1
TMT B (sec)	79	71	42	62	84	72	102	88	136	121	204	162	56.2
Stroop colour word (sec)	83	87	76	73	92	107	115	146	102	109	170	265	34.1
Stroop colour word (error)	1	0	2	2	0	1	5	12	3	0	5	8	2.1
TOL total	36	36	32	34	32	31	28	25	29	26	32	32	2.8
TOL (sec)	146	189	326	181	225	304	191	298	854	703	367	410	259.7
Category fluency	28	20	57	54	36	43	29	31	22	24	20	22	13.4
Letter fluency	31	17	35	44	31	34	40	39	32	28	15	10	3.4

RCI = reliable change indices; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test; TMT = Trail Making Test; ToL = Tower of London test; Sec = seconds; RCI = reliable change indices.

decline will reach the limit associated with disability or handicap in everyday life.

In our study there was one small haemorrhage resulting in vertical gaze difficulty. While the thalamus has been associated with a higher risk of bleeding (Terao *et al*., 2003), Diederich *et al*. (2005) reported one haematoma at the right electrode tip during pallidal stimulation for Tourette syndrome. Intracerebral haemorrhage is one of the most severe albeit rare complications of deep brain stimulation surgery and has a generally accepted incidence of 3% (Binder *et al*., 2005). The fact that the visual symptoms in Patient 2 did not change in the stimulation OFF condition as well as in the stimulation ON condition and that they resolved after 6 months, suggested that symptoms during the cross-over period were not induced by stimulation but by a lesion effect as a result of the haemorrhage. However, this study did not systematically evaluate the effects of unilateral stimulation.

Patient 6 experienced a positive effect of thalamic stimulation on the tics, but he suffered from various motor and psychiatric symptoms and showed a decrease in mental speed. These changes may be related to the progressive cerebral atrophy apparent on serial postoperative imaging. This patient was extensively re-evaluated during his postoperative stay on a psychiatric ward and an external expert was consulted to exclude possible other co-morbidities. Although the patient had a history of alcohol abuse, there was no explanation found for the rapidly progressive cerebral atrophy.

The reported visual problems in patients with Tourette syndrome after stimulation of the centromedian nucleus - substantia periventricularis - nucleus ventro-oralis internus crosspoint of the thalamus may not be due to ocular abnormalities but to visual processing problems. Visual processing difficulties are frequently presented in Tourette syndrome and are thought to be most reflective of underlying frontostriatal dysfunction (Le Vasseur *et al*., 2001). However, previous studies examining saccades in Tourette syndrome reported conflicting results (Le Vasseur *et al*., 2001). Servello *et al*. (2008) also reported subjective vertigo, blurring of vision and upward ocular deviation after thalamic deep brain stimulation, but in their series these symptoms appeared to be transient. Extensive vestibular and oculomotor examinations in our sample did not identify an objective oculomotor dysfunction that could be directly attributed to Tourette syndrome or stimulation. Subjective lack of energy was the other main adverse event in this study, reported previously and by both patients and caregivers (Visser-Vandewalle *et al*., 2003). To understand this effect and to differentiate it from apathy and mood, additional assessments may be indicated in future pre- and postoperative assessments.

The main limitation of the present study concerns its statistical power and external validity in view of the number of included patients and patient drop-out prior to completion of the randomization period. A second and related limitation concerns the randomization process, since five patients completed the trial in Group A, and only one in Group B. This effectively diluted the original cross-over design of the trial. A third methodological issue is that patients might be unblinded to stimulation settings based on their experience during optimization of stimulation during the immediate postoperative period. However, uncertainty about this was a reason for early rescheduling in four patients. The issue of rescheduling is a final methodological issue and might be a specific problem for patients with Tourette syndrome or obsessive–compulsive disorder-like symptoms (Gabriels *et al*., 2003). Given the complexity of Tourette syndrome and difficulties adhering to cross-over protocols, future studies should consider delayed therapy or randomization to OFF or ON groups rather than a cross-over design.

This trial was intended to enrol and implant 15 patients. The consensus of the Dutch–Flemish Tourette Surgery Study Group was to end this trial after the interim analysis, because of slow inclusion as well as the significant results of this analysis. Thalamic stimulation was overall effective at suppressing tics in a sample of six patients, but there were adverse effects on oculomotor function and energy levels. The reduced energy levels had a clear impact on daily living. The effects on oculomotor function were extensively investigated, but could not be objectivized. Given the availability of other potentially promising targets, such as the internal segment of the pallidum (GPi), the paucity of available refractory patients with Tourette syndrome, and the need for double-blind trials, the Dutch–Flemish Tourette Surgery Study Group decided to terminate the trial after obtaining the results of the interim analysis.

In conclusion, the findings from this double-blind randomized trial suggest that stimulation of the centromedian nucleus - substantia periventricularis - nucleus ventro-oralis internus crosspoint of the thalamus may lessen the severity of tics in patients with refractory Tourette syndrome, but with the risk of adverse effects on oculomotor function and reduced energy levels.

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