Thalamic deep brain stimulation in Tourette Syndrome

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Thalamic Deep Brain Stimulation in Tourette Syndrome

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Thalamic Deep Brain Stimulation in Tourette Syndrome

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Ter verkrijging van de graad van doctor
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volgens het besluit van het College van Decanen,
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door

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"He kleine meid op je kinderfiets".....voor Kim

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Chapter 1

General introduction

Tourette syndrome

Tourette syndrome (TS) is a complex chronic neuropsychiatric disorder characterized by motor and vocal tics. Motor tics are sudden, repetitive, stereotyped movements such as eye blinking, facial twitching, and head or shoulder movements, whereas vocal or phonic tics are sounds produced by moving air through the nose, mouth, or throat (e.g. coughing and throat clearing) as well as repeating syllables, words, or phrases.¹ TS typically has an onset in early childhood, and boys are more commonly affected than girls. Symptoms usually start with transient bouts of simple motor tics. Tics can become more "complex" in nature and appear to be purposeful. A fleeting feeling of relief often follows performance of a tic or a series of tics.^{2,3} Tics typically follow a waxing and waning pattern of severity, intensity, and frequency.⁴ Tic severity usually peaks between 8 and 12 years of age, with many patients showing a marked reduction in severity by the end of adolescence.⁵⁻⁷ Less than 20% of children with TS continue to experience a moderate level of impairment of global functioning by the age of 20 years.⁷ TS alone is the exception rather than the rule. Attention deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are the most common co-morbidities. The presence of these co-morbidities can add another layer of complexity, which may make it more difficult to develop a treatment plan that not only addresses the tics, but also the co-occurring disorders.

TS might be interpreted as an overactive abnormal neural activity of both the sensorimotor and the limbic-innervated parts, involving multiple outputs, of the basal ganglia.⁸

Treatment of TS

Frequently, TS is found to be a self-limiting disorder, whereas in a small proportion of patients the tics continue into adult life and require long-term behavioural or drug treatment. Behavioural and drug treatment may provide temporary control of symptoms but certain patients prove to be medically untreatable or will experience unbearable side-effects from the medication. To question to deal with this, surgery may be a therapeutic option.

In the past, Hassler and Dieckmann reported on the beneficial effects of lesioning the intralaminar and midline thalamic nuclei in patients suffering from TS, and, in patients with facial tics, also the nucleus ventro-oralis internus (Voi).⁹

Deep brain stimulation (DBS) can be used for neuromodulation with either activation or inhibition of neuronal networks. The functional outcome of the complex mechanisms of action is uncertain and is probably variable, depending on the specific anatomophysiological arrangements of each target region.

DBS has been introduced in the field of neuropsychiatry to modulate neuronal activity in the same areas as those targeted for lesioning in the past, but in a reversible way. As such it was suggested that DBS of the intralaminar and midline thalamic nuclei, and Voi, might have a good effect on TS symptoms.

The difficulty was that Hassler made up to ten coagulations in the intralaminar and medial thalamic nuclei, so a strategic point had to be found so that as many of the nuclei targeted by Hassler could be stimulated by one electrode for each hemisphere. This strategic point was found, studying the Schaltenbrand-Wahren atlas¹¹, on a coronary slice at 4 mm posterior to the midpoint of the line connecting the anterior commissure (AC) with the posterior commissure (PC) and 5 mm lateral to the AC-PC line, and the dorsolateral plane, at the level of AC-PC. The first target for DBS, the medial part of the thalamus at the crosspoint of the centromedian nucleus (Cm), the substantia periventricularis (Spv) and the nucleus ventro-oralis internus (Voi), has been described by Vandewalle in 1999.¹² The results of thalamic DBS in the first 3 Tourette patients have been described in 2003.¹³

Aim of this thesis

The general aim of this thesis is to continue on the pioneering work of Vandewalle. The focus is on the clinical outcome of thalamic (Cm-Voi-Spv crosspoint) DBS in adults with intractable TS.

Chapter 2 reviews the latest literature until 2010 of DBS in general in TS. Five different brain areas are targeted in order to alleviate the tics and associated behaviour in patients with TS. **Chapter 3** addresses the hypothesis of the thalamic stimulation, and more specifically of the Cm -Voi -Spv crosspoint as a major target in TS. The choice of this target is partially based on the result of a blinded prospective pilot-study in two patients who received pallidal and thalamic stimulation, respectively. Only patients with intractable TS are considered candidates for DBS. This has a number of implications for patient selection. In **chapter 4** the selection criteria for DBS in patients with TS are presented.

Chapter 5 describes the results of a double-blind, randomised controlled trial after thalamic DBS in six male Tourette patients. The effect on tics, associated behaviours, and side-effects are meticulously observed and presented. During our trial we operated on a young Tourette patient with severe co-morbid symptoms with complex results as described in **chapter 6**.

In **chapter 7 and 8** specific side-effects of thalamic stimulation are described in more detail. **Chapter 9** comprises the long term follow-up of 2 of the first 3 patients with thalamic stimulation. The focus is on efficacy and safety.

Finally, overall implications for clinical practice and challenges for future research are discussed in **chapter 10**.

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Chapter 2

Deep brain stimulation in Tourette syndrome

Review

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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 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 behaviour.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 behavioural 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 behaviour, 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 behavioural hyperactivity. Obsessive – compulsive behaviour 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 behaviour often wax and wane during the course of the illness. Robertson³ reported that more than one-third of

clinical TS patients exhibited self-injurious behaviour. The most frequent type of self-injurious behaviour 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, psycho behavioural 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 behaviour. 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 thalamic 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 behavioural 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 cortico-striato-thalamocortical 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 global 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), toward 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 2.1):

- 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 behavioural 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 TS. To date, 28 patients have been reported who have undergone bilateral thalamic stimulation with promising results on tics and associated behavioural 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 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 behaviour 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

centromedian–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 behaviour 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 behavioural 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 behaviour, and self-injurious behaviour. 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 behaviour, 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

Table 2.1 dwars

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 regimes, 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 behavioural 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 behavioural disorders), or mental deficiency. Contraindications for surgical treatment for DBS in TS are severe cardiovascular, pulmonary, or haematological 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 anaesthesia, 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 behavioural 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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Chapter 3

Deep brain stimulation in Tourette syndrome: two targets?

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Introduction

Tourette syndrome is a chronic neuropsychiatric disorder with onset in early childhood and characterized by motor and phonic tics. Tics are involuntary, repetitive muscle contractions that produce stereotyped movements (motor tics) or sounds (phonic tics). Co-occurring disorders of attention and impulse control are common, like Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive Compulsive symptoms (OCs). Although TS is frequently self-limited, some patients remain symptomatic and require chronic treatment.¹ The standard treatment is pharmacological, mainly involving neuroleptics, α 2-adrenergic agonists and dopamine-agonists. Behavioural treatment using techniques such as habit reversal has been shown to be effective as well. In a small percentage, however, symptoms are refractory to any conservative treatment and cause severe distress. Since 1955, various attempts have been made to treat these patients through neurosurgical procedures.² The results were often unsatisfactory or major side effects occurred. In 1999, deep brain stimulation (DBS) has been introduced as a new approach for intractable TS.³ To date, 3 patients have been reported who have undergone bilateral thalamic stimulation with promising results on tics and associated behavioural disorders.⁴ The target was chosen at the level of the medial part of the thalamus on the basis of the good results of thalamotomies described by Hassler in 1970.⁵⁻⁷ In 2002, bilateral stimulation of the posteroventral globus pallidus internus (GPi) was performed in one patient with TS⁸, who is to the best of our knowledge the first patient to undergo GPi DBS for intractable TS. The rationale for the choice of this target was the positive effect of GPi stimulation on hyperkinesias in Parkinson's disease (PD). The long-term effects on tics and OCs of chronic thalamic stimulation in the first patient and of chronic pallidal stimulation in the second patient have been described previously^{4,8}, the latter as an abstract. In the present study, we report on the acute effects of bilateral thalamic stimulation and of bilateral pallidal stimulation in two patients with TS.

Materials and Methods

Patient selection

Two patients suffering from TS according to the criteria of the Tourette Syndrome Classification Study Group (TSCSG), were selected for DBS on the basis of the intractability of the disease: behavioural therapy had failed and various drugs in adequate dose (among others dopamine receptor blocking agents and clonidine) were found to have no effect or had to be stopped after prolonged use because of unbearable side effects. In both patients, there was no co-morbidity except for associated behavioural symptoms (compulsions). Both patients gave informed consent for the study and were hospitalized.

Illustrative Cases

Case 1

This man was 45 years old at the time of surgery. He suffered from tics from the age of 7 (Table 3.1). The first tics appeared as grimaces and tongue pulling while in adulthood the most disabling ones were pounding the stomach, screaming, sniffing and flexion movements of the head. The compulsions were breaking glass. Surgery was performed at the University Hospital Maastricht, The Netherlands by V.V.V. Electrodes (Medtronic, model 3387; Medtronic, Kerkrade, The Netherlands) were implanted bilaterally in the thalamus (target was defined 5 mm lateral to the AC-PC line, 4 mm posterior to the midcommissural point, and at the AC-PC plane) at the level of the nucleus ventro-oralis internus (Voi), the centromedian nucleus (Cm) and substantia periventricularis (Spv), with the patient being sedated with clonidine and lorazepam. The patient's history and surgery are described elsewhere in more detail.⁴

Case 2

This man was 27 years of age at the time of surgery. His first tics appeared as tongue pulling and eye blinking at the age of 7 (Table 3.1). At the time of surgery, the patient's most disabling tics consisted of shoulder elevations, adduction movements of the legs, screaming, and grimaces. The compulsion was sniffing at objects. With the patient under general anaesthesia, four electrodes (model 3387; Medtronic, Kerkrade, The Netherlands) were implanted: two at the aforementioned thalamic nuclei, and two at the posteroventrolateral GPi (target was defined 21.5 mm lateral to the AC-PC line, 4 mm anterior to the midcommissural point, and 3 mm inferior to the AC-PC plane). This procedure was performed at the Sint Lucas Hospital Ghent, Belgium by H.C.

Table 3.1 Overview of patient characteristics and symptomatology in two intractable TS patients who underwent bilateral DBS at the level of the thalamus and GPi

	Patient 1	Patient 2
Age at onset (yrs)	7	7
Dis. Duration (yrs)	38	20
Age at surgery (yrs)	45	27
Main tics		
Motor	pounding stomach flexion movements of head touching head grimaces / tongue pulling	Grimaces elevation movements of shoulders adduction of legs
Vocal	uttering sounds sniffing coughing	uttering sounds Sniffing
Associated behav. Symptoms	compulsions (breaking glasses)	compulsions (sniffing at objects)

After the stereotactic operations, MR imaging confirmed the correct position of the electrodes in both patients, with no abnormalities. Two weeks later, the pulse generators (model 7428; Medtronic, Kerkrade, The Netherlands in patient 1 and model 7425; Medtronic, Kerkrade, The Netherlands in patient 2) were implanted infraclavicularly. In patient 2, the effects of bilateral thalamic and bilateral pallidal stimulation were separately assessed with externalized electrodes. GPI DBS resulted in a greater tic-reduction according to clinical judgement and patient's experience. Only the pallidal electrodes were connected to the pulse generator.

Evaluations

Both patients were evaluated one year after surgery at the University Hospital Maastricht. To confirm the beneficial effects at long-term, patients underwent evaluations with both their stimulators *on* (ON I). These results were compared to their pre-operative score (pre-post comparison). Afterward, the stimulators were turned *off* overnight for 12 h. The second examination started with the OFF I evaluation followed by ON II, OFF II and ON III. Between these conditions a stimulation *on-and-off*-period of one hour was applied. After the last evaluation (ON III), patients were discharged. Finally, both patients were asked to score their OCs two weeks later in their home situation (ON home).

Patients were videotaped during the examinations in the abovementioned conditions. In every stimulation condition we monitored the patient in full frontal body view with the observers in the room. In total, 50 minutes (10 minutes per condition) of video recordings for each patient were randomized in 1-minute fragments. The frequency of motor and phonic tics (tics/min) displayed on these video fragments was later counted by two independent and specially trained investigators, who were blinded for the conditions.

Patients and observers were also blinded for the conditions. Furthermore, in the ON I, OFF I and ON home conditions, the OCs was scored using the Padua Inventory-Revised (PI-R).⁹ The PI-R is a 60-item self-report questionnaire with 5 subscales: impulsivity, washing, checking, rumination and precision. A higher score reflects more symptoms.

Stimulation Parameters

In both studies, the stimulation parameters were set at a level in which patients had the best effect on tics without major side effects. This optimal stimulation condition was systematically determined during the outpatient clinic visits of the patients.

Results

Stimulation Parameters

In patient 1, the optimal parameters were 6,4V (stimulation amplitude), 130Hz (stimulation frequency), 120 μ s (pulse width), for both sides, with a monopolar stimulation (0-, 1-, case +, left; 4-, 5-, case +, right).

In patient 2, the most effective parameters were 3,1V, 170Hz, 210 μ s, for both sides, again with a monopolar stimulation (0-, 1-, 2-, case +, left; 4-, 5-, 6-, case +, right).

Pre-Post Comparison

At one year follow-up, the target tics were reduced from 20 to 3 tics/min in patient 1. Evaluations revealed that the tics at 1 year follow-up in patient 2 were reduced from 28 to 2 tics/min. In both patients, all major tics (phonic and motor) and compulsions disappeared. Major tics such as pounding his stomach, screaming, sniffing, coughing and flexion movements of the head disappeared in patient 1, while some minor tics especially in the facial region such as eye-blinking and grimaces were still present. In patient 2 the shoulder elevations, adduction movements of the legs, grimaces and sniffing disappeared as a result of DBS, but eye-blinking remained. The compulsions, breaking glass in patient 1 and sniffing at objects in patient 2, totally resolved.

Acute Effects

Turning *off* the stimulator for 12 hours, led to an increase in the total number of tics from 33.7 to 72.4 tics/min in patient 1 and from 16.7 to 80.2 tics/min in patient 2 (Figure 3.1A). In the ON II condition, the number of tics decreased in patient 1 from 72.4 to 62.1 tics/min and in patient 2 from 80.2 to 55.5 tics/min. After turning *off* the stimulation for one hour (OFF II), the total number of tics practically remained unchanged in patient 1 (from 62.1 to 65.1 tics/min), whereas in patient 2 a substantial increase was noticed (from 55.5 to 89.4 tics/min). In the final condition (ON III), the number of tics decreased from 65.1 to 57.3 tics/min in patient 1 and from 89.4 to 55.2 tics/min in patient 2.

The PI-R score increased by 62% in patient 1 and by 140% in patient 2 after turning *off* the stimulation for 12hours (OFF I). In their home situation, the PI-R score was comparable to the ON I condition in both patients (Figure 3.1B).

Side Effects

Both patients described a feeling of reduced energy at the stimulus voltage necessary for the best effect on their tics. Patient 1 reported a decrease in sexual functions, which has been extensively reported elsewhere.¹⁰ Patient 2 experienced a sudden, short dystonic jerk of the whole body each time the stimulators were switched *on*.

Figure 3.1 The effects of stimulation conditions on tics and associated behavioural symptoms. **A:** The effects of pallidal and thalamic DBS on tics. Patients were videotaped in stimulation *on* and *off* conditions (see x-axis) and the tics (see y-axis) displayed on the videotapes were measured by two independent and blinded investigators. **B:** The effects of pallidal and thalamic DBS on OCS as assessed by the Padua Inventory, revised (total score PI-R on y-axis).

Discussion

In the present case report of two patients, there was a good effect of chronic bilateral thalamic and pallidal DBS on tics and associated behavioural symptoms. The pallidal stimulation had more abrupt effects on tics when the stimulation was switched on, compared with the thalamic stimulation. OCS increased considerably after switching OFF the stimulator for 12 hours and were reduced again with stimulation, in both patients. Stimulation-related side-effects were acceptable for both patients. These findings are in line with the recent basal-ganglia thalamocortical concepts as proposed by Mink.^{11,12} The striatum and the subthalamic nucleus (STN) are the primary

input structures of the basal ganglia, receiving excitatory input from the cerebral cortex. The GPi and substantia nigra pars reticulata (SNr) are the primary output nuclei, sending inhibitory output to the thalamic nuclei. In TS, a disturbed activity of this basal ganglia-thalamocortical circuit, is thought to be responsible for some of the typical TS symptoms.^{11,12} According to these considerations, interference at the level of one of the output or relay stations within this circuit, the GPi or thalamus, can result in a clinical improvement.

The question whether the thalamus or the GPi is the best target for DBS cannot be answered based on the present case observations. In these patients both targets were effective in reducing symptoms. Our study group has chosen to evaluate the effects of thalamic DBS in a larger group of patients, through a prospective randomized controlled cross-over study. This decision is based on the good effects of thalamotomies⁵⁻⁷ in TS, described earlier, as well as on the positive effects of thalamic stimulation performed in 3 patients.^{3,4}

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Chapter 4

Deep brain stimulation in Tourette syndrome The Dutch-Flemish guidelines

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Deep Brain Stimulation in Tourette Syndrome

The application of deep brain stimulation (DBS) in movement disorders such as Parkinson's disease (PD), essential tremor (ET), and dystonia is currently widespread. Long-term results of DBS of the subthalamic nucleus (STN) in PD, the ventral intermediate nucleus (VIM) of the thalamus in ET¹, and the globus pallidus internus (GPi) in dystonia¹ have shown that this technique is safe and has long-lasting beneficial effects on motor disability. Moreover, the advantages of this technique are widely acknowledged when compared with ablative surgery. In Gilles de la Tourette Syndrome (TS), a disorder in which motor and vocal tics form the core symptoms, hardly any DBS experience has been acquired. TS encompasses a neuropsychiatric disorder, in which, in most cases, symptoms wane before or at onset of adolescence.² However, some patients develop severe and incapacitating tics and other comorbid conditions that are treatment refractory.

In the past, these patients have been candidates for ablative procedures in different parts of the brain, such as the prefrontal lobe, cingulum, thalamus, and zona incerta.³ The results were often unsatisfactory or major side effects, such as hemiplegia or dystonia, occurred.³

In 1999, DBS was introduced by our group as a new therapeutic approach for intractable TS.⁴ To date, three patients who underwent bilateral thalamic stimulation with promising results have been described by Visser-Vandewalle et al.⁵ After these single case studies, the Dutch-Flemish Tourette Surgery Study Group has established guidelines for DBS in TS.

These guidelines are used for a prospective randomized double-blind cross-over study in order to evaluate the efficacy of bilateral thalamic stimulation in a larger group of patients experiencing intractable TS. This study began on February 14, 2005. These guidelines include conditions that collaborative centers should fulfil, as well as inclusion and exclusion criteria for patients to enter the study. Based on the pilot study, experiences in the first patients operated⁵ and in line with the collaborative effort realized with regard to DBS in obsessive compulsive disorder¹, specific terms have been formulated.

General requirements to be met by the study center

First, it is of paramount importance that the execution of DBS be restricted to neurosurgical units experienced in DBS treatment of movement disorders, with established collaborations with neurological and psychiatric departments specializing in the diagnosis and treatment of TS. Secondly, because DBS in TS encompasses an invasive surgical technique in an experimental phase, the patients should be studied in a high quality scientific setting using a blinded study design to ensure that sound answers can be given on short- and long-term treatment effect and prognostic factors involved in DBS. Third, an ethics committee (e.g., Institutional Review Board) of the

participating institute should have given approval of all aspects of the study protocol. Only those patients who are fully capable of deciding on participation are included. Patient consent should be monitored throughout the DBS process and patients can drop out of the procedure whenever they choose.

Requirements with regard to patient selection

The TS patients considered for DBS should comprise only very severe cases; they should be patients who have already fruitlessly received standard therapies. This has a number of implications for patient selection.

Inclusion of patients

The patient has a definite Tourette syndrome, established by two independent clinicians. The diagnosis is being established according to the Diagnostic and Statistical Manual of Mental Disorders-IV criteria⁶ and with the aid of the Diagnostic Confidence Index.⁷ According to Diagnostic Confidence Index standards, the patient should be rated as a definite case of TS. Current as well as past tic status is being evaluated. The patient has severe and incapacitating tics as his primary problem. The treatments of these tics, not of other comorbid behaviours such as obsessive-compulsive disorder, self injurious behaviours, or attention deficit hyperactivity disorder are the main focus of the therapy. Psychiatric and neurological side effects are carefully monitored perioperatively, immediately postoperatively, and at long-term follow-up examinations. To assess tic severity, videotaped tic countings⁸ and the Yale Tic Severity Scale⁹ are being used. Patients with Yale Tic Severity Scale scores on subscale A-E > 20 (scale scores, 0-40), and Yale Tic Severity Scale score on subscale F > 5 (scale scores, 0-10) are included. The patient is treatment refractory. This means that the patient either has not or very partially responded to three different medication regimes, each in adequate doses during at least 12 weeks, or has proven not to tolerate medication due to side-effects after serious attempts at taking medication have been made. With regard to the types of medication tried, three different groups can be distinguished that should be tried:

- 1) "classic" Dopamine-2 antagonists (e.g., haloperidol, pimozide) or clonidine,
- 2) modern antipsychotic medication (e.g., risperidone, olanzapine, tiapride, sulpiride), and
- 3) experimental drugs (e.g., quetiapine, aripiperazole, pergolide).

Finally, a trial of at least 12 sessions of behavioural therapy for tics should have been attempted and failed. Behavioural therapy techniques should entail either self-control procedures (habit reversal)¹⁰ or exposure therapy to premonitory urges.¹¹ The patient should also be over 25 years of age.

Exclusion of patients

Tic disorder other than Tourette syndrome, as well as severe psychiatric co-morbid conditions (e.g., psychotic, dissociative, depressive disorders, substance use disorders), cognitive disorders, and mental deficiency. Patients also have common contraindications for surgery, such as severe cardiovascular, pulmonary, or haematological disorders or structural abnormalities are visible on MRI scans.

Requirements with regard to operation conditions

Surgeons should have substantial experience in DBS treatment of movement disorders to enhance efficacy and minimize complications. Compared with patients suffering from PD or ET, TS patients require special anesthesiological measures because of the tics that hinder the stereotactic procedure. We advise not to bring the patient under general anesthesia because negative side effects reported during test stimulation might lead to alteration of the position of the electrode perioperatively.¹¹ Sedating the patient to obtain tic suppression with maintenance of the possibility to communicate with the patients is preferable.

Finally, the Dutch-Flemish Study Group is taking steps to establish a collaborative working group on DBS in TS. The aim of this collaborative group, essentially being in line with the obsessive-compulsive disorder DBS collaborative group, is to equalize protocol strategy and outcome measures, and to compare data in the future. The collaborative effort taken with respect to this type of treatment requires time, effort, mutual confidence, and respect, all of which are necessary to find high-quality scientific answers to the question of whether DBS is of additional aid in the treatment of treatment-refractory TS patients.

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Chapter 5

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

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Introduction

Tourette syndrome (TS) is a neuropsychiatric disorder characterized by sudden, brief, intermittent, involuntary or semi voluntary movements (motor tics) or sounds (phonic or vocal tics).^{1,2} 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.^{1,2} Patients may also suffer from sleep disturbances, learning disorders, anxiety and depression.³ Moreover, TS is often accompanied by behavioural disorders such as Attention Deficit Hyperactivity Disorder (ADHD), Obsessive-Compulsive Disorder (OCD) and behaviour (OCb), as well as Self-Injurious Behaviour (SIB).¹ Tics and associated disorders can have a serious impact on the overall quality of life. The occurrence of ADHD in TS patients ranges from 21 to 90 %.¹ OCb may be present in up to 75% of TS patients.³ Obsessive behaviour in TS frequently involves sexual, violent, religious, aggressive and symmetrical themes, while compulsive behaviour is often related to checking, counting, forced touching, and self-damage.³ Over one-third of clinical TS patients may suffer from SIB, with head banging being the most frequently reported type.⁴

TS is frequently a self-limiting disorder with remission or significant improvement around 20 years of age. However, in roughly 20% of patients tics continue into adult life and require long-term treatment.⁵ 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 (DBS) was introduced as a new approach to treat intractable TS.⁶ The target was located in the medial part of the thalamus at the Centromedian nucleus - Substantia periventricularis - Nucleus ventro-oralis internus (Cm-Spv-Voi) crosspoint. This was based on thalamotomies performed in TS patients by Hassler⁷ 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)⁸ 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.^{8,9} Long-term evaluation was performed in two patients at six and ten years postoperatively. They demonstrated continued benefit of tic control, respectively 78% and 92%.¹⁰ Clinical observations and neuroimaging suggest that dysfunction of the basal ganglia and related thalamocortical circuits form part of the pathophysiological basis of TS.^{11,12} 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.¹³ 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 TS may therefore be the result of defective inhibitory mechanisms at the level of the basal ganglia circuits. DBS may act by modulating the relay functions of the thalamus between the basal ganglia and the cortex. Although TS

is characterised by difficulty in suppressing involuntary behaviour, the ability to inhibit highly pre-potent voluntary responses suggests impairment in response control mechanisms at the striatal rather than the cortical level.¹⁴

Since 1999, ten different brain areas have been described as a target for DBS in TS, including the Cm-Spv-Voi crosspoint of the thalamus.¹⁵⁻¹⁷ The Milan group¹⁸ targeted a similar area 2 mm more anteriorly. The Paris group^{19,20} targeted the centromedian nucleus, and the dorsomedial thalamus was targeted in a single patient.²¹ Other targets outside the thalamus include the globus pallidus externus²² and internus with both the ventroposterolateral motor and the anteromedial limbic part targeted in refractory TS.^{20,23-28} The nucleus accumbens²⁹⁻³³ and the anterior limb of the internal capsule^{17, 29-32} have also been targeted in TS patients, particularly in those suffering from OCb. Finally, an improvement of tics after DBS of the subthalamic nucleus (STN) was noted in a patient suffering from Parkinson's disease and tics.³⁴

The effect of Cm-Spv-Voi stimulation on tics and associated disorders was examined in a randomised double-blind cross-over trial comparing the effect of stimulation *on* with that of stimulation *off*. Evaluation at one 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 one year postoperatively, in order to evaluate the safety of this procedure with regard to possible side-effects.

Methods

Patients

All enrolled patients had a primary diagnosis of TS as defined by the Diagnostic and Statistical Manual of mental disorders³⁵ and a minimum score of 80 on the Diagnostic Confidence Index.³⁶ Only severe refractory patients older than 25 years and with a minimum score of 25 on the Yale Global Tic Severity Scale (YGTSS)³⁷ were included. These patients had either failed to respond, or could not tolerate, three-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 ten sessions of behavioural therapy including habit reversal or exposure in vivo. Exclusion criteria included tics not related to TS, severe cognitive impairment, major psychiatric disorder (e.g.: schizophrenia, bipolar disorder) and current substance abuse or dependence (except for nicotine), structural abnormalities on brain magnetic resonance imaging (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 TS, in order to ensure appropriate inclusion in the trial.

Randomisation and masking

The trial followed a prospective, randomised, double-blind controlled cross-over design. Pre- and postoperative assessments were conducted at the Maastricht University Medical Centre (MUMC) in The Netherlands. Four patients underwent surgery at MUMC and two at St Lucas Hospital, Ghent in Belgium. The ethics committee of the MUMC 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 three months and was followed by an *off*-stimulation period of three months (ON-OFF group). In group B, stimulation was switched *off* during the first three months, followed by three 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 six months.

Evaluations were performed at the end of each condition, at three and six months after surgery, and at one year post surgery by a clinician (LA) 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 six months of open stimulation.

Target, surgery and stimulation

Target

The hypothesis was that stimulation of the Cm and Spv would suppress excitatory feedback projection to motor and the limbic parts of the striatum⁶, decrease tics and improves behavioural disorders. Stimulation of the Voi 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 sub nuclei.⁶

Surgery

The stereotactic procedure was performed under local anaesthesia and sedation (lorazepam, remifentanyl and clonidine). The target was the Cm-Spv-Voi crosspoint of the thalamus located on fused CT/MRI images with the following coordinates: 5 mm lateral to the anterior commissure (AC) - posterior commissure (PC), 4 mm posterior to the midcommissural point at the level of the AC-PC plane. Target coordinates were adapted according to the width of the third ventricle and AC-PC 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 micro-electrode recordings (MER) 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, U.S.A.) 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 60µsec) 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 definite, 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. DBS 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 approximately one week (Kinetra model 7428, Medtronic).

Stimulation

After the second procedure, stimulation parameters were adjusted during a three 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 µsec and a frequency of 100Hz. 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 (three and six months after surgery) and at one year after surgery (LA). The primary outcome was the total YGTSS score.³⁷ This score provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic tics. Total scores range from 0-50 with higher scores indicating higher severity. The modified Rush Video-Based Rating Scale (mRVRS)³⁸ was used to evaluate tics based on video recordings with ten minutes of video recordings in the blinded conditions and at follow-up after one year. Each of the six thirty-minute epochs was divided into five two-minute 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 one year postoperatively.

ADHD was measured by the Conners Adult ADHD Rating Scale (CAARS)³⁹ and OCB by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).⁴⁰ Anxiety was assessed by the Beck Anxiety Inventory (BAI)⁴¹ and the Dutch version of the Beck Depression Inventory (2nd edition)⁴² was used to assess the existence and severity of depressive symptoms. Because there was no valid scale for SIB available, the patients were asked to fill in a Visual Analogue Scale (VAS), a 100-mm bar, beginning with “no symptoms” on the left hand side.

Cognition

Given the known frontostriatal neuropathology of Tourette, we focused on attention and executive functions.¹⁴

The cognitive test battery was administered before surgery and at one year follow-up. This included a number of subtests (i.e., similarities, digit symbol-coding, digit span, matrix reasoning) of the Wechsler Adult Intelligence Scale-third edition (WAIS III)⁴³, the Wisconsin Card Sorting Test (WCST)⁴⁴, the Stroop Colour Word Test⁴⁵, the Trail Making Test (TMT)⁴⁶, Category⁴⁷ and Letter fluency⁴⁸ and the Tower of London test (ToL) with the procedure proposed by Krikorian.⁴⁹ Post-surgical testing was conducted whilst the patient was *on* stimulation with DBS parameters that were individually optimised.

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 approximately 4 hours 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 one year after surgery. Based on previous experience⁸, 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 DBS. This was considered to be a minimum improvement of 33% compared to baseline or an absolute value of 10 points. To detect this difference with a power of 90%, fifteen 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 (RCI) were calculated for the secondary outcome variables and cognition, in order to ensure a methodology that assessed true changes.⁵⁰ For the YGTSS, true change corresponded with a difference of 10 points, as mentioned above. The RCI 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. RCI therefore measures whether the change in a test score falls beyond the range that could be attributed to measurement variability of the test itself.⁵¹ Based on RCI, 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 RCI.⁵² In accordance with the hypothesis that secondary outcome variables improve and cognition might decrease, a one-sided p-value of less than 0.05 was considered significant. All data were analyzed using SPSS-pc, version 16.0 software (SPSS, Chicago, IL).

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 woman with very serious SIB 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, like including hypertonia, mutism and repeated fainting, which needed extensive diagnostic evaluations and multidisciplinary treatment. Given this complex postoperative outcome, she could not be randomised within the period of follow-up and therefore was considered as lost to follow-up. Patient 8, a 43-year old woman with no associated disorders, was also lost to follow-up. During the first three 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 MUMC. It appeared later that she was randomised for group B.

In total, six patients completed the full trial, including both blinded assessments in the cross-over period and the one year assessment, with five patients in group A, and one (patient 4) in group B. Only two patients (patient 3 and 5) completed the full three months *off* and three months *on*. Four patients (patient 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 three months. Table 1 summarises 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 one year postoperatively in four patients and completely stopped in patient 1 (See Table 5.1 for details).

Electrode localization and stimulation settings

All patients received bilateral stimulation. Due to longer AC-PC 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 5.2. 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 three weeks for five patients as planned. A complex psychiatric situation prolonged this period to five 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 V to 7.3V. (See Table 5.3 for the stimulation parameters). After the cross-over period, all patients except for patient 2 preferred continuously 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 the *off* stimulation period ($p=0.046$) (See Table 5.4). There was also a reduction in the total video-tic counts after *on* stimulation in comparison to *off* stimulation ($p=0.046$). Although the mRVRS was partially based on the video-tic counts, no significant difference was found between *on* and *off* scores (See Table 5.4). At one year follow-up, there was a significant effect on both YGTSS (49%) and mRVRS (35%) scores as compared to preoperative assessments ($p = 0.028$ and 0.046 , respectively).

Table 5.1 dwars

Table 5.2 dwars

Table 5.3, 5.4, 5.5 dwars

Based on individual scores, five patients (except patient 2) showed a substantial reduction of the total YGTSS score (10 points or more) after three months *on* stimulation compared to the *off* condition. All patients, including patient 2, demonstrated a substantial reduction in the total score on the YGTSS, one year postoperatively as compared to preoperative assessment. Individual total scores on the YGTSS are shown in Figure 5.1 and individual motor and vocal tics are shown in Table 5.5. Three patients (patient 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.

Figure 5.1 Individual changes in total YGTSS scores in six patients before surgery, *off*, *on* and 1 year after surgery

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 one year follow-up (See Table 5.6). There was no indication of a stimulation effect, at an individual level, between *on* and *off* conditions or preoperative assessment versus that at one year postoperatively. Based on the RCI, patient 6 experienced the most changes between *on* and *off* stimulation, with an increase in OCb and a decrease in depression and ADHD scores during *on* stimulation (See Table 5.7). At one year after surgery this patient showed an overall improvement.

Table 5.6 Results on secondary outcomes in six Tourette patients

	Before surgery	<i>off</i>	<i>on</i>	1 year	$P(\text{on vs. off})$	$P(\text{before surgery vs. 1 year})$
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). * indicates significant p value < 0.05 . YBOCS: Yale-brown Obsessive Compulsive Scale. CAARS: Conners Adult ADHD Rating Scale. BAI: Beck Anxiety Inventory. BDI: Beck Depression Inventory. SIB: self-injurious behaviour.

Table 5.7 dwars

Effect on cognition

Neuropsychological test scores before surgery and one year after surgery are shown in Table 5.8.

Table 5.8 Cognition before and 1 year after surgery in six Tourette patients

Test	Before surgery	1 year	P value
Cognition	55 (21,4)	50,8 (14,5)	0,599
WAIS digit symbol-coding	18,1 (6,3)	18,1 (4,0)	1
WAIS similarities	16,5 (4,7)	18,6 (3,9)	0,131
WAIS matrix reasoning	13,1 (2,8)	13,0 (3,7)	0,832
WAIS digit span	20,0 (12,5)	15,5 (7,0)	0,249
WCST total error	9,8 (6,3)	7,0 (2,6)	0,207
WCST perseverative error	5,8 (0,4)	6,0 (0)	0,317
WCST category	34,8 (7,0)	38,1 (16,9)	0,75
TMT A (sec)	107,8 (56,2)	96,0 (38,4)	0,249
TMT B (sec)	106,3 (34,1)	131,1 (70,0)	0,046 [†]
Stroop colour word (sec)	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)	32,2 (13,5)	0,916
Letter fluency	30,6 (8,4)	28,6 (13,0)	0,463

Mean (SD). [†] indicates significant p value <0.05. WAIS: Wechsler Adult Intelligence Scale; WCST: Wilconsin Card Sorting Test; TMT: Trail Making Test; TOL: Tower of London test. Sec: seconds.

Scores for the group revealed no significant change from baseline to one 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 one year after surgery. Based on calculated RCI (See Table 9), only one patient (patient 6) showed a substantial increase in time on the colour-word card of the Stroop, whereas two patients (patient 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, also classified as serious by the ethics committee, was a small parenchymal haemorrhage in patient 2, deep at the tip of the left electrode, resulting in vertical gaze palsy. This resolved after six months as seen on objective ophthalmological measurements.⁵³ 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 one 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 six 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. Patient 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 one-year period of evaluation and three 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 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 videonystagmography in a vestibular research laboratory⁵⁴, 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.⁵³

Table 5.9 dwars

Discussion

In this double-blind, cross-over trial, the effects of stimulation of the Cm-Spv-Voi 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 one 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 one 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 one 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 one year after surgery.

Group differences in cognition at baseline and at one 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 RCI 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 (patient 2) resulting in vertical gaze palsy that resolved after six months and subjective changes in the velocity of upward gaze thereafter², one skin infection (patient 3) successfully treated with 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 mRVRS score based on the video-tics ratings did not change significantly. The mRVRS is divided in five sub scores: 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.^{8,55} However, the percentage of improvement at one 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%¹⁷ and 66%¹⁵, respectively, with the first case initially undergoing anterior inferior internal capsule stimulation with minimal results and side effects but later complicated by hardware failure.¹⁷ In an open label study, involving 18 patients with a minimum follow-up of three months, the percentage of improvement was 63%.⁴⁴ In another study¹⁶, 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%, three months after surgery. The relatively high percentages found in the open-label phases, including the present report of 49% improvement at one 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 randomised trials especially since patients with TS are known to be suggestible.⁵⁶

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.¹⁸ 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 OCb (patient 1 and 2) showed improvement, except for patient 6, who showed deterioration when in the stimulation *on* condition. At one 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^{8,55}, OCb and SIB completely disappeared in all three patients, even when the stimulator was switched *off*. The Milan group¹⁸ also reported a decrease in OCb and SIB in their series but a detailed description of the associated disorders and response after thalamic DBS was not provided. Thalamic stimulation resulted in an improvement of 76% on the Y-BOCS at two years after surgery compared with preoperative assessment in one patient with TS in a further report.¹⁵ Measures of anxiety, depression and OCb showed no significant change in another series of five patients; although the noted trend was towards improvement, baseline scores were at best moderate.¹⁶

One year postoperatively, cognitive re-assessments showed a decline in a few of the executive tests with only the Stroop Colour Word Test showing a group effect. In our previous study⁸ visual reaction time and fluency, both tests within the domain of

executive function, also showed a decline after thalamic DBS. These findings are comparable with the decline in frontostriatal cognitive function found after STN DBS in Parkinson's disease.⁵⁷ In line with STN DBS, 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, STN DBS seems to be relatively safe from a cognitive point of view.^{58,59} 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 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 bleeding⁶⁰, Diederich²⁴ reported one haematoma at the right electrode tip during pallidal stimulation for TS. Intracerebral haemorrhage is one of the most severe but rare complications of DBS surgery and has a generally accepted incidence of approximately 3%.⁶¹ 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 six 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 TS patients after stimulation of the Cm-Spv-Voi crosspoint of the thalamus may not be due to ocular abnormalities but to visual processing problems. Visual processing difficulties are frequently presented in TS and are thought to be most reflective of underlying frontostriatal dysfunction.⁶² However, previous studies examining saccades in TS reported conflicting results.⁶² Servello¹⁸ also reported subjective vertigo, blurring of vision and upward ocular deviation after thalamic DBS, 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 TS or stimulation. Subjective lack of energy was the other main adverse event in this study, reported

previously and by both patients and caregivers.⁸ 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 randomisation period. A second and related limitation concerns the randomisation 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 optimisation of stimulation during the immediate postoperative period. However, uncertainty about this was however 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 TS or OCD-like symptoms.⁶³ Given the complexity of TS and difficulties adhering to cross-over protocols, future studies should consider delayed therapy or randomisation to *off* or *on* groups rather than a cross-over design.

This trial was intended to enroll 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 objectivised. Given the availability of other potentially promising targets, such as the GPi, the paucity of available refractory TS patients, 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 randomised trial suggest that stimulation of the Cm-Spv-Voi crosspoint of the thalamus may lessen the severity of tics in patients with refractory TS, but with the risk of adverse effects on oculomotor function and reduced energy levels.

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Chapter 6

Paradoxical results of thalamic stimulation in a Tourette patient with severe comorbidity

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Submitted

Introduction

In 1999, Deep Brain Stimulation (DBS) was introduced as a new therapeutic approach for intractable Tourette Syndrome (TS).¹ Since then, both single and multiple areas have been targeted to deal with tics and comorbid symptoms of TS, including Attention Deficit Hyperactivity Disorder (ADHD), obsessive-compulsive disorder (OCD) and behaviour (OCb), self-injurious behaviour (SIB), depression and anxiety. Most patients had beneficial outcomes and adverse effects, both surgery and stimulation related, were mostly minor and relatively well tolerated or inverted by changing the stimulation parameters.² At present, DBS for TS is still considered to be an experimental option with limited controlled and double blind data.³ While quality of life is often more impaired by comorbidities than by tics³, guidelines for patient selection^{4,5} mainly focused on tics. Also in the recently published revision³, specific recommendations about comorbidity in patient selection are relatively underexposed, which is probably due to insufficient knowledge in the field.

In 2010, we have completed a double-blind trial stimulating the Centromedian nucleus-Substantia periventricularis nucleus-Ventro-oralis internus (Cm – Spv – Voi) crosspoint of the thalamus.⁶ Here we report on an institutionalized patient with intractable TS and severe comorbidity, including life-threatening SIB. Although she was younger than 25 years, she was included in the trial and underwent surgery for clinical urgency. Postoperatively, she could not be randomised within the period of follow-up because of unexplained complications. We discuss the nature of the complications and whether these complications are related to preoperative comorbidity.

Case report

History

The 20-year old female patient was born with a mild spastic diplegia. The diagnosis of TS was made at the age of 10 years with both motor and vocal tics. Comorbidities included depression, pervasive developmental disorder not otherwise specified (PDD-NOS), compulsions and severe SIB, including pounding her head and arm (she had to wear a helmet and a bodyprotector), poking sharp objects into her body and scratching until bleeding. Numerous pharmacological treatments had been administrated and discontinued, due to side effects or lack of response. Behavioural therapy and electroconvulsive therapy were even leading to new tics. In November 2006, she underwent surgery for thalamic DBS. See for the surgical methods Ackermans et al.⁶ and for the final electrode position and stimulation settings Table 6.1.

Table 6.1 Final electrode position and stimulation parameters

		Left	Right
X	mm lateral APC-PC	5	5
Y	mm posterior Mid AC-PC	4	4
Z	mm beneath AC-PC	Contact 1 on target -2	Contact 1 on target -2
Electrode		central	Central
Number of MER		2 (central and lateral)	1
Stimulation pattern		1-,2+	5-,6+
Amplitude (mV)		5	5
Wave (msec)		60	60
Frequency (Hz)		110	110

AC = anterior commissure; MER = microelectrode recording; PC = posterior commissure

Postoperative course

Three weeks after surgery, while adjusting the parameters, she showed an abrupt onset of severe hypertonia in her left leg. In the following days this extended to the right leg and both arms, followed by involuntary movements of the left arm, and on one occasion rotating movements of both arms above the head. The symptoms did not disappear when switching *off* the stimulator. Either with or without stimulation, the hypertonia was present but inconsistent over time and could not be classified within the phenomenology of organic movement disorders such as myoclonus, dystonia or spasticity. During the first month after surgery, she was bedridden and developed an opisthotonus. Rehabilitation with a cognitive behavioural approach was not successful. In May 2007 she developed unexplained disturbances of consciousness, followed by periods of mutism. To exclude a side-effect of stimulation, double-blind stimulation was performed at 19 months after surgery according to the procedure of the trial.⁶ Unblinding the conditions showed an increase in tics (see Table 6.2) but a relief of hypertonia while the stimulator was switched *on*, and *visa versa*. For the patient, the results were completely unexpected and she decided to switch the stimulator *off*. From that time on she showed hypertonia in her legs and alternating in her arms, but relatively few motor and vocal tics. Later, she developed complaints of impaired swallowing, nausea and she could not bear food anymore. Diagnostics (e.g., gastroscopy) did not result in an organic explanation and psychiatric consultation did not reveal a depressive state. In November 2009, she passed away in a nursing home. For personal reasons no autopsy was performed.

Table 6.2 Pre- and postoperative assessment of tics and comorbidities

	Before surgery ^a	Stimulation <i>off</i> ^b	Stimulation <i>on</i> ^c
Tic severity (YGTSS total)	42	12	39
Vocal tics (YGTSS vocal)	17	0	14
Motor tics (YGTSS motor)	25	12	25
OCD (Y-BOCS)	20	8	7
SIB (VAS)	5.7	0	8.9
ADHD (CAARS)	58	41	45
Autism (PDD-SQ)	136	127	124
Depression (BDI)	12	20	15
Anxiety	32	41	44

^a = preoperative medication included duloxetine (30mg/day), alprazolam (0.50mgx4/day), baclofen (20mgx3/day) and pergolide (0.05mg/day); ^b = 22 months after surgery, at the end of the first randomization period of 3 months with stimulation *off*; ^c = 23 months after surgery, at the end of the second randomization period of only 6 weeks with stimulation *on*; ADHD = Attention Deficit Hyperactivity Disorder; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory (2nd edition); CAARS = Conners Adult ADHD Rating Scale; OCD = Obsessive Compulsive Disorder; PDD-SQ = Pervasive Developmental Disorder-Self Questionnaire; SIB = Self Injurious Behaviour; VAS = Visual Analogue Scale; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; YGTSS = Yale Global Tic Severity Scale

Discussion

The most frequently reported side effects for DBS in TS are fatigue and apathy, both related to thalamic stimulation.⁶ So far, there has been no report of physical symptoms with a progressive course after a DBS procedure and a reversed effect during double-blind stimulation. Considering the criteria of Fahn and Williams⁷, the abrupt onset of the hypertonia, its inconsistency and incongruency with organic disorders, the bizarre movements and the concomitant somatizations (loss of consciousness, mutism and later swallowing disturbances) suggest a psychogenic nature. However, clear diagnosis of a psychogenic disorder was difficult in light of the complex neurological and psychiatric history, with a relatively high risk of a false positive interpretation. The symptoms could be seen as progression of unidentified preoperative comorbidity. Alternatively, the surgical procedure or stimulation may have caused a dysbalance in the limbic and associative cortico-basal ganglia-thalamocortical loops⁸, leading to compensatory psychiatric symptoms or disinhibition of preoperatively unidentified psychogenic features. Imitation and simulation are not obvious in our patient, but high expectations, or the loss of tics as a protection to daily demands, might have interfered with the results of DBS. All efforts to optimize postoperative adjustment could however not prevent overall deterioration.

This case demonstrates the complexity of TS and DBS as a therapeutic option. Although DBS is a promising treatment option for severely affected TS patients, it is still in its infancy. Towards a standard neurosurgical procedure, refinement of patient selection is warranted with exclusion criteria for those TS patients at risk of

unfavourable outcomes. Recent guidelines³ recommend treatment of comorbidities prior to surgery, which suggests that comorbidities have predictive value for the postoperative outcome. Our case report supports the assumption that preoperative comorbidities may lead to postoperative complications. Retrospectively, we may have underestimated the impact of her medical history with spastic diplegia and severe psychiatric comorbidity. Moreover, given the complexity of Tourette, it is easy to overlook psychogenic features and symptoms related to personality disorders. Therefore, clinicians should be alert on potential masked psychiatric symptoms during the preoperative selection procedure.

In conclusion, based on the reversed results during double blind stimulation, the present case report emphasizes the need for double blind studies. These studies should take into account comorbidity, both as an outcome and a predictor variable. The clinical message is that clinicians should be alert on potential masked psychiatric symptoms during preoperative screening. Attempts to treat comorbidities prior to surgery for DBS might prevent postoperative complications and disappointment in terms of quality of life and is as such a legitimate excuse to postpone the surgical procedure.

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Chapter 7

Vertical gaze palsy after thalamic stimulation for Tourette Syndrome

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Introduction

Thalamic deep brain stimulation (DBS) is a new therapeutic intervention for Tourette Syndrome (TS).¹ TS is a neuropsychiatric disorder characterized by motor and phonic tics, often associated with behavioural disorders like obsessive compulsive behaviour (OCb), attention-deficit hyperactivity disorder (ADHD) and self-injurious behaviour (SIB).

Vertical gaze function is the result of a complex mechanism involving midbrain and brainstem nuclei.² The oculomotor and trochlear nuclei contain the ocular motoneurons controlling vertical eye movements. The premotor signal for saccadic eye movements is generated by burst cells in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). The riMLF is located close to the midline just above the dorsomedial to the anterior pole of the red nucleus, lateral to the periaqueductal gray matter and the nucleus of Darkschewitsch, and rostral to the interstitial nucleus of Cajal (INC).² We describe a patient who developed a vertical gaze paralysis after DBS performed for intractable TS, due to a small deep bleeding in the upper mesencephalon. In this report, the origin of vertical gaze palsy and the anatomical localization of vertical gaze nuclei are discussed.

Case report

History

A 39-year-old man underwent bilateral thalamic DBS because of intractable TS. For 33 years he was suffering from socially and physically debilitating motor and phonic tics especially coprolalia. He also suffered from Self Injurious Behaviour (SIB) like banging his forehead against a wall or window.

Antipsychotic medication from different pharmacological groups, and clonidine, as well as cognitive behaviour therapy were tried but had to be stopped because of lack of effect or due to side effects.

Operation

Three days pre-operatively a magnetic resonance (MR) imaging with double-contrast gadolinium was performed for optimal visualization of the blood vessels. On the day of surgery, after fixation of the stereotactic frame (CRW-frame), a CT-scan without contrast was performed. The target, in the medial part of the thalamus at the crosspoint of the centromedian nucleus, the ventro-oralis internus and the substantia periventricularis, was set on fused CT-MR-images, in reference to the anterior commissure–posterior commissure (AC-PC)-line. Details of the target and the surgical technique in general can be found elsewhere.¹ Special attention was paid to the

planning of the trajectory, so that even the smallest blood vessels could be avoided. For all our DBS-procedures we use Leadpoint® system (Medtronic, Kerkrade, The Netherlands) allowing the insertion of five micro-electrodes simultaneously. With this system, we perform extracellular single-unit recordings and trial macrostimulation. In this case, during the planning of the target at the left side no trajectory for the medial and anterior electrodes could be found that would avoid a small blood vessel located close to the border of the third ventricle. Therefore, we decided to use only the central, lateral and posterior electrodes. During the operation, with the patient being sedated, a neurologist tested the patient's word fluency, horizontal eye movements and urges to express a tic. The operation was uneventful, at both sides. Immediately postoperatively however, the patient complained about diplopia and dizziness.

Examination

Ophthalmologic examination revealed an up- and downward gaze palsy on saccadic and smooth eye pursuit movements and a small convergence disturbance (see Figure 7.1). Horizontal saccadic and pursuit gaze were normal. The horizontal and vertical optokinetic reflexes were spared. There was no ptosis and the diplopia could not be objectivated. The pupils were isocoric with a scotopic diameter of seven mm. The direct and consensual pupillary responses to light were normal. The confrontational visual fields were complete, with no visual neglect. The other cranial nerve functions were normal. Further neurological examination showed no abnormalities. One day after the DBS-procedure a CT-scan was performed. This showed an area of increased signal intensity medially and distally at the tip of the left electrode, across the midline (see Figure 7.2). When the stimulator was switched *on* the patient noticed a subjective increase of his vertical gaze palsy. In order to assess the deficit, video-recordings were made while the patient was unaware of the stimulation condition. Manipulation of the choice of active electrodes, or switching the stimulation *off*, did not have any influence on the gaze impairment.

Postoperative course

Two weeks later the pulse-generator was implanted. The clinical signs gradually improved spontaneously. Finally, after 3 weeks the patient was discharged from the hospital. At that moment almost 50% of his vertical gaze palsy was resolved. Six months postoperatively an ophthalmologic re-examination was performed with prolonged DBS-stimulation, and after the stimulator being switched *off* for 12 hours. In both conditions there were maximal up-and downward eye-movements on a Hess screen. Within this range the upward saccadic velocities were still reduced by 20-25 degrees, while the downward gaze had completely normalized.

Figure 7.1 Eye positions of gaze one day postoperatively. From top to bottom: forward gaze (A), upward gaze (showing elevation paralysis) (B), downward gaze (showing depression paralysis) (C) right gaze (D), left gaze (E), and convergence (F). Full horizontal gaze is present.

Figure 7.2 Unenhanced CT-scan made 1 day post-operatively. An axial section at the level of the rostral midbrain shows discrete increased intensity (line 1) in the tegmentum adjacent to the third ventricle caudal of the tip of the left electrode (line 2) crossing the midline.

Discussion

We report a patient with TS, who developed vertical gaze palsy, especially in the upward direction, following the implantation of DBS electrodes in the medial part of the thalamus. Taylor et al.⁵ reported on a patient with central nystagmus induced by DBS of the centromedian nucleus of the thalamus for intractable epilepsy.

The presenting symptoms of vertical gaze palsy, in absence of convergence-retraction nystagmus and light-near dissociation (the light reflex is absent or abnormal but the near response is intact), makes the diagnosis of Parinaud syndrome unlikely.²

The postoperative CT-scan (see figure 2) revealed a hyperdense lesion across the midline caudally to the tip of the left electrode. This area corresponds with bilateral pretectal components including the riMLF, without involvement of the oculomotor and red nuclei. A previously described bilateral lesion of the riMLF resulted in bilateral gaze palsy, with preserving of vertical gaze holding, vestibular ocular reflex and pursuit.² The pontine tegmentum was completely spared explaining the normal horizontal eye movements.

Minor intracranial hemorrhages usually recover completely with good neurological clinical outcome. Our patient showed a partial recovery from vertical gaze palsy after six months. A possible explanation of the remaining upward gaze palsy is the difference in the anatomical position of the tracts with the riMLF efferent pathways for up- or downward gaze hypothetically being completely distinct.⁶ The tracts responsible for downward gaze lie medially, with an unknown level of decussation. The upward gaze tracts with decussation in the posterior commissure lie laterally. The longer trajectory of the upward gaze tracts may explain the higher incidence of upward gaze palsies as compared with downward palsies.² This is in contrast with the ipsilateral innervation of depressor muscles and the bilateral innervation of elevator muscles.⁷

Intracerebral hemorrhage is one of the most severe complications of DBS surgery, but rarely occurs and has a generally accepted incidence of 3%. It is known that surgery at the level of the thalamus is accompanied by a higher risk for bleedings.⁸ However, a recent study by Binder et al.⁹ showed that the target of choice within the DBS procedure is the main predictor for hemorrhagic stroke; the globus pallidus internus has the highest risk and the thalamus has the lowest. Another predictor of thalamic stroke is the preexistence of hypertension and intraoperative blood pressure. In our case, the patient's pre- and perioperative blood pressure remained within a normal range. In our experience often small vessels can be visualized on double dose gadolinium MR images, especially at the medial part of the thalamus, close to the border of the third ventricle.

The small hemorrhage under the tip of the left electrode, which extends 3 mm below the target may have been caused during micro-electrode recordings. It remains unclear whether or not the bleeding in this case was the result of the use of the specific microelectrode.

Conclusion

Vertical gaze palsy is an uncommon complication after thalamic DBS for intractable TS. Because the thalamic target for DBS is located near the nuclei responsible for vertical gaze, trajectory planning and electrode positioning should be done with a special focus on vertical eye movements and with extreme accuracy and caution.

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Chapter 8

Thalamic Stimulation and Penile Erection

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Introduction

Penile erection is a complex neurovascular event.¹ It is controlled by a spinal generator network and a supraspinal controlling system and their reciprocal interactions.²⁻⁶ The role of the spinal system has been extensively described.⁷ On the other hand, little is known about the supraspinal control, specifically about the role of the thalamus.

Two patients underwent successful bilateral Deep Brain Stimulation (DBS) of the thalamus for Tourette syndrome (TS). TS is a chronic neurological disorder characterised by vocal and motor tics.⁸ The onset is generally in childhood and the disease is frequently self-limiting. A small number of patients, however, remain symptomatic and usually require pharmacological treatment. In 1999 Vandewalle et al.⁹ introduced DBS as a treatment for intractable TS. There are no specific sexual disorders linked to TS. The two patients of this study experienced changes in penile erection in response to sexual stimuli.

In the present study, penile erection in stimulation *on* and *off* conditions has been examined in a laboratory setting to investigate the role of the thalamus in erection.

Methods

Two patients (male, 42 and 45 years old) with absent co-morbidity underwent deep brain stimulation (DBS) of the thalamus for intractable TS. The patients gave written informed consent for the surgery and this study. Electrodes (Medtronic, model 3387) were implanted bilaterally in the thalamus at the level of the nucleus ventro-oralis internus (Voi), centromedian nucleus (Cm) and substantia periventricularis (Spv) as described earlier.⁹ The final position of the electrode was determined by the clinical response of the patients who were tested by the blinded neurologist. The coordinates were: left 5 mm and right 3 mm in patient 1, left 3 mm and right 5 mm in patient 2, lateral to the anterior-posterior commissure (AC-PC) line, 4 mm posterior to the midcommissural point, and at the AC-PC plane. Post-operative MR imaging confirmed the correct position of the electrodes. Two weeks later, the pulsegenerators (Itrel III, Medtronic model 7425 for patient 1/ Kinetra, Medtronic model 7428 for patient 2) were implanted subcutaneously beneath the clavicle. Extensive neuropsychological testing was performed pre- and postoperatively. The patients were followed for 5 years and 8 months, respectively. The stimulation parameters for patient 1 were: 1.6 V/ 130 Hz / 90 µs, monopolar (electrode 1 and 5 negative) and for patient 2: 6.4 V/ 130 Hz / 120 µs, monopolar (electrode 2 and 6 negative).

Penile erection in both patients was evaluated at the same time of the day, during two sessions on subsequent days with the stimulation *on* and *off*. *Off* stimulation evaluations were performed 12 hours after turning *off* the stimulation. An electromechanical strain gauge, developed by Barlow et al.¹⁰, was used for penile circumference measurement. The gauge was connected to a BIO2-high sensitivity bio-

amplifier (Psylab) and an IBM-compatible computer. Calibration was performed after every session to translate millivolts into cm penile circumference. Participants received instructions on using the rotating dial of a potentiometer to indicate their subjectively experienced sexual arousal. Participants were shown 5 selected clips from erotic films, in color and with sound, each lasting 3 minutes. During another trial they were asked to engage in a sexual fantasy for 3 min., either choosing a favorite fantasy of their own or repeating by imagery (portions of) the previously presented erotic video films. As an internal validity check, film stimuli were accompanied by cognitive tasks of varying difficulty, producing increasing cognitive load, and competing for attention with the erotic stimuli. Previous work in this area demonstrated a robust inhibitory effect of increasing distraction on erectile response in sexually functional men.¹¹ After an adaptation period of 3 minutes, a 60-second penile circumference baseline was established. Between stimulus presentations, a rest period of a minimum of 3 minutes allowed the participant's arousal to return to baseline. The last 60 seconds of every inter-stimulus interval was used to measure pre-stimulus baseline penile circumference.

Results

Evaluation revealed, respectively, a 90% and 92.1%- reduction of tics at 5 years follow-up in patient 1 and at 8 months in patient 2. The general intelligence level for the patients was average to above average (IQ's 108 and 114 resp.). Pre-operatively, the patients showed borderline to low results on verbal memory, and patient 2 performed below average for facial recognition. Postoperatively, patient 1 showed little or no change on the tests. Patient 2 had low scores on most timed tasks, including visual reaction time and word fluency. Verbal memory and facial recognition scores increased, with a possible retest effect.

The patients reported, retrospectively, normal preoperative sexual function. DBS of the thalamus was found to have a profound impact on the genital response to visual erotic stimulation and sexual fantasy under laboratory conditions, as shown in Figure 8.1. Patient 1 experienced almost no penile erection in the stimulation *off* condition whereas patient 2 had a manifest erection. In the stimulation *on* condition, the speed of erection and amplitude of penile circumference was remarkably increased in patient 1. In patient 2, turning *on* the stimulation practically inhibited erection. These findings were consistent for all 5 erotic clips and 1 sexual fantasy within each session. On the whole, subjective sexual arousal (not shown) was found to follow the differential pattern of genital arousal during *on* and *off* conditions in both participants.

Figure 8.1 Time course of the speed of erection and amplitude of penile circumference during the 5 erotic clips and 1 sexual fantasy, while applying various methods of distraction. The test has been performed with stimulation *on* and 12 h *off*.

Discussion

Subjective changes in sexual response to sexual stimuli experienced by both patients have been confirmed by the present study. In laboratory conditions, thalamic stimulation increased erection in patient 1 and reduced it in patient 2. These different reactions of penile erection to visual erotic stimuli may be the result of difference in localization of the electrodes, the stimulation parameters for optimal motor effect, the duration of chronic stimulation, or the inter-individual variation in erectile reactions. With the present localisation of the electrodes and stimulation parameters, however, there is a net effect on tics in both patients. The inter-individual variation may be a plausible explanation as patient 1 experienced a minor erection whereas patient 2 had a manifest erection in the stimulation *off* condition. This difference in the *off* condition may, however, also be induced by long-term stimulation in patient 1 since this patient reported normal sexual function pre-operatively. The difference in electrode position could also cause the difference in penile reactions since the mechanisms of action of tic reduction and penile erection may be completely unrelated.

Several studies hypothesize that a dysfunction of the cortico-basal ganglia-thalamocortical circuits underlies the pathophysiology of TS. The midline and intralaminar thalamic (Spv and Cm) nuclei play an important “gating” role in the

regulation of the basal ganglia- thalamocortical information flow.⁹ DBS probably modulates the properties of this “gate”. Data from preclinical studies suggest that the thalamic caudal and lateral intralaminar nuclei are possibly involved in processing the sexual outflow from the spinothalamic pathway towards the preoptic area, temporal lobe and the frontal cortex.⁴ DBS of this region could interfere with the electrical activity of these “gating” structures resulting in different erectile reactions to sexual stimuli. Furthermore, the possible involvement of the thalamus in human penile erection has also been demonstrated in a recent study using blood oxygenation level-dependent (BOLD) functional MRI.¹²

Our findings confirm that the intralaminar thalamic nuclei play an important role in penile erection and that erection can be modulated by DBS of this region.

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Introduction

Penile erection is a complex event controlled by vascular, hormonal and neuronal systems.^{1,2} The neuronal system involved in erection is often divided into a spinal and supraspinal network. It is generally accepted that the spinal system directly controls erection and that the supraspinal network modulates this control mechanism through different ascending and descending pathways.³ The final step in erection, after these controlling centres, is the local relaxation of smooth muscle and the subsequent several fold increase of penile circulation resulting in an erect phallus. This step at least requires a functionally well-timed and well-tuned nervous system. Defects in this system can give rise to various forms of erectile dysfunction. The spinal cord integrates information from somatic and autonomic afferents, and supplies the penis with regulatory efferents. In turn, the spinal cord receives afferent feedback from somatic and visceral fibres originating from the penis and perigenital area.⁴ The main intraspinal centres involved in this process are the sacral parasympathetic nucleus (Spn), the thoracolumbar sympathetic nuclei (intermediolateral cell column and dorsal grey commissure) and the pudendal motoneurons.⁴ Little is known about the supraspinal network. An excitatory pathway has recently been identified from the lumbosacral spinal cord to the oxytocin secreting parvocellular region of the paraventricular nucleus (Pvn) of the hypothalamus.⁵ Oxytocin seems to be an important neurotransmitter as its intrathecal administration elicits penile erection.⁵ Furthermore, reciprocal connections between the periaqueductal grey, hypothalamus, thalamus, amygdala, hippocampus and various cortical areas are likely to be involved in the brain control of erection.⁶ The general idea is that there is no specific 'erection centre' in the brain and that erection is controlled by widespread interrelated pathways.²

In the past years, most research was mainly focused on the peripheral control of penile erection rather than the central control. This has increased the knowledge of the peripheral physiology and resulted in the introduction of phosphodiesterase 5 inhibitors as an effective treatment for several forms of impotence.⁷ Even though some groups had focused their research on central pathways in the past decades,⁸⁻¹⁰ the brain as a potential therapeutic target has generally been ignored.¹¹ The introduction of apomorphine, a pro-erectile drug acting at supraspinal levels, in the clinical treatment of erectile dysfunction¹²⁻¹⁴ and the recent case report of changes in penile erection following deep brain stimulation (DBS) of the thalamus has raised the question as to what extent direct central modulation of erection is possible.^{12,13,15} Two patients suffering from intractable Tourette Syndrome (TS) underwent DBS of the thalamus. Postoperatively, patients experienced changes in erectile function, which could easily be reversed by turning *off* the stimulator. The thalamus has generally been regarded as a group of relay nuclei that serve as a 'gate' for sexual information from the spinal cord towards higher centres. Recent evidence, however, suggests a more

integrated regulatory function.¹⁵ In this literature review, the role of thalamic nuclei in erection is discussed.

Search strategy

All articles that contained information on the role of the thalamus in erection were reviewed. The reports were found by a Medline search (Pubmed) using the following key words: thalamus and thalamic in combinations with sexual, sexual arousal, sexual function, ejaculation, erection, intercourse and copulation. Only papers published in English were reviewed. Some of the reviewed reports in this article were not found by this search. These were found by analysis of the bibliography of all included papers. Articles containing original information on the thalamus and erection were reviewed thoroughly, whereas reports only mentioning sexual arousal, ejaculation or both, and not erection, are briefly summarized. In total, 13 reports were found describing original data. All data about patients and/or experiments were collected.

Results

The role of the thalamus in erection

—1980. One of the first reports on the cerebral representation of penile erection was by MacLean and Ploog in 1962.¹⁶ They remarked that ‘although the brain has been extensively explored by electrical stimulation, surprisingly little has been learned about the localization of structures involved in penile erection’. Such information could provide more insight into the neuronal mechanisms involved in sexual behaviour. In their experiments, observations were made on 29 *Saimiri sciureus* (squirrel monkey). Electrical stimulation was performed under stereotactic conditions in various parts of the brain. The number of trajectories and stimulation sites were not reported. Erection was graded on a six-point scale, independency and blinding unmentioned. MacLean and Ploog remarked that positive responses were elicited when the electrode entered the thalamic tubercle and was lowered towards the rostral pole of the thalamus. The thalamus was, according to the authors, proerectile like many other forebrain regions. After 1 y, the same authors published another article dealing with the cerebral representation of penile erection.¹⁷ This time special attention was paid to the caudal thalamus, midbrain and pons. Under conditions similar to previous experiments, 30 *S. sciureus* were operated on. Stimulation from the medial dorsal (MD) nucleus to the posterior part of the thalamus was found to elicit erection. In contrast to other brain regions, higher frequencies were required: 60–100 Hz instead of 20–30. The authors concluded that in the midline part of the MD nucleus of the thalamus, a continuity of positive loci could be found from its rostral to its caudal limits. Again, no mention was

made of blinding and independency of erection rating. In addition, the exact anatomical location of the stimulation sites remained unclear as the post-mortem sections only demonstrated trajectories. Along one trajectory multiple targets had been stimulated. In 1968, Robinson and Mishkin¹⁸ described their findings on intracerebral stimulation and penile erection in *Macaca mulatta*. They remarked that electrically evoked penile erection had already been studied intensively by MacLean and co-workers in the squirrel monkey, but that these findings were not confirmed by studies in other primates. Using a stereotactic frame made of acrylic cement, 5880 loci were explored by stimulation through a monopolar electrode in three locally anesthetized three *M. mulatta*. In total, 205 electrode trajectories had been made. Animals were tested by two investigators for erection that was graded as small (penis not fully extended) or as large (rigidly extended), without mentioning blinding and independency. The latency for erection following stimulation varied from 1 to 8 s. Erection occurred at 162 stimulation sites. These areas were summarized as the anterior cingulate region, anterior internal capsule, putamen, lateral and medial preoptic regions, lateral and medial hypothalamus, tegmentum, midline thalamus, amygdala and stria terminalis. In contrast to previous experience, no erection was evoked by stimulation of the mammillary body.¹⁶ In addition, hippocampus, fornix, septum and most of the thalamus were also unresponsive. The authors concluded that the proerectile regions were mainly located within the limbic system and also involved the midline thalamus. No additional information, however, was provided on which nuclei within the midline thalamus were involved. The anatomical localization of the stimulation sites lacked certainty for two reasons. First, no intraoperative recordings had been performed that could give some indication about the anatomical localization. Second, post-mortem sections only demonstrated a trajectory, making it impossible to define where the actual stimulation sites had been. Several years later, Sapolsky and Eichenbaum¹⁹ reported on the thalamocortical mechanisms in odour-guided behaviour. Before and after ablation of brain structures, adult male hamsters were subjected to odorants varying from after-shave to sexual stimuli (odour of adult male or adult ovariectomized, induced estrus, female hamsters). Lesions in the MD nucleus of the thalamus and in the prefrontal cortex inhibited odour-guided erection and intercourse. The authors concluded that the projection from the olfactory cortex to the MD nucleus and from there upwards to the frontal neocortex was involved in the sexual processes. Unfortunately, in this report no sections of the lesions were provided that could have given an indication about the anatomical localization and the extent of the lesions.

—1981. Park et al.¹¹ described the activity of brain regions involved in penile erection using blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI). Twelve sexually potent male volunteers and two hypogonadal impotent patients participated in their study. Two sets of stimuli were used: erotic films (sexual arousal condition) and documentary film (neutral condition). There were

two alternating periods of rest and stimulation. Brain maps were generated during the various periods of stimulation. Penile erection and sexual arousal were assessed using a five-point scale. Blinding and independency were not mentioned. Significant increases in penile erection and in 'perceived sexual arousal' were observed during visual erotic stimulation. In normal patients, BOLD-fMR images demonstrated significant activation in the inferior frontal lobe, cingulate gyrus, insula, corpus callosum, thalamus, caudate nucleus, globus pallidus and inferior temporal lobe as a result of erotic stimulation. The thalamus showed bilateral activation in 10 of the 12 subjects. In hypogonadal patients, activation was observed only in the inferior temporal lobe and thalamus. After testosterone supplementation, however, there was an increase in activated regions in their two patients and the pattern of activation became comparable to that of normal patients. The authors remarked that functional brain imaging bridged the gap between neurobiological systems and behavioural sciences. Furthermore, they stated in their study that sexual activation areas could be divided into limbic and paralimbic areas. The thalamus was a part of the limbic activation. Its involvement in erection was not discussed further, unfortunately. It still remains unclear whether thalamic activation is due to sexual arousal, erection or both. Recently, two papers demonstrated significant thalamic activation as a result of increased sexual arousal measured by the same technique.^{20,21} In these studies, however, it is not described whether sexual arousal was accompanied by erection or not. The situation becomes even more complex when the report by Arnow et al.²² is considered. They also mapped brain activation using BOLD-fMRI following visual erotic stimulation. In their study, no specific changes were noticed at the level of the thalamus in response to erotic clips. Arnow et al. concluded that future studies were required in order to study such discrepancies.

In a recent case report, the involvement of the thalamus in penile erection was reinforced. In two patients suffering from intractable TS, DBS of the thalamus was performed.^{23,24} Electrodes were implanted bilaterally in the thalamus at the level of the nucleus ventro-oralis internus (Voi), centromedian nucleus (Cm: as a part of the intralaminar thalamic nuclei) and substantia periventricularis (Spv: as a part of the midline thalamic nuclei). Evaluation revealed a 90 and 83% reduction of tics at 5 y follow-up in patient 1 and at 8 months in patient 2, respectively. The patients, however, experienced changes in penile erection in response to sexual stimuli after the surgery. Penile erection was measured in stimulation *on* and *off* conditions using an electromechanical strain gauge. Patients were shown selected clips from erotic films. DBS of the thalamus was found to have a profound impact on the genital response to visual erotic stimulation and sexual fantasy. Patient 1 experienced almost no penile erection in the stimulation *off* condition, whereas patient 2 had a manifest erection. In the stimulation *on* condition, the speed of erection and amplitude of penile circumference was remarkably increased in patient 1. In patient 2, turning the stimulation *on* practically inhibited erection. On the whole, subjective sexual arousal was found to follow the differential pattern of genital arousal during *on* and *off*

conditions in both participants. The authors explained these different penile reactions to visual erotic stimuli by differences in the stimulation settings. In patient 1, the location of the left electrode is 2 mm lateral and the right electrode 2 mm medial in relation to the position of the electrodes in patient 2. According to the authors, DBS of the thalamus was probably affecting the neural network involved in sexual processing, which also comprised the amygdala and the orbitofrontal cortex. Different electrode positions could therefore give rise to these opposing effects, as a result of a possible differential organization of 'inhibitory' and 'excitatory' projections in this area. The difference in electrode localization had also been confirmed by postoperative MRI, which clearly demonstrated that the electrodes were placed in the medial part of the thalamus and showed approximately a 2-mm-asymmetric placement in the mediolateral plane. The conclusion drawn from this case report was that the midline and intralaminar thalamic nuclei could play an important role in penile erection. Role of the thalamus in sexual arousal, copulation and ejaculation Pfaus et al.²⁵ reported their findings on cerebral c-fos (messenger RNA) gene expression following sexual stimulation. C-fos is an immediate-early gene that is held to reflect neuronal activation.²⁶ C-fos mapping was performed following copulatory behaviour, manual stimulation of the flank and perineum and vaginocervical stimulation in female rats. Its expression was found to be distributed differently within forebrain regions depending on the type of sexual stimulation. Copulation and vaginocervical stimulation especially, induced expression throughout the reuniens, centromedial and centrolateral nuclei of the thalamus. Heeb et al.²⁷ conducted a similar study. They visualized c-Fos (protein) in the brain of Mongolian male gerbils that had been exposed to various types of sex-related stimuli or that displayed various aspects of sexual behaviour. C-Fos expression was found in the preoptic nucleus, medial amygdala and the parvicellular part of the subparafascicular nucleus (SPF) of the thalamus following ejaculation. These results were also later confirmed by Veening and Coolen²⁸ and Coolen et al.²⁹ In the same year, Ohkura et al.³⁰ reported on central c-fos expression in female sheep following a 5-min exposure to a male and intromissions. Exposure to males significantly increased c-fos levels in cortical areas, hippocampus, amygdala, hypothalamus, nucleus accumbens and MD thalamus.

In the next years, another three preclinical studies were published on the expression of early immediate genes in thalamic nuclei following sexual stimulation.^{31–33} The main findings were in accordance with previously reported literature. The SPF showed significant expression in relation to sexual stimuli. These results supported the hypothesis that the medial SPF is probably one of the main relay stations in which the spinothalamic pathway is further processed towards higher centres.

Discussion

Thalamic involvement in erection

Several clinical and preclinical studies, listed in Table 8.1, have highlighted the involvement of thalamic nuclei in penile erection. In primates, Maclean et al.¹⁷ have shown that electrical stimulation of the midline part of the MD is pro-erectile, and Robinson et al.¹⁸ have evoked erection by stimulation of the midline thalamus. In rodents, Sapolsky et al.¹⁹ have demonstrated that the MD is involved in odour-guided sexual behaviour. In patients, two studies have shown the involvement of the thalamus in erection: Park et al.¹¹ through BOLD-fMRI studies and Temel et al.¹⁵ through DBS of the medial part of the thalamus in TS patients. One important general criticism is that none of the authors was able to identify precisely the nuclei they assume to be involved. The provided post-mortem sections, in the above-mentioned preclinical studies, could not demonstrate the presumed target or were not given at all.¹⁹ Temel et al.¹⁵ mentioned postoperative MRI studies, which showed that the tip of the electrodes were located in the medial part of the thalamus, but it cannot be ruled out that neighbouring structures were also involved. It has been shown that thalamic activation can also be observed during other components of sexual behaviour such as sexual arousal, copulation or ejaculation (Table 8.2). An adequate sexual arousal is usually required for a physiological erection and erection generally precedes ejaculation. In the majority of the reviewed reports, it still remains unclear whether thalamic activation is due to a specific phase of sexual behaviour such as erection, suggesting a well-defined single function, or if it is involved in multiple stages, indicative of a more integrated function.

Organization of the human thalamus

The thalamus, virtually localized at the centre of the brain, is located under the lateral ventricles and sandwiches the third ventricle.³⁴ It consists of two parts interconnected by the which is relatively poorly developed in humans. The thalamus processes most of the information, both sensory and motor, reaching the cerebral cortex from the rest of the central nervous system.³⁵ Classically, the thalamus has been divided into nuclei according to the cyto- or myeloarchitecture and the names generally refer to their anatomical localization. The major nuclear groups are the anterior, medial, midline, intralaminar, lateral, posterior, dorsal and ventral ones (Figure 8.2).³⁴ As described earlier, various thalamic regions are thought to have a possible involvement in erection. The nucleus Voi is a member of the ventro-oralis nuclei (Vo) group and is in close relationship with the mamillothalamic tract and the Cm nucleus. The Vo is more or less equivalent to the ventral lateral (VL) nuclei in primates and rats. Cm, part of the intralaminar nuclei, occupies a large area in the caudal thalamus. It borders ventromedially on the parafascicular (Pf) nucleus, forming a complex often referred as the Cm–Pf complex.

Table 8.1 en 8.2 dwars

Cm has been regarded as one of the most important relay stations in which the anterolateral spinothalamic pathway is further processed.³⁴ Peripheral sexual sensations are most probably transmitted through this ascending pathway originating in the spinal cord.³⁶ The posterior pole of the thalamus is occupied by the pulvinar, the largest nucleus in the thalamus, which is mainly related to the visual system. The second largest nuclear aggregation is the MD complex located within the medial part of the thalamus.³⁷ The MD is often divided into a medial (or pars magnocellularis) and a lateral nucleus (pars parvocellularis). Its medial nucleus largely projects to the rostral and orbital parts of the prefrontal cortex, whereas the lateral nucleus mainly projects to the superior and lateral parts. One of its main inputs comes from the amygdaloid complex. Anatomically, the MD is closely related to the Cm–Pf complex and the Spv.

Synopsis and future perspectives

Considering the reviewed reports and the neuroanatomical organization, the thalamus participates in highly complex integrative activity and does not simply function as a set of relay nuclei. The Cm–Pf complex and the MD nucleus are likely to be the most important thalamic nuclei involved in penile erection (Figure 8.2). Functionally, these nuclei receive their main input from the ascending anterolateral system, cortical areas (depending on the type of sexual stimuli) and limbic structures. After modulating this afferent information, the projection is probably directed towards the cortical areas and limbic structures and from there backwards to the spinal generator system (Figure 8.3).

On the whole, the present data on the role of the thalamus in erection and in other aspects of sexual behaviour are far from complete. Future experiments are required to delineate its involvement and additional data are needed with respect to the organization of the sexual pathway within the thalamic nuclei. Based on the results of DBS in patients, an important question to be addressed is whether parallel organizations of excitatory and inhibitory projections exist. Furthermore, advanced neuroimaging studies in combination with tracing and receptor-binding studies should be executed in order to map the primary areas involved in the different stages of sexual behaviour.

Figure 8.2 Schematic drawing of the bilateral thalamus. Both thalami are interconnected by the massa intermedia (MI). The thalami sandwich the third ventricle (III). MD and the Cm–Pf complex are likely to be involved in erection. Other relevant surrounding nuclei are: LD $\frac{1}{4}$ laterodorsal nucleus, VL $\frac{1}{4}$ ventrolateral nucleus ($\frac{1}{4}$ ventro-oralis nucleus) and VPL $\frac{1}{4}$ ventroposterolateral nucleus.

Figure 8.3 Schematic drawing of the spinothalamic pathway that transmits the sexual information from the spinal cord to higher centres. The main intraspinal centres involved in this process are the Spn, the thoracolumbar sympathetic nuclei (intermediolateral cell column and dorsal grey commissure) and the pudendal motoneurons. The information from the spinal centre is processed at the level of the thalamus (Figure 1) and is further directed towards other cortical and subcortical areas. Finally, the thalamus receives back efferent information, which is passed towards the spinal centre.

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Chapter 9

Long-term outcome of thalamic deep brain stimulation in two patients with Tourette syndrome

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Introduction

Tourette Syndrome (TS) is a chronic complex neuropsychiatric disorder characterized by tics. Tics are sudden, repetitive, stereotyped muscle contractions (motor tics) or sounds (vocal tics).¹ 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 behaviour.² For many patients, especially those with mild symptomatology, medication and/or psychobehavioural strategies are sufficient. For patients, refractory to any treatment, surgery may be the treatment of last resort. Electrical deep brain stimulation (DBS) of the thalamus has been introduced as a new surgical technique for the treatment of intractable TS in 1999.³ Vandewalle et al.³ selected a trajectory that included the centromedian (CM), the ventral oral internal thalamic nuclei (Voi) and the substantia periventricularis (Spv) mimicking the lesions performed by Hassler and Dieckman⁴, who used to perform more than 10 up to 14 lesions in each hemisphere. The promising effects of bilateral thalamic DBS have been described in three patients with a follow-up period of 5 years, and 8 months respectively.⁵ There was a reduction in tics of 72-90% and an improvement of associated behavioural disorders.

Since then, thalamic DBS in TS has received increasing attention. A growing number of patients undergoing thalamic DBS have been reported in the literature.⁵⁻¹³ However, most published series included either few cases or relatively short follow-up periods. The aim of the present study was to describe the long-term effects of bilateral thalamic DBS on tics and overall outcome (i.e., associated behavioural disorders, cognition and mood and possible adverse effects), in 2 of the 3 earlier mentioned patients with TS.

Methods

Patients were selected for thalamic DBS based on the following criteria: the adult patient has definite TS with frequent and disabling motor and vocal tics not responsive to treatment with multiple neuroleptics and psychotherapy. In both patients, there was no co-morbidity except for associated behavioural symptoms. The patient selection criteria and operation procedure have been previously described.³ Two out of 3 patients were evaluated during a period of 10 and 6 years respectively. The third patient was lost to follow up due to emigration.

The target was defined 5 mm lateral to the anterior commissure (AC) – posterior commissure (PC) line, and 4 mm posterior to the midcommissural point, and at the AC-PC plane. Because of a stimulation-induced feeling of fear during test stimulation, in patient 1 the right electrode was placed 2 mm more medial and the left electrode in patient 2 was placed 3 mm lateral to the AC-PC line. We saw the patients every time the internal pulsegenerator (IPG) had to be replaced. The patient in case 1 received 2

IPG replacements in 10 years and the patient in case 2 received 7 replacements in 6 years. We changed stimulation parameters when a satisfactory response was not achieved or if adverse events were thought to be related to stimulation. Both patients were videotaped before and after surgery and were assessed at 3 different time points starting with preoperative assessment and at 5 and 10 years postoperatively in case 1, and 8 months and 6 years postoperatively in case 2. During postoperative follow-up we made 20 minutes video-registrations in chronic bilateral *on*-stimulation and after 12 hours *off*-stimulation. More detailed information about video-protocol and follow-up has been previously described in 2003.⁵ Video-fragments of 10 minutes were scored by 3 blinded investigators (A.W., F.P. and L.A.). Both patients underwent psychological examination at all time points including assessment of cognition and mood. Because of stimulation with increasing voltages in case 2, we made a multi-slices CT-scan to control the position. The same type of CT-scan was performed in case 1 to exclude a cholesteatoma, because of complaints of chronic otitis media and tinnitus. Both CT-scans did not show any abnormalities (see Figure 9.1). In our centre it is contraindicated to perform Magnetic Resonance Imaging (MRI) in patients with any kind of neurostimulator.

Figure 9.1 Post-operative multi-slices CT-scan of both Tourette patients 10 and 6 years respectively.

Results

Effect on tics and associated behavioural disorders

The absolute numbers of tics per 10 minutes for both patients are presented in Table 9.1.

Table 9.1 Total amount of tics per 10 min pre- and postoperatively

Patient	Pre-op		F-U <i>on</i>		Video tics/10 min F-U <i>off</i>		Long term F-U <i>on</i>		Long term F-U <i>off</i>	
	motor	vocal	motor	vocal	motor	vocal	motor	vocal	motor	vocal
1	380	42	23	19	83	23	13	18	71	19
2	142	54	24	10	94	36	36	7	60	30

Pre-op=pre-operative, F-U=follow up

Case 1

This 42 year old male was operated in 1997 by VVV. Before surgery motor tics consisted mainly of turning movements of the neck, licking and biting his shoulder, and adduction movement of the knees. Blowing and uttering sounds were the most prominent phonic tics. Compared to the number of tics prior to surgery, there was a 90.1% tic-reduction at five years after surgery, increasing to 92,6% (from 422/10min to 31/10min) at ten years after surgery.⁵ The patient still demonstrated some turning movements of the head, eye blinking and blowing. During stimulation (*on*) there was no self-injurious behaviour like biting in his shoulder and checking compulsions resolved completely.

Case 2

This 45 year old male was operated in 2002 by VVV. Motor tics like head turning, flexion movements of the head, eye blinking, touching eyelid, contracting the abdominal muscles, and grimacing, and phonic tics like sniffing, coughing and screaming were present before surgery. Pounding the stomach and screaming were the most disabling tics prior to surgery. The patient also had compulsive behaviour like breaking glasses with his hand or head. Eight months after the operation there was a tic-reduction of 82% and 78% (from 196/10min to 42/10min) after 6 years of follow-up.⁵ Major tics such as pounding his stomach, screaming, sniffing, coughing and flexion movements of the head had disappeared but he still demonstrated motor and phonic tics, especially grimacing, abdominal contractures and small uttering sounds. The compulsive behaviour was in control.

In both patients, all major tics and compulsions had disappeared. In the stimulation-*off* condition with the stimulator switched *off* for 12 hours, there was still a tic-reduction in patient 1 of 78% (422/10min to 90/10min) and in patient 2 of 54% (196/min to 90/10min).

Effects on cognition and mood

Case 1

Postoperatively (both 5 years and 10 years after DBS), measures of cognition (e.g., verbal and non-verbal memory, executive function, mental speed and attention) showed little or no change compared to those assessed preoperatively. The Beck Depression Inventory (BDI)¹⁴ was administered during the postoperative follow-up only and showed mild to moderate signs of depression (total scores were 14 and 17, respectively). At 10 years after surgery the patient reported to be very pleased with the results without a need to discard Tourette from his self-image.

Case 2

The neuropsychological assessment battery in case 2 was more extended than that in case 1. Compared to the baseline assessment prior to surgery, there was a postoperative decline in verbal fluency, in particular letter fluency, and in the total number of words learned in five trials of an auditory verbal learning task. Reproduction scores (free recall and recognition) showed no change over time. The time needed to perform the color word task of the Stroop¹⁵, a measure of selective attention, increased substantially at 8 months after surgery but decreased to the baseline level at 6 years after surgery. Psychiatric questionnaires including the BDI¹⁴ (total scores were 19 prior to surgery and after surgery 15 and 10, respectively) and the Minnesota Multiphasic Personality Inventory-2 (MMPI-2)¹⁶ showed a slight decrease in depression but the overall psychopathology based on the clinical scales of the MMPI was still high at 6 years after surgery. Figure 9.2 shows the measures on the respective clinical scales of the MMPI before surgery, 8 months (short-term follow-up) and 6 years (long-term follow-up) after surgery. The measures on the validity scales L (Lie), F (Infrequency) and K (Correction) fulfilled the criteria for interpretation at all moments of follow-up with high F scores indicating a cry for help. Both before and after surgery the profile of measures was pathological with relatively low scores for items related to somatisation and sexual identity. Compared to preoperative levels there was an increase in scores on items related to social adaptation, aggression and anger. Anger scores were very high (T-score=87) at 6 years after surgery and were also confirmed during the interviews. The patient suffered from many events including serious marital problems, recurring financial problems and health problems. Although his energy level had significantly decreased he was content with the effect of surgery at 6 years after surgery. In contrary to the patient in case 1 he was very eager to abandon Tourette from his self-image but so far he could not enjoy a life unrestricted by tics.

Figure 9.2 MMPI of case 2 pre, post DBS.

Stimulation parameters

The stimulation parameters for each patient at 5 years in case 1 and 8 months in case 2 and at long-term follow-up (10 and 6 years respectively) are shown in Table 9.2.

During the follow-up period in case 2, there have been major adjustments to the stimulation parameters with a progression of monopolar stimulation towards bilateral bipolar stimulation. The stimulation has been increased from 2,5 to 8,5V with bipolar stimulation. The patient in case 1 needed a lower voltage to avoid side-effects (dizziness, blurred vision) at long term follow-up.

Table 9.2 Stimulation parameters at follow-up of two Tourette patients who received bilateral thalamic stimulation.

Patient	Electrode settings				amplitude				rate		Pulsewidth	
	F-U		Long term F-U		F-U		Long term F-U		F-U	Long term F-U	F-U	Long term F-U
	L	R	L	R	L	R	L	R				
1	4-,5-/6+,7+	0-,1-/2+,3+	4-,5-/6+,7+	1-/case+	2,2	2,4	1,8	1,5	100	130	210	90
2	5-/case+	1-/case+	5-,6+,7-	1-,2+,3-	2,4	2,8	8,5	8,5	100	100	210	150

Each electrode has 4 poles with 0 most ventral and 3 most dorsal for right stimulation, or 4 most ventral and 7 most dorsal for left stimulation.

When case is +, the stimulation is monopolar.

L=left, R=right, 2m=at 2 months, F-U= at follow-up 5 years and 8 months for patients 1 and 2 resp.

Adverse events

Both patients reported a reduction in energy when the current intensity reached the level necessary for an optimal effect on tics. Therefore the patient in case 1 turned down his stimulation a few times during the day. The patient in case 2 did not adjust the stimulation settings and preferred the feeling of drowsiness above his tics. Both patients had hardware related complications, consisting of traction of the lead in the neck. Multiple revisions of the wound and local injections have been done with partial effect in both patients. Whereas the patient in case 1 received 2 IPG replacements in 10 years, the patient in case 2 received 7 replacements in 6 years due to his high voltage stimulation.

Effects on sexual functioning including an increased sexual drive in case 2 at 8 months after surgery have been described previously in detail.¹⁷⁻¹⁸ Sexual functioning (see Table 9.3) was measured by the International Index of Erectile Function (IIEF) including five domains.¹⁹

At long term follow-up, there was a decrease in erectile and orgasmic function of the patient in case 1 when compared with scores before and 5 years after surgery. The IIEF scores in case 2 showed a substantial improvement in sexual functioning at 8 months after surgery but a slight decrease at the long-term follow-up except for sexual drive that increased to the maximum level.

The patient in case 2 reported difficulty with his visual adaptation and vertigo but both complaints did not interfere with his daily life. Examination by an ophthalmologist did not show any disabilities. Given the complaints in case 2 we made inquiries about vision and vertigo in case 1 and he appeared to have difficulty driving his car with the stimulator *on*, because of a so called blurred vision by looking ahead. Turning down the voltage by his patient programmer reduced these complaints.

Table 9.3 Results of IIEF in two Tourette patients who underwent thalamic DBS.

	Subscore		Patient 1			Patient 2		
	no items	max score	preoperative	postoperative	long term	preoperative	postoperative	long term
Erectile function	6	30	30	30	23	13	20	15
Orgasmic function	2	10	10	10	8	0	10	8
Sexual desire	2	10	8	10	8	5	9	10
Intercourse satisfaction	3	15	12	11	13	6	14	10
Overall satisfaction	2	10	8	8	9	2	10	2

IIEFa=International Index of Erectile Functioning (Rosen et al. 1997). High score suggest a better sexual functioning.

Discussion

In both patients with TS treated by bilateral thalamic stimulation, the substantial improvement in tics observed at the initial 5 year and 8 months follow-up examination (90% and 82% improvement of tic score) was maintained after a total period of 10 and 6 years (92.6% and 78%, respectively). Corresponding to the short term follow-up assessments of the present cases⁵ only video-tic rating scales were used for evaluating the long-term efficacy of surgery. The adverse events observed in both patients were related to the hardware, energy level and vision but were not distressing at long term follow-up. The cognitive decline in case 2 concerning both verbal learning and verbal fluency is in line with findings related to left-sided thalamotomy and thalamic stimulation but the effect on daily functioning is considered small.²⁰ Although there might be involvement of the left thalamus in memory and language function²¹, thalamic stimulation did not affect the postoperative performance of case 1. Besides, a postoperative decline in verbal fluency has also been reported after stimulation of the subthalamic nucleus, but again the impact on daily life is regarded as small.²² The increase of stimulation strength seen during the follow-up period in case 2 could be the result of tolerance. Because of normal long-term follow-up CT-scan compared with the standard CT-scan, immediately after surgery, electrode malposition seems unlikely. As cited by Blomstedt et.al., increased use of bipolar stimulation over time can be interpreted as a consequence of development of tolerance to a level where monopolar stimulation cannot be increased further without eliciting side-effects.²³ This was the case in patient 2: monopolar stimulation of pole 1 and 5 led to bipolar stimulation of pole 1,2,3 and 5,6,7 at long term follow-up.

The present results indicate that bilateral thalamic DBS is effective in producing sustained improvement of tics in Tourette patients followed for more than 6 years. In addition, these results confirm the relevance of this brain area in the pathogenesis of TS. When the stimulator is switched *off*, tics reappear, which indicates that thalamic DBS does not induce permanent tic improvement in TS. However, the tics did not return to the pre-operative level which might be an after stimulation effect. Therefore, when one aims to measure tics in the stimulation *off* condition, it is recommendable to switch the stimulator *off* for a longer period. The duration of this period is still debatable. Although one surgeon (VVV) performed both surgeries, the setting of surgery was different causing the dissimilarity in both time points of postoperative evaluation and pre- and postoperative assessments (e.g., the preoperative assessment of case 1 did not include the BDI).

Although the small number of patients did not allow performing a statistical analysis and confirmation is needed by double blinded randomized trails, our observations provide a rationale for an effective treatment of TS. One major concern however is the success of adaptation after the relatively sudden alleviation of tics. Whereas advances in medicine are aimed at alleviation of untreatable chronic conditions, there have been few attempts to study the process of adaptation which is provoked by such a sudden

relief.²⁴ Given the consequences of TS for social, familial and professional life, patients have to deal with many challenges after surgery as shown by both cases but in particular the patient in case 2. Anticipating on this postoperative adjustment prior to surgery will be helpful to assist patients and their families in benefiting from tic reduction and maximizing the overall outcome and success of surgery.

Conclusion

The present long term follow-up study of two Tourette patients further supports the beneficial effect of bilateral thalamic DBS on tic reduction. Development of tolerance occurred in one of two patients and attention is needed for the adverse effects and in particular whether these are incidental or structural. The results of this open-label study justify a larger, double blinded randomized clinical trial. This study should however include a strategy to deal with the postoperative psychosocial adjustment in order to maximize the overall outcome.

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Chapter 10

General discussion

General discussion

In the last ten years, about 70 patients with TS have been reported to be treated with DBS in the literature, with ten different brain targets, including the Cm-Spv-Voi crosspoint of the thalamus.¹⁻⁴ The group of Servello and Porta⁵ targeted the same area but at a point 2 mm more anteriorly. The group of Houeto et al.⁶, targeted the centre of the centromedian nucleus, and one case is described with DBS of the dorsomedial thalamus.⁷ Besides the thalamus, the globus pallidus externus (GPe)⁸ and both the ventroposterolateral motor, as well as the anteromedial limbic part of the globus pallidus internus (GPi) have been targeted for DBS in refractory TS.⁹⁻¹⁴ Also the nucleus accumbens¹⁵⁻¹⁹, and internal capsule^{4,18,19}, have been described, mostly in TS patients also suffering from OCs. Finally, in a patient suffering from both Parkinson's disease and tics, there was an improvement of tics after DBS of the subthalamic nucleus.²⁰ (Chapter 2)

The general rationale for modulating these areas is based on the assumption that tics and associated behavioural disorders are related to a dysfunction of the cortico-basal ganglia-thalamocortical circuitry. Focal disruption of different functional striatal territories results in abnormal activation of neocortical motor and non-motor areas, producing repeated stereotyped movements and abnormal behaviour.²¹

In the following paragraphs the choice for the target as investigated in this thesis and the selection criteria for inclusion will be explained. Next the results in terms of effects and adverse events will be summarized. Finally the clinical implications and challenges for future research will be discussed.

Target

Three patients undergoing bilateral thalamic stimulation have been reported in a pilot study showing promising results on tics and associated behavioural disorders.¹ The target was chosen at the level of the medial part of the thalamus on the basis of the good results of thalamotomies described by Hassler in 1970.²²⁻²⁴ In 2002, bilateral stimulation of the posteroventral globus pallidus internus (GPi) was performed in 1 patient with TS¹⁴, who is, to the best of our knowledge, the first patient with GPi DBS for intractable TS. The rationale for this specific target was the positive effect of GPi stimulation on hyperkinesias in Parkinson's disease (PD).²⁵ In chapter 3, the effect on tics and associated behavioural symptoms of 2 patients with respectively chronic bilateral thalamic and pallidal DBS is described. The pallidal stimulation had more abrupt effects on tics when the stimulation was switched *on* or *off*, compared with thalamic stimulation. OCs increased considerably after switching *off* the stimulator for 12 hours and was reduced again with stimulation *on* in both patients. Stimulation-related side effect of reduced energy was acceptable for both patients.

These findings are in line with the basal ganglia–thalamocortical concepts as proposed by Mink.^{26,27} The striatum and the subthalamic nucleus (STN) are the primary input structures of the basal ganglia, receiving excitatory input from the cerebral cortex. The GPi and substantia nigra pars reticulata (SNr) are the primary output nuclei, sending inhibitory output to the thalamic nuclei. In TS, a disturbed activity of this basal ganglia–thalamocortical circuit is thought to be responsible for some of the typical TS symptoms.^{26,27} According to these considerations, interference at the level of one of the output or relay stations within this circuit, the GPi or thalamus, may result in a clinical improvement.

The question whether the thalamus or the GPi is the best target for DBS cannot be answered based on two cases. In both patients, the targets, either the GPi or the thalamus, were effective in reducing symptoms. However, based on the promising results of the pilot study stimulating the thalamus¹, we preferred to further focus on thalamic DBS in a larger group of patients using a prospective randomised controlled crossover design.

Patient selection

TS patients considered for DBS should comprise only very severe, intractable cases. Recommendations for both the selection of patients for DBS treatment including the assessment and study design are mainly driven by expert opinion since evidence from trials is scarce. This has a number of implications for patient selection as described in chapter 4. Our selection criteria are patients with certain TS with a minimum age of 25 and a minimum score of 25 on the Yale Global Tic Severity Scale (YTSS), without sufficient effect (or unbearable side effects) of medication and after behavioural therapy were potential candidates for surgery, without common contra-indications for surgery or structural MRI-abnormalities. Only in one exceptional case we have performed surgery before the age of 25, because of very severe and automutilative tics. For different reasons, this patient was not included in the trial.

Effects of Thalamic DBS

Tics

Although the sample size was small (six included patients) in our double blind randomised controlled trial (chapter 5), tic severity during *on* stimulation was significantly lower than during *off* stimulation, with substantial improvement (37%) on the Yale Global Tic Severity Scale. The effect of stimulation 1 year after surgery was sustained with significant improvement (49%) on the Yale Global Tic Severity Scale when compared with preoperative assessments. Associated behaviour conditions 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.

Side-effects / adverse events

Serious adverse events included a small intracranial haemorrhage in one patient resulting in vertical gaze palsy during six months and subjective changes in the velocity of upward gaze afterwards.²⁸ One patient experienced an infection, successfully treated with antibiotics. Although erectile dysfunction has been reported in two patients (chapter 8), none of the patients in the trial reported sexual complaints. All the operated patients reported a substantial restriction in their daily activities due to lack of energy.

Group analysis on cognition between the preoperative assessments and those at one year after surgery showed 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 Index (RCI) showed a decline for only one of the six patients, this group effect needs to be restrained.

In Chapter 6 a complex case is presented of a young woman suffering from intractable TS and severe comorbidity with a contradictory outcome after thalamic DBS. Postoperatively she developed symptoms not congruent with organic disorders and which were not affected by stimulation. This case demonstrates the complexity of TS with its multi-faceted symptoms. Prior to operation clinicians should be alert on potential masked psychiatric symptoms and first treat co-morbidity.

One patient of the randomized controlled trial reported vertical gaze difficulty after thalamic DBS due to a haemorrhage at the end of the left electrode (chapter 7). Vertical gaze palsy is an uncommon complication after thalamic DBS for intractable TS. Because the thalamic target for DBS is located near the nuclei responsible for vertical gaze, trajectory planning and electrode positioning should be performed with a special focus on vertical eye movements and with extreme accuracy and caution. Aside from the proven vertical gaze disturbances, all the other included patients reported visual problems. This may not be due to ocular abnormalities but to visual processing problems. Visual processing difficulties are frequently present in TS and are thought to be most reflective of the underlying frontostriatal dysfunction.²⁹ Previous studies examining saccades in TS have reported however conflicting results.²⁹ Servello et al.¹⁸ also reported about stimulation induced subjective vertigo, blurring of vision and upward ocular deviation after thalamic DBS, but in their sample, these symptoms appeared to be transient. Applying extensive vestibular and oculomotor examinations did not help us to objectify any oculomotor dysfunction that could be directly attributed to either TS or stimulation.

Although the significant effect of stimulation on tics, there are some side-effects, one could wonder whether thalamic DBS is the best suitable target for TS.

Follow-up

After at least 6 years there is still a 78% tic reduction in two patients (chapter 9). The reported side effects were related to the hardware, energy level and vision, but were not distressing at long-term follow-up.

Clinical implications

In total we operated on ten TS patients from 1997 until 2008, and followed them carefully until now. Immediately postoperatively as well as at long-term follow-up there is a significant effect on vocal and motor tics. In our population we have seen side-effects related to DBS and unrelated to the thalamic target like infection, hardware failure and intraparenchymal haemorrhage. There are some persistent and recurrent side-effects as reported by the patients, like reduced energy, visual problems, erectile dysfunction which are probably related to thalamic DBS.

Given the many different targets used for DBS in TS, and the small number of patients suffering from the intractable syndrome, continuous exchange of clinical experience, and an ongoing evaluation is important. A uniform approach with standard inclusion criteria and outcome measures is warranted to find out which the most optimal target is, or whether “tailored” targeting is needed, with a specific target for a specific subtype of patients, as also suggested by Porta et al.³⁰

Given the consequences of TS for social, familial and professional life, patients have to deal with many challenges after surgery. Anticipating on this postoperative adjustment prior to surgery will be helpful to assist patients and their families in benefiting from tic reduction and maximizing the overall outcome and success of surgery.

Future research

A major drawback of this DBS trial is the small patient number and the related limitation concerns the randomisation process. This effectively diluted the original cross-over design of the trial. Another methodological issue is that TS patients are uncertain about the stimulation condition, and this was a reason for early rescheduling in four patients. This might be a specific problem for patients with Tourette syndrome or obsessive-compulsive disorder-like symptoms.³¹ 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.

The results of thalamic DBS in TS (chapter 3, 5 and 9) prove that the technique is effective in the treatment of carefully selected patients (chapter 4). Because of the

occurrence of stimulation related side-effects (chapter 6, 7) the search for the most optimal target is still going on. Patients treated with DBS will need long-term follow-up in order to answer questions regarding long-term efficacy, and outcome. In addition, the phenotypic variability of TS patients and various co-morbidities makes it even more difficult to evaluate exactly what circuits should be modulated depending on the predominant clinical features. A future challenge regarding treatment of TS is to figure out which target has a long-lasting place as a therapeutic options. Other questions still to be addressed are whether tolerance, hardware failure would play a role. So there are a lot of questions and a few answers. Therefore a prospective, multicentre approach may be best to study the questions raised by studying DBS in selected Tourette patients.

Conclusion

This thesis addresses the results of the study on the efficacy and safety of thalamic DBS in patients with intractable Tourette Syndrome. Although the results of a double blind randomised controlled trial are positive and its safety has been shown after at least 6 years, stimulation-induced side-effects make the search for the optimal target still going on.

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Summary

Summary

This thesis addresses the results of thalamic deep brain stimulation in patients with Tourette Syndrome. We comprised selection criteria, both short and long-term follow-up and also side-effects.

Tourette Syndrome (TS) is a neuropsychiatric disorder characterized by motor and vocal tics, often associated with behavioural 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, as reviewed in **chapter 2**.

In **chapter 3**, we describe the effects of bilateral thalamic stimulation in one patient and of bilateral pallidal stimulation in another patient, to find out whether one target is the best therapeutic option. Both patients suffered from intractable Tourette syndrome (TS). Any conservative treatment had failed or had been stopped because of unbearable side-effects in the two patients. In both cases, there was no co-morbidity except for associated behavioural symptoms (compulsions). Electrodes were implanted at the level of the medial part of the thalamus (centromedian nucleus, the substantia periventricularis, and the nucleus ventro-oralis internus) in one patient and in the posteroventral part of the globus pallidus internus (GPi) in the other patient. In both cases, deep brain stimulation (DBS) resulted in a substantial reduction of tics and compulsions. These data show that bilateral DBS of the thalamus as well as of the GPi can have a good effect on tics and behavioural symptoms in patients suffering from intractable TS.

Inclusion and exclusion criteria have been formulated to identify good candidates for DBS as addressed in **chapter 4**. The selected patient should be rated according to Diagnostic Confidence Index as a definite case of TS, should be over 25 years of age, fruitlessly received medication and psychotherapy and have severe Tourette Syndrome, classified by YGTSS without psychiatric comorbidity and no common contraindications for neurosurgery.

Chapter 5 is about six patients with intractable TS were invited to take part in a double-blind randomised 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 three months stimulation followed by three-month *off* stimulation (group A) or vice versa (group B). The cross-over period was followed by

six-months *on* stimulation. Assessments were performed prior to surgery and at three, six months and one 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 one year postoperatively.

Interim analysis was performed on a sample of six male patients with only one patient randomised 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 vs. 25.6 +/- 12.8, $p=0.046$). The effect of stimulation one year after surgery was sustained with significant improvement (49%) on the Yale Global Tic Severity Scale (mean 42.2 +/- 3.1 vs. 21.5 +/- 11.1, $p=0.028$) when compared to 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 one year postoperatively. Cognitive re-assessment at one 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. These 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. We concluded that further randomised controlled trials on other targets are urgently needed since the search for the optimal one is still ongoing.

Chapter 6 describes a case-report of a 20-year old female patient suffering from refractory TS with severe psychiatric comorbidity, who was included in a randomized controlled trial stimulating the thalamus. Postoperatively, she developed symptoms not congruent with organic disorders, including hypertonia and periods of loss of consciousness, mutism and swallowing disturbances. Double blind stimulation resulted in a reduction of mainly vocal tics and an increase of hypertonia in the stimulation *off* condition, whereas tics increased with a relief of hypertonia in the stimulation *on* condition. Both medical and psychological interventions appeared to be unsuccessful. The patient eventually died leaving questions about the exact nature and cause of her complications unanswered. This case report demonstrates the complexity of TS and questions the suitability for DBS in case of severe psychiatric comorbidity. During preoperative screening clinicians should be alert on potential masked psychiatric symptoms and they should try to treat the comorbidities prior to surgery for DBS.

Chapter 7 describes a complication which might demand special attention during the planning of thalamic DBS in TS. A 39-year-old man underwent thalamic deep

brain stimulation (DBS) because of intractable Tourette Syndrome (TS). Immediately post-operatively, he complained about diplopia and dizziness. The neurological examination revealed vertical gaze palsy with preserved vertical oculo-cephalic movements. The post-operative computed tomography (CT)-scan revealed a discrete high-density lesion across the midline at the distal end of the left electrode. This area corresponds with the pretectal area including the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), with sparing of the oculomotor and rubral nuclei. Six months postoperatively maximal up- and downward smooth pursuit eye movements were achieved. Upward saccadic velocities were still reduced by 20-25 degrees. Examination of both horizontal and vertical eye movements during DBS-surgery, especially when the thalamus is targeted, is recommended.

Chapter 8 addresses side-effects reported by two patients after thalamic DBS who were not participants of the trial. Post-operatively, the patients reported changes in penile erection. Laboratory testing of penile erection in response to various erotic video clips was performed in stimulation *on* and *off* conditions. DBS of the thalamus was found to have a profound impact on the genital response to visual erotic stimulation and sexual fantasy under laboratory conditions. Penile erection is a complex neurovascular event. The neuronal system involved is often divided into a spinal (generator) and supraspinal (controller) network. Little is known about the supraspinal control. The recent finding of changes in penile erection following deep brain stimulation of the thalamus in two patients has raised the question as to what extent the thalamus is involved in erectile function. The thalamus has generally been regarded as a group of relay nuclei that served as a 'gate' for sexual information from the spinal cord towards higher centres. Recent evidence, however, suggests a more integrated regulatory function. Our review of the literature from 1960 until 2003 revealed 13 reports describing original data (preclinical and clinical). Various thalamic regions, varying from the midline thalamus to the posterior thalamus, have been reported to be activated during erection. The majority of the reports, however, showed that mainly the mediodorsal (MD) nucleus and the centromedian-parafascicular nucleus (Cm-Pf complex) are involved in penile erection. MD is the second largest nuclear aggregation located within the medial part of the thalamus. Anatomically, the MD is closely related to the Cm-Pf complex. The Cm-Pf complex is one of the most important relay stations in which the anterolateral spinothalamic pathway is further processed. This pathway is thought to transmit peripheral sexual sensations. On the whole, the present data on the role of the thalamus in erection are far from complete and future experiments are required to delineate its involvement.

Chapter 9 describes the long-term (6 and 10 years) outcome in terms of tic reduction, cognition and mood and side-effects of medial thalamic DBS in two previously described Tourette patients. We compared the outcome of two patients at 6 and 10 years after surgery with their preoperative status and after 8 months and 5 years of

treatment, respectively. Standardized video recordings were scored by three independent investigators. Both patients underwent (neuro)psychological assessment at all time points of follow-up.

Tic improvement observed at 5 years in patient 1 (90.1%) was maintained at 10 years (92.6%). In patient 2 the tic improvement at 8 months (82%) was slightly decreased at 6 years (78%). During follow-up, case 1 revealed no changes in cognition, but case 2 showed a decrease in verbal fluency and learning which was in line with his subjective reports. Case 2 showed a slight decrease in depression but overall psychopathology was still high at 6 years after surgery with an increase in anger and aggression together with difficulties in social adaptation. Besides temporary hardware related complications no distressing adverse effects were observed. We concluded that bilateral thalamic stimulation may provide sustained tic benefit after at least 6 years but to maximize overall outcome, attention is needed for postoperative psychosocial adaptation, already prior to surgery.

This thesis addresses the results of the study on the efficacy and safety of thalamic DBS in patients with intractable Tourette Syndrome. Although the results of a double blind randomised controlled trial are positive and its safety has been shown after at least 6 years, stimulation-induced side-effects make the search for the optimal target still going on. In the general discussion (**chapter 10**) we put forward the clinical implications and some future challenges.

Samenvatting

Samenvatting

Dit proefschrift beschrijft de resultaten van thalamische diepe hersenstimulatie bij mensen met het Syndroom van Gilles de la Tourette. We hebben achtereenvolgens selectiecriteria vastgesteld, de korte en lange termijn effecten bekeken, alsmede de neveneffecten.

Het syndroom van Gilles de la Tourette (TS) is een neuropsychiatrische aandoening, welke gekenmerkt wordt door motore en vocale tics, vaak gepaard gaande met geassocieerde gedragsafwijkingen. De symptomen verdwijnen vaak na de puberteit. De pathofysiologie van TS is nog steeds niet opgehelderd en voer voor discussie. Er bestaat een rationale voor het effect van diepe hersenstimulatie (DBS) gebaseerd op de huidige kennis en aannames van het cortico-basale ganglia-thalamocortical circuit. Wanneer patiënten met ernstig TS uitbehandeld zijn, kan neurochirurgie een therapeutische optie zijn. In 1999 is thalamische diepe hersenstimulatie bij een reeds uitbehandelde patiënt met TS voor het eerst beschreven. Sindsdien zijn er meerdere hersengebieden gestimuleerd in een zeer selecte patiëntengroep, zoals globus pallidus internus en nucleus accumbens.

In de literatuur zijn meerdere targets, zoals globus pallidus internus en nucleus accumbens, gekozen voor DBS bij TS. In **hoofdstuk 2** wordt hiervan een overzicht gegeven.

In **hoofdstuk 3** beschrijven we de effecten van DBS in twee patiënten waarvan er één thalamische stimulatie krijgt en de andere pallidale stimulatie, dit om uit te vinden welke target het beste is. Beide TS patiënten zijn uitbehandeld, aangezien conservatieve therapie faalde of onacceptabele bijwerkingen had. Beide patiënten hadden geen co-morbiditeit anders dan de geassocieerde gedragsafwijkingen (compulsies in beide gevallen). In een patiënt werden de electrodes geïmplanteerd in het mediale deel van de thalamus op een kruispunt van drie kernen (de centromedian nucleus, de substantia periventricularis en de nucleus ventro-oralis internus), terwijl de andere patiënt electrodes kreeg geplaatst in de globus pallidus internus. In beide gevallen resulteerde de stimulatie in een substantiële tic-reductie en een verbetering van de compulsies. Uit deze resultaten is geen onderscheid te maken tussen bovengenoemde targets bij de behandeling van patiënten met TS.

De in- en exclusiecriteria om geschikte patiënten te selecteren voor DBS worden in **hoofdstuk 4** beschreven. Samenvattend moet de patiënt een zekere diagnose van TS hebben volgens de 'Diagnostic Confidence Index' en er moet sprake zijn van een ernstige vorm zoals geclassificeerd door de 'Yale Global Tic Severity Scale'. De geselecteerde patiënt moet ouder zijn dan 25 jaar en uitbehandeld zijn, zowel medicamenteus als gedragsmatig, alvorens voor een eventuele operatie in aanmerking te komen. Bijkomend moet de patiënt geen psychiatrische comorbiditeit hebben welke

een neurochirurgische interventie in de weg zou staan. Uiteraard gelden er algemene contra-indicaties voor een operatie die niet specifiek aan TS gebonden zijn.

In **hoofdstuk 5** worden zes Tourette patiënten beschreven welke hebben deelgenomen aan een dubbel-blind gerandomiseerde cross-over studie naar de effecten van thalamisch DBS. Na de operatie werden de patiënten gerandomiseerd in twee groepen, waarbij de stimulatie eerst 3 maanden *aan* en vervolgens *uit* ging (groep A) en vice versa (groep B). Na deze *aan/ uit* periode volgende er een zes maanden durende stimulatie *aan* periode. Steeds werden de patiënten nauwkeurig geobserveerd, zowel voor de operatie, als op 3, 6 en 12 maanden na de operatie. Het primaire doel was om te kijken of de operatie effect had op de ernst van de tics, geobserveerd door de Yale Global Tic Severity Scale (YGTSS) en ten tweede om te kijken naar veranderingen in geassocieerd gedrag en geheugen. Geheugen-testen werden alleen maximaal een maand voor en 12 maanden na de operatie afgenomen. Tussentijdse analyse na zes patiënten werd er uitgevoerd, waarbij er maar 1 patiënt in groep B terecht was gekomen. De ernst van de tics tijdens de stimulatie *aan* was significant lag er dan tijdens stimulatie *uit*, met een verbetering van 37% op de YGTSS (gemiddelde 41.1 +/- 5.4 vs. 25.6 +/- 12.8, $p=0.046$). Het effect van stimulatie op de tics na 1 jaar, persisteerde met een verbetering van 49% op de YGTSS (gemiddelde 42.2 +/- 3.1 vs. 21.5 +/- 11.1, $p=0.028$) in vergelijking met pre-operatief. Secundaire uitkomstmaten veranderde in het geheel niet. Cognitietesten na 1 jaar lieten zien dat er meer tijd nodig was om de Stroop-Kleuren-Woord-Kaart test te voltooien. Dit houdt een geringe verslechtering van selectieve aandacht en impulsiviteit in. Er zijn complicaties opgetreden, zoals een kleine bloeding aan het uiteinde van een electrode, een infectie van de pulsgenerator, subjectieve oogbewegingsstoornissen en een verlies in energie in alle patiënten. Deze resultaten suggereren dat stimulatie van de thalamus, nader gespecificeerd het kruispunt van de Centromedian nucleus - Substantia periventricularis - Nucleus ventro-oralis internus een gunstig effect heeft op de ernst van de tics. Hoewel er kans is op bijwerkingen, zoals oogbewegingsstoornissen en verminderd energieniveau.

Hoofdstuk 6 is gewijd aan een 20 jaar oude patiënte met ernstige psychiatrische comorbiditeit, die was geïncloseerd in de gerandomiseerde studie. Post-operatief ontwikkelde deze patiënte symptomen die niet binnen een organisch kader paste, zoals hypertonie, bewustzijnsveranderingen, mutisme en slikstoornissen. Dubbel-blinde evaluatie van de effecten van de stimulatie liet met name een verbetering van de vocale tics zien, terwijl de stijfheid juist toenam als de stimulatie *UIT* werd gezet. Het tegengestelde gebeurde wanneer de stimulatie *aan* werd gezet. Zowel medisch als psychologisch uitvoerige onderzoeken leverde geen verklaring op. Uiteindelijk is patiënte overleden zonder antwoorden te krijgen op vragen over de tegenstrijdige uitkomsten en onverklaarbare neven-effecten. Deze casus geeft aan hoe complex TS kan zijn. Psychiatrische comorbiditeit is een factor waarmee ernstig rekening

gehouden dient te worden alvorens een patiënt een DBS als therapeutische optie voor te stellen.

Hoofdstuk 7 gaat over een opgetreden complicatie, waardoor speciale aandacht vereist is tijdens de peri-operatieve trajectbepaling bij thalamische DBS in TS. Een 39 jaar oude man onderging thalamische DBS wegens uitbehandelde TS. Direct post-operatief klaagde patiënt over dubbelbeelden en duizeligheid. Neurologisch onderzoek liet een verticale blikparese zien met intacte oculocephale oogbewegingen. Post-operatieve CT-scan liet een zeer geringe hyperdense laesie onder de tip van de linker electrode zien. Deze laesie in het pretectale gebied komt overeen met de 'interstitial nucleus of the medial longitudinal fasciculus (riMLF)', waarbij de nucleus oculomotorisch en nucleus ruber gespaard zijn. Zes maanden post-operatief heeft patiënt weer ongestoorde gladde oogvolgbewegingen in verticale richting, en zijn enkel nog de saccades in opwaartse richting met 20-25 graden verstoord. Uit deze casus leren we dat zowel horizontale als verticale oogvolgbewegingen gedurende de operatie waarbij de thalamus de target is nauwkeurig moeten worden getest.

Hoofdstuk 8 beschrijft bijwerkingen van twee patiënten na thalamische DBS.

Postoperatief bemerkten de twee patiënten thuis een tegengesteld effect van DBS op hun erectie. Zo bemerkte patiënt 1 een stimulerend en patiënt 2 een remmend effect op de erectie. Laboratoriumtesten werden uitgevoerd om de peniele erectie tijdens erotische videofragmenten te meten in de condities waarbij de stimulatie *aan* en *uit* gezet werden. Uit de testen bleek dat DBS van de thalamus onder laboratorium-omstandigheden een duidelijke, zij het niet eenduidige, remmende dan wel stimulerende invloed heeft op de genitale respons tijdens erotische stimuli en seksuele fantasie. Peniele erectie is een complex neurovasculair samenspel. Het neuronale systeem betrokken bij dit proces omvat zowel een spinaal (generator) als een supraspinaal (controller) netwerk. Er is maar weinig bekend over het supraspinale systeem inzake erecties. De recente bevindingen dat er veranderingen in erecties kunnen optreden na thalamische DBS suggereert dat de thalamus betrokken is bij dit proces. De thalamus wordt gezien als een schakelstation van seksuele informatie vanaf spinaal niveau naar hoger gelegen kernen. Recente onderzoeken suggereren een meer gereguleerd regelmechanisme. 13 artikelen met klinische en preklinische data zijn er verschenen van 1960 tot 2006.

Diverse thalamische kernen, variërend van de midline tot posterieure deel, zouden betrokken zijn bij erecties. In de meerderheid van de artikelen wordt de betrokkenheid van mediodorsale kern (MD) alsmede de centromedian-parafascicular kern (Cm-Pf-complex) beschreven tijdens erectie. MD is de tweede grootste kern gelegen in het mediale deel van de thalamus. Anatomisch gezien is de MD nauw betrokken bij het Cm-Pf-complex. Het Cm-Pf-complex is een van de meest belangrijke schakelstations in het spinothalamisch systeem. Dit systeem verzorgt o.a. perifere seksuele sensaties.

Ondanks dit beperkte onderzoek, waarbij de invloed van de thalamus bij erecties is bekeken, is verder onderzoek dan ook aangewezen.

In **hoofdstuk 9** beschrijven we de effecten van thalamische DBS op de tics, geheugen en stemming in twee TS patiënt op lange termijn (na 6 en 10 jaar). We hebben de lange-termijn uitkomsten vergeleken met de eerdere pre-operatieve en post-operatieve resultaten (8 maanden en 5 jaar). Gestandaardiseerde video-opnames zijn gescoord door drie onafhankelijke onderzoekers. Tijdens elk meetmoment zijn er ook neuropsychologische testen afgenomen. Er was er een persisterende tic-reductie van 90.1% na 5 jaar en 92.6% na 10 jaar in patiënt 1. In patiënt 2 was er na 8 maanden een verbetering van tics van 82% en 78% na 6 jaar. Gedurende de follow-up periode was er geen verandering in geheugen bij patiënt 1, terwijl patiënt 2 verminderde verbale fluency en leercapaciteit liet zien, zoals ook door de patiënt was gerapporteerd. Ondanks dat patiënt 2 enige vermindering had van de depressieve klachten bleef er sprake van psychopathologie met name kwaadheid, agressie en moeilijkheden met sociale aanpassing. Er werden tijdelijke hardware gerelateerde complicaties gerapporteerd, zonder beperkende neven-effecten. Uit deze lange termijn evaluatie kunnen we concluderen dat thalamische DBS ook op lange termijn effectief is. Er is speciale aandacht nodig voor psychosociale zorg zowel voor als na de operatie.

Dit proefschrift beschrijft de resultaten van een studie naar de effecten, neveneffecten en veiligheid van thalamische DBS bij patiënten met een ernstige vorm van het syndroom van Gilles de la Tourette. Hoewel de resultaten van een dubbel-blind gerandomiseerd onderzoek positief zijn en de effecten over minstens 6 jaar gekend zijn, zijn er ook stimulatie-gebonden neveneffecten welke onderzoek naar andere potentiële targets rechtvaardigen. In de discussie (**Hoofdstuk 10**) wordt verder nog ingegaan op de klinische relevantie en de verdere uitdagingen bij voortzetten van onderzoek bij mensen met het Syndroom van Gilles de la Tourette.

Dankwoord

Dankwoord

Alle mensen die aan dit proefschrift hebben bijgedragen wil ik hartelijk bedanken. Aan een aantal mensen ben ik bijzonder veel dank verschuldigd.

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List of publications

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Curriculum Vitae

Curriculum Vitae

Linda Ackermans was born on December the 28th, 1979 in Tilburg, The Netherlands. She attended secondary school for 6 years at the 'Cambreurcollege' in Dongen. In 1998 she started to study health sciences at the University Maastricht in Maastricht, The Netherlands for 2 years. In 2000 she switched to study medicine at the University Maastricht where she participated for four years in research alongside her medical studies in the research group of Dr. Y. Temel and Prof. dr. V. Visser-Vandewalle. The author has been awarded as 'talented Medical Student' (Kootstra Fellowship 2005) and received the Research award of the Faculty of Medicine in 2006. During the final year of her medical training, she followed a clerkship neurology, psychiatry and neurosurgery in Queens Square, London. In 2006 she obtained her medical degree. In December 2006 she became resident neurosurgery (Prof. dr. E.A.M. Beuls and Prof. dr. J.J. van Overbeeke) at the department Neurosurgery in the academic hospital of Maastricht. During her residency she started and completed the research described in this thesis under supervision of Prof. dr. V. Visser-Vandewalle.

Linda Ackermans werd op 28 december 1979 geboren in Tilburg. Ze doorliep het atheneum aan de middelbare school het 'Cambreurcollege' in Dongen. In 1998 begon ze aan de studie gezondheidswetenschappen aan de Universiteit van Maastricht. Na 2 jaar, in 2000, stapte ze over naar de opleiding Geneeskunde aan de Universiteit van Maastricht waarbij ze naast haar opleiding ook betrokken was in de onderzoeksgroep van Dr. Y. Temel en Prof. dr. V. Visser-Vandewalle. De auteur ontving in 2005 het Kootstra Fellowship en in 2006 de research award van de faculteit geneeskunde. In het laatste jaar van haar opleiding tot basisarts, liep ze een co-schap neurologie, psychiatrie en neurochirurgie in Queens Square London. In 2006 behaalde ze haar arts-examen. In December 2006 is ze onder leiding van Prof. dr. E.A.M. Beuls in opleiding gekomen tot neurochirurg, welke ze nu voortzet onder leiding van Prof. dr. J.J. van Overbeeke. Tijdens deze opleiding werd, onder begeleiding van Prof. dr. V. Visser-Vandewalle het proefschrift geschreven dat nu voor u ligt.