New insights in deep brain stimulation for Tourette syndrome

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New insights in Deep Brain Stimulation for Tourette Syndrome

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New insights in Deep Brain Stimulation

for Tourette Syndrome

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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Voor mijn lieve opa

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The background is a dark gray with a complex network of white lines resembling a circuit board. These lines form various geometric shapes, including circles, squares, and irregular paths. In the center of the image, there is a glowing, stylized representation of a human brain. The brain is composed of numerous small, bright white dots and lines, giving it a digital or neural appearance. It is surrounded by the circuit-like patterns, suggesting a connection between the brain and technology or a digital neural network.

Chapter 1

Introduction

Adjusted version in press as book chapter for:
“Deep brain stimulation: an interdisciplinary approach”

A.Y.J.M Smeets, A.F.G Leentjens, L Ackermans

Edited by: Y Temel, S Chabardes, R.M.A de Bie, A.F.M Leentjens, J Volkmann

TOURETTE SYNDROME

Clinical picture

George Gilles de la Tourette first described Tourette Syndrome (TS) in 1885 as a clinical triad of multiple tics, coprolalia and echolalia ¹. However, a publication dated 1873 by Armand Trousseau included a detailed account of what is now known as TS ². TS is a childhood-onset complex neuropsychiatric disorder characterized by tics ³⁻⁵. According to the criteria of the fifth edition of the Diagnostic and Statistical Manual of mental disorders (DSM-5) ⁶, multiple motor and one or more vocal tics must be present for more than one year and the onset of tics needs to be before the age of 18. The DSM-5 criteria are listed in Table 1.

Table 1: DSM-5 criteria for Tourette Syndrome.

For a diagnosis of Tourette Syndrome the patient should meet all of the following criteria:

Criterion	Description
A	Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently
B	Tics may wax and wane in frequency, but have persisted for more than one year since first tic onset
C	Onset is before age of 18 years
D	The disturbance is not attributable to the physiological effects of a substance (e.g. cocaine) or another medical condition (e.g. Huntington's disease, post viral encephalitis)

Tics are defined as sudden, rapid, recurrent, non-rhythmic muscle contractions that produce stereotyped movements (motor tics) or sounds (vocal tics). Tics may be abrupt in onset, fast and brief (clonic tics) or slow and sustained (dystonic or tonic tics) ^{7,8}. Tics in TS typically begin as simple motor tics (e.g. eye blinking, facial grimaces) around the age of 4-6 years, followed by simple vocal tics (e.g. throat clearing, sniffing) a year or two later. After onset of tics there is often a progressive pattern of tic worsening, and tics become more complex ³. Coprolalia, one of the most debilitating symptoms, occurs in about 14-20% of patients ⁹. Many patients describe premonitory sensations, the building up of tension just before a tic, and these sensations are often more distressful than the tics themselves. Once the tic has occurred, there is a brief experience of relief ^{7,8}. Most patients can suppress tics for a short while and describe a rebound intensification of tics afterwards. In spite of the fact that many patients describe such a rebound, this phenomenon has not been confirmed in research ^{10,11}. The severity of tics can also be influenced by circumstances, they may increase with stress, anxiety and fatigue, while focused activities and alcohol use may reduce their intensity ^{7,8}.

Course of the disease

The prevalence of TS in childhood (defined here as age < 18 years) is estimated at 0.3 to 0.9% with males being affected two to four times as frequent as women⁹. On average, tics start around the age of 4-6 years, reach their worst-ever period early in the second decade of life, around 8-12 years of age, to be followed by a steady decline in severity³. In the natural course of TS, tics occur many times a day in bouts and wax and wane in severity over time. Overall, TS has a favourable prognosis. About one third of children with TS will experience a significant tic decrease during adolescence and remain with only mild tics that do not require clinical attention, whereas another third of children is completely tic-free³. Yet, a small proportion of patients does not experience this remission, and in this group some individuals not only experience tic worsening during adolescence but they develop the most severe and debilitating forms of TS. In 5% of patient's TS has a serious and even life-threatening nature, called malignant TS. It is characterized by tic-related injuries, Self-Injurious Behaviour (SIB), uncontrollable violence, and suicidal attempts^{3,9,12}.

Comorbidities

TS is accompanied by comorbid disorders in 50-90% of patients causing a heterogeneous phenotype of the disease. In some patients, these comorbid disorders cause even more impairment than the tics themselves. Attention Deficit and Hyperactivity Disorder (ADHD) is present in about 50% of patients and Obsessive-Compulsive behaviour (OCb) in 50-75%^{3,4,13}. Obsessions may involve violent, aggressive, sexual and symmetrical themes. Compulsive behaviour is often related to checking, counting, forceful touching and self-damage. More than one-third of patients with TS exhibits SIB, most frequently head banging. Many TS patients experience developmental disorders, learning disabilities, sleeping disorders, anxiety disorders and depression^{4,13}.

Pathophysiology

The pathophysiology of TS is still largely unknown. In the past few years, a lot of research has been directed towards genetic and auto-immune disorders¹⁴. Functional and structural studies show abnormalities in several cortical and subcortical areas during tics, among which the basal ganglia (BG)¹⁴⁻¹⁸. The BG modulate behaviour through a mechanism that involves changing cortical excitability through different BG circuits. The direct circuit, that extends from the striatum to the internal globus pallidus (GPi) and the substantia nigra pars reticulata (SNr), excites the cortex through the disinhibition of the thalamus. The indirect pathway, extending from the striatum to the external globus pallidus (GPe) and then to the subthalamic nucleus (STN), inhibits the thalamic projections. The hyperdirect pathway bypasses the striatum and sends cortical

signals directly to the STN and then to the GPi/SNr. In general, the direct pathway activates desired programs while the hyperdirect and indirect pathways suppress unwanted competing programs¹⁴. It has been hypothesized that in TS due to a dopaminergic dysfunction, focal aberrations in the striatum cause excessive inhibition of the GPi/SNr in the direct pathway, thereby causing an involuntary motor command to be executed in the cortex due to excessive disinhibition¹⁹. The cortico-basal-ganglia-thalamocortical (CBGT) projections can be divided into five important functional circuits, named for their cortical areas of origin and action, which travel through different parts of the BG nuclei: the motor, the associative, the limbic, the oculomotor and the orbitofrontal circuit. Chapter 2 will be dedicated to the functional anatomy of the BG and the relationship between BG dysfunction and the pathophysiology of TS.

TREATMENT OF TOURETTE SYNDROME

There is no cure for TS. Therefore, treatment aims to diminish or alleviate tics and other comorbid symptoms. The critical first step in making treatment decisions is to select the most appropriate target symptoms, the ones causing the most problems in a patient's daily functioning²⁰. In one patient it may be the tics themselves, in another it may be comorbid ADHD or OCB and in another it may be a combination of target symptoms.

Psychosocial or behavioural treatment

For many patients with mild symptoms, psychosocial or behavioural interventions may be sufficient to bring symptoms to a tolerable level of severity^{5,20}. Psychosocial interventions are for example psychoeducation which has the aim to improve the tolerance for symptoms and to support stress reduction²¹. Behavioural approaches are habit reversal therapy, relaxation training, contingency management, exposure and response prevention, self-monitoring, massed practice, bio(neuro)feedback, and cognitive behavioural treatment^{20,21}. In habit reversal therapy, patients are trained to recognize premonitory urges and respond to these with a voluntary competing or incompatible response, such as contraction of a 'tic-opposing' muscle or relaxation of the 'tic-muscle'. Habit reversal therapy may also comprise relaxation training and contingency management. Relaxation techniques are focused on muscle relaxation in general and in response to premonitory urges. Contingency management consists of the manipulation of environmental contingencies, so that tic-free intervals are positively reinforced and tic behaviours are ignored. Exposure and response prevention consists of exposure to the premonitory sensory urges during prolonged tic suppression and stimulating habituation.

Pharmacological treatment

Pharmacological treatment might be an option if psychosocial or behavioural interventions are not sufficient, for example if a patient experiences: tics that cause subjective discomfort (e.g. pain or injury), tics that cause sustained social problems (e.g. social isolation or bullying), tics that cause emotional problems (e.g. reactive depressive symptoms), or tics that cause functional interference (e.g. impairment of academic achievements)²². It is important to realize that it is still unknown what effect pharmacological treatment has on the natural long-term course of TS and how it might influence the natural course of brain development²². A large number of pharmacological interventions have shown effect in reducing tics in TS patients including typical and atypical antipsychotics, benzamides, noradrenergic agents, tetrabenazine and tetrahydrocannabinol^{4,8,22}. Most widely used drugs are typical antipsychotics (pimozide, haloperidol, sulpiride, tiapride) that block postsynaptic dopamine-D2 receptors. In adult TS patients these are considered the first choice. Benzamides, such as tiapride and sulpiride, also work via the dopaminergic system. Alternatives are atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone) that have more serotonergic and noradrenergic effects. Another noradrenergic agent used in the treatment of tics is clonidine, which is often used as the first choice in children. Mild side effects like sedation and irritability are reported for all these types of drugs. But more severe side effects like extrapyramidal symptoms (e.g. tardive dyskinesia or parkinsonism), weight gain, impaired glucose tolerance and depression are also seen with these antipsychotics. The extrapyramidal side effects are the most pronounced for the typical antipsychotics²². Some evidence also exists for tetrabenazine and tetrahydrocannabinol. If tics are limited to one muscle or one muscle group, botulinum toxin injections can help. Selective serotonin reuptake inhibitors and clomipramine are recommended for the treatment of comorbid OCB and depression. Psychostimulants, such as methylphenidate, are used for the treatment of comorbid ADHD^{4,8,22}.

Deep Brain Stimulation

Despite psychosocial and behavioural therapy and pharmacological treatment, a small sub-group of patients fails to respond to treatment or experiences intolerable side effects. They continue to experience significant symptom burden throughout adolescence and adult life^{21,22}. For those patients, Deep Brain Stimulation (DBS) can be considered. Guidelines for indication have been proposed by the Tourette Syndrome Association (TSA)²³ (see Table 2).

Table 2: Criteria for indicating Deep Brain Stimulation in Tourette Syndrome patients.

	Criterion
Diagnosis	A confirmed diagnosis of Tourette Syndrome according to the DSM-5 criteria
Age	> 18 years
Severity	YGTSS >35/50
Neuropsychiatric comorbidity	<ul style="list-style-type: none"> - Tics must be the predominant complaint. If neuropsychiatric comorbidity is present, this should not be predominant - No suicidal ideation or attempted suicide in the past six months - Comorbid neuropsychiatric disorders must have been stable for at least six months - Comorbid neuropsychiatric morbidity should be scored with valid rating scales, so that these symptoms can be monitored post-operatively
Previous treatment	<ul style="list-style-type: none"> - Treatment with at least three medications must have shown no effects or could not be tolerated <ul style="list-style-type: none"> - D2 receptor antagonists - Atypical antipsychotics - Alpha-adrenergic agonists - Other - Behavioural treatment was not effective <ul style="list-style-type: none"> - Habit reversal therapy - Exposure and response prevention
Psychosocial factors	<ul style="list-style-type: none"> - Adequate social support without any (sub)acute stressors - Willingness to undergo psychological treatment post-operatively if necessary - Preparedness of caregiver to participate in post-operative counselling

DSM-5: fifth edition of the Diagnostic and Statistical Manual of mental disorders; YGTSS: Yale Global Tic Severity Scale; D2: dopamine 2.

Obviously, there are also contra-indications for DBS such as severe systematic diseases or structural abnormalities on the Magnetic Resonance Imaging (MRI) that interfere with optimal or safe electrode placement. The final decision for proceeding to DBS should be made by consensus within a multidisciplinary team in which the neurosurgeon, psychiatrist and preferably the psychologist participates.

Since 1955 attempts have been made to treat TS surgically. A total of 65 patients have been treated with ablative surgery that was targeted at various brain areas, among which the frontal cortex, the thalamus, the globus pallidus and the cerebellum²⁴. The results of these interventions have not been well described and severe complications occurred such as hemiplegia and dystonia. Based on new developments within movement disorder surgery, DBS of the thalamus was first used as treatment for intractable TS in 1999²⁵. The procedure requires the electrical stimulation of deep brain structures by implanted electrodes which receive high-frequency pulses from a subcutaneous implanted pulse generator. The main goal of DBS is to change neuronal firing patterns and to influence the passage of information through the targeted nuclei in the CBGT circuits and to improve symptoms of TS. This has the same effect on symptoms as a lesion, but in a reversible way.

Evidence shows that DBS exerts its effect by causing functional ablation which reduces information flow through the stimulated nucleus^{26,27}.

Since 1999, about 57 DBS studies in TS have been published worldwide, including approximately 156 patients from 23 centres in 13 countries²⁸. A key factor to attaining optimal results from this surgery is target selection, a topic still under debate due to the complex clinical profile presented by TS patients. Nine separate brain areas have been targeted so far:

- The medial part of the thalamus:
 - 1) The centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus (Cm-Spv-Voi) cross point of the thalamus^{25,29-44}.
 - 2) The centromedian nucleus–parafascicular complex (CM-Pf) of the thalamus⁴⁵⁻⁵⁰.
 - 3) The dorsomedian nucleus-parafascicular complex (DM-Pf) of the thalamus⁵¹.
- The internal globus pallidus (GPi):
 - 4) The posterolateral motor part (posterior GPi)⁵²⁻⁶³.
 - 5) The anteromedial limbic part (anterior GPi)^{61,64-71}.
- 6) The external globus pallidus (GPe)⁷².
- 7) The nucleus accumbens (NA)⁷³⁻⁷⁶.
- 8) The anterior limb of the internal capsule (ALIC)^{73-75,77}.
- 9) The subthalamic nucleus (STN)⁷⁸.

Moreover, studies targetting multiple brain areas separate or at the same time have been performed^{52,79-88}. Interfering with DBS at the level of one of the main output or relay stations of the BG seems to result in clinical benefits in refractory TS patients. Overall, DBS results in a significant short-term improvement of 53% on the Yale Global Tic Severity Scale (YGTSS) on all targets (Table 3). The analysis of controlled studies shows a significant improvement in tics during ON stimulation compared to OFF stimulation. In general, the degree of tic improvement appeared to be most robust for the thalamic and the GPi targets²⁸.

Table 3: Effects of Deep Brain Stimulation in Tourette Syndrome patients.

Target	N	Mean change (%)*	≥ 25% response (%)*	≥ 50% response (%)*
Thalamus	78	53 (26)	82	52
Posterior GPi	20	57 (35)	78	61
Anterior GPi	44	52 (55)	77	66
GPe/STN	2	-	-	-
NA/ALIC	9	44 (15)	75	38
Other [#]	3	45 (27)	67	67
Total	156	53 (27)	81	54

* Mean change in score and percentage response on the Yale Global Tic Severity Scale (YGTSS).

[#] Other: area of the GPi targeted was unclear (n=2) and stimulation in both anterior and posterior GPi (n=1).

Abbreviations: N: number; GPi: internal globus pallidus; NA: nucleus accumbens; ALIC: anterior limb of the internal capsule; GPe: external globus pallidus; STN: subthalamic nucleus.

Table adapted from article by Baldermann et al²⁸.

DBS of the medial thalamus

The first DBS implantation for TS in three patients targeted the Cm-Spv-Voi cross point of the thalamus and resulted in a tic reduction of 72%, 83% and 90% on the YGTSS, respectively ⁴³. The choice for this target was based on the successful stereotactic lesioning in a case described by Hassler and Dieckmann ⁸⁹. The hypothesis was that stimulation of the Cm and Spv would suppress excitatory feedback projection to motor and limbic parts of the striatum, decrease tics and improve 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. Since then, 78 patients with thalamic DBS have been reported in 22 studies ²⁸. The mean percentage improvement on the YGTSS was 53%, with 52% of patients reporting at least 50% improvement at the last reported follow-up (Table 3). This follow-up varied widely and only 20% of included patients had a follow-up of more than one year. Reported side effects include loss of libido, lethargy, and weight loss. Cases of psychosis, depression and hypomania have been reported and these may be reversed by adjusting stimulation parameters ⁹⁰.

DBS of the globus pallidus

The globus pallidus consists of an internal and external part (GPi and GPe), and most studies have targeted the GPi. Only one case history reports on stimulation of the GPe in TS with a 70% improvement on the YGTSS after six months ⁷². The GPi consists of a posterolateral motor part (posterior GPi) and an anteromedial limbic part (anterior GPi). Both have been targeted in the DBS treatment of TS. Some studies do not report which part of the GPi is targeted. DBS of the posterior GPi was first done in 2002 with good results ⁵² and since then 20 patients have been described in the literature ²⁸. A mean improvement on the YGTSS of 57% has been reported, with 61% of patients reporting at least 50% improvement at the last reported follow-up (Table 3). By now, more patients have received DBS of the anterior GPi ²⁸. These patients show a mean improvement of 52% on the YGTSS with 66% of patients reporting at least 50% improvement (Table 3). Known side effects of pallidal DBS are anxiety, agitation, weight loss, nausea, vertigo and paraesthesia's of which most appeared to be transient ⁹⁰.

DBS of the nucleus accumbens and the anterior limb of the internal capsule

Only 9 patients have been reported that received DBS of the NA/ALIC with a mean improvement of 44% on the YGTSS, and 38% reporting more than 50% improvement ²⁸ (Table 3). Although the evidence is weak, stimulation of this target seems to be less effective. Potential side effects of DBS of the NA include flushing, anxiety, sweating, hypomania, agitation, and psychosis. Potential side effects of ALIC DBS are euphoria, anxiety, panic, and fear ⁹⁰.

DBS of the subthalamic nucleus

A single case history of a 38-year-old man with Parkinson's disease (PD) who also suffered from tics has been described. After DBS of the STN for his PD, not only parkinsonian motor symptoms improved, but the tic frequency also diminished by 97% at one year⁷⁸.

AIM OF THIS THESIS

The general aim of this thesis is to continue the development of DBS for refractory TS patients by further exploring the effects of surgery in our own centre, including the relationships with the underlying pathophysiology, and both surgical and ethical issues. Open label series and small double-blind trials report positive effects on tics in TS patients after DBS of several brain targets, including the medial thalamus and the anterior GPi. However, DBS for TS is still not approved by the European Commission (EC) and the Food and Drug Administration (FDA) because of the lack of evidence due to the difficulty of performing high quality research in a randomized controlled fashion, coupled with the variable effect of surgery, the large number of targets, and the overall small numbers of TS patients with DBS worldwide. The main focus of this thesis is to continue the follow-up of operated TS patients and TS patients with an indication for DBS, including both thalamic and anterior GPi DBS. The goal is to provide new insights about the effects of thalamic and pallidal DBS for refractory TS patients.

Chapter 2 provides an overview of the functional anatomy of the BG and the connected CBGT pathways and explores the relation between BG dysfunction and the pathophysiology of TS. We explain how targeting different brain areas within the BG might influence these pathways in order to improve symptoms of TS. In **chapter 3** we report on the long-term outcome of seven refractory TS patients who were participants of a double blinded randomized controlled trial, treated with DBS of the medial thalamus between 2001 and 2008. Because of our own results with thalamic DBS, showing an increasing disbalance of therapeutic effects and side effects at long-term follow-up, and the positive results of other groups targeting the anterior GPi, we changed our target. **Chapter 4** describes the results of DBS of the anterior GPi in five refractory TS patients. In **chapter 5** we describe our electrophysiology recordings during DBS surgery targeting the anterior GPi in eight awake TS patients. We have directly observed neuronal activity in the limbic domains of the BG and this chapter focuses on linking the activity of GPi neurons in these domains with the underlying pathophysiology of TS. Every step of the DBS surgery is important, and as such **chapter 6** describes a modified cement-based fixation of the DBS electrode to prevent unintended migration, and consequently displacement of the electrodes. **Chapter 7** deals with the ethical issues associated with DBS of adolescent TS patients. We describe our experiences with the treatment of two adolescent TS patients and systematically review the scarce literature on the subject. Finally, we provide a general discussion in **chapter 8** in which we address questions about the underlying pathophysiology of TS and we provide new insights about the effects of thalamic and pallidal DBS for refractory TS patients.

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Chapter 1

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Chapter 2

The role of the basal ganglia in Tourette Syndrome

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In Tourette Syndrome (TS) dysfunction of the basal ganglia (BG) and the connected cortico-basal-ganglia-thalamocortical (CBGT) pathways plays a major role in the underlying pathophysiology, although the exact mechanisms are not fully understood¹. Knowledge about the basic functional anatomy of the BG and their pathways is essential in understanding the mechanisms and effects of Deep Brain Stimulation (DBS) in TS patients. Therefore, we provide a general anatomical overview of the BG and their pathways, followed by an exploration of the changes in the CBGT circuits in TS patients, and an explanation of the mechanisms of DBS.

ANATOMY OF THE BASAL GANGLIA

The BG are a group of interconnected deep subcortical nuclei which are located symmetrically across the cerebral hemispheres and consist of (Figure 1)²:

- The putamen and nucleus caudatus, together called the striatum.
- The subthalamic nucleus (STN).
- The external globus pallidus (GPe).
- The substantia nigra, pars compacta (SNc).
- The internal globus pallidus (GPi): divided in a posterolateral part, the motor area (posterior GPi), and an anteromedial part, the limbic area (anterior GPi).
- The substantia nigra, pars reticulata (SNr).

Figure 1: Anatomy of the basal ganglia.

The cortex sends information to the BG, where it is processed and sent back to the cortex via the thalamus (Figure 2). The striatum and the STN are the *primary input* structures of the BG. The striatum receives excitatory input from all areas of the cerebral cortex and the STN from motor areas in the frontal lobe. The striatum also receives substantial

afferents from the SNc and the intralaminar thalamic nuclei (mainly the centromedian-parafascicular (Cm-Pf) complex and the ventrolateral thalamic nuclei (VL)), in addition to intrastriatal inputs²⁻⁴.

The GPe and SNc are *intrinsic nuclei* within the BG. The GPe connects the input and output stations and receives excitatory input from the STN and inhibitory input from the striatum. The GPe in turn sends inhibitory output to STN, the GPi and the SNr. The SNc sends inhibitory as well as excitatory output back to the striatum to modulate the function of the BG via dopamine (DA)²⁻⁴.

The GPi and SNr are the *primary output* structures of the BG and they are a single cellular structure divided by the internal capsule. These output nuclei receive fast, excitatory input from the STN and slower, inhibitory input from the striatum. The GPi and SNr in turn send inhibitory signals predominantly to the thalamus, which then sends excitatory signals back to the cortex. Thalamic area's innervated by the BG are the ventro-anterior nucleus (VA), the mediodorsal nucleus (MD), the VL nuclei and the Cm-Pf complex²⁻⁴.

Figure 2: Schematic representation of the cortico-basal-ganglia-thalamocortical pathways.

Abbreviations: Cx: cerebral cortex; STN: subthalamic nucleus; GPe: external globus pallidus; Str: striatum; Th: thalamus; GPi: internal globus pallidus; SNr: substantia nigra, pars reticulata; SNc: substantia nigra, pars compacta; GABA: Gamma-aminobutyric acid. Figure adapted from book chapter written by A.F.G Leentjens.

CORTICO-BASAL-GANGLIA-THALAMOCORTICAL PATHWAYS

Three CBGT pathways have been described (Figure 2), however, anatomical evidence points out that this intrinsic circuitry is far more complex^{1,5}:

- The *direct pathway*, which is a positive feedback loop. In this pathway the cortex sends excitatory signals to the striatum, which inhibits the GPi/SNr complex. These two structures then disinhibit the thalamus, thereby effectively reinforcing the excitatory signals directed back to the cortex.
- The *indirect pathway* constitutes a negative feedback loop. In this pathway, signals from the striatum are redirected to inhibit the GPe. These signals then disinhibit the STN and GPi/SNr complex, which leads to more inhibition of the thalamus and its projections to the cortex.
- The *hyperdirect pathway* also constitutes a negative feedback loop. The striatum is bypassed and signals from the cortex are directly projected onto the STN to excite the GPi/SNr complex, thereby inhibiting the thalamus and its projections to the cortex.

In general, the direct pathway facilitates movement and the indirect and hyperdirect pathways inhibit movement. Via the fast conducting hyperdirect pathway the thalamus is initially inhibited, it is then subsequently disinhibited by the direct pathway, with the indirect pathway finally exerting inhibition once more. This arrangement allows for precise selection of action, with a circumscribed initiation and termination. The direct pathway activates desired programs while the hyperdirect and indirect pathways suppress unwanted competing programs. Therefore, selected movements are enabled and competing postures and movements are prevented from interfering with the one selected³⁻⁵.

The CBGT projections can be divided into five important functional circuits, named for their cortical areas of origin and action: 1) the motor, 2) the associative, 3) the limbic, 4) the oculomotor and 5) the orbitofrontal circuit⁶. The first three circuits seem to be involved in the pathophysiology of TS and are shown in Figure 3. The main cortical inputs to the motor circuit are the primary motor, premotor, supplementary motor (SMA) and somatosensory cortex and signals are sent to the putamen. The main inputs to the oculomotor, associative and orbitofrontal circuit are the dorsolateral prefrontal and lateral orbitofrontal cortex and signals are sent mainly to the nucleus caudatus. Information from these four circuits is conveyed primarily to the posterior GPi/SNr. The main inputs to the limbic circuit are the anterior cingulate and orbitofrontal cortex, the hippocampus, and the amygdala and signals enter via the ventral striatum. The ventral striatum contains the nucleus accumbens (NA), the ventromedial part of the nucleus caudatus, and the medial part of the tuberculum olfactorium. Limbic information is conveyed to the anterior GPi^{2-4,6}.

There is a parallel organisation of these functionally segregated CBGT circuits. Each circuit receives multiple, partially overlapping corticostriatal inputs, which are progressively integrated in their passage through the BG to a restricted portion of the thalamus, and from there back to a single cortical area. Each circuit is partially closed by the restricted thalamocortical projection returned to one of that circuit's multiple sources of corticostriatal inputs⁶.

Figure 3: Anatomical-functional organization of the circuits of the cortico-basal-ganglia-thalamocortical pathways.

Re-entrant circuits from functionally and anatomically distributed, parallel circuits which integrate to perform massive processing in different brain areas. In Tourette Syndrome disturbances are observed in motor, associative and limbic functions and those circuits are shown here.

Abbreviations: GPe: external globus pallidus; GPi: internal globus pallidus; STN: subthalamic nucleus.

Figure adapted from article by Hashemiyoony et al⁷.

BASAL GANGLIA DYSFUNCTION IN TOURETTE SYNDROME

Structural changes have been reported in the BG and in a broad range of connected motor and limbic cortical areas of TS patients⁸⁻¹⁰. Various neuroimaging studies have shown reduced volumes and abnormal asymmetries of the nucleus caudatus, putamen and globus pallidus^{8,11-13}. Volumes of grey matter are abnormal⁹ and white matter analysis show widespread abnormalities in patients with TS^{14,15}. Neuropathological studies have shown structural changes in neurons in the striatum and globus pallidus of TS patients^{16,17}. Morphological changes have also been shown in a broad range of limbic and motor cortical areas, including increased and/or decreased volumes of specific brain areas, decreased grey matter volumes and cortical thickness⁹. Moreover, abnormalities in the dopaminergic neurotransmitter system seem to play a significant

role¹⁸⁻²¹. Dopaminergic neurons in the SNc have contrasting effects on the facilitating and inhibiting pathways since they tend to activate striatal neurons contributing to the direct pathway (D1-receptors) and inhibit striatal neurons in the indirect pathway (D2-receptors). The overall impact of DA on the BG is the enhancement of thalamocortical excitation². Several functional neuroimaging studies have shown abnormalities in DA transporter and DA binding in the striatum of TS patients¹⁸⁻²¹.

Traditionally, TS has been considered a member of the hyperkinetic movement disorder family. They all express an excess of movement with uncontrollable and relatively rapid motor acts and share a common pharmacology, since they are suppressed by DA antagonists. Examples are chorea and athetosis (e.g. due to Huntington's disease), ballism (e.g. due to STN infarction) and tics (e.g. due to TS). Functional models of the BG have suggested potential mechanisms for hyperkinetic movement disorders. They view all hyperkinetic movement disorders as one entity and assume that they have common underlying properties and they have centred on the existence of abnormalities in the motor circuits¹⁴. The *'box and arrow' model* depicts the global neuronal activity modulation of whole brain areas (boxes) along the CBGT pathway as a function of their connectivity (arrows). In this model, hyperkinetic disorders are explained by striatal disinhibition that leads to reduced tonic inhibition exerted by the GPi/SNr on its thalamocortical targets. The *'action selection' model* accounts for the local changes in the inhibition of neuronal sub-groups within the output nuclei. In this model, hyperkinetic symptoms originate from abnormal focal activation of striatal neurons which inhibit the activity of a subpopulation of GPi neurons^{1,5,14}.

In TS, this unwanted inhibition of the main output nuclei of the BG leads to disinhibition of its thalamocortical targets and this in turn can lead to repeated stereotyped unwanted movements like tics (Figure 4)¹⁴. Mechanisms that can be responsible for such an unwanted activation are excessive cortical or thalamic input to the striatum, deficiency of intrastriatal inhibition, abnormal DA transmission, and abnormal membrane excitability. Many features of TS can be explained as a failure to inhibit unwanted movements, behaviours, and thoughts, resulting from these abnormal BG output patterns. For example, abnormal activation of the motor cortex can produce simple tics, abnormal activation of the premotor cortex or SMA can lead to complex tics, abnormal activation of the orbitofrontal cortex can cause compulsions, and abnormal activation of the dorsolateral prefrontal cortex can produce attention deficits

Figure 4: Schematic representation of the abnormalities in the cortico-basal-ganglia-thalamocortical pathways in Tourette Syndrome. (red lines: fat line = enhanced activity, thin line = reduced activity).

Disinhibition within the striatum leads to excessive inhibition of the GPi/SNr in the direct circuit, which in turn leads to less inhibition of the thalamus and as a consequence excessive excitation of the cortical targets. Abbreviations: Cx: cerebral cortex; STN: subthalamic nucleus; GPe: external globus pallidus; Str: striatum; Th: thalamus; GPi: internal globus pallidus; SNr: substantia nigra, pars reticulata; SNc: substantia nigra, pars compacta; GABA: Gamma-aminobutyric acid. Figure adapted from book chapter written by A.F.G Leentjens.

ELECTROPHYSIOLOGY IN TOURETTE SYNDROME

Animal models of TS using electrophysiological recordings are used to better understand the underlying neuronal mechanisms of the disease. Focal striatal disinhibition using microinjections of Gamma-aminobutyric acid-A (GABA_A) antagonists leads to the appearance of motor and vocal tics in non-human primates²²⁻²⁴ and motor tics in rodents^{25,26}. These animals transiently display sudden, rapid, and repetitive movements that resemble the simple motor tics of TS patients. Both phasic increases and decreases in firing rate were found in GPi and GPe neurons in relation to the tics²²⁻²⁴. DBS targeting different areas within the BG and the thalamus provides a rare opportunity to directly observe neuronal activity in TS patients. Intra-operative recordings from drivable microelectrodes present the opportunity for single unit recordings, while post-operative recordings of local field potentials (LFP) can be made from implanted macroelectrodes⁷. Neurophysiological analysis of intra- and post-operative human electrophysiological recordings from clinical DBS studies suggest a link

between tic behaviour and activity in both the thalamus and the GPi^{7,27}. Single unit recordings in the trajectory targeting the nucleus ventro-oralis internus (Voi) of the thalamus showed that it is characterized by a localized pattern of neuronal bursting²⁸. However, these findings were also seen during DBS under general anaesthesia for other indications and are neither unique to the target or to the disorder. Extracellular electrophysiological recordings performed during pallidotomy surgery revealed a decreased overall firing rate in the posterior GPi of TS patients²⁹. In addition to the overall change, a similar bursting activity was seen and almost half of these GPi neurons showed tic-related neuronal changes around the time of the tic. We found comparable results of a reduced baseline firing rate and tic dependent transient rate changes when targeting the anterior GPi in TS patients²⁷. Only one study has performed chronic LFP recordings from implanted thalamic electrodes and correlated these findings with the symptoms. An increase in spectral activity in gamma band power and theta/gamma cross frequency was found in responders of thalamic DBS³⁰.

RATIONALE FOR TARGETING THE THALAMUS AND THE INTERNAL GLOBUS PALLIDUS

The reason for choosing a certain target for DBS in refractory TS patients is based on the focus of the treatment, for example the motor aspects of tics or the compulsive and behavioural elements. A systematic review and meta-analysis from 2016 identified 156 reported cases of TS DBS, of which 78 targeted the thalamus, 44 the anterior GPi, and 20 the posterior GPi³¹. Other targets have been less studied. The thalamus and the GPi are key structures within the CBGT pathways (Figure 2 and 3) and by influencing them through high frequency stimulation the signalling throughout the BG can be adapted. The main goal of DBS is to restore the imbalance present in the CBGT pathways of TS patients and to relieve symptoms. The thalamus is not only the target of integrated BG output and the most important relay station to the cortex, it also projects back to the striatum, and controls the information transmitted to both the cortex and the striatum. The GPi is the primary output nucleus of the BG, and stimulation of this nucleus can modulate the whole CBGT circuit. Moreover, the thalamus and the GPi seem to play a significant role in the underlying pathophysiology of TS^{1,14}, which is supported by clinical evidence showing that the degree of tic improvement is most robust for these targets³¹.

The first DBS target used in TS was the medial thalamus and the selection was motivated by thalamotomies performed in 1970 by Hassler and Dieckmann³². They 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 Voi. The difficulty was that they made up to ten coagulations in each thalamus, so a strategic point had to be found to stimulate as many of the nuclei targeted with one electrode

for each hemisphere. The strategic point chosen was located at the cross point between the anteromedial border of the centromedian nucleus (Cm, as part of the intralaminar thalamic nuclei), the substantia periventricularis (Spv, as part of the medial thalamic nuclei), and the Voi (as part of the ventrolateral thalamic nuclei). This target has been slightly adapted by others, some stimulate a little bit more anterior while others stimulate the centre of the Cm-Pf complex. It is hypothesized that targeting this area would lead to modulation of motor symptoms via stimulation of the Cm (motor circuit), modulation of behavioural symptoms via stimulation of the Spv (projections to the ventral striatum, part of the limbic circuit), and modulation of facial tics via the Voi (direct projections to facial parts of the (pre)motor cortex)³³.

In 2002 the first TS patient was treated with DBS of the GPi³⁴ and several years later this area gained more interest as a potential target for TS. The GPi can be divided in a motor area (posterior GPi) and a limbic area (anterior GPi). The posterior GPi became a readily accepted target given the extensive evidence of the efficacy of this target in other hyperkinetic movement disorders, specifically dyskinesia's in Parkinson's disease³⁵ and dystonia³⁶. These disorders share some underlying mechanisms, but they only centre on the existence of abnormalities in the motor circuits of the BG. It was thought that targeting the posterior GPi would lead to modulation of motor symptoms in TS, but not necessarily to modulation of behavioural symptoms. Recently, more attention is being paid on the role of the associative and limbic circuitry in TS, and it is even thought that motor symptoms of TS can result from abnormal motivational drives from these circuits rather than from dysfunction of the motor circuit^{1,12}. Therefore, it is hypothesized that targeting the anterior GPi might improve both behavioural and motor symptoms of TS and result in even more clinical benefits.

MECHANISMS OF DEEP BRAIN STIMULATION

How does DBS influence the electrophysiological signals in the CBGT circuits and restore the imbalance present in TS patients? Evidence shows that DBS exerts its effect by causing functional ablation, which reduces information flow through the stimulated nucleus^{20,29}. High frequency stimulation inhibits the targeted area because the negative extracellular charge makes it more difficult to generate action potentials. The similarity between findings in Parkinson patients, TS patients and normal animals supports the notion that the mechanisms of DBS are comparable regardless of the underlying disease or the region of stimulation^{20,37}. In TS there seems to be a disbalance in the CBGT circuit as shown in Figure 4. In summary this means that disinhibition within the striatum leads to excessive inhibition of the GPi/SNr complex in the direct circuit, which in turn leads to disinhibition of the thalamus and therefore to enhanced excitation of the cortical targets. DBS of the thalamus can correct this disinhibition by causing functional ablation and reduced signalling through the thalamus, leading to less

excitation of the cortical targets. Moreover, the afferent enhancing projections from several thalamic nuclei (e.g. the Cm-Pf complex) to the striatum might be inhibited by the stimulation. DBS of the GPi is more difficult to be explained by the above-mentioned working mechanisms. It is thought that stimulation of the GPi results in partial temporal blocking of neuronal responses to stimulation pulses. This abolishes the tic-related activity of the neurons and for a short period increases the overall firing rate of the nucleus²⁰. If the firing rate of the GPi during stimulation is increased, this leads to more inhibition of the thalamus and as a result to less excitation of the cortical targets. Studies of long-term electrophysiological changes underlying the progressive effects of DBS in TS are unfortunately still lacking.

CONCLUSION

Although dysfunction of the CBGT pathways seems to play a critical role in the underlying pathophysiology of TS, the exact mechanisms are still unknown. The emerging evidence that TS involves CBGT dysfunction emphasizes that further investigation of the basic neurobiology of the BG is likely to be indispensable for improved understanding of the pathophysiology of TS. Moreover, this might have direct consequences for choosing DBS targets and for treating refractory TS patients.

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Chapter 3

Thalamic Deep Brain Stimulation for
refractory Tourette Syndrome:
clinical evidence for increasing disbalance
of therapeutic effects and side effects
at long-term follow-up

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ABSTRACT

Objective: Thalamic Deep Brain Stimulation is effective in reducing tics in patients with refractory Tourette syndrome at the short-term. Here, we report on the long-term outcome.

Methods: Seven patients underwent bilateral Deep Brain Stimulation between 2001 and 2008. The target was the centromedian nucleus, substantia periventricularis and nucleus ventro-oralis internus cross point of the thalamus. The effect on tics and side effects were evaluated with a variable follow-up duration of 12 to 78 months.

Results: Patient 1 and 2 showed good tic improvements of 81.6% (60 months) and 50% (36 months), respectively. However, side effects like reducing levels of energy and visual disturbances increased. In patient 1 the target was changed to the anterior part of internal globus pallidus and patient 2 switched the stimulator permanently off. Patient 3 experiences still satisfying results with a tic improvement of 88.9% (78 months). Patient 4 and 7 showed minor tic improvements of 34% (16 months) and 9% (60 months), respectively. In both patient's side effects became more severe and the target was changed to the anterior part of the internal globus pallidus. Patient 5 showed a tic improvement of 27.5% (12 months) and went abroad for stimulation of the external globus pallidus. Patient 6 developed cerebellar atrophy. He experienced several non-stimulation related side effects and turned the stimulator off.

Conclusions: There seems to be an increasing disbalance of therapeutic effects and side effects at long-term follow-up, often leading to either switching the stimulator off or new surgery with a different neuro-anatomical target.

INTRODUCTION

Tourette Syndrome (TS) is a childhood-onset neurodevelopmental disorder characterized by multiple motor and vocal tics^{1,2}. Although symptoms usually subside by adulthood, a significant proportion of patients fail to respond to standard medical and behavioural therapies³⁻⁵. For these patients, Deep Brain Stimulation (DBS) has emerged as a therapeutic escalation. At present, six different targets have been stimulated^{6,7}; the medial part of the thalamus, the internal globus pallidus (GPi), the external globus pallidus (GPe), the nucleus accumbens (NA), the anterior limb of internal capsule (ALIC), and the subthalamic nucleus (STN). Most of the TS patients have shown beneficial short-term effects following DBS. Overall, DBS resulted in a significant short-term improvement of 53% on the Yale Global Tic Severity Scale (YGTSS)^{7,8}. In general, the degree of tic improvement appeared to be most robust for the thalamic and the GPi targets⁷.

So far, long-term follow-up data are sparse. Porta et al⁹ described their six years follow-up of thalamic DBS in 18 TS patients and showed a significant improvement on tics and comorbid behavioural disorders. However, long-term complications and difficulties such as noncompliance and differences in opinions between the medical team and the patients as to their satisfaction with the outcome were reported⁹⁻¹⁰. Motlagh et al¹¹ reported their experiences with DBS of the medial thalamus (n=5) or the GPi (n=3) in eight TS patients over seven years. Only three patients experienced more than 50% tic reduction (thalamic target in all three patients) and two patients had their DBS leads removed, one due to an infection and one to due lack of effect (thalamic target in both patients).

Given the small amount of published data, it is difficult to consider the gain for future individual TS patients. Therefore, rigorous reporting of all available data, and especially long-term follow-up data, is highly needed. The present paper reports on the long-term outcome of seven refractory TS patients treated with DBS of the medial thalamus between 2001 and 2008. The initial one-year outcome of six patients¹² and the six years outcome of the seventh patient¹³ have been reported previously.

METHODS

Patient selection

Seven patients with refractory TS were referred to the Maastricht University Medical Centre (MUMC) and selected for bilateral DBS of the medial thalamus between 2001 and 2008. One other patient underwent thalamic DBS during that period. This was a 20-year-old institutionalized female patient with intractable TS and severe comorbidity, including life-threatening self-injurious behaviour. She underwent surgery for clinical urgency in 2006. Postoperative she experienced abrupt onset hypertension, inconsistent

and incongruent with organic disorders, bizarre movements and concomitant somatizations, suggesting a psychogenic nature. In 2009 she passed away in a nursing home. No follow-up data are available and the details have been described in a case report¹⁴.

Inclusion criteria for surgery were: 1) a primary diagnosis of TS according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders criteria (fourth edition) (DSM-IV)¹⁵, 2) minimum age of 25 years, 3) a minimum score of 80 on the Diagnostic Confidence Index¹⁶, 4) a minimum score of 25 on the YGTSS¹⁷, 5) failure to respond to, or intolerable side effects of three-months trials of adequately dosed typical (e.g. haloperidol) or atypical (e.g. risperidone, olanzapine, quetiapine) antipsychotic medication or clonidine, 6) completed at least ten sessions of behavioural therapy. Exclusion criteria included: 1) tics not related to TS, 2) major psychiatric disorders, 3) current substance abuse or dependence (except for nicotine), 4) severe cognitive impairment, 5) structural abnormalities on brain Magnetic Resonance Imaging (MRI), 6) general contraindications for surgery or anaesthesia. All patients were evaluated by a multidisciplinary team, a collaboration of neurologists, neurosurgeons, psychiatrists and neuropsychologists with special interest in TS, in order to ensure appropriate selection. These results represent a systematic audit of routine outcome measurements and formal approval by a medical ethics committee was therefore not required. The short-term results of all patients have been published previously^{12,13}, and all patients gave written informed consent to report their results and to retrieve data from their medical records. To retrieve these long-term follow-up data all patients gave oral informed consent.

Surgery

Stereotactic bilateral DBS of the medial thalamus was performed under local anaesthesia and sedation in all seven patients. Target was the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus (Cm-Spv-Voi) cross point of the thalamus, using the following standard coordinates; x = 5 mm lateral of the anterior commissure – posterior commissure (AC-PC) midline, y = 4 mm posterior to the mid-commissural point at the level of the AC-PC plane, z = at the level of the AC-PC plane. Target coordinates were adapted according to the width of the third ventricle and the AC-PC length (Table 1). The trajectory with the best clinical outcome and no stimulation induced side effects was determined using extracellular single-unit micro-electrode recordings (MER) and test stimulation. Full details of our neurosurgical procedure are published previously¹².

Table 1: Stereotactic coordinates and stimulation parameters.

patient	lead	left electrode			right electrode										
		x	y	z	active contacts	voltage (V)	pulse (μs)	frequency (Hz)	x	y	z	active contacts	voltage (V)	pulse (μs)	frequency (Hz)
1	3387	3	4.8	contact 1: target -4	0-, 1-, 2+, 3+	6	120	110	3	4.8	contact 1: target -2	4-, 5-, 6+, 7+	6	120	110
2	3387	5	4	contact 1: target	0+, 1-, 2-, 3+	1	60	70	5	6	contact 1: target +2	4-, 5-, 6+, 7+	2.1	60	70
3	3387	5	4	contact 1: target -3	1-, 2-, C+	1.7	210	100	5	6	contact 1: target -2	5-, 6-, C+	1.7	210	100
4	3387	7	4	contact 1: target -1	2-, C+	6.6	180	90	7	4	contact 1: target -1	5-, C+	6.6	150	90
5	3389	5	4	contact 1: target	1-, 2-, C+	2.6	90	130	5	4	contact 1: target	5-, 6-, C+	2.6	90	130
6	3387	9	4	contact 1: target -3	1-, C+	1	60	110	9	4	contact 1: target -3	5-, C+	1	60	110
7	3387	5	4	contact 1: target	1-, 2+, 3-	9.3	150	100	5	4	contact 1: target	5-, 6+, 7-	9.3	150	100

Active contacts and stimulation parameters are shown at final follow-up; x = number of mm lateral of the anterior commissure – posterior commissure (AC-PC) midline; y = number of mm posterior to the mid-commissural point at the level of the AC-PC plane; z = number of mm deeper (+) or more superficial (-) than the AC-PC plane.

Postoperative management

Outpatient visits and programming sessions were performed as frequently as needed and wanted. Patients received a patient-programmer, which allowed them to change the stimulation voltage between individually assigned ranges. The initial goal was to evaluate all patients once a year, but due to non-compliance we were not able to collect data on a yearly basis. During visits to the outpatient clinic the effect on tics, side effects, complications and stimulations parameters were evaluated. At some moments, the YGTSS was completed by a neurosurgeon (LA) which provides an evaluation of number, frequency, intensity, complexity, and interference of motor and vocal tics. Total scores range from 0 to 50 with higher scores indicating higher severity¹⁷.

RESULTS

Patient 1 (male, 48 years at time of surgery)

This patient developed his first tics at the age of six. Motor tics consisted mainly of facial grimaces, eye blinking, and shoulders shrugs. Vocal tics were coughing and making uttering sounds. His tics were not responsive to medication or behavioural therapy. No comorbid disorders were present. In 2005 bilateral DBS of the thalamus was performed. After surgery, tics diminished and the YGTSS improved from 38 to 2 (94.7%) at one-year follow-up (Table 2). However, he experienced many psychosocial stressors since he lost his job a few months after surgery. He suffered from several periods of minor depression during the following years. At 60 months of follow-up tic improvement was maintained with a score of 7 on the YGTSS (81.6%). However, from 2009 he needed higher voltage stimulation to obtain the same effect on his tics. As a consequence, more frequent battery changes were needed, including a rechargeable battery. He was admitted to the hospital several times to obtain the most effective stimulation parameters without success. Side effects like a reduced level of energy, sleeping disorders and gaze disturbances became more severe, making stimulation at adequate parameters impossible. The active contacts and stimulation parameters at final follow-up are shown in Table 1. He was not satisfied with the effects of the stimulation anymore and bilateral DBS of the anterior GPi was carried out in 2012. The thalamic leads remained in situ but switched off. We were not able to reach a satisfying effect with pallidal stimulation on tics so far, even after rigorous adjusting of stimulation parameters. Finally, we decided to switch off the pallidal DBS and turn on the thalamic DBS again. No data, including the YGTSS, have been obtained during this period.

Patient 2 (male, 39 years at time of surgery)

This patient developed tics around the age of six. He suffered from socially and physically debilitating motor and vocal tics, especially spitting and coprolalia. He also exhibited self-injurious behaviour like banging his forehead against a wall. He did not suffer from comorbidities. Medication and cognitive behavioural therapy were not effective. In 2005, he was selected for bilateral DBS of the thalamus. After surgery he developed a vertical gaze paralysis due to a small deep bleeding in the upper mesencephalon at the tip of the left electrode, which improved spontaneously¹⁸. The YGTSS improved from 44 to 19 (56.8%) at 12 months of follow-up, and it improved even further at 24 months of follow-up (YGTSS of 11 (75%)). Coprolalia and self-injurious behaviour disappeared after surgery. Although the vertical gaze palsy had resolved, he continued having visual disturbances and pressure behind his eyes during stimulation. He also experienced a reduction in his energy level. The YGTSS remained 22 (50%) at 36 months of follow-up. However, due to these side effects and the burden of visiting the outpatient clinic, he eventually decided to switch the stimulator permanently off.

Patient 3 (male, 40 years at time of surgery)

This patient developed tics at the age of seven. He suffered from several motor tics like shoulder shrugs and neck extensions; however, most debilitating were his vocal tics, mainly coprolalia. He had a history of substance abuse, but no other comorbidities. In 2005 bilateral DBS of the thalamus was carried out. Postoperative he developed an infection of his infraclavicular pulse generator (*staphylococcus aureus*), which was successfully treated with six weeks of intravenous antibiotics. Tics progressively diminished after surgery and the YGTSS decreased from 45 to 12 (73.3%) and further to 5 (88.9%) at respectively 45 and 78 months of follow-up. This patient still experiences some side effects like reduced levels of energy and minor visual disturbances, especially with higher voltage stimulation. However, with the current stimulation parameters these side effects are acceptable and he is still satisfied with the effect of the DBS.

Patient 4 (male, 35 years at time of surgery)

This patient experienced his first tics at the age of seven. Motor tics included flexion with both arms and jumping and vocal tics included shouting, coprolalia and echolalia. Most debilitating were his vocal tics. He had a positive family history for TS and a history of depression and ADHD. In 2006 bilateral DBS of the thalamus was performed, with an improvement from 46 to 30 (34.8%) on the YGTSS at 16 months of follow-up. From 2009 he started to suffer from more serious side effects like reduced levels of energy and visual disturbances, making daily activities impossible. Due to these side effects and the burden of the disease, he did not tolerate the same voltage stimulation as before

anymore and the positive effects of stimulation began to decrease. In September 2012 the whole system had to be removed due to a persisting hardware infection after a pulse generator replacement, not treatable with antibiotics. Tics increased to the preoperative level with a score of 48 on the YGTSS. In December 2012 DBS of the anterior GPi was carried out. An improvement from 48 to 17 (64.5%) was observed on the YGTSS after 12 months¹⁹.

Patient 5 (*male, 40 years at time of surgery*)

This patient suffered from severe motor tics since the age of 12, most debilitating were forceful jerks of legs, arms and abdomen, facial grimaces and jumping. No comorbidities were present. In 2008 he was selected for bilateral DBS of the thalamus. His YGTSS showed a minor improvement from 40 to 29 (27.5%) at 12 months after surgery. This patient was discontented with the results and went to Belgium for DBS of the GPe and was lost to follow-up.

Patient 6 (*male, 40 years at time of surgery*)

This patient developed tics at the age of six, during childhood motor tics decreased but vocal tics became more pronounced. Most debilitating were coprolalia, echolalia and uttering sounds. He had a history of substance abuse, but no other comorbidities. Bilateral DBS of the thalamus was carried out in 2008. Both motor and vocal tics diminished during stimulation, but almost all tics remained present to some extent. The YGTSS improved from 41 to 27 (34.1%) at 26 months of follow-up. Postoperative, he experienced several symptoms like binge eating, lethargy, dysarthria, gait disturbances and apathy up to one year after surgery. These symptoms were not related to adjustments in stimulation settings and their interpretation was complicated by inconsistencies in his subjective report during the interviews and the complexity. A CT-scan performed six months after surgery revealed cerebellar atrophy, not present at preoperative imaging. Due to all these other symptoms and the lack of effect we turned the stimulator off and as such he was lost to follow-up.

Patient 7 (*male, 45 years at time of surgery*)

This patient developed tics at the age of eight which gradually worsened around adolescence. His most debilitating symptoms consisted of forceful head movements, leading to cervical myelopathy, and screaming. Moreover, sexual obsessions and compulsions such as breaking glasses were troublesome. In 2001 he was selected for bilateral DBS of the thalamus, which resulted in an improvement from 43 to 26 on the YGTSS (39.5%) at eight months of follow-up. During follow-up, major adjustments to the stimulation parameters were made with a progression of monopolar stimulation

towards bilateral bipolar stimulation and an increase from 2.4 to 9.3 V. However, this caused serious side effects including reduced levels of energy, gaze disturbances and alteration of sexual function, making stimulation at adequate parameters impossible. After three to six years higher scores on the YGTSS were observed (44, 35, 39). Moreover, with lower voltage stimulation serious side effects remained. In 2010 a hardware defect in the left electrode was detected and, consequently, the whole DBS system was removed. Since a satisfying situation with thalamic DBS had not been reached in the last years, DBS of the anterior GPi was carried out in September 2010, at the age of 54. With pallidal DBS he experienced a large improvement on the YGTSS from 46 till 9 (80.4%), which was maintained after 38 months of follow-up¹⁹.

Table 2: Yale Global Tic Severity Scale.

	YGTSS total (motor/vocal)						
	Baseline	6-12 m	12-24 m	24-36 m	36-48 m	48-60 m	60-78 m
Patient 1	38(19/19)	2(0/2)	-	5(0/5)	8 (4/4)	7 (4/3)	ND
Patient 2	44(25/19)	19(19/0)	11 (10/1)	22(16/6)	22 (16/6)	ND	ND
Patient 3	45(20/25)	19(13/6)	22(18/4)	-	12 (12/0)	-	5 (5/0)
Patient 4	46(21/25)	34(15/19)	30(15/15)	ND	ND	ND	ND
Patient 5	40(22/18)	29(14/15)	ND	ND	ND	ND	ND
Patient 6	41(16/25)	26(10/16)	-	27(13/14)	ND	ND	ND
Patient 7	43 (20/23)	26 (16/10)	-	-	44 (23/21)	35 (19/16)	39 (21/18)

YGTSS: Yale Global Tic Severity Scale; m: months; ND: No Data (because stimulator removed or switched off).

DISCUSSION

These seven cases show that thalamic DBS in patients with severe TS can be effective in reducing tics at the short-term¹². However, at the long-term in only one patient (patient 3) the stimulator is still active. In three patients (patient 1, 4 and 7) the target has been changed to the anterior GPi due to side effects (e.g. reduced level of energy, sleeping disorders, gaze disturbances and alteration of sexual function). In one of those patients (patient 1) a satisfying effect on tics during pallidal stimulation could not be reached and finally we switched off the pallidal DBS and turned on the thalamic DBS again. Three patients (patient 2, 5, and 6) were not satisfied with the results of the DBS and decided to switch off their stimulator. Two of them (patient 5 and 6) showed only minor improvement during stimulation, whereas the third patient (patient 2) had a good effect but suffered from the adverse effects. These results are partially in line with the results of Motlagh et al¹¹, with an improvement of more than 50% in three out of eight cases versus three out of seven cases in our sample. However, they did not report on side effects over the course of time, which appeared to increase in our sample and were often responsible for changing the target or switching off the stimulator. Porta et

al⁹ reported a significant reduction in tic severity (pre-DBS 80.83 ± 11.98 , post-DBS 22.11 ± 14.19 , $p < 0.001$) at six years follow-up, but also difficulties like noncompliance and differences in the opinions between the patients and the medical team^{9,10}. In their sample side effects have been reported only as minor and not being a cause of the dissatisfaction, which is in contrast with our results.

At long-term follow-up we also found differences in opinions between the medical team and the patients as to what a satisfactory outcome is. Whereas professionals mainly focus on tic reduction, a patient's wellbeing does not only depend on tic reduction^{10,20}. In our group we noticed that patients with tic improvements between 9% and 34% generally were dissatisfied with the results and end their stimulation. We also observed that patients who responded well in terms of tic reduction ($>50\%$), but experienced increasing side effects were dissatisfied too. The YGTSS is a quantitative method to determine the effect on tics¹⁷, but it does not necessarily represent the patient's satisfaction with the treatment. Satisfaction may concern many factors, which can be different for the individual patients. Besides, there will be a response shift with respect to expectations and ambitions, which may explain changes in satisfaction over time. Therefore, qualitative research concerning the perception of satisfaction, expectations, and ambitions in TS patients undergoing DBS is highly needed²⁰.

In the earlier years of DBS, professionals often mentioned the 'burden of normality' as an explanation for dissatisfaction after surgery²¹. On being rendered 'disease' free, the process of successful adjustment primarily depends on the patient's ability to discard the roles associated with the disease and his capacity to adjust to leading a normal life. For TS patients this may be especially difficult since they suffer from a lifelong disabling condition, and the tics have played a major role in the development of their personality, education and both social and professional life. In addition, DBS in TS improves the symptoms (tics), with a collateral improvement of comorbid behavioural disorders in only a minority of patients. In the early period after surgery the relief of tic improvement may distract from essential other premorbid problems and side effects. However, these problems and side effects may become more obvious after a longer time, and at that time more difficult to accept. In general, one easily can get used to 'success', but it is hard to accept 'losses'.

Saleh et al⁵ analysed all reported complications and adverse events after DBS for TS and other psychiatric diseases. Long-term morbidity was reported in 16.5% of cases, in 6.2% this was related to the surgery or hardware and in 10.2% to chronic stimulation^{5,12}. Stimulation related side effects included; anxiety ($n=7$), mood changes ($n=2$), psychosis ($n=1$), apathy ($n=13$), and alteration of sexual function ($n=6$). Notably, apathy was observed only in patients with thalamic DBS. The majority of reported side effects appeared to be transitory or resolved with adjustments of stimulation settings. This is not in line with our experience during the long-term follow-up. The side effects in our group did most often not respond to adjustments in stimulation settings. Moreover, the

side effects, though based on self-report, became more pronounced with increasing treatment duration.

Thoughtful programming of the stimulator is very important to achieve an optimal clinical outcome¹¹. Due to natural symptom fluctuations, variability in patient's responses to treatment and expectations, adjustment in stimulation settings is often a temporary solution⁹⁻¹¹. In our experience TS patients tend to blame the stimulator for almost all negative symptoms and maybe professionals reinforce them to do so by adjusting the stimulation settings every time they report complaints. Given the experimental status of DBS in TS and their clinical responsibility to treat side effects, professionals might feel the pressure to intervene and as such maintain dissatisfaction. Intensive guidance, multidisciplinary, already early after surgery, is needed to differentiate between stimulation related changes and problems in coping with the postoperative situation. Standard postoperative psychoeducation for the patient and his system, either individual or in a group, will be helpful to shift the focus from the stimulator to the person and his environment and as such reduce blaming the stimulator and unnecessary adjustment of the stimulation settings.

The main limitation of this case series is that we report on observational data of a small sample and case descriptions from routine clinical practice with variable follow-up duration. Specialized Tourette clinics have reported only a handful of appropriate DBS candidates each year, rendering it nearly impossible to draw critical conclusions about the effects. However, the importance of these data for our daily practice cannot be underestimated. Thorough reporting on small groups and long-term follow-up data is essential, particularly in dealing with a complex disease like TS. Our experience highlights the need for more qualitative studies and the incorporation of additional outcome parameters other than reduction of tics and comorbid symptoms. To overcome some of these problems an International DBS Registry and Database for TS is being developed, with the idea that the statistical power necessary to refine and improve this procedure could only be achieved through the collection of a large worldwide community of cases²².

CONCLUSION

In our group of patients receiving thalamic DBS for TS there seems to be an increasing disbalance of therapeutic effects and side effects at long-term follow-up, often leading to either switching off the stimulator or new surgery with a different neuro-anatomic target. The reported cases reflect the strong heterogeneity of the disease and comorbidity, the still underrated impact of individual expectations and ambitions and the caution of the professionals, all interfering with effects and side effects and the overall success of DBS.

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Chapter 4

Deep Brain Stimulation of the internal globus pallidus in refractory Tourette Syndrome

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ABSTRACT

Objective: Deep Brain Stimulation in psychiatric disorders is becoming an increasingly performed surgery. At present, six different targets have been stimulated in Tourette Syndrome, including the internal globus pallidus. We describe the effects on tics and comorbid behavioural disorders of Deep Brain Stimulation of the anterior internal globus pallidus in five patients with refractory Tourette Syndrome.

Methods: This study was performed as an open label study with follow-up assessments between 12 and 38 months. Patients were evaluated twice, one month before surgery and at long-term follow-up. Primary outcome was tic severity, assessed by several scales. Secondary outcomes were comorbid behavioural disorders, mood and cognition. The final position of the active contacts of the implanted electrodes was investigated and side effects were reported.

Results: Three males and two females were included with a mean age of 41.6 years (SD 9.7). The total post-operative score on the Yale Global Tic Severity Scale was significantly lower than the pre-operative score (42.2 ± 4.8 versus 12.8 ± 3.8 , $P=0.043$). There was also a significant reduction on the modified Rush Video-Based Tic Rating Scale (13.0 ± 2.0 versus 7.0 ± 1.6 , $P=0.041$) and in the total number of video-rated tics (259.6 ± 107.3 versus 49.6 ± 24.8 , $P=0.043$). No significant difference on the secondary outcomes was found, however, there was an improvement on an individual level for Obsessive-Compulsive behaviour. The final position of the active contacts was variable in our sample and no relationship between position and stimulation effects could be established.

Conclusion: Our study suggests that Deep Brain Stimulation of the anterior internal globus pallidus is effective in reducing tic severity, and possibly also Obsessive-Compulsive behaviour, in refractory Tourette patients without serious adverse events or side effects.

INTRODUCTION

Tourette Syndrome (TS) is a complex childhood-onset neuropsychiatric disorder characterized by multiple motor tics plus one or more vocal tics ¹⁻³. More than half of patients with TS show evidence of psychiatric comorbidity, exhibiting symptoms of Attention Deficit and Hyperactivity Disorder (ADHD), Obsessive-Compulsive behaviour (OCb), and anxiety or mood disorders ^{2,3}. TS is often self-limiting ⁴, but in about 20% of patients tics continue in adult life and require chronic treatment ¹. Behavioural therapy and medication may provide relief, but some patients remain refractory or experience unbearable side effects ². For those patients, surgery might be the treatment of last resort.

Deep Brain Stimulation (DBS) of the medial thalamus was introduced in 1999 as a new approach for refractory TS patients ⁵. At present, six different targets have been stimulated, including the internal globus pallidus (GPi), which is divided in a posterolateral part, the motor area (posterior GPi), and an anteromedial part, the limbic area (anterior GPi) ⁶. Although the majority of studies have targeted the medial thalamus with positive effects on tics, the effects on comorbid behavioural disorders are indistinct and serious side effects, such as reduced levels of energy, visual disturbances, sleeping disorders, and erectile dysfunction, have been reported ^{7,8}. Recent open-label studies and small double-blind trials suggest that DBS of the anterior GPi is an effective and well-tolerated treatment for refractory TS ⁹⁻¹³. Sachdev et al ¹¹ reported their long-term follow-up of 17 patients with DBS in the anteromedial GPi. Overall, they showed a significant tic reduction around 45% at one month of follow-up which was maintained up to four years. Side effects related to the stimulation were mostly temporary and attenuated with adjustment of stimulation parameters (e.g. anxiety, agitation, dizziness). Kefalopoulou et al ¹² performed a relative large randomized, double-blind, crossover trial of anterior GPi stimulation in 13 refractory TS patients. They reported significant improvement on the Yale Global Tic Severity Scale (YGTSS) of 15.3% during the blinded off-stimulation versus on-stimulation, which further improved during the open label stimulation phase (40.1%). Side effects were comparable to those described previously.

Based on these promising results and pathophysiological considerations we decided to perform anterior GPi stimulation in five patients with refractory TS. The effects on tics, associated behavioural disorders, mood and cognition are described in this paper.

METHODS

Patient selection

Patients with refractory TS were referred to the Maastricht University Medical Centre (MUMC) and selected for bilateral DBS of the anterior GPI. Inclusion criteria for surgery were: 1) a primary diagnosis of TS according to the Diagnostic and Statistical Manual of Mental Disorders criteria (fourth edition) (DSM-IV)³, 2) a minimum score of 80 on the Diagnostic Confidence Index¹⁴, 3) a minimum age of 25 years, 4) a minimum score of 25 on the YGTSS¹⁵, 5) failure to respond to, or intolerable side effects of three-months trials of adequately dosed typical (e.g. haloperidol) and atypical (e.g. risperidone, olanzapine, quetiapine) antipsychotic medication or clonidine, 6) completed at least ten sessions of behavioural therapy (e.g. exposure in vivo or habit reversal). Exclusion criteria included: 1) tics not related to TS, 2) major psychiatric disorders (e.g. schizophrenia, bipolar disorder), 3) current substance abuse or dependence (except for nicotine), 4) severe cognitive impairment, 5) structural abnormalities on brain Magnetic Resonance Imaging (MRI), 6) general contraindications for surgery or anaesthesia. These criteria are in line with the European guidelines for TS and previously published research^{6,7,16}. All patients were seen by a neurosurgeon, psychiatrist and neuropsychologist, and patient selection was based on a multidisciplinary decision. These results represent a systematic audit of our outcomes and ethical approval was therefore not required. However, all patients gave written informed consent to report the results and to retrieve data from their medical records.

Surgery

The surgery was performed under local anaesthesia and sedation (lorazepam, remifentanyl and clonidine), using a Leksell stereotactic frame. The following stereotactic coordinates were obtained: 12 mm lateral, 6-9 mm anterior, and 0-3 mm superior to the midcommissural point. Target coordinates were visualized and adapted on high field T2 W MRI images. A burr hole was placed in line with the planned trajectory and multiple-electrode extracellular single-unit micro-electrode recordings (MER) were performed. Recording took place from 10 mm above target to 4 mm beneath target in 0.5 to 1.0 mm steps. Subsequently, test stimulation was performed along the trajectories with the best MER recordings to assess stimulation-induced side effects. Finally, test electrodes were replaced by a final, quadripolar electrode (model 3389 or 3387, Medtronic Kerkrade, the Netherlands) with the second deepest contact (contact 1) at the level of the pallidal target that gave no side effects or only at highest stimulus intensity. Subsequently, the pulse generator (Activa PC, Medtronic) was implanted in a separate procedure under general anaesthesia. On the second post-operative day an MRI-scan was performed to detect asymptomatic haemorrhages and

to evaluate the position of the electrodes. Stimulation parameters were adjusted after surgery. More details about the stereotactic neurosurgical procedure have been published previously by Ackermans et al⁷.

Electrode localization

The final position of the active contacts of the implanted electrodes was visualized. To this end, the coordinates of the active contacts were calculated in the post-operative images by manually defined coordinates of the most distal point of the electrode artefact, and of a proximal point in the centre of the electrode artefact. Next, the brains of the pre- and post-operative MRI images were extracted with FSL's brain extraction tool (BET)¹⁷ to rigidly fuse the post-operative images with the pre-operative images, using FSL's Linear Image Registration Tool (FLIRT)¹⁸. Based on this registration the post-operative active contact coordinates were converted to the pre-operative image space. Finally, ITK-SNAP segmentation software was used to visualize the final position of the active contacts on the pre-operative MRI scans¹⁹.

Outcome measures

Patients were evaluated twice, within one month before surgery and minimal twelve months after surgery on all primary and secondary outcomes. All evaluations were performed by the same examiners (AS, AD, LA).

The primary outcome was tic severity assessed by the YGTSS¹⁵, the modified Rush Video-Based Tic Rating Scale (mRVRS)²⁰, and the number of video-rated tics in 10 minutes. The YGTSS provides an evaluation of number, frequency, intensity, complexity, and interference of motor and vocal tics. Total scores range from 0-50 with higher scores indicating higher severity. The mRVRS and the number of video-rated tics were based on five 2-minute video fragments in three different conditions: interview, sitting alone, and walking. The mRVRS scores tic frequency, severity of tics, and the number of body areas involved. Scores range from 0-25 with higher scores indicating higher severity. Secondary outcomes were comorbid behavioural disorders, mood and cognition. OCB was measured by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)²¹ and ADHD by the Conner's Adult ADHD Rating Scale (CAARS)²². Depressive symptoms were assessed by the Dutch version of the Beck Depression Inventory 2th edition (BDI-II)²³ and anxiety by the Beck Anxiety Inventory (BAI)²⁴. A neuropsychological examination was performed to assess cognition. Given the known frontostriatal dysfunction in TS and results on cognition in the past, the examination focused on attention and executive functions⁷. The test battery included the digit symbol coding and digit span subtest of the Wechsler Adult Intelligence Scale-third edition (WAIS III)²⁵, the Trail Making Test (TMT)²⁶, the Stroop Colour Word Test²⁷, and Category²⁸ and Letter fluency²⁶.

Adverse events, meaning complications related to the surgery or side effects related to the stimulation, were monitored carefully and frequently by interview on the outpatient clinic.

Statistical analyses

Pair-wise comparisons of the respective pre- and post-operative outcome variables were performed with Wilcoxon signed-rank tests and a P-value < 0.05 was considered significant. All data were analysed using Statistical Package for the Social Sciences version 20.0 software (SPSS, Chicago, IL, USA).

RESULTS

Study population

In total five patients, three males and two females, were indicated for bilateral DBS of the anterior GPi between 2010 and 2013. Mean age of the group was 41.6 years (SD 9.7, range 35-57) and mean disease duration was 33.2 years (SD 8.9, range 23-46). Three patients were on medication for TS pre-operative (patient 2, 3 and 4). This medication was reduced by approximately 50% post-operatively in all patients. Follow-up duration ranged from 12 to 38 months (SD 13.7).

Patient 1: This divorced and unemployed male developed tics at the age of eight which gradually worsened around adolescence. Most debilitating symptoms were forceful head movements and screaming. Moreover, sexual obsessions and compulsions such as breaking glasses were troublesome. In 2002, at the age of 45, he was selected for bilateral DBS of the thalamus (centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus (CM-Spv-Voi) cross point), which resulted in a tic reduction of 82% at 8 months of follow-up. During follow-up, major adjustments in stimulation parameters have been made with a progression of monopolar stimulation towards bilateral bipolar stimulation and an increase from 2.4 to 8.5 V. However, this caused serious side effects like reduced levels of energy and gaze disturbances. At six years of follow-up tic reduction remained 78%, but even with lower voltage stimulation serious side effects remained. In 2010 a hardware defect in the left electrode was detected and, consequently, the whole DBS system was removed. Since a satisfying result of the thalamic DBS had not been reached anymore the last years, DBS of the anterior GPi was carried out at the age of 54 in 2010. Follow-up duration was 38 months.

Patient 2: This unmarried and unemployed female, with a positive family history of tics and ADHD, suffered from tics since the age of five, becoming more severe around the

age of 25. Motor tics were mainly facial grimaces and eye blinking. Vocal tics like grunting and severe coprolalia caused most impairment. She also suffered from self-mutilating behaviour (e.g. touching hot pans and sharp knives) and OCB (e.g. repeating other people, checking). In 2010, at the age of 29, she was selected for DBS of the anterior GPi. Follow-up duration was 34 months.

Patient 3: This unmarried and unemployed female suffered from tics since the age of seven, which waxed and waned during childhood. From the age of 18 tic severity increased. Motor tics such as head banging and jerks throughout her whole body were most disabling. Vocal tics included coprolalia and uttering sounds. Serious OCB like checking doors and counting made daily activities difficult. DBS of the anterior GPi was performed in 2011 at the age of 41. Follow-up duration was 29 months.

Patient 4: This unemployed and married male with one child, had tics since the age of seven. Most disabling were his vocal tics, including shouting, coprolalia and echolalia. But he also suffered from severe motor tics like jumping and jerks of the arms. In 2006, at the age of 35, DBS of the thalamus (CM-Spv-Voi cross point) was performed with an improvement in tics of 35% one year after surgery. Although the effect on tics remained stable, he was not satisfied with the results due to side effects like gaze disturbances and reduced levels of energy. He felt like a different person and was not able to perform his daily tasks. Many adjustments in stimulation settings were made without sustained satisfying results. In 2012 the pulse generator and the extra-cranial leads had to be removed due to a persisting hardware infection after an internal pulse generator replacement. Because of the disappointing results of thalamic DBS at long-term follow-up, we choose not to replace the thalamic leads. In 2012, at the age of 41, he was selected for DBS of the anterior GPi. Follow-up duration was 12 months.

Patient 5: This employed and married male with one child experienced facial tics since the age of 12. In his late twenties both motor and vocal tics became more severe and jerks throughout his whole body were the most disabling symptom. He also suffered from vocal tics like uttering sounds and coughing. Tic frequency was extremely high, mainly due to persisting bouts of combined tics. DBS of the anterior GPi was performed in 2013, at the age of 35. Follow-up duration was 12 months.

Final position of the implanted electrodes

Details of the final electrode position and stimulation parameters are shown in Table 1 and Table 2. Moreover, the position of the active contacts is shown in Figure 1a-1f. In patient 1, the left and right active contacts are located around 2mm anterior in the external globus pallidus (GPe). In patient 2, both active contacts are located cranial in the anterior part of the GPi. In patient 3, the left active contact is located in the cranial part of the anterior GPi, however, the right active contact is situated in the posterior part of the anterior GPi. In patient 4, both active contacts are located in the anterior GPi, stimulating both the cranial and caudal parts since three active contacts are used. In patient 5, the active contacts are located at the medial border of the anterior GPi with the internal capsule.

Table 1: Final electrode position.

Patient	Left electrode				electrode	number of MER
	Lead	x	y	z		
1	3387	12	8	contact 1 on target -1.0	central	5
2	3387	12	9	contact 1 on target	medial	3 (except lat/pos)
3	3389	12	6.6	contact 1 on target -3.0	central	3 (except ant/med)
4	3389	13.2	10.9	contact 1 on target +1.5	central	3 (except ant/pos)
5	3389	11.2	8.9	contact 1 on target -0.5	lateral	3 (except ant/med)
Patient	Right electrode				electrode	number of MER
	Lead	x	y	z		
1	3387	12	8	contact 1 on target -1.0	anterior	5
2	3387	12	11	contact 1 on target	central	2 (cen/med)
3	3389	12	6.6	contact 1 on target -3.5	lateral	3 (except ant/med)
4	3389	14.4	9.6	contact 1 on target +1.5	anterior	4 (except pos)
5	3389	11	8.9	contact 1 on target - 0.5	central	3 (except ant/med)

MER: microelectrode recordings; ant: anterior; lat: lateral; med: medial; pos: posterior; x = number of mm lateral of the anterior commissure – posterior commissure (AC-PC) midline; y = number of mm anterior to the mid-commissural point at the level of the AC-PC plane; z = number of mm deeper (+) or more superficial (-) than the AC-PC plane.

Table 2: Stimulation parameters.

Patient	Left electrode					Right electrode					Voltage (V)	Pulse (μ s)	Frequency (Hz)
	0	1	2	3	case	4	5	6	7	case			
1				-	+				-	+	3.2	360	130
2		-			+		-			+	5.6	330	180
3				-	+				-	+	4.7	330	100
4	-	-		+		-	-		+		5.0	180	130
5			-	-	+	-	-			+	2.2	330	130

V: Volt; μ s: microseconds; Hz: Hertz.

Figure 1: Final position of the active contacts of the implanted electrodes on the pre-operative inversion recovery MRI-scans of the five patients, respectively.

(A): Anatomical overview around the internal globus pallidus. (B) Patient 1. (C) Patient 2. (D) Patient 3. (E) Patient 4. (F) Patient 5.

Abbreviations: Pu: Putamen; GPe: external globus pallidus; GPi: internal globus pallidus; Th: Thalamus.

Pre-operative inversion recovery MR images were acquired with a 1.5T MR scanner (patients 1, 2, and 5) and a 3T MR scanner (patient 3 and 4) (Intera, Philips Medical Systems, Eindhoven, the Netherlands). The inversion time was 400 msec, and the echo time, repetition time, and resolution varied from 10-15 msec, 2000-8807 msec, and 0.34x0.34-0.45x0.45 mm, respectively.

Primary outcomes

On a group level, the post-operative score on the YGTSS was significantly lower than the pre-operative score (42.2 ± 4.8 versus 12.8 ± 3.8 , $P=0.043$). There was also a significant reduction on the mRVRS (13.0 ± 2.0 versus 7.0 ± 1.6 , $P=0.041$) and on the total number of video-rated tics (259.6 ± 107.3 versus 49.6 ± 24.8 , $P=0.043$). The YGTSS and the number of video-rated tics were divided into motor and vocal sub scores. For the video-rated tics, improvements on both sub scores were comparable (79.7% and 81.0%, respectively). On the YGTSS the percentage of reduced motor scores was lower than that

of the reduced vocal scores (64.8% and 78.2%, respectively). The evaluators were not blinded for the stimulation condition. Individual primary outcomes are shown in Table 3.

Table 3: Results on primary outcomes.

		YGTS			Video-rated tics			mRVRS
		<i>Motor</i>	<i>Vocal</i>	<i>Total</i>	<i>Motor</i>	<i>Vocal</i>	<i>Total</i>	
Patient 1	<i>Pre-op</i>	24	22	46	182	33	215	12
	<i>Post-op</i>	9	0	9	31	0	31	5
Patient 2	<i>Pre-op</i>	13	23	36	88	25	113	10
	<i>Post-op</i>	7	6	13	28	12	40	6
Patient 3	<i>Pre-op</i>	25	17	42	273	73	310	15
	<i>Post-op</i>	7	2	9	68	4	72	9
Patient 4	<i>Pre-op</i>	23	25	48	167	92	259	14
	<i>Post-op</i>	8	9	17	19	6	25	8
Patient 5	<i>Pre-op</i>	23	17	40	327	74	401	14
	<i>Post-op</i>	8	8	16	54	26	80	7
		P = 0.043			P = 0.041			P = 0.043

Pre-op: pre-operative; Post-op: post-operative; YGTSS: Yale Global Tic Severity Scale; mRVRS: modified Rush Video-Based Rating Scale.

Secondary outcomes

No significant differences were found between pre-operative and post-operative assessments of anxiety, depression and ADHD (Table 4). However, those patients (three of five) with clinically relevant symptoms of OCB prior to surgery (Y-BOCS > 16) showed improvement after surgery (12%, 35% and 100%). Neuropsychological test scores revealed no significant differences between pre- and postoperative assessment (Table 5).

Table 4: Results on behavioural disorders and mood.

		Y-BOCS		CAARS		BAI		BDI	
		Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Patient 1		16	14	109	91	60	53	20	22
Patient 2		31	0	17	36	22	25	9	3
Patient 3		20	13	104	101	34	38	8	14
Patient 4		10	0	99	65	32	32	5	8
Patient 5		0	0	MD	35	MD	22	MD	1
Mean	(SD)	15.4 (11.5)	5.4 (7.4)	82.3 (43.7)	65.5 (29.8)	37.0 (16.2)	34.0 (12.3)	10.5 (6.6)	9.6 (8.6)
P-value		0.068		0.465		1.000		0.581	

Mean (SD); Pre-op: pre-operative; Post-op: post-operative; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; CAARS: Conner's Adult ADHD Rating Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; MD: Missing Data.

Table 5: Results on cognition.

		WAIS digit symbol coding	WAIS digit span	TMT A (sec)	TMT B (sec)	Stroop colour word (sec)	Stroop colour word (error)	Category fluency	Letter fluency
Patient 1	Pre-op	42	11	40	101	80	0	37	32
	Post-op	45	15	40	110	102	0	35	25
Patient 2	Pre-op	52	11	35	97	118	1	37	27
	Post-op	67	11	40	72	80	0	34	22
Patient 3	Pre-op	99	23	12	30	50	0	59	72
	Post-op	83	24	13	59	62	0	47	58
Patient 4	Pre-op	63	13	17	95	122	6	37	45
	Post-op	60	16	33	MD	101	3	36	39
Patient 5	Pre-op	78	14	22	46	85	1	35	41
	Post-op	81	16	20	34	86	1	43	45
P-value		0.891	0.068	0.237	1.000	0.686	0.180	0.345	0.080

Pre-op: pre-operative; Post-op: post-operative; sec: seconds; WAIS: Wechsler Adult Intelligence Scale; TMT: Trial Making Test.

Adverse events

Patient 1 developed a coagulase-negative staphylococcus infection of the abdominal pulse generator six months after surgery, which was successfully treated with intravenous antibiotics. Moreover, he experienced pain on the left side of his neck due to lead traction. Three patients experienced side effects related to the stimulation. Patient 1 and 3 reported a feeling of apathy leading to passive behaviour and not related to adjustments in stimulation parameters. Patient 4 experienced weight loss and stimulation-related agitation.

DISCUSSION

In this paper the effects of DBS of the anterior GPi were analysed in five refractory TS patients. Even though we performed an open label study with a small sample size, there was a significant beneficial group effect on tics. The improvement in YGTSS (70%) is in line ¹³ or even more ^{11,12} than most previous studies targeting the same area report. Controlled data, although in a small sample, have even suggested that DBS of the anterior GPi could bring larger benefits than thalamic ¹³ or posterior GPi ¹⁰ stimulation. Although there were no significant effects for comorbid behavioural disorders, mood and cognition at the group level in our patients, those patients with pre-operative clinically relevant OCB showed post-operative improvement at an individual level. Effects of anterior GPi DBS on OCB have often not been described and are overall indistinct. Only Sachdev et al ¹¹ showed significant improvement in OCB during

stimulation. So far, DBS in TS has not been associated with significant cognitive decline on a group level, providing support for its cognitive safety²⁹.

Adverse events related to the surgery were minor and occurred in only one patient who developed an infection of his abdominal pulse generator. Stimulation induced side effects reported were apathy in two patients, not responsive to changes in stimulation settings. These patients were still able to perform all necessary daily tasks, with a higher threshold to initiate them. One patient suffered from agitation and weight loss, which was extensively investigated by several specialists, but no cause could be found. As such we believe the weight loss might be stimulation related, although adjustment of the parameters did not affect the weight. Apathy has been reported in other studies as a possible stimulation induced side effect¹². Moreover, side effects like anxiety, agitation, and dizziness have been reported, which were not present in our group^{10-13,30}.

The location of the active contacts differs between our five patients, ranging from the anterior part of the GPi to the GPe and the internal capsule. We could not establish a relation between the anatomical position of the active contacts and the effects of the stimulation. Larger sample sizes will be needed to clarify which anatomical structures relating to an anterior GPi trajectory provide optimal tic control. Our findings suggest that applying electrical stimulation to the region of the anterior parts of the GPe and GPi produces therapeutic effects on tics, and in patients with OCb possibly also on these symptoms.

This study has a number of limitations. We reported observational data from routine clinical practice with variable follow-up durations. As such no power calculation was performed and the statistical comparisons are based on five patients. There was no control group or control condition that would allow definite attribution of change in symptoms and side effects related to the implantation or stimulation. The paucity of available refractory TS patients, however, makes it difficult to perform highly needed randomized controlled trials with sufficient power.

CONCLUSION

Our study contributes to the sparse evidence in this field suggesting that anterior GPi DBS is an effective treatment in refractory TS^{10,13,30,31}. We are cautious in over interpreting these data, but based on the present results, our experience with thalamic stimulation and other published evidence, we will continue targeting the anterior GPi as first choice in future refractory Tourette patients.

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Chapter 5

Tonic and phasic changes in pallidal activity in Tourette Syndrome

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ABSTRACT

Background: Tourette Syndrome is a hyperkinetic neurodevelopmental disorder characterized by tics.

Objective: Assess the neuronal changes in the limbic globus pallidus associated with Tourette syndrome.

Methods: Neurophysiological recordings were performed from the anterior (limbic) external globus pallidus and internal globus pallidus of eight awake patients during Deep Brain Stimulation electrode implantation surgeries.

Results: The baseline firing rate of the neurons was low in a state dependent manner in both segments of the globus pallidus. Tic dependent transient rate changes were found in the activity of individual neurons of both segments around the time of the tic. Neither oscillatory activity of individual neurons nor correlations in their interactions were observed.

Conclusions: The results demonstrate the involvement of the limbic pathway in the underlying pathophysiology of Tourette Syndrome and point to tonic and phasic modulations of basal-ganglia output as a key mechanism underlying the abnormal state of the disorder and the expression of individual tics, respectively.

INTRODUCTION

Tourette syndrome (TS) is a childhood-onset neurodevelopmental disorder characterized by motor and vocal tics¹. The underlying mechanism of TS is still largely unknown; however, multiple lines of evidence have linked it to malfunctions in the cortico-basal-ganglia-thalamocortical (CBGT) pathway^{2,3} and specifically to reduced inhibition within the striatum, the primary input nucleus of the basal ganglia (BG)^{2,4,5}. The striatum controls the output of the BG through two pathways: the direct pathway to the output nucleus of the BG, the globus pallidus internus (GPi) and the indirect pathway to the GPi through the globus pallidus externus (GPe)^{6,7}. These pathways are further subdivided into functional pathways that convey motor information primarily to the posterolateral GPi (posterior GPi) and limbic information to the anteromedial GPi (anterior GPi)⁸.

Currently, there is scant neurophysiological data from TS patients. Extracellular neuronal recordings performed during pallidotomy surgery revealed a decreased overall firing-rate in the posterior GPi of TS patients complemented by phasic firing-rate changes around the time of the tic⁹. Deep Brain Stimulation (DBS) targeting the anterior GPi in TS patients provides a rare opportunity to directly observe neuronal activity in the limbic domains of the BG. The current study focuses on linking the activity of GPe/GPi neurons in these domains with TS pathophysiology.

METHODS

Patients

The data were collected from eight patients, aged 19-55 years (37 ± 14 , mean $\pm$ SD) who underwent surgery for the bilateral implantation of DBS electrodes in the anterior GPi, as treatment for TS (Table 1). Patients with refractory TS were referred to the Maastricht University Medical Centre (MUMC) and selected for bilateral DBS of the anterior GPi. Inclusion criteria for surgery were: 1) a primary diagnosis of TS according to the Diagnostic and Statistical Manual of Mental Disorders criteria (fourth and later fifth edition)^{10,11}, 2) a minimum score of 80 on the Diagnostic Confidence Index¹², 3) a minimum score of 25 on the Yale Global Tic Severity Scale (YGTSS)¹³, 4) failure to respond to, or intolerable side effects of three-months trials of adequately dosed typical (e.g. haloperidol), and atypical antipsychotic medication (e.g. risperidone, olanzapine, quetiapine) or clonidine, 5) completed at least ten sessions of behavioural therapy (e.g. exposure in vivo or habit reversal). Exclusion criteria included: 1) tics not related to TS, 2) major psychiatric disorders (e.g. schizophrenia, bipolar disorder), 3) current substance abuse or dependence (except for nicotine), 4) severe cognitive impairment, 5) structural abnormalities on brain Magnetic Resonance Imaging (MRI), 6) general contraindications

for surgery or anaesthesia. These criteria are in line with the European guidelines for TS^{14,15}. Based on new insights and recommendations we have waived the previously suggested 25-years-old age limit since 2014, with the specification that a multidisciplinary team approach for screening is employed¹⁵. In this study, the neurophysiological results represent an overview of routine measurements performed during DBS surgery for TS and formal approval by a medical ethics committee was therefore not required. All patients gave written informed consent to report these results and to retrieve data from their medical records.

Surgery

Details about the neurosurgical procedure and the surgery outcomes are described in previous work^{16,17}. The surgery was performed under local anaesthesia and sedation while the patients were awake. The following stereotactic coordinates were obtained: 12 mm lateral, 6-9 mm anterior, and 0-3 mm superior to the midcommissural point. Target coordinates were visualized and adapted on high field T2 weighted images. The angle of the track is adapted to T1 weighted images with contrast, to avoid blood vessels as well as the head of the nucleus caudatus and in order to enter the frontal lobes. Up to five micro-electrodes were used to record the neuronal activity along the trajectory for mapping purposes. Recording took place from 10mm above target to 4mm beneath target in 0.5–1.0mm steps. The electrode signal was bandpass filtered (160–5000Hz), and sampled at 20/25kHz (InoMed, V3.15). Movement during the neuronal recordings was monitored by simultaneous electromyogram (EMG) recordings, sampled at 2 kHz. EMG recordings were available only in three surgeries (patients V, K & O). The recordings were performed from the extensor digitorum communis and flexor carpi radialis (patient V), from the masseter (patient's K and O) and the deltoideus, rectus abdominus and femoralis (vastus medialis) on bilateral muscles (patient O). In addition, a simultaneous video recording of the face was available in one surgery (patient K).

Data pre-processing and analysis

The anatomic location of the individual neurons was reconstructed based on the MRI scan, the overlaid trajectory and the trajectory history including border cells and areas of reduced neuronal activity (white matter). The signals were sorted offline (Offline Sorter, V2.8.8; Plexon) into multiple single-unit spike trains. All additional analyses were performed using custom-written MATLAB code (V2012B; MathWorks). Neurons were accepted for further analysis if they met the following criteria: 1) the recording was from a location within the GPe or the GPi, 2) the acquired cells' action potentials were of a consistent distinct shape that could be fully separated with a high degree of certainty from the spike waveforms of other neurons and the background noise, 3) the

cells' inter-spike intervals were confirmed to have a refractory period, and 4) stable neuronal recording was available for at least 3 continuous seconds (coefficient of variation (CV) or Fano factor (FF) < 4). Low-frequency bursting (LFB) neurons from the GPe were excluded from the database.

The firing rate, CV and FF of each neuron were calculated for the entire recording period of the neuron. As movement was not monitored for most patients, the time of the tics was unknown. Thus, the analyses were performed on a signal that was not free of the tics' effect on the overall baseline. FF was calculated using windows of 100ms.

Neuronal oscillations were assessed by estimating the power spectrum density (PSD) of the spike trains using Welch's method (Hamming window, 1s, 50% overlap). A shuffling method was used to compensate for the distortion in the spectrum of spike trains which occurs due to the refractory period of the neurons. The mean of the PSD of each neuron was reduced from its PSD. Cross-correlation function between simultaneously recorded pairs of neurons was calculated using 1ms bins and was smoothed with a Gaussian window ($SD=2ms$). The population correlations were assessed by calculating the Pearson's product-moment-correlation-coefficient (PCC) between the spike trains (bin size: 10ms) of simultaneously recorded neurons ($>2s$ overlap).

Changes in the neuronal firing rate around the tics were assessed by calculating the firing rate of each neuron during time windows of 1.5s around the tics (0.5s pre–1s post tic onset time) and comparing this to the firing rate at all other times. The recordings used in our dataset were performed for mapping purposes, thus we only have a short recording period for each neuron containing very few tics (2.7 ± 2.2 tics, mean $\pm$ SD). This precluded the use of methods with high temporal resolution, such as peri-tic time histogram, for the analysis of significant changes. We overcame the sparsity of the data by using broader windows thereby sacrificing temporal resolution for statistical significance. Tic onset times were calculated using threshold crossing of the EMG envelope (3/10 SD over the steady state mean value, for at least 3 consecutive bins). The EMG signals were processed offline and the envelope of the signal was estimated after low pass filtering (8Hz, four-pole Butterworth filter) on the absolute values of the signal. EMG detected tics with a short time gap ($<1s$) from the previous tic onset were excluded. Frame-by-frame video analysis was used to characterize the motor tics in one patient (patient K). The video detections were then aligned to the EMG tic-detection and EMG detected tics that were not accompanied (preceded by $<250ms$) by a video detected tic (of type: eye blink) were excluded from the analysis. The significance level of the tic-related changes was determined by calculating the distribution of a dataset containing 1000 sequences of sham tics for each neuron. Each sham tic sequence included random times which excluded the times of real tics. The number of sham tics within each sequence was set to the number of actual tics that occurred during the recording of each neuron.

Table 1: Clinical characteristics of the Tourette Syndrome patients.

Pt	Sex	Age	Disease time (years)	Tic symptoms	YGTS (motor/ vocal)	Associated behavioural disorders	Medication before surgery	Thalamic DBS	Sedation during surgery
R	M	41	34	shouting, coprolalia, echolalia, flexion arms, jumping	48 (23/25)	history of depression	Zopiclon 7.5mg/day Risperdal 1mg/day	6 years prior to surgery	Remifentanyl 0.02-0.03 µg/kg/min Propofol 2-4 mg/kg/h Missing data
A	F	29	24	coprolalia, grunting, facial grimaces, eye blinking	36 (13/23)	OCb, auto mutilation, history of depression	Pimozide 2mg/day	-	Remifentanyl 0.02-0.03 µg/kg/min Propofol 1-3mg/kg/h
V	M	35	23	jerks of arms/legs, elevation of shoulders, contraction of abdomen, coughing	40 (23/17)	none	none	-	Remifentanyl 0.02-0.03 µg/kg/min Propofol 1-3mg/kg/h
S	M	55	49	coughing, sniffing, facial grimaces, eye blinking, jerks of neck/arms/abdomen	40 (23/17)	none	none	7 years prior to surgery	Remifentanyl 0.1 µg/kg/min Propofol 1-3 mg/kg/h
D	M	54	46	facial grimaces, eye blinking, head banging, jerks of abdomen, coughing, uttering sounds	46 (24/22)	OCb	none	9 years prior to surgery	Remifentanyl 0.01-0.02 µg/kg/min Clonidine 0.003-0.008 µg/kg/min Midazolam 1mg/h
G	F	41	34	eye blinking, facial grimaces, jerks of neck/arms/legs, head banging, uttering sounds, coprolalia	42 (25/17)	autism, OCb, history of depression	Paroxetine 50mg/day Quetiapine 50mg/day Oxazepam 10mg/day	-	Remifentanyl 0.07-0.1 µg/kg/min
K	M	19	13	eye blinking, jerks of head/neck, barking, coprolalia	39 (15/24)	none	none	-	Remifentanyl 0.12 µg/kg/min
O	M	19	11	head shaking, eye blinking, jerks of neck/ arms/legs, coughing	28 (23/5)	none	none	-	Dexmedetomidine 0.5 µg/kg/h

Pt: Patient; YGTSS: Yale Global Tic Severity Scale; ADHD: Attention Deficit and Hyperactivity Disorder; OCb: Obsessive-Compulsive behaviour.

* The use of Propofol as a sedative during three surgeries (of patients R, V and S) was stopped or lowered to a dosage of maximum 1-2 mg/kg/hr, about 15 minutes before the micro-electrode recordings.

RESULTS

Firing rate and pattern

A total of 235 single neurons were recorded from eight awake TS patients during neurophysiological mapping for placement of DBS electrodes in the anterior GPi. Clinical characteristics of the patients are shown in Table 1. The neurons were identified as GPe (n=77) or GPi (n=158) neurons based on their location and trajectory history including border cells and low background activity between the GPe and GPi (Figure 1A).

The firing rates were 48.25 ± 3.4 spikes/s and 50.9 ± 2.6 spikes/s (mean $\pm$ SEM) for GPe and GPi, neurons respectively. The firing rate distributions were positively skewed indicating that the firing rate of most neurons was even lower, with a small subpopulation of high frequency discharge neurons. While the firing rates were similar between GPe and GPi neurons, the firing patterns of the neurons in each nucleus were different. Both the CV and the FF were higher in GPe neurons, in line with their typical pauses, as compared to GPi neurons which presented Poisson-like values of CV and FF (~ 1) (Figure 1B). Different pathologies of the BG, most notably Parkinson's disease (PD), are associated with enhanced oscillatory activity. We found no significant oscillations in the spike trains of neither GPe nor GPi neurons using power spectral estimation methods.

A

i)

ii)

B

Figure 1A: Recording track.

(A) An example of the recording electrode track overlaid on (i) sagittal and (ii) axial MRI for purposes of illustration. Blue – GPe, red – GPi. Abbreviations: GPe: external globus pallidus; GPi: internal globus pallidus. (B) Examples of neurons recorded from several locations along one track. The electrode depth is shown in relation to the location of the stimulation electrode implantation site (0mm).

Figure 1B: Firing characteristics of globus pallidus neurons.

(A) Mean baseline firing rate (i), CV (ii) and FF (iii) of GPe and GPi neurons. Abbreviations: CV: coefficient of variation; FF: Fano factor; GPe: external globus pallidus; GPi: internal globus pallidus.

(B) Firing rate distributions of GPe and GPi neurons (bin size=10 spikes/s). The mean (dashed vertical line) and median (dotted vertical line) of each distribution are overlaid.

Neuronal interactions

Neuronal activity in the GPe/GPi of the normal non-human primate is uncorrelated^{18,19}. However, positive correlations between these neurons appear in PD patients^{20,21} and in the primate model of the disorder¹⁹. To examine whether changes in firing synchrony play a role in the pathophysiology of tics, we examined the correlation in spike firing between simultaneously recorded neurons. Cross-correlation functions were calculated between the spike trains of 63 pairs (GPe:18, GPi:45) of simultaneously recorded single neurons. The activity of the neurons was found to be uncorrelated as none of the cross-correlation functions had significant peaks (Figure 2A). We calculated the Pearson's product-moment-correlation-coefficient (PCC) between the spike trains of each pair of neurons. The average correlation coefficient for the whole population of pairs was zero with narrow margins (0 ± 0.03 , mean $\pm$ SD) (Figure 2B). Coherence was used to study the degree of neuronal interaction as a function of frequency. The mean coherence

between all simultaneously recorded pairs was flat with no significant peak at any frequency (Figure 2C).

Figure 2: No correlations in the globus pallidus.

Tic-related changes in neuronal activity

The expression of tics was associated with altered neuronal activity throughout the globus pallidus (Figure 3A). Tic times were identified using EMG recordings from three patients (patients V, O and K; patient K had in addition a video recording). The mean firing rate of each neuron during 1.5 seconds (-0.5s→+1s) around tics onset was compared to the mean firing rate of the neuron during the rest of the time (using 100ms time windows). A large fraction (44.1%, 15/34) of GPe neurons significantly changed their firing rate around the time of the tic (two-sample t-test; 10/15 with

$p < 0.01$, and 5/15 with $p < 0.05$). Similarly, 41.7% (15/36) of GPi neurons significantly changed their firing rate around the time of the tic (6/15 with $p < 0.01$, and 9/15 with $p < 0.05$) (Figure 3A-B). In both nuclei, half of the responding neurons (8/15 GPe, 7/15 GPi) displayed a decrease in activity around the time of the tic. The fraction of neurons displaying tic-related activity was significantly higher than expected by the distribution of changes around random time events (z-score, GPe $P < 0.05$; GPi $P < 0.01$). In contrast to the significant firing rate changes of individual neurons, the mean response of GPe as well as of GPi population to the tics was not significantly different from the baseline activity (paired-sample t-test, $P > 0.05$) (Figure 3B-C, bar plot). Thus, despite phasic tic-related changes in the firing rate of individual neurons, the mean firing rate of both nuclei did not phasically change during tic occurrence.

Figure 3: Tic-related changes in firing rate.

DISCUSSION

In this study, we examined neuronal activity in the anterior (limbic) GPe and GPi in TS patients. The baseline firing rate was low and the firing rate distribution of the neurons was skewed. In addition to the tonic reduction in the firing rates, a large fraction of the neurons displayed phasic tic dependent changes. These changes included transient increases and decreases in activity in both segments of the globus pallidus. In contrast to other BG related disorders, oscillatory activity of individual neurons as well as abnormal synchronization between neurons were not observed.

No studies of the limbic (anterior) GPi or any part of the GPe tonic activity during TS have been previously conducted. Tonic activity changes in the motor (posterior) GPi during TS have been partially addressed in previous studies of anesthetized²² and awake²³ patients undergoing a mapping procedure. Our results are in line with both studies which found a rate decrease in the GPi compared to rates recorded in PD patients²³ or normal non-human primates¹⁹. Interestingly, the reduced firing rates that we observed in the GPe are comparable to those previously seen in awake patients suffering from other hyperkinetic disorders such as dystonia^{22,24-26} and hemiballismus²⁷.

Functional models of hyperkinetic movement disorders have tended to focus solely on the existence of abnormalities in the motor circuits of the BG. Here we found changes in the activity of the anterior (limbic) domains of both segments of the globus pallidus resembling those seen in the motor domain⁹. This points to a clear functional interaction between the motor and limbic circuits within the CBGT loop which is consistent with the symptomatology of TS that links limbic, e.g. psychiatric comorbidities, and motor, e.g. tics, properties^{28,29}.

Hyperkinetic disorders in general, and TS in particular, are hypothesized to be associated with enhanced activity of the direct pathway and reduced activity of the indirect pathway which together leads to over-activation of the cortex^{6,7}. In line with this assumption, imaging studies have found abnormal activity in the globus pallidus and enhanced excitation of the direct pathway³⁰⁻³². Our results support this assumption in that the GPi neurons displayed reduced activity. However, the GPe baseline, tonic, activity was also reduced, contradicting the current perception of the indirect pathway involvement in hyperkinetic disorders^{6,7}. Interestingly, this co-modulation of both segments of the globus pallidus is not unique to TS, but has also been observed in other hyperkinetic disorders such as dystonia^{25,26} and hemiballismus²⁷. The reduced activity in both segments can be explained by later theoretical models^{33,34} and experimental data from animal models^{35,36} that point to striatal disinhibition as a key factor driving the appearance of tics. This disinhibition, affecting striatal projection neurons contributing to both the direct and indirect pathways, is thus expected to exercise increased inhibition on both the GPe and GPi driving their firing rates down, in line with our findings. The mixture of phasic responses around the time of the tic indicates that

the neurons within each nucleus form a heterogenic network, in line with previous findings in animal models of the disorder^{35,36}.

CONCLUSION

Our results support and extend existing theoretical, clinical and experimental data suggesting tonic and phasic changes in the neuronal activity throughout the BG during TS. Moreover, our results are unique in demonstrating that these changes affect not only motor pathways but also limbic pathways reflecting the complexity of the disorder. The departure of our findings from the classic perception of hyperkinetic disorders thus calls for the development of a more comprehensive model of BG functionality linking the activity in different domains of the BG in general and during hyperkinetic disorders in particular.

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Chapter 6

Modified cement-based fixation of the Deep Brain Stimulation electrode

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Deep Brain Stimulation (DBS) is becoming an increasingly performed surgery in daily neurosurgical practice. There are several important steps in DBS, such as patient selection, planning of the target, type of anaesthesia, microelectrode recording if performed, and the fixation of the final electrode (lead). Suboptimal fixation can result in electrode migration shortly after the surgery. Unintended migration, and consequently displacement of the electrodes, occurs in up to 10% of the cases and is a serious complication in DBS surgery^{1,2}. This may result in no or suboptimal therapeutic effects, making a second surgery necessary¹⁻³. There are generally two methods for the fixation of the electrode to the skull. The first is using a burr-hole device provided by the hardware manufacturers. For this, the form of the burr hole must be tailored to allow the placement of the burr-hole device³⁻⁵. The second is acrylic-based cementation^{4,6}. This provides the surgeon with a certain degree of freedom in the choice of the form and size of the burr hole. Some of the acrylics contain antibiotics and may form a barrier against infections. In the past 15 years, we have been using antibiotic-containing acrylic⁷. Besides some of its advantages, as outlined above, we experienced a disadvantage, which is the low degree of attachment of the acrylic to the bone, even with undercutting of the tabula interna to achieve a sandwich construction of the cement versus the burr hole. Frequently, we observed small movements of the acrylic construction related to the cerebrospinal fluid/parenchyma pulsations intraoperatively. To overcome this issue, we applied one to two anchoring titanium screws before applying the acrylic cement. This experience was derived from our laboratory studies, where we implanted cannulas and electrodes for long-term experiments and found out that anchoring screws are crucial in achieving a robust construction⁸. Here, we describe a rather simple modification of our previously reported antibiotic-containing cement-based fixation technique⁷ to achieve rigorous anchoring of the DBS electrode.

After having determined the optimal implantation site during DBS surgery, the microelectrode recording/test stimulation electrode is removed and fluoroscopy is performed. Then, the final DBS electrode is lowered to the optimal stimulation site. After placing two layers of oxidized cellulose polymer (Surgicel), one or two titanium screws (2 × 5 mm, the size might depend on individual preferences) are placed close to the burr hole and the acrylic is applied (Figure 1A-C). Finally, the internal guide is removed and a second layer of acrylic is used to fix the electrode. We have performed eight surgeries (16 electrode fixations) with this method and have not observed any movements of the acrylic construct related to cerebrospinal fluid/parenchyma pulsations. The construction was extremely solid. This was independent of whether one or two screws were used. We did not compare the effectiveness of using one or two screws in a randomized fashion.

Adequate fixation of the DBS electrode is essential to prevent postoperative migration. The acrylic-based fixation method has been our method of choice for the last 15 years for several reasons. We modified this method by adding anchoring screws to increase the robustness. This change is in line with other attempts in the field to improve DBS surgery.

Figure 1A: Placement of one of the two screws partially in the skull, nearby the edge of the burr hole and in the opposite direction.

Figure 1B: Final position of the two screws which will connect the cement to the surrounding skull.

Figure 1C: The first layer of cement is placed and surrounds the electrode over the already inserted screws.

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Chapter 7

Ethics of Deep Brain Stimulation in adolescent patients with refractory Tourette Syndrome: a systematic review and two case discussions

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ABSTRACT

Introduction: Tourette Syndrome is a childhood onset disorder characterized by vocal and motor tics and often remits spontaneously during adolescence. For treatment refractory patients, Deep Brain Stimulation may be considered.

Methods and results: We discuss ethical problems encountered in two adolescent Tourette Syndrome patients treated with Deep Brain Stimulation and systematically review the literature on the topic. Following surgery one patient experienced side effects without sufficient therapeutic effects and the stimulator was turned off. After a second series of behavioural treatment, he experienced a tic reduction of more than 50%. The second patient went through a period of behavioural disturbances that interfered with optimal programming, but eventually experienced a 70% tic reduction. Sixteen Deep Brain Stimulation surgeries in adolescent Tourette Syndrome patients have been reported, none of which pays attention to ethical aspects.

Discussion: Specific ethical issues arise in adolescent Tourette Syndrome patients undergoing Deep Brain Stimulation relating both to clinical practice as well as to research. Attention should be paid to selecting patients fairly, thorough examination and weighing of risks and benefits, protecting the health of children and adolescents receiving Deep Brain Stimulation, special issues concerning patient's autonomy, and the normative impact of quality of life. In research, registration of all Tourette Syndrome cases in a central database covering a range of standardized information will facilitate further development of Deep Brain Stimulation for this indication.

Conclusion: Clinical practice should be accompanied by ongoing ethical reflection, preferably covering not only theoretical thought but providing also insights in the views and perspectives of those concerned, that is patients, family members and professionals.

INTRODUCTION

Tourette Syndrome (TS) is a childhood onset neuropsychiatric disorder with multiple motor tics and one or more vocal tics, lasting longer than one year. It affects approximately 0.3 – 1.0 % of the general population¹⁻³. The majority of patients suffer from associated comorbid conditions such as Attention Deficit and Hyperactivity Disorder (ADHD), Obsessive-Compulsive behaviour (OCb), anxiety, and affective disorders⁴. Typically, tics start around the age of 4-6 years, multiply and worsen until the age of 12-14 years and are then followed by a steady decline in severity. TS is often self-limiting, with symptoms remitting around the late adolescence. However, in about 20% of patients, tics continue in adult life and require chronic treatment^{1,3}. Despite behavioural therapy or pharmacological treatment, a small subgroup of patients fails to respond to treatment and continue to experience significant symptom burden throughout life⁵⁻⁷. For those patients, Deep Brain Stimulation (DBS) surgery can be an effective last resort treatment⁸. It must be realized however, that TS is not (yet) a recognized indication for DBS treatment by the Food and Drug Administration (FDA) and the European Commission (EC). We have a longstanding experience with DBS surgery in TS patients since in our centre we performed 16 surgeries in the past 18 years, which is 10% of all reported cases worldwide⁹⁻¹³.

The emergence of psychiatric disorders, such as depressive disorder, Alzheimer's disease and anorexia nervosa, as potential indications for DBS as well as the application of DBS in younger patients has created new interest in ethical questions and social challenges^{14,15}. For most of these indications, ethical considerations have been published¹⁶⁻¹⁸. To date, no ethical considerations have been published on DBS in TS patients, let alone for younger TS patients. The minimum age for considering DBS in TS patients has been widely debated. In 2006, the first guidelines of the Tourette Syndrome Association (TSA)¹⁹ proposed a minimum age of 25 years to ensure that individuals who might experience spontaneous tic remission would not be implanted with a surgical device. More recently, compelling arguments have been made for consideration of surgical intervention at younger ages in certain cases of severe TS. Especially during adolescence, the impact of severe and refractory tics on daily functioning is large. Patients are often not able to go to school or work, they tend to avoid social activities, are not able to develop friendships or an affective relationship, and have a low self-esteem. This developmental interference may have long-lasting effects in later life. Another reason to consider DBS earlier in life is the risk of self-injurious tics, e.g. violent cervical tics which may cause cervical myelopathy and secondary neurological deficits²⁰⁻²². This form is sometimes called 'malignant' TS and occurs in about 5% of patients²³. Delaying or not performing DBS in these patients could eventually lead to irreparable harm. Therefore, in more recent TSA recommendations²⁴ the age guideline has been adjusted and they recommend a multidisciplinary evaluation and discussion, without setting a strict minimum age.

This paper deals with ethical issues associated with DBS of adolescent TS patients. Adolescence is the period of transition from childhood to adulthood. The World Health Organization (WHO) defines adolescence as the age period between 10 and 19 years^{25,26}, however the period of adolescence has often been extended to include the ages of 10 through 22 - 25 years, with most researchers dividing this age span into early (10 - 13), middle (14 - 17) and late (18 - mid-20s) adolescence²⁷. Therefore, we define adolescence as the age period between 10 and 25 years in this paper. We describe our experiences with the treatment of two adolescent TS patients, both 19 years old, and systematically review the scarce literature on this subject. We discuss the ethical issues and specific difficulties that physicians may encounter when treating adolescent patients.

METHODS AND RESULTS

Patient 1

Patient 1 is a 19-year-old male who experienced tics since the age of five. No other diseases or comorbidities were present, and he had a negative family history for tic syndromes. The tics started with sniffing sounds and tapping his chest, but gradually expanded and increased over the years. At the age of 18, vocal tics, such as almost continuous and loud barking and coprolalia, were the most debilitating. He also suffered from frequent motor tics such as eye blinking and head shaking. Because of the disruptive nature of the tics, he had to leave school and avoided social activities. Different pharmacological treatments as well as behavioural therapy had not been effective in the past. From 2005 till 2013 he used clonidine, risperidone, pimozide and aripiprazole, either solely or in combination, without a positive effect on tics and/or with severe side effects. Moreover, botulin injections did not result in tic improvement. In 2010, he received cognitive behavioural therapy for several months without any improvement. He fulfilled all our criteria for DBS surgery (Table 1), which are in line with the TSA guidelines for DBS in TS²⁴. After a multidisciplinary evaluation, he was indicated for bilateral DBS of the anterior internal globus pallidus (GPi) and the surgery was carried out successfully in March 2014 (at the age of 19). Details about the neurosurgical procedure have been published previously^{10,11}. Preoperative he scored 39 (motor/vocal = 14/25) on the Yale Global Tic Severity Scale (YGTSS)²⁸.

A few days after surgery, the stimulator was turned on and different contact points and stimulation parameters were tested. With increasing voltages, he experienced side effects such as hyperkinesia, dyskinesia in the legs and a dejected mood, complicating the programming. Therefore, the voltage was reduced before he was discharged, accepting a suboptimal tic reduction at that moment. The expectation was that these side effects would diminish due to habituation and that the voltage could be increased

slowly at the outpatient department. However, after six months of intensive outpatient visits and a second admission at the hospital to systematically check all possible stimulation parameters, he still experienced the same side effects at all contacts without sufficient therapeutic effects. We decided to turn the stimulator off. At that time, his score on the YGTSS was 24 (motor/vocal = 10/14), which was a relevant reduction compared to the pre-operative score. However, he still suffered from severe tics, e.g. constantly loud barking and headshaking, he felt ashamed and avoided social activities. In September 2016, at the age of 21, he started behaviour therapy again for three months with a further relevant improvement in tics, self-confidence and overall functioning. His YGTSS further declined to 18 (motor/vocal = 8/10), two years after surgery. In a last outpatient appointment, he was satisfied with his current disease severity and stated that with this symptom severity he would in retrospect not have considered DBS. At this moment, he does not want the stimulator removed since he experiences no burdens and does not want to undergo surgery again.

Table 1: Inclusion and exclusion criteria for Deep Brain Stimulation in Tourette Syndrome.

<i>Inclusion criteria *</i>	<i>Exclusion criteria *</i>
<ul style="list-style-type: none"> - Primary diagnosis of TS according to the DSM-V criteria ⁵⁷ - A minimum score of 80 on the Diagnostic Confidence Index ⁵⁸ - A minimum score of 25 on the Yale Global Tic Severity Scale ²⁷ - Failure to respond to, or intolerable side effects of three-months trials of adequately dosed classical (e.g. haloperidol) and atypical (e.g. risperidone, olanzapine, quetiapine) antipsychotic medication or clonidine - Completed at least ten sessions of behavioural therapy (e.g. exposure and response prevention or habit reversal) - A stable psychosocial environment - Neuropsychological profile indicates candidate can tolerate demands of surgery, postoperative follow-up, and possibility of poor outcome - Age is not a strict criterion. Local ethics committee involvement for cases involving persons < 18 years, and for cases considered "urgent" (e.g. impending paralysis from head-snapping tics) 	<ul style="list-style-type: none"> - Tics not related to TS - Major psychiatric disorders (e.g. schizophrenia or bipolar disorder). - Current substance abuse of dependence (except for nicotine) - Severe cognitive impairment - Structural abnormalities on brain Magnetic Resonance Imaging - General contraindications for surgery or anaesthesia

* These criteria are in line with the latest worldwide recommendations for DBS in Tourette Syndrome ²⁴. DBS: Deep Brain Stimulation; TS: Tourette Syndrome; DSM-V: Diagnostic and Statistical Manual of Mental Disorders criteria (fifth edition).

Patient 2

Patient 2 is a 19-year-old male adolescent that developed his first motor tics at the age of eight. No other comorbidities were present, and he had a negative family history for

tic disorders. Tics started with head shaking, followed by eye blinking and grimaces, and later progressed to his shoulders, arms, trunk and legs. The most debilitating tics were persistent bouts of motor tics in his entire body. He also experienced mild vocal tics like coughing, sniffing and grumbling. At the age of 18, he had to quit school since he was not able to concentrate anymore due to the severity of the tics and because his tics were an unacceptable distraction to fellow students. Medication and behavioural therapy had not been effective in the past. He had used clonidine, pimozide, haloperidol and quetiapine either without lasting positive effects or with intolerable side effects. Between 2007 and 2009 he underwent several psychotherapeutic therapies, among which exposure and response prevention, habit reversal and relaxation training. He was using cannabis daily since he felt it calmed him. This patient fulfilled our selection criteria (Table 1) and was indicated for bilateral DBS of the anterior GPi. He agreed to stop using cannabis as part of the treatment agreement, so that better evaluation of symptoms during programming would become possible. The surgery was carried out without complications in March 2016 (at the age of 19).

Within one week after the surgery the stimulator was turned on and systematically different stimulation parameters were tested. Initially he experienced increased agitation, but also an increase in tic frequency and severity. Despite he was informed that finding the correct stimulation parameters would take time, he had hoped for an immediate effect on his tics and was disappointed. This resulted in tension, anger and arguments with his supporting parents, making the programming sessions more difficult. In the following weeks, we had several programming sessions at the outpatient department, mainly decreasing the voltage and slowly increasing it at home, and finally with a voltage of 3.0 a significant tic reduction was established and the agitated feeling had almost disappeared. However, at home the situation escalated, mainly due to the daily excessive use of cannabis, with increasingly quarrelsome and aggressive behaviour. He still lived at home with his parents and siblings who tried to support him and this led to severe conflicts. The exact reason why he started using drugs again is uncertain, but he told us he was overwhelmed, felt a lot of pressure to succeed with the therapy, and needed the cannabis to calm down, even though he knew it caused him more problems. We offered psychological treatment, which he rejected.

In July 2016, we arranged a meeting with the Committee on Medical Ethical Issues of our hospital to discuss how to proceed: we were not able to reliably evaluate the effects of the DBS due to the excessive use of cannabis and non-compliance of the patient and doubted whether continued treatment was useful. Also, the potential contribution of the DBS to the aggressive behaviour was discussed. He was known with aggressive behaviour following cannabis use and it seemed unlikely that the DBS settings were the cause of his behavioural problems. Therefore, we decided to continue treatment because of its positive effect on tics. However, we discussed with the patient that we would not further adjust the stimulation settings if he would not be compliant with all aspects of the treatment agreement, including stopping cannabis usage. A few

months later, his behaviour drastically changed in a positive way. He stopped smoking cannabis, his aggressive behaviour as well as the relationship with his parents improved, and he found a job and started working again. One year after surgery, he was quite satisfied with the effects of DBS. All tics were still present, but much less frequent and intense and he could suppress them better. He did not suffer from side-effects anymore. At that moment, his YGTSS was reduced from 32 preoperatively (motor/vocal = 23/9) to 10 postoperatively (motor/vocal = 8/2).

Overview of the ethical literature

We systematically searched the literature for papers discussing ethical issues in young TS patients treated with DBS. We searched PubMed with the search strategy; (Tourette's syndrome OR Tourette syndrome OR Gilles de la Tourette syndrome OR Tourette's disorder OR Tourette OR tic disorder) AND (Deep brain stimulation OR DBS) without any time or language restriction (Figure 1).

Since 1999, 156 cases of DBS treatment in TS patients have been published²⁹. Of these, only 16 surgeries in patients under 25 years of age have been described in case reports (Table 2)^{20-22,30-40}. These reports mainly focus on target selection, stimulation parameters, and effects on tics and comorbid psychiatric disorders. The most common reasons for operating on these young patients were the severity and intractability of the disease, the considerable influence on daily functioning (e.g. not able to go to school or work, avoiding social activities, not able to develop friendships, and low self-esteem), and severe motor tics causing self-injurious behaviour^{20-22,32-35,37,39,40}. None of these reports discussed the ethical aspects of DBS in adolescent patients. Moreover, minimal attention was paid on to the specific difficulties encountered in these younger patients.

Most research groups used the minimum age of 25 years as an inclusion criterion for surgery, but some groups did not follow this advice and therefore larger studies might have also included some younger patients⁴¹⁻⁵⁰. In the latest TSA guidelines, 33 patients were reported that had DBS before the age of 25 years. The risk of surgical complications and adverse events did not appear to be higher in this age group compared with older patients²⁴. Servello et al⁴² concluded that in their series of 18 patients implanted with thalamic DBS electrodes, three of the four cases who were implanted before the age of 20 years had less satisfactory results after 3 to 6 months than those older than 20 years. This was most likely due to spontaneous waxing and waning of symptoms requiring frequent DBS programming. So far, detailed case descriptions are lacking and no attention has been paid on the ethical issues and specific difficulties that physicians may encounter when treating adolescent TS patients. As such we conclude that there is yet no literature on ethical aspects of performing DBS on TS patients, let alone on adolescent TS patients.

Figure 1: Literature search.

Table 2: Overview of the literature about Deep Brain Stimulation in Tourette patients ≤ 25 years

Author (year)	Number of patients	Age (years)	Sex	Target	Comorbidities	Follow-up (months)	YGTS (% improvement)	Complications of the surgery	Side effects	Ethical aspects
Shahed (2007)	1	16	M	GPI (posterior)	Anxiety, depression, ADHD	6	84%	None	Not mentioned	Not considered
Dueck (2009)	1	16	M	GPI (posterior)	Mental retardation (IQ 60)	12	No change	None	Nausea, dizziness, anxiety (high V)	Not considered
Vernaleken (2009)	1	22	M	Thalamus (pf, dm, lm)	ADHD, OCB, depression	6	36%	Not mentioned	Not mentioned	Not considered
Idris (2010)	1	24	M	Thalamus (voi, cm, pf)	None	2	Not performed	Intracerebral hematoma	Not mentioned	Not considered
Kaido (2010)	3	19/20/21	1M, 2F	Thalamus (voi, cm, pf)	OCB/depression in 1 patient	12	44%/31%/29%	None	Blurred vision (high amplitude)	Not considered
Pullen (2011)	1	17	M	Thalamus (cm, pf)	ADHD, OCB, borderline	18	82%	None	Not mentioned	Not considered
Hwynn (2012)	1	15	M	GPI (posterior)	Dystonia	36	Not performed	None	Not mentioned	Not considered
Savica (2012)	2	17/17	2M	Thalamus (cm, pf)	OCB, ADHD, depression, SIB	12	69%/80%	None	Transient paraesthesia	Self-injurious tics
Duits (2012)	1	20	F	Thalamus (voi, cm, pf)	Depression, autism, OCB, SIB	36	Not performed	None	Hypertonia, mutism, unconsciousness	Severe comorbidity as exclusion criteria
Dong (2012)	1	22	M	Unilateral GPI (posterior)	None	12	53%	None	None	Not considered
Massano (2013)	1	15	M	GPI (anterior)	OCB, anxiety, depression	24	61%	None	None	Not considered
Huasen (2014)	1	19	F	GPI (anterior)	None	12	55%	Not mentioned	Not mentioned	Cervical myelopathy due to tics
Zekaj (2015)	1	17	M	Thalamus (voi, cm, pf)	ADHD	72	98% (without DBS)	None	None	Temporary DBS during adolescence
Hauseux (2016)	3	12/17/18	3M	GPI (anterior & posterior), thalamus (cm, pf)	ADHD, OCB, depression, anxiety	47/40/69	18%/6%/32%	None	Dysarthria, worsening OCB/mood	Not considered

YGTS: Yale Global Tic Severity Scale; M: Male; F: Female; GPI: globus pallidus internus; Pf: parafascicular nucleus; DMN: dorsomedial nucleus; LM: Lamella Medialis; Voi: nucleus ventro-oralis internus; CM: centromedian nucleus; ADHD: Attention Deficit Hyperactivity Disorder; IQ: Intelligence Quotient; OCB: Obsessive-Compulsive behaviour; SIB: Self-Injurious Behaviour; V: Voltage.

DISCUSSION

We have described our experiences with DBS in two severely affected and refractory adolescent TS patients. Three years after surgery one patient experienced a tic reduction of more than 50% with the stimulator turned off. The reduction may be due to natural waning of tics that often follows adolescence and due to an additional behavioural treatment for tics after the DBS. At present, he is satisfied with the level of symptoms and would not consider the surgery anymore. The second patient is responding well to the stimulation, but went through a period of behavioural disturbances which are not uncommon during adolescence but interfered with optimal programming. We believe that the experienced stress before, around, and after the surgery might have provoked the excessive use of cannabis and caused the related behavioural disturbances.

DBS in TS seems to have a promising future in terms of tic reduction, however, it raises several ethical questions that need continuing discussion especially in adolescent patients. *Five major topics* concerning the ethics of DBS in clinical practice have been identified previously: 1) selecting patients fairly, 2) thorough examination and weighing of risks and benefits, 3) protecting the health of children in paediatric DBS, 4) special issues concerning patient's autonomy, and 5) the normative impact of quality of life measurements⁵¹.

When discussing the *first topic*: selecting patients fairly, one of the first questions is whether DBS should be indicated for adolescent patients with TS, given the chances of natural remission during adolescence. In 40% of TS patient's tics decrease during adolescence, in another 40% they may disappear completely and only in 20% they remain in their full intensity and require chronic treatment^{1,3}. Chronic treatment may include pharmacotherapy and behavioural or psychosocial therapy^{6,7}, but there is a small subset of patients who fail to show clinical improvement, and experience intolerable side-effects or potentially life-threatening tics or self-injurious behaviour. These patients are potential candidates for a surgical intervention. The available research shows that DBS of different targets in TS is effective and results in a mean tic improvement of 53% on the YGTSS²⁹.

Based on the new insights and guidelines we have waived our previous age limit of 25 years²⁴. This brings us to incorporating the *second topic*: thorough examination and weighing of risks and benefits. Our motivation for waiving this age limit was that severe TS in adolescence can be severely disruptive to development, often jeopardizing educational and job opportunities, social interactions and relationships. Delaying surgery in these younger incapacitated TS patients could potentially result in permanent harm to social, psychological, and intellectual development, even if the symptoms eventually subside with age. Similarly, in rare cases of 'malignant TS', the tics themselves may carry greater risk for bodily harm or even death^{20-22,24}. An early intervention with positive results may bring significant benefits on the individual's

development and future. On the other hand, DBS is an invasive treatment with potential surgical complications and adverse events. Stimulating the anterior GPi has been related to side-effects such as higher anxiety levels, dyskinesia, fatigue, dizziness and a case of hypomania^{29,52}. Stimulating different targets can cause other side-effects such as gaze disturbances, mood deterioration, apathy and dysarthria²⁹. In many instances adjustment of the stimulation parameters can diminish or eradicate these side-effects. Surgical complications mostly centre around hardware malfunction and infections^{53,54}. In general DBS is considered as a safe surgical procedure with a minimal risk (<1%) of serious complications (e.g. bleeding, neurological deficits)^{24,29,53}. Thorough selection of patients who should be offered DBS is an essential requirement for a successful intervention from a clinical as well as an ethical perspective. In general, patient selection should optimize the individual risk–benefit ratio⁵¹.

Both our patients suffered from severe and refractory TS for many years and were selected for DBS after a thorough multidisciplinary evaluation. Patient 1 had received behavioural treatment and several medications without success and hence he met the DBS inclusion criteria. After unsuccessful DBS, he tried a behavioural treatment again, from which he reported a positive effect on tic severity, self-confidence and quality of life. Behaviour therapy implies doing homework exercises, which this patient reported he had not done the first time he underwent this treatment, because at that time he could not focus on this treatment since he was too busy with school and his parents were in a divorce. Although this patient met the inclusion criteria for DBS, an additional step before starting DBS could have been thorough evaluation of which interventions for tics have been done before and why the patient did not profit from it. After optimizing these first-line less invasive interventions [7] DBS might be an option for further treatment.

A gap in our current state of knowledge is that it is not possible to predict the natural course of tics in TS, so that expected chronicity cannot be used to indicate DBS treatment. At present it remains unclear whether (and to what extent) severely affected patients at the age of 18 may or may not await a significant improvement until the age of 25⁸. Clinicians selecting DBS candidates would benefit from knowledge of predictive factors, both epidemiological as well as biomarkers, that would allow identification of patients who will remain severely affected into adulthood, but so far this is not possible. Therefore, the advantages and disadvantages of DBS should be evaluated multidisciplinary for every individual adolescent TS patient who may be a surgical candidate. Our patients were informed about the possibility of natural improvement or remission and the possibility of limited or no effect of the surgery on tics. Apparently, they chose to have the operation because of their actual suffering, and not because of the chance of chronicity. In patient 1 as well as in the case described by Zekaj et al⁴⁰, tic severity significantly declined during adolescence, to such an extent that the stimulator in these patients was turned off and they would not be eligible for DBS anymore. Should we not have operated on these patients? With the knowledge of hindsight probably not, but that does not help in the decision making beforehand. On the other hand, if

DBS resulted in positive stimulation effects in this very important period of life, would it be ethical to deprive them from this therapeutic option? Moreover, would it be ethical to consider DBS a temporary therapeutic application? And if so, should we remove the stimulator when, after turning off the system, there is no increase in tics for a certain period? It is important to realize that since DBS may be an effective procedure in selected treatment-resistant adolescent TS patients, one may do harm to patients not only by performing DBS, but also by not performing it. It seems to be justified to leave traditional reticence (based on the substantial chance of natural remission) behind and allow earlier intervention in view of the combination of acute suffering and the chance of irreparable harm. The patient's benefit is central in the ethical evaluation. This criterion can outweigh risks and side effects, and can make DBS appropriate even in adolescent TS patients with a chance of natural remission⁵¹.

The *third topic* is protecting the health of children in paediatric DBS. This can be expanded to protecting the health of adolescent TS patients selected for DBS (age 10 - 25 years). Local ethics committee involvement is necessary for cases involving persons under 18 years and for cases considered "urgent" in our centre²⁴. Moreover, following all the in- and exclusion criteria and basing the decision on a multidisciplinary decision is mandatory. Successful application of the DBS procedure requires much more than the surgery itself. In addition, guidance before, during and after surgery and defining realistic expectations are of major importance. Programming the stimulator to gain the settings with the best effects on tics and no or minor side-effects may take months to a year²⁴. This is clearly different from, for example, Parkinson's disease or essential tremor in which an immediate effect can be observed. Significant spontaneous waxing and waning of symptoms in TS requiring frequent DBS programming makes it even more difficult. The influence of this might be greater during adolescence and spontaneous waning may even be a first sign of spontaneous remission^{1,55}. Therefore, the inclusion criteria for surgery should go much further than being purely clinical criteria and consider certain psychological, social and environmental factors too. To get through all the problems and challenges (e.g. school issues and interpersonal relationships) during the period from childhood to adulthood and handle the related stress, it is very helpful for adolescents not only to have the understanding and support from peers and adults, but also to be able to manage the stressors and hassles of everyday life by themselves. The development of coping strategies may support or inhibit positive adolescent adaptation.

Adolescents who lack adequate coping strategies are more likely to show deviant behaviour (e.g. substance use) and use avoiding and distancing coping strategies, whereas adolescents with healthy coping try to solve the problems or seek for social support⁵⁶. Ideally, adolescent candidates for DBS surgery have a stable psychosocial environment and an effective and positive coping style. Patients should be able to tolerate the demands of surgery and the postoperative follow-up, and also the ability to cope with the possibility of a poor outcome. As such it is important for all DBS centres who operate on

TS patients with a multidisciplinary approach to include an extensive (neuro)psychological evaluation. Since adolescent patients often still live with their parents, a supporting attitude of parents and other relatives is also of significant importance. Even though formally informed consent lies with the young patient only, especially these young patients can profit from an approach in which both the patient and parents, or other close caregivers, are consulted during the DBS trajectory and involved in treatment and follow-up. In patient 2 the stress experienced before, around and after the surgery might have provoked the excessive use of cannabis and the related behavioural disturbances as a result of an avoiding coping style. Psychological support already prior to surgery can help those patients and parents with a less effective coping style to deal with the stress that can accompany the surgery. Psychological support is also helpful to improve overall compliance and other difficulties that may impede successful DBS.

The *fourth topic* concerns the patient's autonomy and the decision for surgery should be based upon autonomous decision-making of the potential patient ^{57,58}. Respect for patient's autonomy is expressed by safeguarding for informed consent. Some aspects of DBS should be given special attention, namely the complexity of the treatment, the expectations of the patient and his relatives, compliance, and the operating technique ⁵¹. A specific problem in the latter context is the so-called therapeutic misconception, which implies that patients expect evident personal benefit, but fail to realize the innovative character of the treatment and undervaluing the fact that individual treatment response is uncertain and long-term cognitive, emotional and behavioural effects are largely unknown. Desperation is often very high in severely affected TS patients which increases to hope for improvement by DBS. Moreover, depression occurs frequently in adolescent TS patients ⁵⁹, and their preferences can be more strongly influenced by affective components. Combined, this could lead to the danger of overhasty decisions in favour of undergoing DBS surgery. In addition to informed consent, DBS could have an impact on patient's autonomy in a separate way. Faced with decision conflicts DBS patients might fail to slow down and make impulsive decisions for their disadvantage ⁵¹. This might have played a role in our second patient. Although he was informed that finding the correct stimulation settings would take time and that we did not expect an immediate effect on his tics, he was very disappointed. This disappointment became part or maybe even the cause of the behavioural problems complicating the treatment even more. Moreover, a stable psychosocial environment, such as supportive parents, is one of the inclusion criteria for DBS and especially important in adolescent patients. Despite being of importance for a positive outcome of DBS, this same environment could also undermine autonomous decision making of the patient. Adolescence is a period of understanding the 'self' in relation to the social world with a desire to find a balance ²⁶. Adolescents can base their decision to take part and undergo treatment on external forms of pressure, either perceived or actual. They may feel ashamed and a burden to their family. These feelings may make them suffer even more than the tics themselves. This may influence their decision to participate and

undermines autonomous decision-making and voluntary participation. To address these issues, a good relationship between researcher and patient is essential, given also that life-long treatment and follow-up within the same institution will be needed.

DBS is an elective intervention in TS that is neither life-saving, nor can it cure the disease, and the goal for patients is usually to improve their quality of life, which is greatly limited in refractory TS patients. This brings us to the *fifth topic*: the normative impact of quality of life measurements. Enquiring for the quality of life of the patients in treatment, additionally to the effectiveness of the intervention, is an important aspect from an ethical point of view. In Parkinson's disease and other movement disorders, the pure effectiveness of the intervention regarding the motor functions has been considered normatively meaningless⁵¹. At this point, the question rises whether this also holds in case of TS. In patients with TS the deterioration of their quality of life does not merely consist in the very fact that they do experience these tics, but also in the negative effects the tics have on their surroundings as well as reactions of other people on the tics, resulting in low self-esteem. In addition, DBS treatment in adolescent TS patients has a normative impact on young patient's long-term quality of life comparable to those described for patients with movement disorders. Delaying the surgery might lead to deterioration of quality of life during this important period of life. Even though the effects of DBS might be even successful several years after adolescence, irreparable personal and social harm might be done. Tics that are experienced as insulting or disturbing, for example coprolalia or severe motor tics in class room settings, are normatively meaningful because they also affect other persons. Such social consequences and the reactions of others contribute to the fact that young TS patients end up with having their educational and job opportunities ruined and their social interactions and relationships potentially even irreparably harmed. Therefore, the effectiveness of the DBS intervention might be normatively meaningful in itself. The first patient experienced an improvement in tics and quality of life three years after surgery, which seemed to be independent of the DBS. The second patient experienced a beneficial effect on his tics which allowed him to start working again and to improve his social contacts, eventually leading to an improvement of his quality of life. At the same time, as discussed before, normatively relevant risks and benefits go further than effectiveness. Too high expectations, disappointment in case there is no immediate success, great suffering pressing patients to seek solutions, troubles with coping with surgery- and treatment-related stress, are all issues that are relevant in this regard.

Although ethical criteria for evaluating psychiatric DBS are principally similar to those discussed for other movement disorders, the experimental character of DBS in TS raises additional questions of research ethics. DBS for TS is not (yet) a recognized indication by regulating authorities and it must be considered a treatment that should only be done in a *research setting*. This triggers several structural challenges that DBS trials in this domain will unavoidably face. In addition to safeguarding the rights and interests of vulnerable research participants, it would be important to initiate set-up and promotion of high-

quality scientific research that could serve the interest of future patients⁵⁷. Today, such trials are not performed worldwide, and such a trial set-up faces several challenges. Even experienced DBS centres perform only a handful of DBS surgeries in TS patients each year, using different techniques and targets, making it difficult to obtain and interpret large-scale outcomes. Multicentre randomised controlled trials would theoretically be desirable, but difficult to realize due to practical reasons and would stretch over many years, and often do not provide conclusive evidence in heterogeneous populations, such as TS patients⁵⁰. Currently the inclusion process, surgical techniques, targets, programming and postoperative care differ largely between different institutions and countries. Moreover, during such study new insights might be gained, e.g. pointing to different surgical targets or other changes in the procedure, which would be unethical to withhold from later participants. Because of these limitations, coupled with the variable effect of surgery, and the overall small numbers of TS patients with DBS worldwide, there is no regulatory agency approval from the FDA and the EC to date. To overcome these structural limitations and to take steps towards larger scale analyses, the TSA recently launched an international Tourette DBS registry and database⁶⁰. The main goal of the project is to share data, uncover best practices, improve outcomes, and provide critical information to regulatory agencies. Such a database can also allow for an analysis of adolescent TS patients to determine for which group of younger patients DBS would be beneficial, either temporarily or lifelong lasting.

CONCLUSION

DBS surgery for TS patients has lately been considered at an earlier age because more stress has been placed on the potential long lasting harmful effects of the disorder. Specific ethical issues arise in this age-group relating both to clinical practice as well as to research. In clinical practice attention should be paid to selecting patients fairly, thorough examination and weighing of risks and benefits, including evaluation of adequacy of former applied first-line interventions, protecting the health of children and adolescents receiving DBS, special issues concerning patient's autonomy, and the normative impact of quality of life. Realistic expectations, consideration of the psychological, social and environmental conditions of adolescent TS patients and the adequate inclusion of relatives in the process of decision-making and care are important. In research, registration of all TS cases in a central database covering a range of standardized information will facilitate the further development of DBS for this indication. Clinical practice should be accompanied by ongoing ethical reflection, preferably covering not only theoretical thought but providing also insights in the views and perspectives of those concerned, that is patients, family members and professionals. Examining the ethical issues of DBS may help to realize its entire potential for benefiting severely suffering TS patients.

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Chapter 8

Discussion

In this thesis we have addressed questions about the role of the basal ganglia (BG) and the connected cortico-basal-ganglia-thalamocortical (CBGT) pathways in the underlying pathophysiology of TS, which is still matter of considerable debate. Knowledge about the basic functional anatomy of these pathways is essential in understanding the mechanisms and effects of Deep Brain Stimulation (DBS) in TS patients. The main goal of DBS is to restore the imbalance present in the BG of TS patients and to relieve symptoms. After many years of thalamic stimulation, we now tend to favour stimulation of the anterior internal globus pallidus (GPi), since especially the long-term effects appear to be more promising than those for thalamic stimulation.

THE UNDERLYING PATHOPHYSIOLOGY OF TOURETTE SYNDROME

Neural activity in the basal ganglia of Tourette Syndrome patients

Recording electrophysiological activity from TS patients during DBS surgery provides a unique opportunity to directly characterize the neuronal activity underlying the disorder. Extracellular neuronal recordings performed during pallidotomy surgery revealed a decreased overall firing-rate in the posterior/motor GPi of TS patients, complemented by phasic firing-rate changes around the time of the tic¹. We were the first to perform these electrophysiology measures during DBS of the anterior/limbic GPi in TS patients. We found the same baseline firing-rate decrease in the anterior GPi as previously observed in the posterior GPi¹, which is not reported in Parkinson patients² or healthy non-human primates³. We also found tic dependent transient rate changes in the activity of the individual neurons of the anterior GPi, which is in line with previous measures of the posterior GPi in TS patients¹. Interestingly, we also observed reduced firing rates in the anterior GPe, comparable to those previously seen in awake patients suffering from other hyperkinetic disorders such as dystonia⁴⁻⁷ and hemiballismus⁸. These results point to tonic and phasic modulations of the BG output as a key mechanism underlying the abnormal state of TS and the expression of tics, respectively. Moreover, it clearly demonstrates the involvement of the limbic pathway in the underlying pathophysiology of TS. Evidence points out that reduced inhibition in the striatum seems to play a significant role in the underlying pathophysiology of TS⁹⁻¹¹. Therefore, we do not view these abnormal BG output signals as the cause of TS, but as a consequence of an imbalance higher in the CBGT circuit. An imbalance in for example the primary input structure of the BG, the striatum, can lead to alterations throughout the whole CBGT circuit. These electrophysiological studies in the acute phase of the intervention suffer from two major flaws. First, they are potentially confounded by a notable microlesion effect, which can induce biochemical responses in neurons and persist up to three months postoperatively. Second, they do not explain the underlying neurophysiological dynamics that support the pathology and how these are altered

because of therapy. Such information must come from chronic recordings from in-dwelling electrodes¹². Only one study has performed chronic local field potential (LFP) recordings from implanted thalamic electrodes and correlated these findings with the symptoms. Their results suggest that dynamic changes in gamma band power are relevant to the pathophysiology underlying TS and that the therapeutic effect of DBS may be the functional restoration of effective communication, since gamma band activity is characteristic of normal thalamic information processing¹³.

Models of basal ganglia dysfunction in relation to Tourette Syndrome

Are our results of neuronal activity in the anterior GPi and GPe in TS patients in line with the existing functional models of the BG that have suggested potential mechanisms for hyperkinetic movement disorders? The *'box and arrow' model* defines the CBGT pathway as a feedback loop with two main competing elements: a positive feedback loop mediated by the direct pathway and a negative feedback loop mediated by the indirect pathway. Thus, hyperkinetic disorders like TS are associated with increased activity of the direct pathway and reduced activity of the indirect pathway, resulting in a reduction of GPi activity, which subsequently leads to disinhibition of the thalamus and overactivation of the cortex¹⁴⁻¹⁶. Our results support this assumption in that the GPi neurons in TS patients displayed reduced baseline activity. However, the GPe baseline activity was also reduced, contradicting the current perception of the indirect pathway involvement in hyperkinetic disorders. Interestingly, this co-modulation of both segments of the globus pallidus is not unique to TS, but has also been observed in other hyperkinetic disorders such as dystonia and hemiballismus⁶⁻⁸. The reduced activity in both segments of the globus pallidus can be explained by later theoretical models^{16,17} and experimental data from animal models^{3,18}. The *'action selection' model* suggests that a subset of excited striatal neurons leads to the release of a selected action, while inhibiting all other potential actions. In this model, hyperkinetic symptoms originate from abnormal focal activation of striatal neurons which inhibit the activity of a subpopulation of GPi neurons^{16,17,19}. In TS, this disinhibition, affecting striatal projection neurons contributing to both the direct and indirect pathways, is thus expected to exercise increased inhibition on both the GPe and GPi driving their firing rates down, in line with our findings. Increased inhibition of the GPi leads to disinhibition of its thalamo-cortical targets and this in turn can lead to repeated stereotyped unwanted movements like tics. Next to these tonic baseline firing-rate decreases in the anterior GPi and GPe, we found a mixture of responses in both nuclei around the time of the tic, roughly equally distributed between increases and decreases. This cannot be explained by applying the above-mentioned models of BG functioning.

In summary, this points to a tonic and phasic modulation of the basal-ganglia output as a key mechanism underlying the abnormal state of TS and the expression of individual tics, respectively. Moreover, it shows that the intrinsic circuitry of the BG is

far more complex and not all the electrophysiological findings can be explained by the existing models of BG dysfunction.

Towards new models of basal ganglia function/dysfunction

Our electrophysiology recordings highlight the differences between TS and other hyperkinetic movement disorders. The departure of our findings from the classic BG models of hyperkinetic disorders thus calls for the development of novel concepts and models of the BG, which can capture the heterogeneous nature of the different disorders as well as the different neurons within each nucleus. The emerging evidence that TS involves CBGT dysfunction in the motor and limbic domains emphasizes that further investigation of the basic neurobiology of the BG is likely to be indispensable for improved understanding of the pathophysiology of TS. Moreover, this might have direct consequences for the DBS targets and for treating refractory TS patients.

DEEP BRAIN STIMULATION IN TOURETTE SYNDROME

Target selection

Since the first DBS surgery in a refractory TS patient was performed in 1999²⁰, about 156 TS patients have been reported to be treated with DBS. Nine separate brain areas have been targeted so far: the medial part of the thalamus (three different areas: the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus (Cm-Spv-Voi) cross point²⁰⁻³⁶, the centromedian nucleus–parafascicular complex (CM-Pf)³⁷⁻⁴², the dorsomedial nucleus–parafascicular complex (DM-Pf)⁴³), the anterior/limbic GPi⁴⁴⁻⁵², the posterior/motor GPi^{48,53-63}, the GPe⁶⁴, the nucleus accumbens (NA)⁶⁵⁻⁶⁸, the anterior limb of the internal capsule (ALIC)^{65-67,69}, and the subthalamic nucleus (STN)⁷⁰. Moreover, studies targetting multiple brain areas separate or at the same time have been performed^{53,71-80}. More than 10% of these surgeries have been performed in our centre during the past 18 years^{20-23,25,34,35,51,71,81,82}, of which we have targeted the medial thalamus in nine patients (Cm-Spv-Voi cross point) and the anterior GPi in eight patients. Target selection is a topic still under debate due to the complex clinical profile presented by TS patients¹². The thalamus and the GPi have been targeted the most. These are key structures within the CBGT pathways and by influencing them through high frequency stimulation, the signalling might be adapted and the imbalance present in the BG of TS patients restored in order to relieve symptoms.

Patient selection

Apart from target selection, another relevant question is which patients should be selected for DBS. TS patients considered for DBS should comprise only very severe, intractable cases since it is a last resort and experimental treatment. In 2006, the Dutch-Flemish Tourette Surgery Study Group has established guidelines for DBS in TS²², comparable to the guidelines from the Tourette Syndrome Association (TSA)⁸³. We have followed the recommended in- and exclusion criteria in all our patients to ensure adequate selection of DBS candidates. In 2014, the TSA updated the recommendations for patient's selection and assessment based on a critical review of the existing literature⁸³. A major change in these new recommendations is that the age limit has been adjusted from a minimum age of 25 years towards a multidisciplinary evaluation without setting a firm age limit. As such younger patients have been treated with DBS. This gives rise to discussion about ethical dilemmas, specific problems encountered in this age group and effect differences between adolescent and adult patients, which we will further address later in this chapter.

Effects of Deep Brain Stimulation

A meta-analysis published in 2016 by Baldermann et al⁸⁴ included 156 cases of DBS in refractory TS patients. Seventy-eight cases targeted the medial thalamus, 44 the anterior GPi, 20 the posterior GPi and 9 the NA/ALIC. Highly significant changes were found after thalamic DBS (mean Yale Global Tic Severity Scale (YGTSS) improvement of 53%). Comparable results were seen for the posterior GPi (57%) and the anterior GPi (52%). Changes after DBS of the ALIC/NA showed less improvement (44%). Regarding comorbid symptoms, the data revealed a median reduction of 31% on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and subgroup analysis did not show significant differences between targets.

Thalamic Deep Brain Stimulation

The first TS patient who underwent thalamic DBS in our centre showed a tic reduction of 90% after 12 months²⁰. In 2003, we reported on three patients showing a 72-90% improvement in tics eight months to five years post-operative³⁵. In two of these three patients, Obsessive-Compulsive behaviour (OCb) and self-injurious behaviour (SIB) were no longer present. Long-term evaluation in two patients at six and ten years post-operative demonstrated continued benefit of tic control (78% and 92%)⁷¹. In a larger series of 18 patients, performed by Servello et al³³, who were followed up between three and 18 months, YGTSS improvement varied between 24% and 79% with a concurrent improvement in comorbidities. Follow-up of the same patients group⁷⁵ showed a mean YGTSS improvement of 73% and a mean Y-BOCS improvement of 42%

five to six years after surgery. These and other open-label studies strongly indicate that thalamic DBS may have beneficial effects in TS for tics as well as comorbid behavioural disorders^{21,24,25,27-29,36-38,41,71,74,76,80}.

The results of two randomized controlled trials (RCT's) showed a more variable response. In 2007, Macuinas et al³⁰ performed a prospective double-blind RCT targeting the thalamus (Cm-Pf complex) in five patients. They were randomized and evaluated in one of four states of unilateral or bilateral stimulation (both stimulators ON, left ON-right OFF, right ON-left OFF, both OFF) for one week each. In the randomized phase of the trial, a statistically significant reduction in tics was observed in the bilateral ON state. For three months open label stimulation three of the five patients responded with a 50% average reduction of tics. Measures of OCB, depression and anxiety showed a trend towards improvement, with a 45% improvement on the Y-BOCS. A double-blind crossover RCT performed in our centre by Ackermans et al²² targeted the Cm-Spv-Voi cross point of the thalamus in six TS patients who were randomly assigned to three months ON stimulation and three months OFF stimulation or vice versa. At a group level improvement in tic control during ON vs. OFF stimulation was 39% and 3%, respectively. After one-year open label follow-up, these levels were maintained at 49% on the YGTSS. Secondary outcome measures included associated behavioural disorders and mood and they did not show any effect at a group level, either between ON and OFF stimulation or between pre-operative and one-year post-operative.

We published our long-term follow-up data of these six patients²², together with a seventh patient²¹ (follow-up between 24 and 78 months) and found that in only one patient the DBS is still active. In three patients the target has been changed to the anterior GPi due to side effects (e.g. reduced level of energy, sleeping disorders, gaze disturbances and alteration of sexual function). Three patients were not satisfied with the results of the DBS and decided to switch off their stimulator. Two of them showed only minor improvement during stimulation, whereas the third patient had a beneficial effect but suffered from side effects. These results are in line with the long-term follow-up results of Mothlagh et al⁷⁴, with an improvement of more than 50% in only three out of eight cases versus three out of seven cases in our sample. However, other groups did not experience more negative long-term results with thalamic DBS and did not report these or other severe side effects in their patients^{75,80}.

Pallidal Deep Brain Stimulation

The GPi is divided in a posterolateral part, the motor area (posterior GPi), and an anteromedial part, the limbic area (anterior GPi). There has been much debate as to which sub region might respond best to DBS in TS patients. We have decided to target the anterior GPi based on pathophysiological considerations in which the limbic circuit seems to be of major importance in TS and based on positive results of other groups

targeting this area⁸⁴. Controlled data, although in a small sample, have even suggested that DBS of the anterior GPi could bring larger benefits than thalamic^{73,79} or posterior GPi⁴⁸ stimulation. Moreover, we decided to switch our preferred target from the thalamus to the anterior GPi based on our disappointing long-term results with thalamic DBS.

Open label studies targeting the anterior GPi demonstrate a tic improvement ranging from 38% to 72% with a follow-up duration between 4 to 46 months^{44,46,48,50}. This is in line with our results of five TS patients treated with anterior GPi DBS, showing a significant beneficial effect on tics (mean tic improvement of 70%). We found no significant difference on comorbid behavioural disorders, mood and cognition, but there was an improvement on an individual level for OCb. The results of anterior GPi DBS were less pronounced in two RCT's. Kefalopoulou et al⁴⁷ analysed anterior GPi DBS in 15 TS patients. They compared blinded ON stimulation vs. OFF stimulation periods and showed a mean YGTSS improvement of only 15% on a group level, although with substantial variability between patients (from -3% to 57%). No significant effect on OCb was observed. In the open label stimulation period of 8 to 36 months patients showed a 40% improvement in tics. This significant tic improvement was maintained at long-term follow-up⁸⁵. The change in OCb did not reach statistical significance, however, subgroup analysis revealed that four patients with the most severe OCb had the greatest improvement⁸⁵, which is in line with our results of anterior GPi DBS⁵¹. Welter et al⁵² performed a double-blind RCT in which they enrolled 16 refractory TS patients who received anterior GPi DBS. Three months later they were randomly assigned to receive either active or sham stimulation for the subsequent three months. All patients then received open-label active stimulation for six months. No significant difference in YGTSS score between the beginning and the end of the three-months double-blind period between groups was found, with a mean improvement of 10% on the YGTSS for patients with active stimulation and 4% for patients with sham stimulation. YGTSS total scores for all patients in both groups combined improved with 40% at the end of the open-label period.

Data from the double-blinded period of these two RCT's targeting the anterior GPi in refractory TS patients do not support the positive effects found during their open-label phase and in other open label studies. One explanation might be that they suffer from problems concerning blinded programming, which is common in trials of DBS^{47,52}. Adjustment of stimulation while maintaining treatment blinding can compromise the identification or use of the optimum settings. Both groups deliberately constrained the stimulation amplitudes and voltages to avoid unmasking the patient's stimulation status during this phase. Additionally, anxiety associated with uncertainty about whether stimulation was switched off or on can be an issue for some patients. During the open label phase, stimulation was further adjusted in all patients to achieve maximum symptom control. The reduction in tic severity during this period was correlated with the increase in stimulation electrical charge⁵². Follow-up during the blinded on and off

phases is only three months, which seems to be insufficient to decrease tic severity for refractory TS patients. This is in line with our own experiences in which programming to reach a satisfying stimulation effect in TS patients might take months, and even up to one year. However, blinding patients for such a long period would not be acceptable or tolerated. Moreover, the inclusion period in both studies was quite long (4 years⁴⁷ and 5 years⁵²), and publishing the data took another 5 years in the study performed by Welter et al⁵².

Kefalopoulou et al⁴⁷ reported that stimulation through the most dorsal contacts on the electrodes was frequently associated with optimum tic responses, possibly suggesting that stimulation of the GPe might be involved in the mechanisms of tic relieve. In their long-term follow-up analysis they investigated whether a specific anatomical site within the anterior GPi correlated with optimal clinical outcomes for tics, mood and OCB⁸⁵. A region within the anterior limbic GPi, on the medial medullary lamina in the pallidum (between the border of GPi and GPe) at the level of AC-PC plane, was significantly associated with improved tics, and on an individual level with OCB. In our case series of five patients targeting the anterior GPi⁵¹, the location of the active contacts differed between patients, ranging from the anterior part of the GPi to the GPe. We could not establish a relation between the anatomical position of the active contacts and the effects of stimulation. These findings suggest that applying electrical stimulation to the region of the anterior parts of the GPe and GPi produces therapeutic effects on tics. Moreover, the stimulation effect is not limited to the area of the active contacts since the current has a range of a few millimetres around the contact, depending on the stimulation parameters. The GPe has also been shown to be a possible effective DBS target in refractory TS patients^{64,86}.

Side effects

We have observed significant stimulation related side effects in almost all patients who underwent thalamic DBS in our centre. These side effects included reduction of energy levels, subjective gaze disturbances, and alteration of sexual function^{20,22,35}. During long-term follow-up of these patients we saw an increasing disbalance of therapeutic effects and side effects over time, often leading to either switching the stimulator off or new surgery with a different target³⁴. Servello et al³³ 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. Other side effects reported with thalamic DBS are anxiety, mood changes and apathy. The majority of these reported side effects appeared to be transitory or resolved with adjustments of stimulation settings^{74,84}, which is in contrast with our results. Thoughtful programming of the stimulator is very important to achieve an optimal clinical outcome. Due to natural symptom fluctuations, variability in patient's responses to treatment and expectations, adjustment in stimulation settings is often a temporary solution. In our

experience TS patients tend to blame the stimulator for almost all negative symptoms and maybe professionals reinforce them to do so by adjusting the stimulation settings every time they report complaints. This gives patients the feeling that every negative symptom is a side effect of the stimulator, when it might be due to a completely different cause.

We observed less severe side effects with anterior GPi DBS compared to thalamic DBS. In our group of five TS patients who underwent pallidal DBS, stimulation induced side effects were mild apathy in two patients, not responsive to changes in stimulation settings, and weight loss in another patient. Of the two adolescent patients we treated with anterior GPi DBS, one experienced side effects like dyskinesia in the legs and a dejected mood with increasing voltages, complicating the programming, and eventually leading to turning off the stimulator. Moreover, side effects did not seem to increase with longer follow-up duration and did not influence the daily functioning of patients. Others found side effects such as anxiety, agitation, apathy, mood changes and dizziness during anterior GPi DBS^{47,48,50,73,79,87}. Most of these side effects appeared to be minor or resolved with adjustments of stimulation settings. Long-term follow-up data of anterior GPi DBS are scarce since most groups started targeting the anterior GPi only from 2011.

Ethical issues

An important point of ethical debate is the fact that evidence of the efficacy of DBS for TS is limited and it is not (yet) a recognized indication for DBS treatment by the Food and Drug Administration (FDA) and the European Commission (EC). Consequently, it must be considered an experimental treatment, which implies that only patients with the most severe symptoms that have been proven resistant to conservative treatment, can be considered candidates for DBS. Patients should be informed about the relative lack of evidence and special care should be taken avoid the so-called 'therapeutic misconception' in patients. This means that patients expect evident personal benefit, but fail to realize the experimental character of the treatment and undervaluing the fact that individual treatment response is uncertain and long-term cognitive, emotional and behavioural effects are largely unknown.

Another ethical debate has evolved around the minimum age at which DBS should be considered for refractory TS patients, especially since the guidelines do not set a strict age limit anymore. Given the serious and sometimes irreparable harm that tics can cause to the social, psychological, and intellectual development of children, surgery at younger ages is increasingly considered. However, given the natural course of TS, with improvement during and after adolescence, this may lead to implantation of DBS devices that will only be used for a few years and subsequently inactivated because tics have spontaneously remitted. Also, behavioural disturbances during puberty may interfere with compliance during programming. However, it seems to be justified,

according to the TSA guidelines, to leave traditional reticence behind and allow earlier intervention in view of the combination of acute suffering and the chance of irreparable harm. Since 2014, we have performed DBS surgery in two adolescent TS patients. Although we have experienced spontaneous waning of symptoms making the DBS not necessary anymore in one patient and behavioural disturbances that interfered with optimal programming in the other patient, we still support that there should be no strict age limit for indicating DBS and decisions should be made on individual circumstances and symptomatology. Waiting for an eventual spontaneous regression around adolescence might cause irreparable damages to the patient's future life. Treating these adolescent TS patients underlines even more the importance of a multidisciplinary approach, maintaining strict in- and exclusion criteria, adequate social support and the preparedness of a caregiver to participate in the counselling.

Ethical reflection should accompany present and future clinical practices, preferably covering not only theoretical thought but providing also insights in the views and perspective of those concerned, that is patients, family members and professionals in order to improve this treatment.

New insights and future perspectives

The general aim of this thesis was to continue the development of DBS for refractory TS patients by further exploring the effects of surgery in our own centre. We have continued reporting new cases and the follow-up of all operated TS patients during the past 18 years. Based on the available evidence, DBS of the medial thalamus and the anterior GPi seems to be a safe and effective treatment in well-selected TS patients. Both targets are comparable with regard to tic reduction with improvements around 52% on the YGTSS, and no significant differences in improvement of comorbid behavioural disorders have been reported⁸⁴. After many years of thalamic stimulation, the preferred surgical target in our centre was changed to the anterior GPi, based on our long-term results with thalamic DBS showing that there is an increasing disbalance of therapeutic effects and side effects at long-term follow-up³⁴, and on positive results of other groups targeting this area^{52,73,79}. We found that DBS of the anterior GPi is effective in reducing tic severity, and possibly also OCb, in refractory TS patients without serious side effects⁵¹. These results are confirmed by other open label studies⁸⁴, but contradicted by data from the double-blinded period of two RCT's^{47,52}. During this blinded period, suboptimum stimulation parameters were used out of necessity to ensure blinding, which might explain the more positive results during their open-label phase. Moreover, the short duration of the blinded on and off phases seems to be insufficient to decrease tic severity. We are cautious in over interpreting our own and other open-label data, but will continue targeting the anterior GPi as first choice in future refractory TS patients.

On the other hand, we believe that the choice for one single DBS target in TS is unfeasible due to the complexity of the syndrome and its associated comorbidities. We probably have to switch towards tailored targeting instead of trying to find one optimal target for all patients. This tailored targeting should be based on the main symptoms of a patient. Targeting the medial thalamus might resolve a range of motor and behavioural symptoms, whereas targeting the limbic system by stimulation of the anterior GPi might influence both behavioural symptoms like OCB and motor symptoms. Targeting the posterior GPi could be selected for patients seeking to relieve robust motor symptoms or for patients with dystonic tics. Targeting the NA and/or ALIC might address severe behavioural symptoms in a selected group of patients. The fact that DBS of limbic structures within the CBGT circuitry, such as the anterior GPi, induces improvements comparable to DBS of motor structures favours the hypothesis that modulation of the neuronal activity within the limbic CBGT circuit provokes tic reduction. Moreover, increasing evidence shows that motor symptoms of TS can result from abnormal motivational drives from limbic circuits. In line with these considerations, we believe there is a high need for more qualitative studies and standardized incorporation of additional outcome parameters (e.g. scales for OCB, ADHD and mood disorders), other than solely focusing on the reduction of tics. In some patients, improvement of quality of life might not only be due to tic reduction, but even more due to improvement of these comorbidities.

So far there is no established consensus on stimulation targets, stimulation settings, and long-term efficacy in DBS for TS. Until that has been achieved, DBS in TS will still be experimental and must be considered a last resort treatment that should only take place in specialized treatment centres. Further research should provide more clarity in these areas and also investigate the efficacy of DBS for TS patients over longer periods with optimal stimulation parameters and also identify potential predictors of the therapeutic response, which might help adequate selection of adolescent TS patients that would benefit most from early DBS. The development of DBS in TS proceeds slowly since it is still not approved by the EC and FDA because of the lack of evidence due to the difficulty of performing high quality research in a randomized controlled fashion, coupled with the variable effect of surgery, the large number of targets, and the overall small numbers of TS patients with DBS worldwide. The experimental character of the treatment holds up further steps towards this approval. Since patients might be more cautious in undergoing the treatment, the number of operated TS patients remains low, making it very difficult to obtain enough high-quality evidence. Large scale RCT's and multicentre trials are at present not feasible, but the importance of thorough reporting of small open-label series for our daily practice cannot be underestimated. A blinded multicentred RCT including a large group of refractory TS patients, comparing the efficacy of DBS of the medial thalamus and the anterior GPi with blinded on and off periods of at least six months and an open label phase of 10 years would be desirable. However, this is impossible to realize due to practical reasons, it would stretch over 15

to 20 years and blinding patients for such a long period would not be tolerated. Moreover, during such trial new insights might be gained, e.g. pointing to different surgical targets or other changes in the procedure, which would be unethical to withhold from later participants. In order to overcome these structural limitations, to take steps towards larger scale analyses, and to optimally benefit from the clinical experience gathered so far, we argue that all cases of DBS performed in TS patients are registered in a central database covering a range of standardized information. The TSA has launched such an international Tourette DBS registry and database and the main goal is to uncover best practices, improve outcomes, and provide critical information to regulatory agencies⁸⁸.

CONCLUSION

Despite the difficulties and uncertainties about DBS in refractory TS patients, we believe that DBS holds a promise for becoming an established treatment. Further insights should come from rigorous reporting of all available data worldwide, if possible performing DBS in a blinded and RCT fashion with longer blinded periods and follow-up durations and collecting all these data in the TSA database. We will participate in continuing the development of DBS for refractory TS patients by further exploring the effects of surgery in our own centre and by contributing to the TSA database. We believe this eventually will lead to tailored targeting of brain structures for each individual TS patient based on their main symptoms.

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Summary

This general aim of this thesis is to continue the development of DBS for refractory TS patients by further exploring the effects of surgery in our own centre, including the relationships with the underlying pathophysiology, and both surgical and ethical issues. The main focus is to continue the follow-up of operated TS patients and TS patients with an indication for DBS, including both thalamic and anterior GPi DBS.

In **chapter 2** we have investigated the role of the basal ganglia (BG) and the connected cortico-basal-ganglia-thalamocortical (CBGT) pathways in the underlying pathophysiology of TS, which is still matter of considerable debate. The BG modulate movement and behaviour through a mechanism that involves changing cortical excitability. The striatum is the main input structure of the BG and controls their output through two pathways: the direct pathway from the striatum to the output nuclei (internal globus pallidus (GPi)/ substantia nigra pars reticulata (SNr)), and the indirect pathway from the striatum to the GPi/SNr through the external globus pallidus (GPe). Moreover, there is a hyperdirect pathway which bypasses the striatum and sends cortical signals directly to the subthalamic nucleus (STN) and then to the GPi/SNr. These pathways are further subdivided into functional circuits that convey motor information primarily to the posterior GPi and limbic information to the anterior GPi. Functional models of the BG have suggested potential mechanisms for hyperkinetic movement disorders like TS, which have centred on the existence of abnormalities in the motor circuits. The 'box and arrow' model depicts the global neuronal activity modulation of whole brain areas (boxes) along the CBGT pathways as a function of their connectivity (arrows). In this model, TS is explained by striatal disinhibition that leads to reduced tonic inhibition exerted by the GPi/SNr on its thalamocortical targets. The 'action selection' model accounts for the local changes in the inhibition of neuronal sub-groups within the output nuclei. In this model, TS symptoms originate from abnormal focal activation of striatal neurons, mainly due to dopaminergic dysfunction, which inhibit the activity of a sub-population of GPi neurons. This unwanted inhibition leads to disinhibition of its thalamocortical targets and can lead to an involuntary motor command to be executed in the cortex which can lead to a tic. Electrophysiology data show that the thalamus and the GPi seem to play a significant role in the underlying pathophysiology of TS. These are key structures within the CBGT pathways and by influencing them through high frequency stimulation, the signalling can be adapted and the imbalance present in the BG of TS patients restored in order to relieve symptoms. DBS seems to exert its effect by causing functional ablation which reduces information flow through the stimulated nucleus.

In **chapter 3** we report on the long-term outcome of seven refractory TS patients treated with DBS of the medial thalamus between 2001 and 2008. The target was the centromedian nucleus, substantia periventricularis and nucleus ventro-oralis internus (Cm-Spv-Voi) cross point of the thalamus. The effect on tics and side effects was evaluated with a variable follow-up duration of 12 to 78 months. Patient 1 and 2

showed good tic improvements on the Yale Global Tic Severity Scale (YGTSS) of 81.6% (60 months) and 50% (36 months), respectively. However, side effects like reducing levels of energy and visual disturbances increased. In patient 1 the target was changed to the anterior GPi and patient 2 switched the stimulator permanently off. Patient 3 experiences still satisfying results with a tic improvement of 88.9% on the YGTSS (78 months). Patient 4 and 7 showed minor tic improvements of 34% (16 months) and 9% (60 months), respectively, and in both patients, side effects like reduced levels of energy, gaze disturbances and alteration of sexual function became more severe over time. Moreover, both patients suffered from a hardware complication; in patient 4 the entire system had to be removed due to a persisting hardware infection after a pulse generator replacement (6 years after surgery), and in patient 7 a hardware defect in the left electrode was detected and consequently the whole DBS system was removed (9 years after surgery). Since a satisfying situation with thalamic DBS had not been reached in the last years in both patients, the target was changed to the anterior GPi. Patient 5 showed a tic improvement of 27.5% on the YGTSS (12 months), was discontent with the results and went abroad for stimulation of the GPe. Patient 6 experienced several non-stimulation related side effects and developed cerebellar atrophy. Due to all these other symptoms and the lack of effect (tic improvement of 27.5% after 26 months) he turned the stimulator off and as such was lost to follow-up. Based on these results, we conclude that there seems to be an increasing disbalance of therapeutic effects and side effects at long-term follow-up after thalamic DBS, often leading to either switching the stimulator off or new surgery with a different neuro-anatomical target.

Chapter 4 reports on the results of DBS of the anterior GPi in five refractory TS patients. The target choice was based on the positive results of other groups targeting this area and our negative long-term results with thalamic DBS. This study was performed as an open label study with follow-up assessments between 12 and 38 months. Three males and two females were included with a mean age of 41.6 years (SD 9.7). The total post-operative score on the YGTSS was significantly lower than the pre-operative score (42.2 ± 4.8 versus 12.8 ± 3.8 , $P=0.043$). There was also a significant reduction on the modified Rush Video-Based Tic Rating Scale (13.0 ± 2.0 versus 7.0 ± 1.6 , $P=0.041$) and in the total number of video-rated tics (259.6 ± 107.3 versus 49.6 ± 24.8 , $P=0.043$). No significant difference on the comorbid behavioural disorders, mood and cognition was found, however, there was an improvement on an individual level for Obsessive-Compulsive behaviour (OCb). The final position of the active contacts within the anterior GPi was variable in our sample and no relationship between position and stimulation effects could be established. These results suggest that DBS of the anterior GPi is effective in reducing tic severity, and possibly also OCb, in refractory TS patients without serious adverse events or side effects.

Chapter 5 describes our electrophysiology recordings during DBS surgery targeting the anterior GPi in eight awake TS patients. The neuronal activity in the anterior GPe/GPi,

part of the limbic BG circuit, was analysed. A total of 235 single neurons were recorded and the neurons were identified as GPe (n=77) or GPi (n=158) neurons based on their location and trajectory history. The baseline firing rate of the globus pallidus neurons was low in TS patients. We found firing rates of 48.25 ± 3.4 spikes/sec and 50.9 ± 2.6 spikes/sec (mean $\pm$ SEM) for GPe and GPi neurons, respectively. While the firing rates were similar between GPe and GPi neurons, the firing patterns of the neurons in each nucleus were different. Tic dependent transient rate changes were found in the activity of the individual neurons of both segments around the time of the tic (in 44.1% of GPe neurons and in 41.7% of GPi neurons). In both nuclei, half of the responding neurons displayed a decrease in activity around the time of a tic. Despite phasic tic-related changes in the firing rate of individual neurons, the mean firing rate of both nuclei did not phasically change during tic occurrence. Neither oscillatory activity of individual neurons nor correlations in their interactions were observed. Our results demonstrate the involvement of the limbic pathway in the underlying pathophysiology of TS and point to tonic and phasic modulations BG of output as a key mechanism underlying the abnormal state of the disorder and the expression of individual tics, respectively.

Chapter 6 describes a modified cement-based fixation of the DBS electrode to prevent unintended migration. This unintended electrode migration occurs in up to 10% of cases and may result in no or suboptimal therapeutic effects making a second surgery necessary. The cement-based fixation method has been our method of choice several years and we modified this method by adding anchoring screws to increase the robustness.

Chapter 7 deals with the ethical issues associated with DBS of adolescent TS patients. We discuss ethical problems encountered in two adolescent TS patients treated with DBS of the anterior GPi and systematically review the scarce literature on the topic. Three years after surgery one patient experienced a spontaneous tic reduction of more than 50% and did not require stimulation anymore. The second patient went through a period of behavioural disturbances that interfered with optimal programming, but eventually experienced a 70% tic reduction. Only 16 surgeries in TS patients under 25 years have been reported, none of which pays attention to ethical aspects of this treatment. In adolescent TS patients, DBS carries the risk of becoming unnecessary later due to spontaneous remission. Unfortunately, since chronicity cannot be predicted, it cannot be used to indicate DBS. Moreover, reduced compliance due to behavioural disturbances that may occur in this age period can interfere with treatment. The ethical discussion about DBS in adolescent TS patients is important and should precede future practices and accompany the current practice of indication and treatment.

The general discussion in **chapter 8** addresses questions about the underlying pathophysiology of TS and reflects on what has been learned thus far about thalamic and anterior GPi DBS in refractory TS patients. Recommendations for clinical practice and challenges for future research are discussed.

Samenvatting

Het algemene doel van dit proefschrift is bij te dragen aan de ontwikkeling van diepe hersenstimulatie (DBS) bij patiënten met een refractaire vorm van het Syndroom van Gilles de la Tourette (TS). De focus ligt op het beschrijven van nieuwe bevindingen over de onderliggende pathofysiologie en het verkrijgen van nieuwe inzichten over de effecten van thalamische en pallidale DBS bij refractaire TS patiënten.

In **hoofdstuk 2** hebben we de rol van de basale ganglia (BG), en de daarmee verbonden cortico-basale-ganglia-thalamocorticale (CBGT) circuits, onderzocht in de onderliggende pathofysiologie van TS, een onderwerp van continue discussie. De BG moduleren beweging en gedrag door het veranderen van de corticale prikkelbaarheid. Het striatum is de belangrijkste input structuur van de BG en controleert de output door middel van twee pathways: de directe pathway van het striatum naar de output kernen van de BG (globus pallidus internus (GPI)/substantia nigra pars reticulata (SNr)), en de indirecte pathway van het striatum naar de GPI/SNr door de globus pallidus externus (GPe). Daarnaast is er nog een hyperdirecte pathway welke corticale signalen direct naar de nucleus subthalamicus (STN) stuurt en dan naar de GPI/SNr. Deze pathways worden verder onderverdeeld in functionele pathways waarbij motorische informatie voornamelijk naar de posterieure GPI gestuurd wordt en limbische informatie naar de anterieure GPI. Functionele modellen van de BG hebben potentiële mechanismen voor hyperkinetische bewegingsstoornissen zoals TS voorgesteld, welke zich concentreren op afwijkingen binnen de motorische circuits. Het 'box and arrow' model beschrijft de globale modulatie van de neuronale activiteit van hele hersengebieden (boxes) langs de CBGT circuits als een functie van hun connectiviteit (arrows). In dit model wordt TS verklaard door disinhibitie in het striatum wat leidt tot verminderde tonische inhibitie van de GPI/SNr op de thalamocorticale doelgebieden. Het 'action selection' model beschrijft lokale veranderingen in de inhibitie van neuronale subgroepen binnen de output kernen. In dit model ontstaan de symptomen van TS vanuit abnormale focale activatie van neuronen in het striatum, met name door dopaminerge dysfunctie, welke de activiteit van een subpopulatie van GPI neuronen inhiberen. Deze ongewilde inhibitie leidt tot disinhibitie van de thalamocorticale doelgebieden en kan leiden tot een onwillekeurige motorische opdracht in de cortex en tot het ontstaan van een tic. Elektrofysiologie data tonen dat de thalamus en de GPI een significante rol spelen in de onderliggende pathofysiologie van TS. Beide zijn belangrijke structuren binnen het CBGT circuit en door ze te beïnvloeden met hoogfrequente stimulatie, kan de signalering door de BG aangepast worden. DBS lijkt zijn effect uit te voeren door functionele ablatie te veroorzaken waardoor de informatie geleiding door de gestimuleerde kern verminderd wordt. Het voornaamste doel van DBS is om de disbalans in de BG, welke aanwezig is bij TS, te herstellen en symptomen te verlichten.

In **hoofdstuk 3** beschrijven we de langetermijnresultaten van zeven patiënten met een refractaire vorm van TS welke behandeld zijn middels DBS van de mediale thalamus tussen 2001 en 2008. De target was het kruispunt van centromediane nucleus –

substantia periventricularis – nucleus ventro-oralis internus (Cm-Spv-Voi) van de thalamus. Het effect op tics en bijwerkingen werd geëvalueerd met een variabele follow-up duur van 12 tot 78 maanden. Patiënt 1 en 2 toonden een goede verbetering in tics van 81.6% (60 maanden) en 50% (36 maanden) op de Yale Global Tic Severity Scale (YGTSS), respectievelijk. Echter, bijwerkingen zoals energieverlies en visuele stoornissen namen in de loop van de tijd toe. Bij patiënt 1 werd daarop de target aangepast middels een 2^e DBS operatie naar de anterieure GPI. Bij patiënt 2 werd in overleg besloten om de stimulator definitief uit te zetten. Patiënt 3 ervaart nog steeds een goed effect van zijn DBS met een verbetering van 88.9% op de YGTSS (78 maanden). Patiënt 4 en 7 toonden een minimale verbetering van tics van respectievelijk 34% (16 maanden) en 9% (60 maanden). Bij beide patiënten namen bijwerkingen, waaronder energieverlies, visusstoornissen en seksuele functiestoornissen toe in de loop van de tijd. Daarnaast trad in beide gevallen een hardware complicatie op; bij patiënt 4 moest het hele DBS systeem verwijderd worden door een persisterende hardware infectie na het vervangen van de pulsgenerator (6 jaar postoperatief), en bij patiënt 7 werd een hardware defect in de linker elektrode gevonden waardoor het hele systeem verwijderd werd (9 jaar postoperatief). Bij beide patiënten was er de laatste jaren geen sprake meer van een acceptabel effect van de DBS en daarom werd besloten de target te wijzigen naar de anterieure GPI. Patiënt 5 toonde een verbetering van 27.5% op de YGTSS (12 maanden) en is naar het buitenland gegaan om een DBS van de globus pallidus externus te laten verrichten. Verdere follow-upgegevens ontbreken. Patiënt 6 ontwikkelde postoperatief cerebellaire atrofie met een scala aan klachten (onder andere lethargie, dysarthrie en loopstoornissen), die geen relatie hadden met de stimulatie. Daarnaast was het effect op tics minimaal (34% verbetering na 26 maanden) en is besloten om de stimulator uit te zetten. Deze resultaten tonen dat er op de lange termijn een toenemende disbalans lijkt te zijn tussen therapeutische effecten en bijwerkingen van thalamische DBS. Dit zorgt er vaak voor dat de stimulator of uitgezet worden of dat er een nieuwe operatie plaatsvindt met een andere neuroanatomisch target.

Hoofdstuk 4 beschrijft de resultaten van DBS van de anterieure GPI in vijf patiënten met een refractaire vorm van TS. De target keuze was gebaseerd op de positieve resultaten van anderen welke dit gebied stimuleren en onze eigen negatievere lange termijn resultaten met thalamische DBS. Deze studie is uitgevoerd als een open label studie met een variabele follow-up duur van 12 tot 38 maanden. Drie mannen en twee vrouwen werden geïnccludeerd met een gemiddelde leeftijd van 41.6 jaar (SD 9.7). De totale postoperatieve score op de YGTSS was significant lager dan de preoperatieve score (42.2 ± 4.8 versus 12.8 ± 3.8 , $P=0.043$). Er was ook een significante verbetering op de modified Rush Video-Based Tic Rating Scale (13.0 ± 2.0 versus 7.0 ± 1.6 , $P=0.041$) en in het totale aantal video-gescorede tics (259.6 ± 107.3 versus 49.6 ± 24.8 , $P=0.043$). Er werden geen significante verschillen gevonden in comorbide gedragsstoornissen, stemming en

cognitie. Echter, er op een individueel level was er een verbetering in obsessief-compulsief gedrag. De uiteindelijke positie van de actieve contacten van de definitieve elektrode binnen de anterieure GPi was variabel in onze groep en er kon geen relatie gevonden worden tussen de positie en de stimulatie effecten. Deze resultaten tonen aan dat DBS van de anterieure GPi effectief is in het verminderen van tics, en mogelijk ook obsessief-compulsief gedrag, bij refractaire TS patiënten zonder dat er sprake is van ernstige bijwerkingen.

Hoofdstuk 5 gaat over onze elektrofysiologie metingen tijdens DBS operaties van acht wakkere TS patiënten met als target de anterieure GPi. De neuronale activiteit in de anterieure GPe/GPi, onderdeel van het limbische CBGT circuit, werd geanalyseerd. In totaal werden 235 afzonderlijke neuronen geregistreerd en deze werden geïdentificeerd als GPe (n=77) of GPi (n=158), gebaseerd op locatie en traject geschiedenis. De basis vuursnelheid van de globus pallidus neuronen was laag in TS patiënten. We vonden vuursnelheden van 48.25 ± 3.4 pieken/sec en 50.9 ± 2.6 pieken/sec (gemiddelde $\pm$ SEM) voor GPe neuronen en GPi neuronen, respectievelijk. Terwijl de vuursnelheden gelijk waren tussen de GPe en GPi neuronen, waren de vuurpatronen van de neuronen in de afzonderlijke kernen verschillend. Tic gerelateerde en voorbijgaande veranderingen in vuursnelheid werden gezien in de activiteit van de individuele neuronen van beide kernen rond het moment van de tic (bij 44.1% van de GPe neuronen en bij 41.7% van de GPi neuronen). In zowel de GPe als de GPi liet de helft van deze reagerende neuronen een afname in activiteit zien rond het moment van de tic. Ondanks deze fasische tic-gerelateerde veranderingen in vuursnelheid van individuele neuronen, veranderde de gemiddelde vuursnelheid van beide kernen niet tijdens een tic. Zowel oscillaties van individuele neuronen als correlaties in hun interacties werden niet gevonden. Onze resultaten demonstreren dat het limbische circuit betrokken is bij de onderliggende pathofysiologie van TS. Daarnaast tonen ze aan dat tonische en fasische verandering van de BG output een sleutelmechanisme is in de onderliggende abnormale status van de ziekte en de expressie van individuele tics, respectievelijk.

Hoofdstuk 6 beschrijft een gemodificeerde cement-fixatie van de DBS-electrode om ongewilde migratie te voorkomen. Deze ongewilde migratie treedt op bij circa 10% van de operaties en dit kan resulteren in geen of suboptimale therapeutische effecten, waardoor een tweede operatie noodzakelijk is. We hebben de afgelopen 15 jaar gebruik gemaakt van cement-fixatie en hebben deze procedure gemodificeerd door verankeringsschroeven toe te voegen om de stevigheid van de constructie te verbeteren.

Hoofdstuk 7 gaat over ethische kwesties welke geassocieerd zijn met DBS bij adolescente TS patiënten. Wij bediscussiëren de ethische problemen welke wij tegengekomen zijn bij de behandeling van twee adolescente TS patiënten met DBS van de anterieure GPi. Daarnaast analyseren we de spaarzame literatuur over dit

onderwerp. Drie jaar na de operatie was er bij één patiënt sprake van een spontane tic verbetering van 50% en hij had de stimulatie niet meer nodig. De tweede patiënt heeft postoperatief een periode van gedragsproblemen doorgemaakt welke interfereerden met optimale programmering, maar uiteindelijk was er sprake van 70% tic vermindering. Slechts 16 operaties in TS patiënten < 25 jaar zijn beschreven waarvan geen enkele aandacht bestaat aan de ethische aspecten van deze behandeling. Bij adolescenten bestaat er een risico dat DBS op termijn niet meer noodzakelijk is door spontane remissie van de ziekte. Helaas kan chroniciteit bij TS niet voorspeld worden en kan het dus ook niet gebruikt worden om de indicatie voor DBS te stellen. Daarnaast kan verminderde compliantie door gedragsproblemen sneller optreden in deze levensfase wat een negatieve invloed kan hebben op de behandeling. De ethische discussie rondom DBS bij adolescente TS patiënten is belangrijk en hier moet meer aandacht voor zijn bij toekomstig onderzoek.

In de algemene discussie in **hoofdstuk 8** beschrijven we nieuwe ideeën over de onderliggende pathofysiologie van het TS. Daarnaast trekken we lering uit onze eigen ervaringen met DBS van de thalamus en de anterieure GPI bij TS patiënten. Adviezen voor de klinische praktijk en uitdagingen voor toekomstig onderzoek worden besproken.

Valorisation

Tourette Syndrome (TS) is a childhood-onset neurodevelopmental disorder characterized by multiple motor and one or more vocal tics. It is frequently accompanied by comorbid behavioural disorders and they often cause even more impairment than the tics themselves. TS affects between 0.4% - 3.8 % of the general population. Mainly children between 5 and 18 years of age suffer from the disease and the prevalence in this group lies around 1%. Individuals in all countries worldwide can be affected, although to different degrees. Fortunately, TS is often self-limiting around adolescence. About one third of children experiences a significant tic reduction during adolescence and another third becomes completely tic-free. Yet, still one third of children does not experience this remission, and some not only experience tic worsening during adolescence but they develop the most severe forms of TS. In those patients, TS has a devastating influence on their lives and social environments. Since there is no cure for TS, treatment aims to diminish or alleviate tics and comorbid symptoms. Despite behavioural therapy and pharmacological treatment, a small subgroup of patients fails to respond to treatment or experiences intolerable side effects. These patients are often not able to go to school or work, tend to avoid social activities, are not able to develop friendships or an affective relationship, and have a low self-esteem. For those severely affected TS patients, Deep Brain Stimulation (DBS) has emerged as a therapeutic escalation. In refractory cases of well selected TS patients, DBS of different targets within the thalamus and the basal ganglia (BG) seems to be a promising treatment. A key factor in attaining optimal results is target selection, a topic still under debate due to the complex clinical profile presented by TS patients. Nine separate brain areas have been targeted with DBS so far in TS patients.

This thesis contributes to the clinical evidence that DBS, targeting the medial thalamus and the anterior internal globus pallidus (GPi), seems to be a safe and effective treatment in strictly selected TS patients at the short-term. We found an increasing disbalance of therapeutic effects and side effects at long-term follow-up with thalamic DBS, often leading to either switching the stimulator off or new surgery with a different target. DBS of the anterior GPi was found to be effective in reducing tic severity, and possibly also Obsessive-Compulsive behaviour (OCb), without serious side effects, at both the short-term and the long-term. Because of this we think that DBS for future refractory TS patients should target the anterior GPi and not the thalamus. However, we believe that the choice for a single DBS target in TS is unfeasible given the heterogeneity of the disease. As such we need to switch towards tailored targeting instead of trying to find the optimal target for all patients. This tailored targeting should be based on the main symptoms of a patient, e.g. tics or comorbid behavioural disorders. Besides the specific target another clinical issue considers the age limit for DBS in TS. In spite of our experienced difficulties with adolescent DBS for TS, we think that there should be no strict age limit for indicating DBS and decisions should be made on individual circumstances and symptomatology. Waiting for an eventual spontaneous regression around adolescence might cause irreparable damages to the patient's future

life. We think that ongoing ethical discussion is of major importance and should precede future practices and accompany the current practice of indication and treatment.

The development of DBS in TS proceeds slowly since it is not (yet) approved by the Food and Drug Administration (FDA) and the European Commission (EC), because of the lack of evidence due to the difficulty of performing high quality research in a randomized controlled fashion, coupled with the variable effect of surgery, the large number of targets, and the overall small numbers of TS patients with DBS worldwide. The experimental character of the treatment holds up further steps towards approval. Since patients are more cautious in undergoing the treatment and they can only be operated in a research setting, the numbers of included TS patients remain low, making it very difficult to obtain enough high-quality evidence for approval by the regulatory agencies. The various centres use different techniques and targets, making it difficult to obtain and interpret large-scale outcomes. Multicentre randomized controlled trials would theoretically be desirable, but difficult to realize due to practical reasons and would stretch over many years. Moreover, during such trial new insights might be gained, e.g. pointing to different surgical targets or other changes in the procedure, which would be unethical to withhold from later participants. In order to optimally benefit from the clinical experience, we think that all cases of DBS for TS should be entered in a central database covering a range of standardized information, initiated by the Tourette Syndrome Association (TSA). The main goal is to share data, uncover best practices, improve outcomes, and provide critical information to regulatory agencies. Despite the difficulties and uncertainties about DBS in refractory TS patients, we believe that DBS holds a promise for becoming an established treatment. We will participate in continuing the development of DBS for refractory TS patients by further exploring the effects of surgery in our own centre and by contributing to the TSA database.

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Curriculum Vitae

Anouk (Yvonne Jacqueline Maria) Smeets was born on March 24th, 1989 in Heerlen, the Netherlands. She attended secondary school for six years at the 'Bernardinuscollege' in Heerlen. In 2007 she started to study medicine at the Faculty of Health, Medicine and Life Sciences at the Maastricht University. At the end of her medical studies she completed her research internship about Deep Brain Stimulation in refractory Tourette Syndrome and the beginning of this thesis was set. In December 2013 she received her medical doctor degree and in February 2014 she started working as a resident at the Neurosurgery department at the Maastricht University Medical Centre. In October 2015 she started her specialist training in Neurosurgery at the same department. During her residency she continued and completed the research described in this thesis under supervision of Prof. Temel, Dr. Ackermans, Dr. Duits, and Dr. Leentjens.

Anouk (Yvonne Jacqueline Maria) Smeets werd op 24 maart 1989 geboren in Heerlen. Ze doorliep het gymnasium aan de middelbare school het 'Bernardinuscollege' in Heerlen. In 2007 begon ze met de studie Geneeskunde aan de Faculty of Health, Medicine and Life Sciences van de Universiteit Maastricht. Gedurende het laatste jaar van haar studie bestond haar wetenschapsparticipatie uit onderzoek naar diepe hersenstimulatie bij het syndroom van Gilles de la Tourette, dit was eveneens het begin van deze thesis. In december 2013 behaalde ze haar artsendiploma en in februari 2014 begon ze met werken als arts-assistent bij de afdeling Neurochirurgie in het Maastricht Universitair Medisch Centrum. In oktober 2015 werd ze aldaar aangenomen voor de opleiding tot neurochirurg. Tijdens deze opleiding werd, onder begeleiding van Prof. Temel, Dr. Ackermans, Dr. Duits, en Dr. Leentjens het proefschrift geschreven dat nu voor u ligt.

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