The stimulated brain: A psychological perspective on deep brain stimulation for treatment-refractory obsessive-compulsive disorder

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Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder with an estimated lifetime prevalence of 2%. Severe OCD leads to pronounced suffering and has a major impact on family relationships, social life and the capacity to function at work. At present, clinical management of OCD consists of pharmacological treatment and cognitive behavioural therapy. Although both treatments are often effective, approximately 10% of patients remain severely affected and suffer from treatment-refractory OCD. A new and last-resort treatment option for this group of treatment-refractory patients is deep brain stimulation (DBS). DBS is a treatment in which two electrodes are implanted in specific brain areas. The activity of the electrodes can be programmed externally, which permits the modulation of dysfunctional neural networks that are involved in the pathophysiology of OCD. This thesis describes our journey of discovery and research findings of the past ten years, regarding the effectiveness, safety and mechanism of action of DBS, with an emphasis on the psychological perspective. Therewith, the aim of this thesis is to add to the knowledge about DBS for treatment-refractory OCD.
THE STIMULATED BRAIN
A PSYCHOLOGICAL PERSPECTIVE ON DEEP BRAIN STIMULATION FOR TREATMENT-REFRACTORY OBSESSIVE-COMPULSIVE DISORDER

MARISKA H.M. MANTIONE
The studies described in this thesis were performed at the Department of Psychiatry, in collaboration with the Department of Neurosurgery, Academic Medical Center, the Netherlands, with financial support from the Netherlands Organization for Scientific Research (NWO) ZON-MW VENI program, grant 916.66.095.


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THE STIMULATED BRAIN
A PSYCHOLOGICAL PERSPECTIVE ON DEEP BRAIN STIMULATION FOR TREATMENT-REFRACTORY OBSESSIVE-COMPULSIVE DISORDER

ACADEMISCH PROEFSCHRIFT

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ten overstaan van een door het college voor promoties
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in het openbaar te verdedigen in de Agnietenkapel
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Faculteit der Geneeskunde
Ogni grande viaggio inizia con un primo passo

Vecchio proverbio Italiano

Elke grote reis begint met een eerste stap

Oud Italiaans gezegde
# TABLE OF CONTENTS

| CHAPTER 1 | General introduction and outline of the thesis | 9 |
| PART I: Efficacy of deep brain stimulation in obsessive-compulsive disorder |
| CHAPTER 2 | Targets for deep brain stimulation in obsessive-compulsive disorder | 25 |
| CHAPTER 3 | Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder | 39 |
| CHAPTER 4 | Cognitive behavioural therapy augments the effects of deep brain stimulation in obsessive-compulsive disorder | 59 |
| PART II: Cognition and deep brain stimulation |
| CHAPTER 5 | Cognitive effects of deep brain stimulation in obsessive-compulsive disorder | 77 |
| CHAPTER 6 | The link between obsessive-compulsive disorder and cognition: lessons from deep brain stimulation | 97 |
| PART III: Side effects of deep brain stimulation in obsessive-compulsive disorder |
| CHAPTER 7 | Smoking cessation and weight loss following chronic deep brain stimulation of the nucleus accumbens: therapeutic and research implications. | 111 |
| CHAPTER 8 | A case of musical preference for Johnny Cash following deep brain stimulation of the nucleus accumbens | 121 |
| PART IV: Discussion and summary |
| CHAPTER 9 | General Discussion | 133 |
| Summary | 147 |
| PART V APPENDIX |
| Nederlandse samenvatting | 157 |
| List of publications | 165 |
| Dankwoord | 171 |
| Curriculum Vitae | 177 |
CHAPTER 1

GENERAL INTRODUCTION
This thesis has been a journey of (self-)discovery. It commenced in April 2005 when I was appointed to support an experimental study on the effectiveness of deep brain stimulation (DBS) of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder (OCD). At that time, deep brain stimulation (DBS) was a promising treatment. It was already used extensively as treatment of Parkinson’s disease (PD), and clinical experience suggested that DBS also could improve psychiatric symptoms, in particular OCD. Given these beneficial effects, OCD was the first psychiatric disorder to be treated with DBS. In 2005, only a handful case studies on the effectiveness of DBS in treatment-refractory OCD were published or ongoing.\(^1\)-\(^8\) Nothing was known about the clinical management of severe treatment-refractory patients, optimal targets for stimulation, efficacy and safety of the treatment, or its mechanism of action. This thesis tells the story of ten years of pioneering research in DBS. It tells about the theory and practice of DBS as last resort treatment, the search for the best possible outcome, and what we have learned so far. Therewith, it aims to contribute to the knowledge about the effectiveness and safety of DBS for treatment-refractory OCD patients and its mechanism of action.

1.1 TO START WITH

OCD is a chronic psychiatric disorder, characterized by persistent thoughts (obsessions) that are frequently recognized as irrational, and repetitive ritualistic behaviors (compulsions) that usually represent attempts to minimize distress caused by obsessions. OCD has a life-time prevalence of 2% and affects women and men equally. Severe OCD leads to pronounced suffering and has a major impact on family relationships, social life and the capacity to function at work.\(^9\) At present, clinical management of OCD consists of pharmacological treatment, in particular selective serotonin reuptake inhibitors, and cognitive behavioural therapy (CBT).\(^10\)-\(^14\) Although often effective, both treatments have their limitations. First, patients usually have only a partial response to medication\(^15\) and CBT.\(^16,17\) Across all pharmacological treatments, the percentage of responders in placebo-controlled studies is around 40%.\(^18\) Approximately 60% of patients have a partial response to CBT and only 25% of patients are in full remission following CBT.\(^19\) Furthermore, medication may have significant side effects, and exposure and response prevention in CBT often provokes intense anxiety, resulting in a 25% drop out of patients.\(^20\) Even when the best available treatments are applied, approximately 10% of patients remain severely affected and suffer from treatment-refractory OCD.\(^21\) For this group of treatment-refractory patients, DBS can be considered as a last resort treatment option.
In practice, given the high prevalence of treatment-refractory OCD patients, already a
dozen of patients had enrolled before the study was announced and actually started. Of
the hundred who where interested in the following years, only sixteen patients could
participate. We were flooded with telephone calls. Patients wanted to know when
the study would commence and how they could apply for eligibility. Family called,
emotional and compelling, to emphasize that the situation was intolerable and their
relatives had to be helped urgently, often accompanied with treats of suicide if not
included. The screening for eligibility proved to be a challenge: patients were unable to
come to appointments in the morning due their excessive washing rituals, or refused
to come to appointments at the 13th of the month or at 13.00, because of their obsessive
thoughts that otherwise something terrible might happen to their loved ones. It took
us months to schedule and manage requests and appointments. It took patients days
to perfectly fill out our questionnaires and they brought refuse bags to put at our dirty
hospital chairs. But they came. DBS seemed to be a last hope.

1.2 DEEP BRAIN STIMULATION

Therapeutic options for treatment-refractory OCD patients were previously limited
to ablative neurosurgery, such as anterior capsulotomy and anterior cingulotomy.21
Although also DBS may be considered an invasive procedure, it attracted increasing
interest due to the success of DBS for PD, the small risk of the operation, the reversible
nature of the technique and the possibility of optimizing stimulation to increase the
therapeutic effect and decrease possible side effects. Technically, DBS consists of
two parts: implantation and neuromodulation. Usually, one or two electrodes are
implanted in specific brain areas and connected with an extension cable to a pulse
generator, which is inserted into a pocket under the clavicle. The activity of the
electrodes can be programmed externally with a remote control, communicating with
the pulse generator through telemetry. The electrodes have four contact points, which
can be stimulated separately. Additionally, voltage, pulse width and frequency can be
programmed whereby the anatomic reach of the stimulation area can be adjusted.
This permits the modulation of dysfunctional neural networks that are involved in the
pathophysiology of OCD.22

1.3 TARGETS FOR DEEP BRAIN STIMULATION

In 2005, literature about targets for DBS in OCD and their effectiveness was limited.
Initially, the anterior limb of the internal capsule (ALIC) had been proposed as the target
of choice, based on the lesion target for anterior capsulotomy. In 1998, Nuttin et al.\(^1\) had published the first article on bilateral DBS of the ALIC in four OCD patients. Three of four patients showed beneficial effects. Furthermore, in 2003 they had published the long term results of these patients together with the results of two subsequent patients.\(^2\) Three of four patients that participated in a cross-over design had been responding with an improvement of at least 35% in OCD symptoms. A case study of Anderson and Ahmed\(^3\) in 2003 had confirmed these initial beneficial results of DBS of the ALIC, with a reduction of 79% of OCD symptoms after open stimulation. Less impressive results on DBS of the ALIC had been published by Abelson et al.\(^4\) in 2005, showing that only one in four patients responded with at least 35% in the cross-over phase of the study.

Secondly, the nucleus subthalamicus (STN), part of the basal ganglia, had been proposed as a possible target for DBS in OCD, given the reduction of repetitive behaviours and OCD symptoms after DBS of the STN in PD.\(^5\) Two case studies had underlined the possible effectiveness of DBS of the STN in treatment-refractory OCD. Mallet et al.\(^6\) had reported an average decrease of 82% in OCD symptoms in 2002 and Fontaine et al.\(^7\) had reported a reduction of 97% of OCD symptoms in 2004.

Finally, the nucleus accumbens (NAc), part of the ventral striatum, had been suggested as a target for DBS in OCD. It was considered a promising target because of its involvement in reward processing, motivation and addiction and the evidence of

**Figure 1** Implantation of electrodes and pulse generator.
dysfunction of the reward system in OCD. Sturm et al. had reported in 2003 on the results of unilateral DBS of the NAc in four patients, whereby three of four patients were considered responders after open stimulation. The possible effectiveness of the NAc as a target for OCD was confirmed by a case study of Aouizerate et al. in 2004, showing a 52% decrease of OCD symptoms after DBS of the NAc/ventral caudate in a patient with OCD and depression.

In 2005, there had already been several years of careful consideration between the Academic Medical Center (AMC) in Amsterdam, the University Medical Center Utrecht (UMCU) and Medtronic, the medical technology company. The AMC (Rick Schuurman and Andries Bosch) had an explicit interest in DBS for psychiatric disorders because of its long-standing experience in DBS of movement disorders and the UMCU (Damiaan Denys and Herman Westenberg) because of its extensive knowledge and clinical experience with treatment-refractory OCD. At that centre, OCD was innovatively perceived as a behavioural addiction, associated with a dopaminergic dysregulation and dysfunctional reward processing. This resulted in an interest and agreement to target the NAc as brain area of choice for DBS in OCD.

1.4 SEARCH FOR EFFICACY

In three years, we screened 101 patients for eligibility. Some of them had no OCD, some of them had severe co-morbid disorders and many of them did not fulfill the criteria for treatment-refractoriness. Surprisingly, many patients rather preferred to undergo DBS than starting again with medication or CBT. Eventually, we selected 16 patients that fulfilled the inclusion criteria for the study and were ready to undergo surgery.

In April and May 2005 our first two patients underwent DBS of the NAc: Mrs. L., a 54-year-old woman and Mr. D., a 43-year-old man. Mrs. L. suffered from OCD since 1972. She was obsessed with the number thirteen, left-right issues and had extensive counting compulsions. Mr. D. suffered from OCD since 1971. He had obsessions about contamination, washing and cleaning rituals and compulsively asked reassurance. OCD hindered them both in all aspects of their life. Two weeks after surgery we saw both of them at the psychiatry department of the UMCU. After the electrodes were implanted, we needed to adjust the stimulation to optimize its effect. However, we had not the slightest experience with the remote control and the adjustment of stimulation parameters. There was no guideline to follow and we as, well as the patients, did not know what to expect. Traditionally, as was done in PD, the two lowest contact points of the electrode were activated at basic parameter settings (3.5 V, 90 μsec and 130 Hz). Patients always left the hospital with high hopes. Unfortunately, they failed to
experience any improvement in the first weeks following implantation. In the coming months, we had clinical visits on a weekly basis with the patients to observe changes, assess side-effects, and adjust stimulation settings. In this intensive treatment period, no significant change was observed, leaving the patients desperate.

In September 2005, after three months of extensive labor, our enthusiasm about DBS was completely tempered. Patients were implanted and treated extensively without any response. We considered a next step: changing stimulation parameters to higher current, as was done by Nuttin et al. or changing the contact points from the lower contact points to the upper contact points, which were located more into the ventral capsule. In one week, we activated the upper contact points of both patients. Two days later, we received two unexpected telephone calls. Mrs. L. called. She explained that she felt depressed on the journey to the hospital and felt suddenly happy on the way back. Coming home she realized that she felt calm despite it being week 39 (that is thirteen times three). She told us that she felt less anxious in general. Mr. D. called also. He explained that he felt happier and less rushed. Obsessions had disturbed him, but surprisingly did not persist. Mr. B. described that he felt less anxious. In the next couple of days Mrs. L. contacted the local political party to enter political life. For the first time in 15 years she ate the thirteenth Dutch crispbake of the packet. Mr. B. went to do the groceries for the first time in 10 years and for the first time in 20 years he went to bed without performing his washing ritual.

1.5 ADDITIONAL TREATMENT

Though these initial DBS effects greatly improved anxiety, mood and obsessions, regarding compulsive behaviour we hardly observed improvement in our first patients. Mrs. L. still crossed every doorstep with her right foot. Mr. D. still performed his cleaning rituals after he has left his house. Despite a sustained improved in mood and less anxiety they reported being afraid that stopping their compulsions would result in more obsessions and anxiety.

For the second time, our team was confronted with an unforeseen problem: anxiety and obsessive symptoms decreased spectacularly, but compulsions and avoidance behaviour persisted. As I was the only psychologist with a background of CBT in our team I wondered whether an individual exposure program in which patients are confronted with their feared situations could be used, to help patients to overcome their compulsions and withdraw from their long-lasting avoidance strategies. That is were I basically filled an essential gap in the current treatment approach of DBS. At that time, no one added CBT to DBS since it was seen as a pure neurobiological treatment. There even was severe criticism on adding CBT to DBS by the medical company and
other DBS centres, because it might bias the treatment outcome. However, I believed that the two components of CBT, cognitive therapy and exposure and response prevention (ERP), would perfectly fit and augment the initial response of DBS.

Cognitive therapy is used to challenge and correct the underlying dysfunctional beliefs in OCD. In ERP, patients are systematically confronted with stimuli that provoke anxiety while being encouraged to refrain from performing compulsions. Formerly, the aim of ERP was to teach patients that anxiety does not persist indefinitely and that compulsions and avoidance are unnecessary to prevent harm. In the past years there has been an emphasis on inhibitory learning, the forming of new corrective associations, as aim of ERP. CBT had already been used as an augmentation strategy to increase the general partial response of pharmacotherapy in OCD. The combination of medication and CBT had proven to be more effective than medication alone. I developed a CBT program especially designed to enhance DBS responses and hypothesized that similar to medication, the combination of DBS and CBT would be more effective than either CBT or DBS alone.

1.6 DEEP BRAIN STIMULATION AND COGNITION

During the course of the study we were confronted with side effects of DBS. Regularly, patients complained of forgetfulness, word-finding problems and having difficulties to concentrate during conversations. Little was known about the effect of DBS on cognition. Only Gabriëls et al. and Abelson et al. had been studying the cognitive effects of DBS in OCD. Gabriëls et al. found no negative effect of DBS on measures of intelligence and executive functioning and Abelson et al. found no consistent patterns of change associated with stimulation. However, these studies were very preliminary and we knew from the literature of DBS in PD that there could possibly be cognitive side effects of DBS. Therefore I decided to perform several neuropsychological assessments at different time points in the study to establish the cognitive safety of DBS of the NAc.

Besides, I was wondering how the profound improvement in clinical symptoms after DBS was accomplished. The majority of research on cognition in OCD points to a deficit in organizational strategies in general, suggesting problems with executive functioning. It is proposed that the interaction between organizational strategy deficits and the effort to recall unstructured information may contribute to doubting, an important feature of OCD. Therewith it is possible that these deficits are involved in the maintenance of OCD symptoms. I wondered whether DBS of the NAc, that can have a fast and pronounced effect on symptoms, could influence the underlying cognitive
deficits in OCD and whether the improvement after DBS may be accomplished by an improvement of the cognitive deficits in OCD. To study these two questions I developed a trial in which we investigated the impact of DBS of the NAc on cognition.

1.6 TO END WITH

In April 2015, my thesis and journey about the effectiveness of DBS of the NAc for treatment-refractory OCD will be completed. At that time, 50 treatment-refractory OCD patients will have undergone DBS at our department. In the past ten years we assessed patients with numerous clinical scales and neuropsychological tests. We have learned from clinical studies and our own experiences: which patients are more likely to improve clinically, how to manage the care of treatment-refractory OCD patients and how DBS can be best applied to improve the quality of life of our patients. We developed a guideline for the adjustment of stimulation parameters and a protocol for additional CBT treatment. Our work has resulted in a theoretical contribution understanding treatment-refractory OCD, but as well a direct societal consequence since we succeeded in approving reimbursement of DBS for OCD by the Dutch health insurance company.

For me, DBS has fulfilled its promise as a last resort treatment. Working with DBS can be challenging but it is full of little miracles. DBS is also equivalent to unexpected challenges and situations. Which treatment can put change of accent, quitting smoking, weight loss and a preference for Johnny Cash as side effects at its instructions for use?

1.7 AIMS AND QUESTIONS OF THE STUDY

The overall aim of this study was to add to the knowledge about DBS for treatment-refractory OCD patients. We considered the NAc a promising DBS target given its involvement in reward processing and the evidence of dysfunction of the reward system in OCD. Therefore, we aimed to investigate the effectiveness and safety of DBS of the NAc for treatment-refractory OCD patients. During this trajectory I observed that DBS had minimal impact on compulsive and avoidance behaviours, which made me investigate the effect of the augmentation of CBT to DBS of the NAc. Patients’ complaints of cognitive problems led to the development of a trial that investigated the impact of DBS of the NAc on cognitive functioning. Finally, specific side effects of the treatment made that we carefully examined the role of the NAc and its mechanism of action.
This resulted in the following fundamental clinical questions:

- Is DBS of the NAc an effective treatment for treatment-refractory OCD patients?
- Do we need additional CBT to improve the effect of DBS of the NAc?
- Is DBS of the NAc a safe treatment in terms of cognition?
- Is there a relation between changes in clinical symptoms and changes in cognition?
- What can we learn from the specific side effects of DBS of the NAc?

1.8 GENERAL OUTLINE OF THIS THESIS

Chapter 2 reviews the existing literature on DBS for treatment-refractory OCD. Therewith it aims to give a general introduction to the effectiveness, mechanism of action and side effects of the treatment and discuss the efficacy of various targets. Chapter 3 investigates whether DBS of the NAc is an effective and safe treatment for treatment-refractory OCD. It describes the clinical outcome of DBS of the NAc after an open eight month treatment phase, double-blind cross-over phase and open 12 month maintenance phase. Chapter 4 evaluates the efficacy of CBT as augmentation to DBS of the NAc. A standardized 24-week CBT program was added to DBS in the open treatment phase of eight months and the change of OCD-, anxiety and depressive symptoms was evaluated. In Chapter 5 cognitive functioning is examined over the course of DBS. Treatment-refractory OCD patients that underwent DBS of the NAc were examined at baseline, three weeks postoperatively and following eight months of stimulation and compared with treatment-refractory OCD patients, treated with care as usual. Chapter 6 explores the effect of stimulation on cognition in a double-blind cross-over phase and investigates the relation between cognitive functioning and severity of OCD symptoms. Chapter 7 is a case report of a patient that underwent DBS and quit smoking and lost weight without any effort. It discusses the role of the NAc in addictive behaviours. Chapter 8 is a case report describing an other patient that underwent DBS and developed a sudden and distinct musical preference for Johnny Cash. It discusses the involvement of the NAc in the rewarding properties of music and how DBS may change musical preference. In Chapter 9 we summarize the findings of all previous chapters. It describes the clinical implications of our study and discusses directions for further research.
REFERENCES


PART I

EFFICACY OF DEEP BRAIN STIMULATION IN OBSESSIVE-COMPULSIVE DISORDER
CHAPTER 2

TARGETS FOR DEEP BRAIN STIMULATION IN OBSESSIVE-COMPULSIVE DISORDER

Martijn Figee, Mariska Mantione, Pepijn van den Munckhof, Rick Schuurman, Damiaan Denys


ABSTRACT

Since its introduction for treatment of treatment-refractory obsessive-compulsive disorder (OCD) in 1998, it is estimated that deep brain stimulation (DBS) has been applied to 80 OCD patients worldwide using various brain targets. This paper reviews the effects of five different targets in OCD. The combined preliminary results suggest a 40 to 60% symptom decrease in at least half the patients. The efficacy, the time to response and the type of symptoms that improve, depend on the target of choice. Although side effects occur, most of these are transitory and linked to specific stimulation parameters that may be changed. DBS research has opened up the opportunity to investigate how various symptom layers of OCD, such as anxiety, obsessions, compulsions, and depressed mood are related to brain activities within the cortico-striato-thalamo-cortical network.
2.1. INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by obsessions and compulsions. Obsessions are recurrent and disturbing thoughts causing anxiety or unease, such as the fear to be contaminated or to hurt someone, and the need for symmetry or perfectionism. Compulsions are acts with a ritual character that are performed to neutralize the anxiety caused by the obsessions, such as cleaning, washing, checking, classifying or counting. Approximately two percent of the general population suffers from OCD.\(^1\)\(^2\) Though three out of four patients experience an average symptom decrease of 35% with selective serotonin reuptake inhibitors or behavioral therapy, eventually, one out of ten patients cannot be helped with these regular treatments.\(^3\)

In case of severe treatment-refractory OCD that is incapacitating in all aspects of daily life, an OCD patient might be candidate for neurosurgical treatment. For decades, neurosurgeons have made lesions in the anterior limb of the internal capsule (ALIC) and the basal ganglia by means of classic, ablative neurosurgery.\(^4\) During the past two decades, a shift has occurred in the field of stereotactic neurosurgery since deep brain stimulation (DBS) became an established reversible and adjustable method for the alleviation of movement disorders. For the first deep brain stimulation to be performed, it was plausible to choose selective stimulation of the ALIC in order to imitate the effects of earlier capsulotomies. Since then, more targets have been explored, and as OCD is one of the few diseases in psychiatry in which more functional data on neuroanatomical correlates are becoming available linking specific brain areas to its pathophysiology, DBS can nowadays be applied in OCD with a more rational approach. This article presents a review of various DBS targets in treatment refractory OCD.

2.2 EFFICACY OF DBS IN OCD

At present, approximately 80 patients with treatment refractory OCD have received experimental DBS treatment. Efficacy of DBS has been reported in seven double-blind controlled studies\(^5\)\(^\text{-}\)\(^12\) and six case studies.\(^10\)\(^\text{-}\)\(^17\) Five targets have been used for DBS in OCD: the anterior limb of the internal capsule (ALIC), the ventral capsule/ventral striatum (VC/CS), the nucleus accumbens (NAcc), the subthalamic nucleus (STN) and the inferior thalamic peduncle (ITP). Efficacy results are summarized in Table 1.

**ALIC**

DBS in OCD was initiated in 1998 at the Karolinska institute in Stockholm where two patients received bilateral implantation in the ALIC, but the results were never published
(personal communication S. Andreewitch). In 1999, the Leuven Group reported on bilateral ALIC DBS in four patients. In a subsequent paper, these four patients and two others were followed-up for a period of 21 months. Three out of four patients who completed the study experienced a 35% decrease of symptoms. An average symptom change of 40% was observed in the double-blind controlled part of the study in which the stimulator was put on and off. In 2005, the Michigan Group reported another study of implantation of electrodes in the ALIC of four patients. Patients were stimulated in a double blind way in a phase of four times three weeks with the stimulator on or off, followed by an open phase. Only one patient had a decrease of more than 35% in the double-blind phase. In the open phase, this patient progressed from severe disability to relatively normal life with 73% improvement over baseline in 8 months. Another patient who experienced only a 17% decline in the double-blind phase, showed improvement in the open phase with a final reduction of 44% after completing an intensive behavioral treatment program. In the two patients who were considered responders, PET scans showed decreased activity of the orbitofrontal cortex. In another case study of ALIC DBS, a patient experienced 79% reduction of symptoms at three-month follow up. At 10-month follow-up, the patient was able to return to work with compulsions in complete remission. These first studies show that the ALIC is a potential effective target for the treatment of treatment-refractory OCD. However, the effects are modest and subsequent targets were localized in a more ventral position.

VC/VS
In 2006, an American-Belgian group published the results of ten patients with bilateral stimulation of the VC/VS. Eight of them were followed during three years after bilateral implantation. Over these three years, OCD symptoms improved from severe to moderate with a 30% decrease on average. Four of eight patients were considered responders with a symptom reduction of at least 35%. The Leuven Group, the American-Belgian Group and a group from the university of Florida published the combined results of VC/VS DBS in 26 patients. During this period, targeting within the VC/VS evolved from anterior to a more posterior area. The percentage of responders was 62% at 36 months with more effective stimulation at lower currents at the more posterior targets. A recent pilot study reported on VC/VS in six treatment-refractory OCD patients. Patients were stimulated at either 30 or 60 days post-surgery under blinded conditions. Four of six patients (67%) were responders with a decrease of at least 35% of symptoms. Interestingly, depressive symptoms improved significantly in all patients.

NAcc
A German Group aimed at the right NAcc as stimulation target in four OCD patients. In three out of four patients, open stimulation resulted in nearly total recovery from
both anxiety- and OCD symptoms at 24 to 30 months. The lack of effect in the fourth patient appeared to be caused by a displacement of the electrode in the caudo-ventral direction thereby missing the target area. The same group subsequently published a double-blind study on unilateral right-sided NAcc DBS in 10 OCD patients. A modest improvement of merely 10% was observed in the double-blind part of the study, which was initiated six months after the stimulator had been implanted. At one-year follow-up, five out of ten patients showed symptom decreases of more than 25%, and one patient more than 35%. Depression scores improved within one year, but anxiety failed to respond. A case study on one patient with OCD and depression reported a marked but delayed reduction of symptoms up to 52% at 15 months follow up. An Italian group recently reported delayed effects of NAcc stimulation in two OCD patients. On average, symptoms improved by 38% after one year of stimulation in the first patient and after two years in the second patient with depression scores improving concomitantly.

**STN**

The STN was long known as an effective target for DBS in Parkinson treatment, and in some patients positive effects of STN stimulation on OCD symptoms were reported. In 2008, the French Group reported on the efficacy of bilateral STN stimulation in 18 OCD patients. STN DBS resulted in positive effects on compulsive behavior but appeared to have no effect on mood and global functioning within the first six months.

**THALAMIC PEDUNCLE**

In 2004 and 2007, two case reports in patients with OCD and major depression were published targeting the ventral caudate nucleus/nucleus accumbens and inferior thalamic peduncle. In the first study, a marked but delayed reduction of symptoms up to 52% was seen at 15 months follow-up. Likewise, in the second study, stimulation showed a significant reduction of obsessive and compulsive symptoms. The last finding was substantiated by the same Mexican group that described a 49% reduction of symptoms following open stimulation of the bilateral inferior thalamic peduncle in five patients with OCD.

In conclusion, DBS in ALIC, VC/VS, NAcc, STN and inferior thalamic peduncle has shown to be effective in treatment-refractory OCD. Forty-nine of 78 reported patients experienced a 35% reduction of obsessive-compulsive symptoms. Sixty-three percent of the patients are thus considered responders making DBS a promising technique. However, efficacy varied strongly, not only between different brain targets but also among patients targeted at the same area. Moreover, DBS at different targets appears to modulate different symptoms of OCD: VC/VS DBS improved mood, obsessions and compulsions whereas STN DBS predominantly improved compulsions. Another significant difference was the time to response between the different studies. In the
Table 1 Studies on deep brain stimulation in obsessive-compulsive disorder (OCD)

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Side</th>
<th>Target</th>
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<td>2006</td>
<td>Greenberg et al</td>
<td>Bilateral</td>
<td>Anterior limb of capsula interna</td>
<td>10</td>
</tr>
<tr>
<td>2008</td>
<td>Greenberg et al</td>
<td>Bilateral</td>
<td>Capsula interna/ ventral striatum</td>
<td>26</td>
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<tr>
<td>2010</td>
<td>Goodman et al</td>
<td>Bilateral</td>
<td>Capsula interna/ ventral striatum</td>
<td>6</td>
</tr>
<tr>
<td>2003</td>
<td>Sturm et al</td>
<td>Unilateral</td>
<td>Nucleus accumbens (right)</td>
<td>4</td>
</tr>
<tr>
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<td>Unilateral</td>
<td>Nucleus accumbens (right)</td>
<td>10</td>
</tr>
<tr>
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<td>Denys et al</td>
<td>Bilateral</td>
<td>Nucleus accumbens</td>
<td>16</td>
</tr>
<tr>
<td>2004</td>
<td>Aouizerate et al</td>
<td>Bilateral</td>
<td>Nucleus accumbens + caudate nucleus</td>
<td>1</td>
</tr>
<tr>
<td>2010</td>
<td>Franzini et al</td>
<td>Bilateral</td>
<td>Nucleus accumbens</td>
<td>2</td>
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<tr>
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<td>Mallet et al</td>
<td>Bilateral</td>
<td>Subthalamic nucleus</td>
<td>2</td>
</tr>
<tr>
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<td>1</td>
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<tr>
<td>2008</td>
<td>Mallet et al</td>
<td>Bilateral</td>
<td>Subthalamic nucleus</td>
<td>18</td>
</tr>
<tr>
<td>2009</td>
<td>Jiménez et al</td>
<td>Bilateral</td>
<td>Inferior thalamic peduncle</td>
<td>5</td>
</tr>
</tbody>
</table>

earlier studies, Mallet et al.\textsuperscript{10} and Nuttin et al.\textsuperscript{5,7} reported an acute relief of anxiety and obsessions whereas in the later studies of Nuttin et al., reduction of obsessions and compulsions was not observed until a week of stimulation.\textsuperscript{7} Sturm et al.\textsuperscript{19} reported onset of clinical improvement a few days to several weeks after the beginning of the stimulation. In the study from Abelson et al.,\textsuperscript{1} beneficial effects were seen within the three-week blinded study-period, whereas Mallet et al.\textsuperscript{20} reported improvement of symptoms after three months, Aouizerate et al.\textsuperscript{15} after nine months, and Franzini et al.\textsuperscript{7} only after one year up to two years.
2.3 MECHANISM OF ACTION OF DBS IN OCD

Since OCD has been associated with hyperactivity of the CSTC network,\textsuperscript{23} efficacy of DBS in OCD is most likely related to functional changes within this network. Electrical stimulation appears to be effective because it is assumed to induce a reset of network oscillatory patterns across the CSTC network.\textsuperscript{24} Studies in OCD combining DBS treatment with neuroimaging methods have confirmed changes within the CSTC network. A positron emission tomography (PET) study in six OCD patients, which was carried out two weeks after implantation of electrodes in the VC/VS demonstrated DBS-induced activation of the orbitofrontal cortex (OFC), anterior cingulate cortex, striatum, pallidus
and thalamus. It is of note, however, that at that moment no clinical effects of DBS had been occurred. Post-operative functional magnetic resonance imaging (MRI) in an OCD patient with ALIC DBS showed increased activity in the frontal cortex and striatum compared to pre-operative brain activity. In the same study, clinical response after three months of continuous stimulation was related to a relative decrease of hyperactivity in the OFC. A study by Abelson et al. showed decreased PET activity in the OFC after three to six weeks of ALIC DBS in two OCD responders, but not in the non-responders. In conclusion, sparse neuroimaging research suggests that DBS is effective in OCD because it induces functional changes, not limited to the target area, but observable in the complete CSTC network such as decreased activity in the OFC.

2.4 SIDE EFFECTS OF DBS IN OCD

Potential complications of DBS can arise (1) as a result of surgery (‘procedure related’), (2) due to the implanted device (‘device related’) or (3) due to stimulation or cessation of stimulation. A potential risk of surgery is intra-cerebral hemorrhage. This was reported in one out of ten patients by Greenberg et al. and in one patient in the sample of Mallet et al. One patient had a single intraoperative generalized tonic-clonic seizure following electrode implantation. Superficial surgical wound infection after implantation was reported in one of ten patients by Greenberg et al. and in two of sixteen patients by Mallet et al. In the latter study, the implanted electrodes had to be removed. Other studies did not mention procedure related complications. Device-related side effects were reported by Greenberg et al. where a break in the electrode and subcutaneous extension cable required a replacement in one patient. Also, patients have reported that they disturbingly feel the material within their body, to the extent that some patients wanted it to be removed (one out of four patients: Nuttin et al.). Side effects of stimulation can be divided in acute effects and effects of chronic stimulation. The latter can be subdivided in effects on mood, cognition and personality. Stimulation may cause various acute physical and mental side effects, most of which are transitory and disappear after adaptation of stimulation parameters. Okun et al. reported acute olfactory, gustatory and motor sensations which were strongly associated with the most ventral electrode positions, as well as physiological responses such as autonomic changes, increased breath rate, sweating, nausea, cold sensation, heat sensation, fear, and panic episodes. All effects reversed when DBS was stopped or parameters were changed. Acute mood changes during the first few days of stimulation of the ALIC and NAcc have been reported by Okun et al. such as transient sadness, anxiety, euphoria or giddiness, sometimes to the extent of hypomanic symptoms (five of ten patients: Greenberg et al.; two of ten patients: Huff et al.; four of six patients: Goodman et
al.12). Chronic mood improvement is an unintended but favorable side effect of DBS since most treatment-refractory OCD patients suffer from comorbid major depression. Patients start to laugh, experience blissful feelings and describe that they can see the world more bright and clear within seconds after stimulation. Abelson et al.5 reported improvement of depression in one out of four patients while stimulating the ALIC. Decreased depression scores following VC/VS stimulation were found by Greenberg et al.8 Anti-depressive effects seem to be especially related to DBS of the ventral striatum.12,16,17,20 No improvement of depression was found following STN stimulation.20

Apart from transient diminished concentration and verbal perseverations,18 DBS has not been associated with cognitive decline. Some patients did complain about memory and language problems but this has not been confirmed with neuropsychological tests. Gabriëls et al.,26 Abelson et al.,5 Aouizerate et al.,16 Goodman et al.12 and Greenberg et al.8 reported no decline in cognitive and executive functioning. On the contrary, in the latter study, a group analysis revealed significant improvements in memory recall. Gabriëls et al.26 reported no major adverse or harmful personality changes after one year of DBS using the Minnesota Multiphasic Personality Inventory (MMPI). Neither patients nor family members did report changes in personality in the study of Abelson et al.5 Finally, remission of alcohol dependency27 and unintended, effortless smoking cessation was observed following bilateral stimulation of the NAcc,28,29 supporting the idea of compulsivity with common circuitry in the processing of diverse rewards.

2.5 FOLLOW-UP TREATMENT

Although studies indicate that DBS has the potential to significantly improve OCD symptoms in treatment-refractory patients, they also show that complete remission rarely is achieved. In addition, patients often continue having problems in daily life functioning after DBS, even when most OCD symptoms have disappeared. Compulsions and avoidance behavior that have been around almost life-long in most treatment-refractory OCD patients may have become habitual. Therefore, follow-up treatment with behavioral therapy may be essential to motivate patients implementing the effects of DBS in their daily lives.3,26(Denys et al, in progress) Studies are needed to investigate the additional efficacy of behavioral therapy following DBS.

2.6 CONCLUSION

DBS has been applied in treatment-refractory OCD in an experimental setting for approximately a decade in approximately 80 patients. Stimulation of five different
targets resulted in variable efficacy, from no response till almost complete remission of symptoms. Overall, DBS in OCD may effectuate a decrease of 40 to 60% of symptoms in at least half of patients. Stimulating the VC/VS improves mood, obsessions and compulsions, whereas STN stimulation only improves compulsions. Most side effects are transitory and reverse after adaptation of stimulation parameters. The various stimulated brain areas, in many cases developed empirically, are still in agreement with recent theoretical findings on the neuroanatomy of OCD. DBS is probably effective in OCD because it modulates pathological activity within the CSTC network, resulting in a decrease of hyperactivity. DBS may be more effective when patients are followed up with behavioral therapy after surgery. DBS certainly has the potential of becoming preferential treatment for a specific group of seriously ill, treatment-refractory OCD patients, due to the small risk of the operation, the reversible nature of the technique, and the possibility to optimize treatment postoperatively.
REFERENCES


CHAPTER 3

DEEP BRAIN STIMULATION OF THE NUCLEUS ACCUMBENS FOR TREATMENT-REFRACTORY OBSESSIVE-COMPULSIVE DISORDER

Damiaan Denys, Mariska Mantione, Martijn Figee, Pepijn van den Munckhof, Frank Koerselman, Herman Westenberg, Andries Bosch, Rick Schuurman

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ABSTRACT

BACKGROUND
Obsessive-Compulsive Disorder (OCD) is a chronic psychiatric disorder that affects 2% of the general population. Even when the best available treatments are applied, approximately 10% of patients remain severely afflicted and run a long-term deteriorating course of OCD. The aim of the present study was to determine whether bilateral deep brain stimulation of the nucleus accumbens is an effective and safe treatment for treatment-refractory OCD.

METHODS
The study consisted of an open eight month treatment phase, followed by a double-blind cross-over phase with randomly assigned two-week periods of active and sham stimulation, ending with an open twelve month maintenance phase. Sixteen patients (age range, 18-65 years) with OCD according to DSM-IV criteria, meeting stringent criteria for refractoriness to treatment, were included in the study and underwent treatment with bilateral deep brain stimulation of the nucleus accumbens. Primary efficacy was assessed by change from baseline on the Yale-Brown obsessive-compulsive scale (Y-BOCS). A responder was defined by a decrease of at least 35% on the Y-BOCS.

RESULTS
In the open phase, the mean (SD) Y-BOCS score decreased by 46% from 33.7 (3.6) at baseline to 18.0 (11.4) after eight months (P< 0.01). Nine out of 16 patients were responders with a mean (SD) Y-BOCS score decrease of 23.7 (7.0), or 72%. In the double-blind, sham-controlled phase (n=14), the mean (SD) Y-BOCS score difference between active and sham stimulation was 8.3 (2.3) or 25% (P=0.04). Depression and anxiety decreased significantly. Except for mild forgetfulness and word-finding problems, no permanent adverse events were reported.

CONCLUSION
Bilateral deep brain stimulation of the nucleus accumbens may be an effective and safe treatment for treatment-refractory OCD.
3.1 INTRODUCTION

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by persistent thoughts (obsessions) and repetitive ritualistic behaviors (compulsions). It has an estimated lifetime prevalence of 2% and affects men and women equally. If left untreated, OCD can destroy a person’s capacity to function at work, socially, and even at home. Specific treatments for OCD have been developed, such as cognitive-behavioral therapy (CBT) and pharmacotherapy with serotonin reuptake inhibitors. It is estimated that these treatments provide an average 40–60% symptom reduction in half of patients. However, even when the best available treatments are applied, approximately 10% of patients remain severely affected and experience treatment-refractory OCD.1

For a small proportion of treatment-refractory patients, deep brain stimulation (DBS) may be appropriate. DBS is a neurosurgical treatment involving the implantation of electrodes, that send electrical impulses to specific locations in the brain, selected according to the type of symptoms to be addressed. Presently, there is evidence that DBS is effective in patients with treatment-refractory OCD when it is targeted to the anterior limb of the internal capsule, the ventral striatum, the nucleus accumbens, or the subthalamic nucleus.2–7 Since there is evidence of dysfunction of the reward system in OCD, DBS to the nucleus accumbens might be promising.8 In a pilot series, stimulation of the nucleus accumbens, which is thought to play a critical role in the pathophysiology of OCD, led to significant reduction in the severity of symptoms in three out of four patients.9

The objective of the present study was to confirm these results in a larger series. We also assessed the efficacy and tolerability of bilateral DBS of the nucleus accumbens in severely disabled patients with treatment-refractory OCD.

3.2 METHODS

PATIENTS

Patients were recruited from the outpatient clinic for anxiety disorders at our university hospital. All patients consented to participate in this study and signed an informed consent form. The Medical Ethical Review committee of our hospital approved the study, which was registered under trial number ISRCTN23255677 in the international controlled trial registry.

INCLUSION CRITERIA

Participants were female or male outpatients, aged between 18 and 65 years, who were
diagnosed with primary OCD according to the DSM-IV criteria, using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I). Only patients with a score of at least 28 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), measured twice at least two weeks apart, were included in the study. Patients were required to have at least a five year history of OCD, and to experience substantial functional impairment according to the DSM-IV criterion C, and a Global Assessment of Function (GAF) score of 45 or less. Refractoriness to treatment was defined as no response or insufficient response following at least two treatments with a selective serotonin reuptake inhibitor (SSRI) at maximum dosage for at least 12 weeks, plus one treatment with clomipramine at maximum dose for at least 12 weeks with assessment of plasma levels to control for sufficient bioavailability, plus at least one augmentation trial with an atypical antipsychotic for eight weeks in combination with an SSRI, plus at least one CBT trial for a minimum of 16 sessions.

EXCLUSION CRITERIA
Except for those with major depressive disorder and mild anxiety disorders, patients with clinically significant comorbid DSM-IV diagnoses (such as schizophrenia, bipolar II disorder, alcohol or substance abuse in the last 6 months, current tic disorder and body dysmorphic disorder) were excluded from the study. Patients with severe personality disorders, assessed using the Structured Clinical Interview for DSM-IV Axis II disorders (SCID-II), were excluded. Other reasons for exclusion were clinically significant and unstable neurological or medical illnesses.

STUDY DESIGN
The study consisted of three sequential treatment phases. After electrode implantation, patients entered an open phase of eight months during which they were evaluated every two weeks for severity of symptoms and optimal stimulation parameters. Once an initial and substantial decrease (on average six points) in Y-BOCS score had been obtained, which was usually after 8 weeks of stimulation, a standardized CBT program was added. Since OCD is a context-related disorder, it is common for OCD patients to actively avoid stimuli or social contexts in order to cope with their disease. To realize the full potential of the DBS treatment, the program was designed to confront patients with their feared stimuli and consequently force patients to deal with their obsessive-compulsive symptoms. Treatment with CBT consisted of weekly individual sessions of 60 minutes for 24 weeks and was conducted by a cognitive behavioural therapist and a trained nurse. After the open phase, patients entered a one month, double-blind, sham-controlled phase. Patients were randomly allocated to two periods of two weeks with the stimulators blindly turned on (active stimulation) in one period and turned off (sham stimulation) in the other. Block-randomization was used with computer-
generated random sequence, providing adequate concealment. Patients were assessed three times (at baseline, after a two week period of active or sham stimulation, and after the second two week period of reversed active or sham stimulation). The assessor was blind to stimulation conditions. Treatment with CBT was continued during the cross-over period. The ensuing maintenance phase lasted twelve months, during which patients were evaluated at three-month intervals. The stimulators were turned on for all patients and stimulation parameters were adjusted if necessary.

SURGICAL PROCEDURE
The implantation of the electrodes was performed according to standard stereotactic procedures using frame-based MRI for target determination. All patients underwent bilateral implantation of four-contact electrodes (model 3389; Medtronic, Minneapolis), with contact points being 1.5 mm long and separated from adjacent contacts by 0.5 mm. The contacts are coded from 0 (ventral) to 3 (dorsal) and are independently programmable. Target coordinates for the electrode tip were 7 mm lateral to the midline, 3 mm anterior to the anterior border of the anterior commissure, and 4 mm inferior to the intercommissural line. Electrodes were implanted following the anterior limb of the internal capsule into the target nucleus, with an anterior angle of approximately 75° to the intercommissural line. The target coordinates were uniformly used in all patients, as there was not yet a rationale available for relative positioning within the nucleus accumbens, given the individual variation of anatomy in relation to the stereotactic atlases. Electrodes were connected via subcutaneous extensions to stimulators (Soletra; Medtronic, Minneapolis) placed bilaterally in an infraclavicular pocket under general anesthesia. Post-operative frame-based computed tomography images (n=9) or plain X-rays (n=7) were used to verify the position of the implanted electrodes, which were all located at a distance from the intended target smaller than the size of the electrode contact, with an error within the limits of precision of the imaging technique. To restrict the variability of the study design, stimulation parameters were standardized to a frequency of 130 Hz and a pulse width of 90 µsec. Optimization was limited to changes in active contact points and voltage, ranging to a maximum 5.0 V.

OUTCOME MEASURES
Obsessive-compulsive symptoms were measured with the Y-BOCS with scores ranging from 0 to 40; higher scores indicated more severe symptoms. Patients were defined as a responder if they had a decrease on the Y-BOCS of at least 35%. Depression was rated with the 17-item Hamilton Rating scale for Depression (HAM-D), and anxiety was evaluated with the Hamilton Anxiety Scale (HAM-A). The Brown Assessment of Belief Scale (BABS) was used to assess delusional characteristics of obsessions. The Sheehan Disability
Scale (SDS)\textsuperscript{17} was used to assess overall symptomatic and functional impairment; the SDS consists of three separate ratings which evaluate the effect of symptoms on work, social life, and family life. A trained blind investigator completed the scales at baseline and at each visit. Information on adverse events was derived during each visit by questioning the subjects in general terms, by spontaneous reports of the subjects or by observation. Any change of behavior reported by the patient was rated as an adverse event.

**STATISTICAL ANALYSIS**

The sample size was based on the assumption that a mean (SD) reduction of 9 (6) points on the Y-BOCS (based on drug studies\textsuperscript{1}) is a clinically relevant response, and that a placebo response in this treatment refractory group will be close to zero. Therefore, 16 patients were judged to be sufficient to assess the potential efficacy of this procedure with a type I error of 0.05 and a type II error of 0.8.

In the open phase, the primary outcome measure (the Y-BOCS score) was analyzed for all patients using a paired t-test. Categorical analyses determined the number of responders based on at least a 35% decrease in the Y-BOCS score. Pearson $\chi^2$, Fisher’s exact tests, or one-way ANOVAs were used to compare clinical characteristics and responders rates for the treatment groups. In the blinded, sham controlled phase, the absolute difference between active and sham stimulation in the whole group was calculated by comparing the endpoint of week 3-4 in the on-off group and of week 1-2 in the off-on group with the endpoint of week 1-2 in the on-off group and of week 3-4 in the off-on group, using a paired t-test. To control for period effects, we used a mixed model regression analysis in line with that by Diaz-Uriarte\textsuperscript{18} with Y-BOCS weekly comparison cores as dependent variables and with period and treatment as independent variables. Dependency between data at weeks 1 and 2 vs at weeks 3 and 4 is modeled by a compound symmetry covariance matrix specification. The interaction term treatment x period tests for carry-over effects. An analogous procedure was performed for the HAM-A and the HAM-D. Data are presented as mean (SD) at 2-tailed 5\% level of significance. All statistical analyses were conducted using commercially available statistical software (SPSS, version 16.0; SPSS Inc, Chicago, Illinois).

### 3.3 RESULTS

**DEMOGRAPHIC AND CLINICAL CHARACTERISTICS**

One hundred and one patients were screened for eligibility, and 16 were included in this study (Figure 1). The demographic and clinical characteristics of the sample are summarized in Table 1. Patient 4 fulfilled the DSM-IV criteria for obsessive-compulsive and avoidant personality disorder. To cover different subtypes of OCD, we deliberately
included patients with a wide diversity of content and type of obsessive-compulsive symptoms.

**OUTCOME MEASURES OF THE OPEN PHASE**

Stimulation in the open phase resulted in a mean Y-BOCS decrease of 15.7 (10.8) (95% confidence interval [CI], 9.9-21.5) points (46%) (P<0.01) (Table 2). A categorical analysis revealed nine patients with at least a 35% decrease on the Y-BOCS with a mean decrease of 23.7 (7.0) points (72%), compared with a mean decrease of 5.4 (3.1) points (24%) in the non-responder group. In the open phase, six out of 16 patients reached a final Y-BOCS score below 10 (mean decrease of 81%), three patients reached a final Y-BOCS score between 10 and 20 (mean decrease of 51%), three patients ended up with a final Y-BOCS score between 20 and 30 (mean decrease of 22%), and four patients stayed above a Y-BOCS score of 30 (mean decrease of 10%). None of the patients worsened under stimulation. To test which electrode contacts were to be used, all patients started with monopolar stimulation with ventral contacts 0 and 1 set negative and case (i.e. battery) set positive, at which setting no changes were observed in any of the patients. In all patients, active contacts were then switched to the dorsal contracts 2 and 3 after two weeks of stimulation, after which the improvements described in the paper were achieved. Contacts used were limited to a change from contact 0 and 1 to contact 2 and 3 at 2 weeks after implantation. Voltage ranged from 3.5 V to maximum 5.0 V with

![Figure 1](image.png)

**Figure 1** Change in absolute Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Hamilton Anxiety Scale (HAM-A), and Hamilton Scale for Depression (HAM-D) scores across the study (84 weeks). A, Change in the open phase (32 weeks). B, Summed increases (weeks 32-34) and decreases (weeks 34-36) during the crossover phase. C, Changes in the maintenance phase (weeks 36-84).
Table 1 Baseline demographic and clinical characteristics of the allocated sample

<table>
<thead>
<tr>
<th>Patient No./Sex/Age/y</th>
<th>Age at onset, y</th>
<th>Duration of illness, y</th>
<th>Axis I comorbidity</th>
<th>Obsessions</th>
<th>Compulsions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/54</td>
<td>21</td>
<td>33</td>
<td>-</td>
<td>Believing in magic numbers</td>
<td>Counting, walking with right foot over lines</td>
</tr>
<tr>
<td>2/M/44</td>
<td>10</td>
<td>34</td>
<td>MDD</td>
<td>Fear of contamination, intrusive images of sex and violence</td>
<td>Washing, cleaning, seeking reassurance</td>
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<tr>
<td>3/M/51</td>
<td>13</td>
<td>38</td>
<td>MDD</td>
<td>Fear of contamination</td>
<td>Washing</td>
</tr>
<tr>
<td>4/F/26</td>
<td>5</td>
<td>21</td>
<td>Dysthymia</td>
<td>Perfectionism</td>
<td>Obsessional slowness, recurring acts</td>
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<tr>
<td>5/M/40</td>
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<td>37</td>
<td>MDD</td>
<td>Fear of harming others, fear of contamination</td>
<td>Checking, washing</td>
</tr>
<tr>
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<td>4</td>
<td>50</td>
<td>MDD</td>
<td>Fear of contamination</td>
<td>Washing, cleaning</td>
</tr>
<tr>
<td>7/F/21</td>
<td>13</td>
<td>8</td>
<td>-</td>
<td>Fear of contamination, fear of harming others</td>
<td>Checking, mental compulsions</td>
</tr>
<tr>
<td>8/F/34</td>
<td>14</td>
<td>20</td>
<td>-</td>
<td>Fear of contamination, perfectionism</td>
<td>Washing, cleaning</td>
</tr>
<tr>
<td>9/M/35</td>
<td>16</td>
<td>19</td>
<td>MDD</td>
<td>Need for symmetry, perfectionism ‘Just right’ behavior</td>
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<td>10/F/32</td>
<td>18</td>
<td>14</td>
<td>-</td>
<td>Believing in magic numbers, fear of predictions</td>
<td>Seeking reassurance</td>
</tr>
<tr>
<td>11/F/45</td>
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<td>25</td>
<td>Panic Disorder</td>
<td>Fear of dirt, need for symmetry</td>
<td>Cleaning, ordering</td>
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<td>12/M/59</td>
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<td>46</td>
<td>-</td>
<td>Fear of coincidence and illogical things</td>
<td>Seeking reassurance, hoarding</td>
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<tr>
<td>13/M/35</td>
<td>14</td>
<td>21</td>
<td>-</td>
<td>Somatic obsessions</td>
<td>Checking</td>
</tr>
<tr>
<td>14/M/42</td>
<td>12</td>
<td>30</td>
<td>-</td>
<td>Fear of contamination</td>
<td>Washing, cleaning</td>
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<tr>
<td>15/M/55</td>
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<td>20</td>
<td>MDD</td>
<td>Fear of contamination, intrusive images of sex and violence, need for symmetry</td>
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<tr>
<td>16/M/54</td>
<td>6</td>
<td>48</td>
<td>-</td>
<td>Need to know everything</td>
<td>Hoarding</td>
</tr>
</tbody>
</table>

A mean voltage setting of 4.3 V. With the voltage set at 3.5 V, the mean life span of the batteries is estimated to be 2 years. With amplitudes higher than 3.7 V the mean life span of the batteries was between 1 year and 2 months and 2 years.

There were no differences in the demographic and clinical characteristics between responders and non-responders, except for the content of the OCD symptoms. Patients suffering from egosyntonic obsessive-compulsive symptoms such as perfectionism, the need for symmetry and hoarding (patients 4, 9, 10 and 16) had a mean decrease of 10% on the Y-BOCS. At baseline, these 4 patients scored significantly higher on the BABS, 11.5 (2.5) versus 6.6 (5.8) (P=0.04) (BABS, 95% CI, 0.3-9.5). Baseline scores, end point scores and the mean changes on the HAM-A, HAM-D, BABS and SDS are listed in Table 2. A significant decrease was observed in all outcome measures.
<table>
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<th>Drug therapy (mg)</th>
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<th># previous CBT trials</th>
<th>Y-BOCS</th>
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<td>paroxetine 60, risperdal 1.5</td>
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<td>21</td>
</tr>
<tr>
<td>clomipramine 125, haloperidol 5</td>
<td>8</td>
<td>2</td>
<td>30</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>paroxetine 60, quetiapine 250</td>
<td>5</td>
<td>1</td>
<td>38</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>citalopram 60, quetiapine 300</td>
<td>4</td>
<td>2</td>
<td>33</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>mirtazepine 45</td>
<td>9</td>
<td>6</td>
<td>35</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>citalopram 60, quetiapine 300</td>
<td>6</td>
<td>3</td>
<td>28</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>-</td>
<td>3</td>
<td>4</td>
<td>29</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td>clomipramine 225, quetiapine 600</td>
<td>5</td>
<td>1</td>
<td>32</td>
<td>18</td>
<td>23</td>
</tr>
</tbody>
</table>

**OUTCOME MEASURES OF THE DOUBLE-BLIND, SHAM-CONTROLLED PHASE**

In the original protocol, a cross-over period of three months was planned, but after the noted effects of stimulation in the open phase, it was deemed impossible to acquire continuing patient cooperation for a period of three months of sham stimulation. Even with this shortened cross-over period, one patient 7 refused to participate in the double-blind, sham-controlled phase because of the risk of losing the improvements gained during the open phase (Y-BOCS decrease of 90%). Patient 9 refused to participate because of disappointment due to lack of efficacy (Y-BOCS decrease of 23%). Therefore, 14 of the 16 patients entered phase II of the study. The mean difference between active and sham stimulation in the whole sample on the Y-BOCS was 8.8 (9.1) (95% CI, 3.6-14.1) points (P=.003) (Table 3). Because we found no carry-over effect (P=.32 for treatment by
### Table 2
Changes in OCD, anxiety, depression, delusional characteristics of obsessions, and overall symptomatic and functional impairment during the open-label and maintenance period of the study.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>8 months</th>
<th>Mean change open period (%)</th>
<th>Confidence Interval</th>
<th>P-value</th>
<th>cross-over period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y-BOCS total</td>
<td>33.7 ± 3.6</td>
<td>18.0 ± 11.4</td>
<td>15.7 ± 10.8 (46%)</td>
<td>9.9 – 21.5</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Obsessions</td>
<td>16.9 ± 1.9</td>
<td>8.3 ± 5.8</td>
<td>8.5 ± 5.6 (50%)</td>
<td>5.5 – 11.5</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Compulsions</td>
<td>16.9 ± 1.8</td>
<td>9.7 ± 5.7</td>
<td>7.2 ± 5.5 (43%)</td>
<td>4.1 – 10.0</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>HAM-A</td>
<td>20.9 ± 5.9</td>
<td>10.1 ± 8.3</td>
<td>10.7 ± 8.1 (51%)</td>
<td>6.4 – 15.0</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>HAM-D</td>
<td>19.5 ± 6.7</td>
<td>10.5 ± 7.8</td>
<td>9.0 ± 6.2 (46%)</td>
<td>5.6 – 12.3</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>BABS</td>
<td>7.8 ± 5.6</td>
<td>4.1 ± 5.0</td>
<td>3.7 ± 5.5 (47%)</td>
<td>0.8 – 6.6</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>SDS work</td>
<td>8.9 ± 1.1</td>
<td>6.0 ± 3.5</td>
<td>2.9 ± 3.1 (32%)</td>
<td>1.2 – 4.6</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>SDS social life</td>
<td>9.0 ± 1.0</td>
<td>5.2 ± 3.3</td>
<td>3.7 ± 2.5 (41%)</td>
<td>1.9 – 5.5</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>SDS family life</td>
<td>7.9 ± 1.5</td>
<td>5.0 ± 3.5</td>
<td>1.4 ± 2.7 (17%)</td>
<td>1.4 – 4.3</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3
Changes in OCD, anxiety, depression, delusional characteristics of obsessions, and overall symptomatic and functional impairment during the open-label and maintenance period of the study.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Start of cross-over</th>
<th>Week 1 - 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>After 8 months of stimulation</td>
<td>After stimulation off</td>
</tr>
<tr>
<td>n = 6</td>
<td></td>
<td>After stimulation on</td>
<td></td>
</tr>
<tr>
<td>Y-BOCS total</td>
<td>34.2 ± 3.6</td>
<td>23.3 ± 9.9</td>
<td>25.8 ± 9.3</td>
</tr>
<tr>
<td>Obsessions</td>
<td>17.5 ± 1.7</td>
<td>11.8 ± 4.7</td>
<td>13.0 ± 4.5</td>
</tr>
<tr>
<td>Compulsions</td>
<td>16.7 ± 2.0</td>
<td>11.5 ± 5.2</td>
<td>12.8 ± 4.7</td>
</tr>
<tr>
<td>HAM-A</td>
<td>21.3 ± 7.7</td>
<td>12.0 ± 8.0</td>
<td>14.3 ± 6.9</td>
</tr>
<tr>
<td>HAM-D</td>
<td>19.7 ± 5.4</td>
<td>10.8 ± 7.0</td>
<td>12.7 ± 5.4</td>
</tr>
<tr>
<td>n = 8</td>
<td></td>
<td>After 8 months of stimulation</td>
<td>After stimulation off</td>
</tr>
<tr>
<td>Y-BOCS total</td>
<td>33.4 ± 3.6</td>
<td>18.7 ± 10.6</td>
<td>29.5 ± 11.4</td>
</tr>
<tr>
<td>Obsessions</td>
<td>16.4 ± 2.1</td>
<td>8.7 ± 5.5</td>
<td>15.2 ± 5.9</td>
</tr>
<tr>
<td>Compulsions</td>
<td>17.0 ± 1.7</td>
<td>10.0 ± 5.3</td>
<td>14.2 ± 5.6</td>
</tr>
<tr>
<td>HAM-A</td>
<td>21.5 ± 4.9</td>
<td>14.2 ± 5.8</td>
<td>27.4 ± 12.0</td>
</tr>
<tr>
<td>HAM-D</td>
<td>21.0 ± 6.5</td>
<td>14.6 ± 5.8</td>
<td>24.6 ± 9.9</td>
</tr>
</tbody>
</table>

-48-
### Table 1: y-BOCS mean change over time

<table>
<thead>
<tr>
<th>Period</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
<th>21 months</th>
<th>Mean change maintenance period (%)</th>
<th>Confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessions</td>
<td>16.9 ± 1.9</td>
<td>9.7 ± 5.9</td>
<td>7.3 ± 0.8</td>
<td>8.9 ± 5.4</td>
<td>12.0 ± 9.3 (57%)</td>
<td>30.7 – 3.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Compulsions</td>
<td>16.9 ± 1.8</td>
<td>10.3 ± 7.3</td>
<td>9.1 ± 6.1</td>
<td>8.9 ± 6.0</td>
<td>10.7 ± 9.1 (55%)</td>
<td>13.1 – 22.0</td>
<td>0.001</td>
</tr>
<tr>
<td>y-BOCS total</td>
<td>34.2 ± 3.6</td>
<td>21.0 ± 3.2</td>
<td>17.0 ± 3.6</td>
<td>22.2 ± 2.6</td>
<td>23.6 ± 2.5 (49%)</td>
<td>23.1 – 4.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Obsessions</td>
<td>17.5 ± 2.1</td>
<td>11.9 ± 3.4</td>
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<td>0.001</td>
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<tr>
<td>Compulsions</td>
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<td>9.0 ± 5.7</td>
<td>8.7 ± 4.7</td>
<td>8.7 ± 4.7 (52%)</td>
<td>5.8 – 15.5</td>
<td>0.001</td>
</tr>
<tr>
<td>y-BOCS total</td>
<td>33.4 ± 3.6</td>
<td>20.7 ± 3.2</td>
<td>16.8 ± 3.6</td>
<td>21.4 ± 2.6</td>
<td>22.3 ± 2.5 (49%)</td>
<td>25.8 – 3.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 2: y-BOCS mean change over time

<table>
<thead>
<tr>
<th>Period</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
<th>21 months</th>
<th>Mean change maintenance period (%)</th>
<th>Confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessions</td>
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<td>9.7 ± 5.9</td>
<td>7.3 ± 0.8</td>
<td>8.9 ± 5.4</td>
<td>12.0 ± 9.3 (57%)</td>
<td>30.7 – 3.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Compulsions</td>
<td>16.9 ± 1.8</td>
<td>10.3 ± 7.3</td>
<td>9.1 ± 6.1</td>
<td>8.9 ± 6.0</td>
<td>10.7 ± 9.1 (55%)</td>
<td>13.1 – 22.0</td>
<td>0.001</td>
</tr>
<tr>
<td>y-BOCS total</td>
<td>34.2 ± 3.6</td>
<td>21.0 ± 3.2</td>
<td>17.0 ± 3.6</td>
<td>22.2 ± 2.6</td>
<td>23.6 ± 2.5 (49%)</td>
<td>23.1 – 4.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Obsessions</td>
<td>17.5 ± 2.1</td>
<td>11.9 ± 3.4</td>
<td>7.3 ± 0.8</td>
<td>8.9 ± 5.4</td>
<td>12.0 ± 9.3 (57%)</td>
<td>30.7 – 3.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Compulsions</td>
<td>16.7 ± 2.0</td>
<td>10.0 ± 6.1</td>
<td>9.0 ± 5.7</td>
<td>8.7 ± 4.7</td>
<td>8.7 ± 4.7 (52%)</td>
<td>5.8 – 15.5</td>
<td>0.001</td>
</tr>
<tr>
<td>y-BOCS total</td>
<td>33.4 ± 3.6</td>
<td>20.7 ± 3.2</td>
<td>16.8 ± 3.6</td>
<td>21.4 ± 2.6</td>
<td>22.3 ± 2.5 (49%)</td>
<td>25.8 – 3.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 3: y-BOCS mean change over time

<table>
<thead>
<tr>
<th>Week 3 - 4</th>
<th>Mean change</th>
<th>Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After stimulation off</td>
<td>30.7 ± 4.5</td>
<td>4.8 ± 7.6</td>
<td>-12.9 – 3.2</td>
</tr>
<tr>
<td>15.3 ± 2.3</td>
<td>2.3 ± 3.6</td>
<td>-6.1 – 1.4</td>
<td>0.175</td>
</tr>
<tr>
<td>15.3 ± 2.4</td>
<td>2.5 ± 4.2</td>
<td>-6.9 – 1.9</td>
<td>0.203</td>
</tr>
<tr>
<td>26.3 ± 9.2</td>
<td>12.0 ± 10.8</td>
<td>-23.3 – -0.7</td>
<td>0.042</td>
</tr>
<tr>
<td>23.5 ± 3.6</td>
<td>10.8 ± 6.0</td>
<td>-17.1 – -4.5</td>
<td>0.007</td>
</tr>
<tr>
<td>After stimulation on</td>
<td>17.6 ± 10.1</td>
<td>11.8 ± 9.3</td>
<td>4.0 – 19.7</td>
</tr>
<tr>
<td>8.0 ± 5.4</td>
<td>7.2 ± 5.5</td>
<td>2.6 – 11.8</td>
<td>0.007</td>
</tr>
<tr>
<td>9.6 ± 4.8</td>
<td>4.6 ± 4.0</td>
<td>1.2 – 8.0</td>
<td>0.015</td>
</tr>
<tr>
<td>15.2 ± 13.5</td>
<td>12.1 ± 8.4</td>
<td>5.0 – 19.2</td>
<td>0.005</td>
</tr>
<tr>
<td>12.9 ± 10.1</td>
<td>11.7 ± 8.4</td>
<td>4.7 – 18.7</td>
<td>0.005</td>
</tr>
</tbody>
</table>
period interaction), the effect of stimulation on Y-BOCS score was assessed using a mixed model regression analysis with treatment and period as independent variables. After correction for period effects, treatment (stimulation) caused a substantial (mean 8.3 [2.3] points [25%]) and statistical significant (P = .004) reduction in the Y-BOCS total score. Adding pre randomization Y-BOCS score as a covariate (to adjust for initial differences between sequence groups) had no effect on the treatment effect estimate nor on its SD. The mean difference in HAM-A scorer between active and sham stimulation was 12.1 (9.1) (95% CI, 6.8-17.3) (P<.01); the mean difference in HAM-D scores between active and sham stimulation was 11.3 (7.2) (95% CI, 7.1-15.5) (P<.01). Due to hypomania, or abrupt worsening of symptoms the blinded status of the stimulators was lifted for most, but not all patients. The status of the stimulators remained unclear for patients 4, 11, 12 and 16, in whom the effect of stimulation was not subjectively noticeable.

OUTCOME MEASURES OF THE MAINTENANCE PHASE
As summarized in Table 2, the improvement observed in the open phase was sustained over the twelve months maintenance phase, in which all outcome measures showed a statistically significant mean reduction versus preoperative baseline. It is of note that Y-BOCS scores throughout the study and at the endpoint were significantly associated with HAM-A scores (rho= 0.772; P= 0.001) and HAM-D scores (rho= 0.745; P= 0.001), suggesting a strong relationship between change in obsessive-compulsive and anxiety and mood symptoms.

TOLERABILITY AND SIDE EFFECTS
All reported adverse events are presented in Table 4, regardless of their relationship with the treatment procedure. The most prominent transient adverse event related to stimulation was elevated mood or hypomania. This occurred shortly after the switch of the contact points from 0-1 to 2-3 and lasted for two days. Elevated mood or hypomania never required the addition of a mood stabilizer and the adverse event was rated as mild. Elevated mood was frequently reported during reactivation of the stimulation after an off period. Permanent adverse events were all related to stimulation and disappeared during the off phases. Increased libido was reported by seven patients, but this was not experienced as uncomfortable. Mild forgetfulness was reported by five patients and word-finding problems by three patients. An extensive neuropsychological test battery was performed in the DBS- treated sample and in a control sample at fixed time points (pre- and post-operatively, at the double-blind cross-over phase, and at the end of the maintenance phase). Given the extensiveness of the data, the outcome of the neuropsychological effects will be published in a separate article.
### Table 4 Number of patients reporting permanent and transient side effects

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Transient</th>
<th>Permanent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery related effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound infection at incision</td>
<td>1 (pt 11)</td>
<td>0</td>
</tr>
<tr>
<td>Tiredness</td>
<td>4 (pt 2, 5, 7, 11)</td>
<td>0</td>
</tr>
<tr>
<td>Feeling of numbness at incision site</td>
<td>7 (pt 2, 4, 6, 8, 9, 11, 12)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (pt 7)</td>
<td>0</td>
</tr>
<tr>
<td>Headaches</td>
<td>2 (pt 9, 16)</td>
<td>0</td>
</tr>
<tr>
<td>Increase in depressive symptoms</td>
<td>2 (pt 5, 9)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Device related effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling of extension leads (mainly with stress)</td>
<td>7 (pt 2, 3, 4, 5, 7, 10, 12)</td>
<td>1 (pt 8)</td>
</tr>
<tr>
<td>Feeling of electric current around neurostimulator</td>
<td>3 (pt 3, 6, 14)</td>
<td>0</td>
</tr>
<tr>
<td>Feeling of neurostimulator in chest</td>
<td>0</td>
<td>3 (pt 7, 8, 10)</td>
</tr>
<tr>
<td><strong>Stimulation related effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypomanic symptoms</td>
<td>8 (pt 2, 4, 5, 11, 12, 13, 14, 15)</td>
<td>0</td>
</tr>
<tr>
<td>Headaches</td>
<td>3 (pt 2, 3, 5)</td>
<td>0</td>
</tr>
<tr>
<td>Cold shivers</td>
<td>2 (pt 3, 4)</td>
<td>0</td>
</tr>
<tr>
<td>Sexual intrusions</td>
<td>1 (pt 3)</td>
<td>0</td>
</tr>
<tr>
<td>Stomach aches</td>
<td>4 (pt 3, 5, 6, 14)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (pt 5)</td>
<td>0</td>
</tr>
<tr>
<td>Taste reduction</td>
<td>3 (pt 5, 8, 16)</td>
<td>0</td>
</tr>
<tr>
<td>Feeling that the face is asymmetrical</td>
<td>1 (pt 5)</td>
<td>0</td>
</tr>
<tr>
<td>Itch in right arm</td>
<td>1 (pt 5)</td>
<td>0</td>
</tr>
<tr>
<td>Menstruation after one year of menopause</td>
<td>1 (pt 6)</td>
<td>0</td>
</tr>
<tr>
<td>Menstruation after 4 years of contraceptive injection</td>
<td>1 (pt 7)</td>
<td>0</td>
</tr>
<tr>
<td>Less blood flow during menstruation</td>
<td>1 (pt 6)</td>
<td>0</td>
</tr>
<tr>
<td>Increase in allergy</td>
<td>1 (pt 7)</td>
<td>0</td>
</tr>
<tr>
<td>Difficulty to reach an orgasm (only at higher voltages)</td>
<td>1 (pt 13)</td>
<td>0</td>
</tr>
<tr>
<td>Increased libido</td>
<td>0</td>
<td>7 (pt 2, 3, 4, 5, 12, 14, 15)</td>
</tr>
<tr>
<td>Increase in sneezing</td>
<td>1 (pt 16)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (pt 7, 10)</td>
<td>0</td>
</tr>
<tr>
<td>Difficulty falling asleep</td>
<td>3 (pt 4, 8,12)</td>
<td>0</td>
</tr>
<tr>
<td>Micturition problems (enuresis, polyuria)</td>
<td>0</td>
<td>2 (pt 1, 12)</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>1 (pt 8)</td>
<td>5 (pt 2, 5, 12, 14, 16)</td>
</tr>
<tr>
<td>Difficulty finding words</td>
<td>0</td>
<td>3 (pt 8, 14, 16)</td>
</tr>
<tr>
<td>Paresthesias in hands and/or feet</td>
<td>3 (pt 4, 11, 16)</td>
<td>0</td>
</tr>
</tbody>
</table>
3.4 DISCUSSION

To our knowledge, this study is the first double-blind, sham-controlled trial to demonstrate that bilateral stimulation of the nucleus accumbens can be an effective and safe treatment in treatment-refractory OCD patients. All patients underwent electrode implantation in the same target area, and stimulation settings were applied uniformly throughout the study. During the treatment period of 21 months, obsessive-compulsive symptoms decreased by 52%, and nine out of sixteen patients responded with a mean improvement of 72%. Anxiety and depressive symptoms decreased by half. The surgical procedure and stimulation were well tolerated. Permanent adverse events were limited to mild forgetfulness and word-finding problems. Increased libido was reported by several patients, but may be interpreted as a return to normal functioning rather than an adverse event.

Our results are consistent with previous reports on DBS in treatment-refractory OCD patients. Greenberg et al. described 26 OCD patients, in whom targeting was progressively more posterior over time, moving from the internal capsule to the ventral striatum. On average, they observed a decrease of 12.5 points on the Y-BOCS, a 53% decrease in HAM-A scores, and a 40.0% decrease in HAM-D scores, with better results obtained with more posteriorly located electrodes, comparable to our surgical target. In the recent study by Mallet et al., 16 OCD-patients were stimulated bilaterally in the subthalamic nucleus. The mean Y-BOCS change between sham and active stimulation was 8.9 points. Contrary to our results, neither anxiety and depression scales nor functional impairment (measured by the Sheehan Disability Scale) showed improvement. Transient hypomania has been a consistent finding in DBS for OCD, as was also seen in our study. We did not observe deterioration of depression or suicidal ideation as had been previously reported.

In the blinded, sham-controlled phase, there was a difference between patients who were assigned to the stimulation on-off group versus the patients who were assigned to the stimulation off-on group. The patients whose stimulators were turned off in the first two weeks immediately experienced an increase of symptoms and then rapidly regained clinical improvement during the ensuing blinded active stimulation. Patients who continued having active stimulation during the first two weeks showed a minor increase in obsessive-compulsive symptoms, probably due to uncertainty and doubt about entering the blinded phase of the study. In this group, the baseline Y-BOCS scores at the start of the cross-over period were higher, which was in part explained by the higher proportion of non-responders from the open phase. Four of six were non-responders in the on-off group versus two of eight in the off-on group. These factors, along with small sample size, may have contributed to the non-significant difference between active and sham stimulation in the on-off group. The changes on the HAM-A
and HAM-D were statistically significant, suggesting a more robust and immediate effect on anxiety and mood than on obsessive-compulsive symptoms.

The beneficial effects on mood and anxiety, along with improvement in obsessions and compulsions, are striking. All patients, even non-responders, experienced substantial mood improvement. Therefore, none of the patients requested to discontinue stimulation, despite lack of response of obsessive-compulsive symptoms. It is not unlikely that improvement of obsessive-compulsive symptoms depends upon changes in mood and anxiety. We observed in our sample a fixed pattern in treatment response and time of onset of response. Symptoms decreased in a sequential order (depressive symptoms first, anxiety symptoms second, obsessions third, and compulsions fourth), and in a fixed time sequence (mood improved within seconds, anxiety within minutes, obsessions within days, and compulsions took weeks and even months to improve). Finally, avoidance failed to decrease spontaneously and required CBT to disappear. For most patients in this study, compulsive behaviour and avoidance had been present for decades; they gradually became part of a ‘normal’ daily pattern and a force of habit. CBT proved itself particularly in decreasing compulsive behavior and avoidance. Interestingly, without stimulation (such as in the placebo-controlled phase) the gained successes with the addition of CBT disappeared rapidly, suggesting that efficacy of CBT depends upon stimulation. Our observation of an immediate and profound effect with accumbens stimulation, along with the reported specific effect of STN stimulation on compulsions, observed in the French sample, hints at the involvement of two different anatomical circuits in OCD. One circuit might be associated with a mood-anxiety spectrum responding to accumbens stimulation, and a second circuit could be related to a compulsive-habit spectrum responding to subthalamic nucleus stimulation.

Obsessions and compulsions are heterogeneous symptoms and a large body of work has delineated subtypes for OCD. We found a clear relation between DBS non-response and type of OCD. Patients with perfectionism, hoarding or symmetry did not respond well to the treatment. Patients with this subtype of OCD believe in the worthiness and soundness of their symptoms and were more likely to describe their obsessions and compulsions as egosyntonic, in harmony with the needs and goals of themselves and consistent with oneself. The robustness of their obsessions and lack of insight into the meaninglessness of their obsessions was expressed in higher BABS-scores, the only baseline score that was significantly different from baseline scores of other patients. High baseline scores on the BABS predicted non-response in our sample, and may be of value for selection of patients.

The great appeal of DBS in comparison with lesions is that it permits focal and adjustable
modulation of the brain. In our sample, improvement was observed using only the dorsal electrode contacts 2 and 3, with active stimulation more in the area of the nucleus accumbens core around the border with the internal capsule and bed nucleus stria terminalis rather than in the shell of the accumbens as previously published.9 The difference in location of the center of the brain tissue volume that is being stimulated between the lower en upper contacts with the 3389 electrode is four millimeters, and seemed to determine non-response or response in our sample. This finding clearly demonstrates the significance and importance of exact targeting with DBS. In future studies, larger samples are needed to further narrow the ‘target space’ so that the most efficient DBS parameters may be used.

A limitation of this study is that the double-blind periods were short, giving rise to the possibility of a carry-over effect, which may have led to an underestimation of the effect of stimulation. This study was originally planned in a sham-controlled design with periods of three months on-off stimulation. We changed the length of three months to two weeks because, once a considerable improvement had been experienced in the open phase, patients did not tolerate off phases due to massive worsening of symptoms. These findings are consistent with the observations of the Koln group treating major depression with nucleus accumbens stimulation.20 Another aspect that may have led to an underestimation of the effect of stimulation is that the currently used rating scales such as the Y-BOCS do not fully reflect improvement in patients with extremely severe OCD. The Y-BOCS typically attributes a maximum score of 4 points to duration of symptoms of eight hours or more. OCD patients in our study suffered sometimes 14 to 16 hours a day of obsessions or compulsions. Because the Y-BOCS fails to detect changes above eight hours, reductions remain unnoticed by the Y-BOCS. New scales designed to capture changes in severe obsessive-compulsive symptoms are needed.

In summary, the results of this study indicate that bilateral stimulation of the nucleus accumbens may be an effective and safe treatment in highly refractory OCD patients, and support the therapeutic potential of DBS in patients suffering from incapacitating chronic psychiatric disorders. Further research is necessary to optimize this therapy with respect to patient selection and management, target location and investigation of new potential indications.
REFERENCES


CHAPTER 4

COGNITIVE BEHAVIOURAL THERAPY AUGMENTS THE EFFECTS OF DEEP BRAIN STIMULATION IN OBSESSIVE-COMPULSIVE DISORDER

Mariska Mantione, Dorien Nieman, Martijn Figee, Damiaan Denys

Psychological Medicine 2014;44(16):3515-22
ABSTRACT

BACKGROUND
Deep brain stimulation (DBS) is a promising new treatment for patients with treatment-refractory obsessive-compulsive disorder (OCD). However, since most DBS patients only show a partial response, the treatment still needs to be improved. In this study we hypothesized that cognitive behavioural therapy (CBT) could optimize the post-operative management in DBS and we evaluated the efficacy of CBT as augmentation to DBS targeted at the nucleus accumbens.

METHODS
Sixteen patients with treatment-refractory OCD were treated with DBS targeted at the nucleus accumbens. After stabilization of improvement in OCD symptoms, a standardized 24-week CBT treatment program was added to DBS in an open phase trial of eight months. Change in obsessive-compulsive-, anxiety- and depressive symptoms was evaluated, using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Hamilton Anxiety Scale (HAM-A) and Hamilton Rating Scale for Depression (HAM-D).

RESULTS
Following addition of CBT to DBS, a significant decrease in obsessive-compulsive symptoms was observed, but not in anxiety and depressive symptoms. In a subsequent double-blind phase, in which stimulation was discontinued, OCD symptoms returned to baseline (relapse) and anxiety and depressive symptoms worsened (rebound) compared to baseline.

CONCLUSION
The results of this explorative study suggest that a combined treatment of accumbens DBS and CBT may be optimal for improving obsessive-compulsive symptoms in treatment-refractory OCD. However, a subsequent RCT is necessary to draw firm conclusions. It seems that DBS results in affective changes that may be required to enable response prevention in CBT. This may indicate that DBS and CBT act as two complementary treatments.
4.1 INTRODUCTION

Obsessive-compulsive disorder (OCD) is a disabling psychiatric disorder that, if left untreated, has a chronic course. At present, clinical management of OCD consists of pharmacotherapy and cognitive behavioural therapy (CBT). Although often effective, both treatments have their limitations. Patients usually have only a partial response to medication and CBT. In addition, medication can have significant side effects and the exposure and response prevention in CBT often provokes intense anxiety, resulting in a 25% drop out of patients. Eventually, 10% of patients with OCD do not respond adequately to current treatments and remain severely affected.

In the last decade, a new treatment for treatment-refractory OCD patients has emerged: deep brain stimulation (DBS). DBS is an adjustable, reversible, non-destructive neurosurgical intervention using implanted electrodes to deliver electrical pulses to areas in the brain. DBS at different brain targets has demonstrated to be an effective treatment for treatment-refractory OCD patients, with a mean responder rate of approximately 60%.

DBS certainly is a promising technique, but patients often show only a partial response. Therefore, the treatment still needs to be improved by optimizing the brain target, the adjustment of electrode settings, the selection of patients and the post-operative management. We have previously reported on the clinical outcome of accumbens DBS in sixteen treatment-refractory OCD patients. In this study we hypothesized that the addition of CBT augments the effectiveness of the post-operative management in DBS. Since CBT has proven to be effective as an augmentation strategy to increase the general partial response of pharmacotherapy in OCD, we assume that it could possibly be used in a similar approach to extend the partial response of DBS. The aim of the present study is to evaluate the addition of CBT to DBS and to discuss the methodology of the CBT program.

4.2 METHODS

PATIENTS

Patients were recruited through the outpatient clinic for anxiety disorders of the Academic Medical Center (AMC) in Amsterdam. The study population consisted of sixteen treatment-refractory OCD patients who participated in a trial in which the effectiveness of DBS for therapy-refractory OCD was assessed in a double-blind crossover design. Pre-treatment demographic and clinical characteristics are presented in Table 1. A full description of inclusion and exclusion criteria may be found in the paper by Denys et al. Informed consent of the participants was obtained after the nature of the procedures had been fully explained.
### Table 1: Demographic and clinical characteristics of each patient in the DBS group (n=16) at baseline

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Age of onset (years)</th>
<th>Duration of illness (years)</th>
<th>Number of previous CBT trials</th>
<th>Number of previous drug trials</th>
<th>Medication during course of study (dose, mg)</th>
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<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>F</td>
<td>21</td>
<td>33</td>
<td>8</td>
<td>6</td>
<td>Clomipramine hydrochloride (75), Quetiapine fumarate (200)</td>
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<tr>
<td>2</td>
<td>44</td>
<td>M</td>
<td>10</td>
<td>34</td>
<td>4(^a)</td>
<td>9</td>
<td>Clomipramine (125)</td>
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<tr>
<td>3</td>
<td>51</td>
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<td>13</td>
<td>38</td>
<td>5(^b,c)</td>
<td>8</td>
<td>Fluvoxamine maleate (300)</td>
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<td>26</td>
<td>F</td>
<td>5</td>
<td>21</td>
<td>5(^b,c)</td>
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<td>40</td>
<td>M</td>
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<td>3(^c)</td>
<td>6</td>
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<td>6</td>
<td>54</td>
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<td>4</td>
<td>40</td>
<td>3(^c)</td>
<td>6</td>
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</tr>
<tr>
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<td>21</td>
<td>F</td>
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<td>8</td>
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<tr>
<td>9</td>
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<td>16</td>
<td>19</td>
<td>4(^c)</td>
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</tr>
<tr>
<td>10</td>
<td>32</td>
<td>F</td>
<td>18</td>
<td>14</td>
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<td>8</td>
<td>Clomipramine (125), haloperidol (5)</td>
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<td>F</td>
<td>20</td>
<td>25</td>
<td>1(^c)</td>
<td>5</td>
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<tr>
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<td>59</td>
<td>M</td>
<td>13</td>
<td>46</td>
<td>2(^c)</td>
<td>4</td>
<td>Citalopram (60), quetiapine (300)</td>
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<tr>
<td>13</td>
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<td>M</td>
<td>14</td>
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<td>9</td>
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<td>Citalopram (60), quetiapine (300)</td>
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<tr>
<td>15</td>
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<td>M</td>
<td>35</td>
<td>20</td>
<td>4(^c)</td>
<td>3</td>
<td>...</td>
</tr>
<tr>
<td>16</td>
<td>54</td>
<td>M</td>
<td>6</td>
<td>48</td>
<td>1(^c)</td>
<td>5</td>
<td>Clomipramine (225), quetiapine (600)</td>
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</table>

DBS, Deep brain stimulation; CBT, cognitive–behavioural therapy.
\(a\) = Outpatient treatment,
\(b\) = Day treatment,
\(c\) = Clinical admission

**PROCEDURE**

The study consisted of three sequential treatment phases: an open phase of eight months, a double-blind cross-over period of 4 weeks and a maintenance phase of 1 year. After surgery, patients entered an open phase of eight months during which they were evaluated every two weeks to assess severity of symptoms and to determine optimal stimulation parameters. In the open phase, a standardized 24-week cognitive behavioural treatment program was added (figure 1). CBT was started when three
conditions were fulfilled. First, a clinical significant decrease in OCD symptoms had to be obtained. This was determined as a decrease of at least 6 points on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Second, there had to be no further decrease in symptoms, i.e. a stable score on the Y-BOCS for three successive visits (six weeks). And third, it had to be observed that patients avoided to resist their compulsions and avoided anxiety provoking exposure situations. Treatment with CBT consisted of weekly individual sessions of 60 minutes. During CBT, we aimed to keep stimulation parameters constant and limited the adjustments of stimulation parameters to small increases in voltage with a maximum of 5.0 V. After finishing the open phase, patients entered a double-blind cross-over period of four weeks. Patients were allocated to 2 periods of 2 weeks with stimulation blindly turned on (active stimulation) in one period and stimulation blindly turned off (sham stimulation) in the other period. Patients were evaluated after each condition. CBT was continued during the cross-over period. This period was followed by a maintenance phase of one year in which CBT was reduced on the basis of individual needs and the number of CBT sessions varied between patients. When ending the maintenance phase, patients were assessed again for severity of symptoms. During the whole study, besides CBT, no other psychological treatments were allowed. Patients were allowed to use medication (see table 1 for a specification of medication). When serotonin re-uptake inhibitors (SSRI’s) were used, they were tapered off pre-operatively to minimize the risk of haemorrhage during surgery. Immediate after surgery they were build up to levels similar as before surgery.

CBT was conducted by a cognitive behavioural therapist and a behavioural nurse therapist specialised in the treating patients with OCD. The treatment manual was adapted from Verbraak et al. Treatment started with exposure and response prevention (ERP) in order to confront patients gradually with their feared stimuli and feared social contexts (e.g. ‘touch the doorknob without hand washing’). Cognitive therapy and behavioural experiments were added subsequently and were used to challenge dysfunctional beliefs (e.g. ‘if I touch the doorknob, I will become sick’). The treatment manual was adjusted on several points to suit this group of severely ill, therapy-refractory patients. First, since patients were reluctant to start again with CBT because of earlier negative CBT experiences, the treatment started with an extensive evaluation of their motivation to reduce their symptoms. Common questions to discuss patients’ motivation were: ‘what do you expect from therapy?’ and ‘what are you going to do with your life when OCD symptoms have diminished?’ Secondly, during the optimization of stimulation parameters in the open phase, it appeared that patients tended to filter out positive experiences and that acknowledgement of the initial positive effect of DBS was essential in further improvement of symptoms: a change in focus had to be realized to enhance motivation for treatment. Therefore, before
the actual start of ERP, patients were asked to keep a diary of positive experiences
to shift their focus from symptoms that did not (yet) improve to symptoms that did
improve after DBS. Thirdly, compulsions had become extremely elaborate and time-
consuming in the course of their disease and patients had developed an extensive
pattern of avoidance to prevent themselves from the need to perform their rituals.
For this reason, the start of exposure therapy aimed at the reduction of compulsions
while patients were still allowed to avoid anxiety provoking situations. Rituals were
decreased step by step while patients were encouraged to remain in each exposure
situation until the distress decreased noticeably. Fourth, it was observed that part of
the compulsions had become habits rather than rational avoidance responses triggered
by obsessions: e.g. patients repeatedly washed their hands because they did so for the
past 20 years, not because of a clear irrational belief about contamination. Therefore,
the start of cognitive therapy aimed explicitly at revealing the original obsessions (e.g.
‘if I touch the doorknob, I will become sick’), whereby the absurdness of the behaviour
could brought up easier for discussion.

OUTCOME MEASURES
Obsessive-compulsive symptoms were assessed with the Y-BOCS. A patient was rated as
a responder in case of a ≥ 35% decrease on the Y-BOCS. Depression was rated with the
17-item Hamilton Rating scale for Depression (HAM-D) and anxiety was evaluated with
the Hamilton Anxiety Scale (HAM-A). A trained and blinded investigator completed the
scales at baseline and at each visit.

STATISTICAL ANALYSIS
The primary outcome measures, the Y-BOCS score, HAM-A score and HAM-D score, were
analysed using a repeated measurements analysis. The difference between stimulation
effects and effect of treatment with CBT was calculated with post-hoc paired t-tests.
The data are presented as mean ± SD at 5% level of significance. All statistical analyses
were conducted with the SPSS statistical package version 18.0.

4.3 RESULTS
Table 2 shows mean baseline scores before implantation, mean scores following DBS
optimization, mean scores following CBT treatment, mean scores in the cross-over
phase, and mean scores at the end of the maintenance phase on respectively the Y-BOCS,
the HAM-A and the HAM-D. All symptom scores decreased during the course of DBS
treatment. The Y-BOCS diminished with 52%, from 33.8 ± 3.6, corresponding with very
severe OCD, to 16.2 ± 8.6, indicating mild OCD at the end of the maintenance phase, i.e.
1 year after the cross-over phase (repeated measures analysis: F(24, 360) = 9.74, p<0.001). The HAM-A decreased with 57% from 20.9 ± 5.9, corresponding with moderate anxiety, to 8.9 ± 5.4, indicating mild anxiety at the end of the maintenance phase (repeated measures analysis: F(24, 360) = 9.65, p<0.001). The HAM-D decreased with 46% from 19.5 ± 6.7, corresponding with moderate depression to 10.6 ± 6.0, indicating mild depression at the end of the maintenance phase (repeated measures analysis: F(24, 360 = 7.07, p<0.001).

![Figure 1](image_url)

**Figure 1** Course of OCD- symptoms, anxiety symptoms and depression symptoms during DBS, additional CBT, double-blind cross-over phase and follow-up phase of the study.

The time needed to optimize stimulation parameters and obtain a significant decrease in Y-BOCS score varied between patients, but was on average 8 weeks. Optimization of DBS stimulation parameters without CBT treatment resulted in a 25% decrease (8.3 ± 7.8 points, p < 0.001) of mean Y-BOCS scores compared to baseline. The mean HAM-A score decreased 41% (8.6 ± 9.0 points, p = 0.002) and the mean HAM-D score decreased 32% (6.3 ± 8.0 points, p = 0.006). Six out of sixteen patients were considered responders with a mean decrease of 49.6% ± 8.7% on the Y-BOCS. With addition of 24 weeks of CBT to ongoing DBS treatment, there was a supplementary 22% mean decrease of total Y-BOCS score (7.3 ± 11.3 points, p = 0.021) although no significant additional decrease of HAM-A score (decrease of 2.3 ± 8.7 points, p = 0.317), and HAM-D
Table 2 Mean and SD of outcome measures in the open phase, double-blind cross-over phase and maintenance phase.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Start CBT</th>
<th>Mean change during adjustment of stimulation</th>
<th>P-value</th>
<th>End CBT</th>
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</thead>
<tbody>
<tr>
<td>Y-BOCS total</td>
<td>33.7 ± 3.6</td>
<td>25.4 ± 7.8</td>
<td>8.3 ± 7.8</td>
<td>0.001</td>
<td>18.1 ± 11.4</td>
</tr>
<tr>
<td>Y-BOCS obsessions</td>
<td>16.9 ± 2.0</td>
<td>12.4 ± 4.0</td>
<td>4.4 ± 3.9</td>
<td>0.001</td>
<td>8.4 ± 5.9</td>
</tr>
<tr>
<td>Y-BOCS compulsions</td>
<td>16.9 ± 1.8</td>
<td>13.0 ± 4.1</td>
<td>3.9 ± 4.1</td>
<td>0.002</td>
<td>9.8 ± 5.8</td>
</tr>
<tr>
<td>HAM-A</td>
<td>20.9 ± 5.9</td>
<td>12.3 ± 7.1</td>
<td>8.6 ± 9.0</td>
<td>0.002</td>
<td>10.1 ± 8.3</td>
</tr>
<tr>
<td>HAM-D</td>
<td>19.5 ± 6.7</td>
<td>13.2 ± 6.8</td>
<td>6.3 ± 8.0</td>
<td>0.006</td>
<td>10.5 ± 7.8</td>
</tr>
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</table>

Data are given as mean (standard deviation).
CBT=cognitive behavioural therapy; Y-BOCS=Yale-Brown obsessive-compulsive scale; HAM-A= Hamilton Anxiety Scale; HAM-D= Hamilton Rating Scale for Depression

score (decrease of 2.8 ± 7.7 points, p = 0.158) was observed. With addition of CBT, the number of responders increased from six to nine out of 16 patients, with a mean decrease in the total Y-BOCS score of 72% ± 17.3%. Two patients refused to participate in the double-blind cross-over phase and were excluded from further assessments. In the crossover phase, the mean-Y-BOCS score, HAM-A score and HAM-D score increased significantly. Due to the relapse in symptoms, most patients were unable to apply CBT techniques during off-stimulation.

4.4 DISCUSSION

In this explorative study of combined DBS and CBT treatment, we evaluated the effectiveness of CBT as an augmentation strategy to DBS. Three interesting observations were made. First, we have an indication that CBT as addition to DBS results in a significant additional reduction of obsessions and compulsions, suggesting that CBT may be required to accomplish further improvement of obsessive-compulsive symptoms following the initial effect of optimization of stimulation. Second, CBT as addition to DBS did not seem to affect anxiety and depressive symptoms but seems to be uniquely associated with a reduction of OCD symptoms. Third, discontinuation of stimulation in the double-blind cross-over phase resulted in a complete and rapid disappearance of the overall effect, i.e. the initial effect of DBS on obsessive-compulsive-, anxiety- and depressive symptoms as well as the gained successes of additional CBT.

No prior study reported the effects of CBT augmentation to DBS. However, our
observation that DBS targeted at the accumbens has a profound effect on anxiety and depressive symptoms and a moderate effect on OCD symptoms, can be compared with other studies. Comparable with our findings, immediate anhedonic, antidepressive and anxiolytic effects were observed after accumbens stimulation in major depressive disorder (MDD).\(^2\) Interestingly, DBS of the subthalamic nucleus in OCD specifically decreased compulsions without significant effects on anxiety and depressive symptoms.\(^1\) Thereby it is possible that the selective efficacy of CBT, as addition to DBS treatment in our study, depends on our target of stimulation.

The mechanism of action of behaviour therapy for OCD may clarify the positive effects of additional CBT in this study. It is assumed that two associations maintain the symptoms in OCD: first, the association between specific stimuli and the provocation of anxiety and second, the association between the ritualistic behaviours and the reduction in anxiety.\(^2\) Behaviour therapy, e.g. ERP, aims to break these associations, preventing the transient and negative reinforcement that occurs when patients reduce their anxiety through compulsions. It has been widely assumed that as a result, exposure based treatment disrupts the obsessive-compulsive cycle and leads to habituation and therefore decrease of anxiety.\(^2\) However, presently it has been suggested that habituation of anxiety does not predict therapeutic outcome and it has been postulated that inhibitory learning, the forming of new corrective associations, underlies the mechanism of action of ERP.\(^2\)

It is likely that the first association between stimuli and anxiety is rapidly weakened by DBS alone, because of its initial effect on anxiety symptoms. However, it is unlikely that DBS solely is able to completely inhibit the second association between ritualistic behaviours and reduction of anxiety, because part of the OCD symptoms remained after effective DBS. Recent research indicates that compulsivity in OCD may arise from excessive stimulus-response habit formation.\(^2\) Our results suggest that

<table>
<thead>
<tr>
<th>Mean change during CBT</th>
<th>P-value</th>
<th>Start cross-over phase</th>
<th>Stimulation on cross-over phase</th>
<th>Stimulation off cross-over phase</th>
<th>1 year follow-up</th>
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<tr>
<td>7.3 ± 1.1</td>
<td>0.021</td>
<td>20.7 ± 10.3</td>
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<td>30.0 ± 8.8</td>
<td>16.2 ± 8.6</td>
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<td>4.1 ± 6.2</td>
<td>0.018</td>
<td>10.1 ± 5.3</td>
<td>10.1 ± 5.5</td>
<td>15.3 ± 4.6</td>
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<td>3.3 ± 5.6</td>
<td>0.035</td>
<td>10.6 ± 5.2</td>
<td>11.0 ± 4.9</td>
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<tr>
<td>2.3 ± 8.7</td>
<td>0.317</td>
<td>13.3 ± 6.6</td>
<td>14.9 ± 10.8</td>
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<td>2.8 ± 7.7</td>
<td>0.158</td>
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</tbody>
</table>
there are goal-directed compulsions fuelled by anxiety that are affected by DBS as well as long existent repetitive compulsive behaviour, which has a more habitual nature, that is more difficult to treat with DBS. It is our clinical observation that during DBS further improvement of OCD symptoms stabilized because patients were unable to intentionally stop their remaining habitual behaviour. It was reported that ERP prior to DBS led to extreme and intolerable anxiety symptoms that eventually resulted in compulsions and hindered successful response prevention. This is supported by the high number of unsuccessful CBT trials before DBS in our sample (table 1). With CBT post-DBS, patients were encouraged to stop their remaining habitual compulsions and were able to experience that the level of anxiety after ERP does not become intolerable as in previous CBT’s. CBT post-DBS appears thus to be necessary to stop habitual behaviour and to enable patients to experience that they can manage anxiety.

The above described mechanism of action of CBT in accumbens DBS is strengthened by a recent animal study\textsuperscript{27} which showed that DBS of the dorsomedial ventral striatum applied during extinction training, decreases fear responses and facilitates the extinction of conditioned fear in rats. It has therefore been suggested that DBS could augment the effectiveness of cognitive behavioural therapies in OCD. In line with Rodriguez-Romaguerra et al.\textsuperscript{27} our results suggest that DBS enables CBT and therefore, CBT could augment the effectiveness of DBS.

We have recently demonstrated that accumbens DBS in OCD restores ventral striatal reward responses and connectivity with the prefrontal cortex.\textsuperscript{28} In MDD, accumbens stimulation reduced anxiety and depression by modulation of amygdala and prefrontal metabolism.\textsuperscript{21} Together, these findings indicate that DBS restores motivational and affective control in a broader limbic-striatal-cortical network. CBT, on the other hand, primarily affects hyperactivity in the orbitofrontal cortex,\textsuperscript{29} an area that is thought to mediate the affective appraisal of stimuli and therefore plays an important role in the mediation of extinction.\textsuperscript{30} In addition, recent evidence suggests that CBT influences brain activity in the caudate nucleus and the pallidum, core regions that have been shown to be directly involved both in the acquisition of repetitive behaviour and thus in the pathophysiology of OCD.\textsuperscript{31} Thus, accumbens DBS and CBT may collaborate in a complementary process in which DBS restores affective and motivational control over unwanted behaviours, paving the way for further extinction of habitual behaviours by CBT.

A complementary relation of DBS and CBT is confirmed by our third observation that OCD- as well as anxiety-, and depressive symptoms completely relapsed in the double-blind cross-over phase. In spite of newly learned associations during CBT, patients were not able to preserve their gained improvement. Although patients have a risk to relapse after treatment discontinuation following combined therapy of medication and CBT for OCD, additional CBT results in a lower relapse rate and a longer
time to relapse compared to medication therapy alone. The fast and complete relapse in the double-blind cross-over phase of DBS treatment, despite the addition of CBT, is in sharp contrast with these findings. In our study, after discontinuation of stimulation, anxiety and depressive symptoms returned acutely and moreover, worsened compared to baseline. This worsening might be an overestimation of symptoms, because patients compare their condition with their symptoms post-DBS instead of pre-DBS, or it might be the result of a rebound effect. The fact that discontinuation of stimulation overrules the gained effect of CBT in the open phase suggests that efficacy of CBT depends on stimulation. On the other hand, with stimulation on again, OCD symptoms improved to a level comparable to post-CBT instead of post-optimization, which suggests that CBT techniques were saved during off-stimulation and which emphasizes the complementariness of both treatments.

LIMITATIONS

A limitation of this study is the exploratory nature of the CBT treatment. All 16 patients received complementary CBT and therefore a comparison between DBS as a stand-alone treatment and DBS and CBT as a combination treatment, is not possible. However, the mean Y-BOCS total score decrease of 72% in 56% of the responding patients in our study is the largest follow up Y-BOCS decrease published to date in DBS studies. In addition, our response rate of 56% is significantly higher than the response rate of 10% reported in a comparable study of accumbens DBS. These results suggest that the combination of DBS and CBT could be most effective in reducing symptoms in treatment-refractory OCD patients. However, we strongly recommend to explore the additional effect of CBT by means of a randomized controlled clinical trial. A second limitation of this study is the small sample size, although our patient group is relatively large compared to previous DBS studies.

4.5 CONCLUSION

The results of this explorative study suggest that DBS targeted at the accumbens may not be optimal as a stand-alone treatment but that the clinical improvement of DBS could be enhanced by the addition of CBT. Since our study is the first to investigate the addition of CBT to DBS, we did not employ a RCT design. Therefore, no firm conclusions can be drawn. However, the positive results of our exploratory study indicate that a subsequent RCT investigating the addition of CBT to DBS is warranted. It seems that accumbens DBS results in fast profound affective changes enabling patients to engage in CBT augmentation for further extinction of compulsive acts that have a habitual nature, allowing patients to regain control of their own behaviour.
REFERENCES


PART II

COGNITION AND
DEEP BRAIN STIMULATION
CHAPTER 5

COGNITIVE EFFECTS OF DEEP BRAIN STIMULATION IN OBSESSIVE-COMPULSIVE DISORDER

Mariska Mantione, Dorien Nieman, Martijn Fjee, Pepijn van den Munckhof, Rick Schuurman, Damiaan Denys

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ABSTRACT

BACKGROUND
Deep Brain Stimulation (DBS) is a promising treatment for treatment-refractory obsessive-compulsive disorder (OCD). However, the effects of DBS on cognitive functioning remain unclear. Therefore, this study aimed to assess cognitive safety of DBS for treatment-refractory OCD and the relation between clinical changes and cognitive functioning.

METHODS
Sixteen patients with treatment-refractory OCD, treated with DBS targeted at the nucleus accumbens (NAcc), were compared with a control group of fourteen patients with treatment-refractory OCD, treated with care as usual. Cognitive functioning was assessed at baseline, three weeks postoperatively and following eight months of stimulation. Change in clinical symptoms was compared with cognitive changes.

RESULTS
Three weeks postoperatively, the DBS group showed a significant reduced performance on measures of visual organization and verbal fluency and a trend toward reduced performance on measures of visual memory and abstract reasoning. Cognitive functioning was found to be stable on all other measures. After eight months of stimulation, reduced performances persisted, except for a significant improvement in verbal fluency. Cognitive functioning in all other domains remained unaffected. No correlation was found between improvement of clinical symptoms and cognitive changes.

CONCLUSION
Firstly, DBS targeted at the NAcc may be considered as a safe method in terms of cognition since cognitive functioning was unaffected on the majority of neuropsychological measures. Nevertheless, we observed some minor reduced performances on specific measures of executive functioning, possibly related to surgical intervention. Thirdly, our results suggest that severity of OCD symptoms is independent of cognitive functioning.
5.1 INTRODUCTION

Recently, several studies have shown that deep brain stimulation (DBS), targeting the anterior limbs of the internal capsule, the ventral striatum, the nucleus accumbens (NAcc), the inferior thalamic peduncle and the subthalamic nucleus is effective in patients with treatment-refractory obsessive-compulsive disorder (OCD). To date, the results of 7 controlled studies have been published worldwide, showing that 34 of 63 patients experience a reduction of at least 35% of OCD symptoms. Consequently, half of the treated patients can be considered as responders, making DBS a promising technique.

Neuropsychological evaluation in DBS treatment plays a vital role in pre-operative neuropsychological screening of potential DBS candidates, in evaluation of outcome and in research. Its contribution in research is twofold: neuropsychological assessment may firstly establish the cognitive safety of DBS treatment and secondly demonstrate whether DBS alters the underlying cognitive deficits in OCD. Presently, there is evidence that the clinical effectiveness of DBS in OCD patients is achieved with stable and even improvement in cognitive functioning. However, since small sample sizes, lack of a control group and the use of a limited range of tests hinder the interpretation of the results, the effect of DBS in OCD on cognitive functioning is still unknown.

We conducted a prospective, controlled study investigating the cognitive effects of bilateral DBS targeted at the NAcc three weeks and eight months postoperatively, allowing a discrimination of short term and long term effects of DBS. In addition we investigated if clinical changes after DBS treatment were associated with changes in cognitive functioning. Changes were compared at three time points with a matched control group of treatment-refractory OCD patients.

5.2 METHODS

PATIENTS

Patients were recruited through the outpatient clinic for anxiety disorders at the Academic Medical Center (AMC), Amsterdam, the Netherlands. The study population consisted of 16 treatment-refractory OCD patients who participated in a trial in which the effectiveness and safety of DBS for treatment-refractory OCD was assessed. Alongside the DBS group, we formed a control group consisting of treatment-refractory OCD patients treated as usual, who were on a waiting list for the DBS study. Both groups were matched on mean age, premorbid intelligence and Y-BOCS score. The investigation was carried out in accordance with the latest version of the Declaration of
Helsinki. The study was part of a registered clinical trial (trial number ISRCTN23255677) and approved by the Medical Ethical Committee of the AMC. Informed consent of the participants, patients as well as controls, was obtained after the nature of the procedures had been fully explained.

Inclusion criteria for patients were: age between 18 and 65 years, primary OCD according to the DSM-IV criteria, severe illness with a total score of at least 28 on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)\textsuperscript{16, 17} and at least a five year history of OCD. All patients had insufficient response to a minimum of 2 different selective serotonin reuptake inhibitors (SSRI's), clomipramine, augmentation with an atypical antipsychotic and a minimum of 16 sessions of cognitive behavioural therapy (CBT).

Exclusion criteria were: significant comorbid DSM-IV diagnosis (except major depressive disorder and mild anxiety disorders) as well as severe personality disorders and substance abuse within the past 6 months. The Structured Clinical Interview for DSM-IV axis I disorders\textsuperscript{18} and the Structured Clinical Interview for DSM-IV axis II disorders\textsuperscript{19} were administered to validate diagnosis.

**PROCEDURE**

A neuropsychological test battery was administered between three to one months pre-operatively, three weeks postoperatively and after an open eight-month treatment phase. To minimize the risk of hemorrhage during surgery for the DBS group, serotonin re-uptake inhibitors were tapered off pre-operatively. Immediate after surgery medication was build up. Medication was kept constant for the DBS group as well as the control group. Before postoperative testing was performed, medication levels were similar as before surgery. The surgical procedure was described previously\textsuperscript{9}, electrodes (model 3389, Medtronic Inc, Minneapolis) being targeted with the deepest contact at the original NAcc target of Sturm, et al.\textsuperscript{2} After electrode implantation, monopolar stimulation was started using ventral contact points 0 and 1. Consistently, no changes in symptoms were observed on these parameters. Three weeks after surgery the neuropsychological test battery was repeated to investigate possible effects of surgery. After post-operative neuropsychological assessment patients entered an open phase of eight months. Since no improvement was observed in any of the patients when stimulating the ventral contacts, the active contacts were switched to dorsal contacts 2 and 3, delivering active stimulation in the ventral part of the anterior limb of the internal capsule. After this switch in contacts clinical improvement on OCD symptoms was apparent in all patients. Stimulation parameters were then standardized to dorsal contacts 2 and 3, a frequency of 130 Hz and pulse width of 90 microseconds. Voltage ranged from 3.5 V to a maximum of 5.0 V. At the end of the open phase the same neuropsychological test battery was repeated to investigate the effects of stimulation.
Where available, we used alternated forms of the neuropsychological tests in a balanced order across patients to minimize practice effects. Patients in the control group were assessed at similar time points as the DBS group.

NEUROPSYCHOLOGICAL TESTS

Measures of intelligence
The Dutch version of the National Adult Reading Test (DART)\(^{20,21}\) assesses premorbid intelligence and was used to match the DBS group and control group. The variable used in the statistical analysis was the intelligence quotient.

The short 12-problem version (set I) of the Raven Advanced Progressive Matrices (RAPM)\(^{22}\) was used to assess abstract reasoning. The number of correct items was scored.

Memory
The Dutch version of the California Verbal Learning Test (CVLT)\(^{23,24}\) is a verbal memory task that yields information on several aspects of verbal learning, organization and memory. The variable used in the analysis was the total recall in five trials. To prevent practice effects due to multiple assessments, the parallel version of the test was used in a counter-balanced design.

The digit span is a subtest of the Wechsler Adult Intelligence Scale (WAIS-III)\(^{25}\) and was used as a measure of short term verbal learning and working memory. Total number of correct items was analyzed.

Visuoconstructual function and memory
The Rey Complex Figure Task (RCFT)\(^{26}\) is a test measuring visual memory and organization. Accuracy for the copy and the immediate recall condition was quantified using a scoring system, resulting in scores ranging from 0 to 36 (Meyers and Meyers, 1995; Spreen and Strauss, 1998).\(^{27,28}\)

Executive functions and inhibition
The Stroop Color Word Test\(^{29}\) consists of three trials measuring selective attention, perceptual interference and response inhibition. The outcome measure used in the analysis was the time needed for the third trial minus time needed for the second trial. Verbal fluency\(^{30,31}\) has been used to investigate a wide variety of cognitive functions, such as long-term verbal memory, attention, vocabulary size and executive functioning.\(^{32}\) The number of generated words in one minute for phonemic (‘N’ and ‘A’) and semantic cues (animals and occupations) were used as dependent variables.

The Trail Making Test (TMT)\(^{33}\) consists of two trials of which the first is considered as a measure of mental speed and the second as a measure of alternated attention. As
the performance in both parts exhibits a close linear relationship, time B divided by

time A was used as an outcome variable for set shifting.\textsuperscript{34}

The Wisconsin Card Sorting Test (WCST)\textsuperscript{35} is one of the most widely used tasks
in the assessment of neurocognitive function. It assesses among others set-shifting,
category formation and set maintenance. Outcome variables used in the analysis were
the number of categories completed and percentage of perseverative errors.

The Tower of London (ToL)\textsuperscript{36} was administered to assess planning ability. The outcome
variable was the total number of steps needed to complete problem-solving tasks.

**Attention**

The Continuous Performance Test – identical pairs\textsuperscript{37,38} assesses sustained visual
attention. Response style (’log-B’) and the ability to discriminate between target and
non-target (’d-prime’) were used as outcome variables.

The Digit Symbol Substitution\textsuperscript{39} is a subtest of the Wechsler Adult Intelligence
Scale measuring attention. The outcome variable used was the number of digits
correctly filled out.

**Motor system**

The Purdue Pegboard\textsuperscript{40} measures upper-extremity fine motor dexterity as well as gross
motor coordination. The number of pegs in the dominant hand and nondominant hand
subtests were used as outcome measures.

**CLINICAL SYMPTOMS**

Obsessive-compulsive-, anxiety- and depressive symptoms of the DBS group and control
group were assessed with the Y-BOCS\textsuperscript{16,17}, the Hamilton Anxiety Scale (HAM-A)\textsuperscript{40}
and the Hamilton Depression Scale (HAM-D)\textsuperscript{41} respectively.

**ADVERSE EVENTS**

Information about adverse events was collected in the open phase of the study as part
of the original clinical trial.\textsuperscript{9} Each visit (every 2 weeks) patients were asked the general
question: ‘Have you experienced a change in behaviour in the last two weeks?’ Any
change in behaviour reported by the patient was rated as an adverse event. Changes
regarding cognitive functioning were also regularly brought up by patients when they
answered question 5 of the HAM-A: ‘Have you experienced difficulties in concentration
or memory?’ Patients were always asked to rate the adverse events they mentioned
(mild – moderate – severe).

**STATISTICAL ANALYSIS**

All data were analysed using the SPSS statistical package for Windows (version 20.0;
IBM Company Chicago, IL, USA). At baseline, differences between the DBS group and control group in age and clinical symptoms were examined by means of independent two-tailed T tests. Gender differences were analysed using a Chi-square test. A linear mixed model analysis was conducted to assess changes in cognitive test parameters over three different time points (at baseline, three weeks postoperatively and eight months post-operatively). Considering the small sample sizes in both groups we decided to correct for baseline differences in our analysis. We conducted a mixed model analysis with change scores as dependent variables and baseline scores as covariate. The change score at three weeks postoperatively was defined as the score at three weeks postoperatively minus baseline score and the change score at eight months postoperatively was defined as the score at eight months postoperatively minus baseline score. Raw test scores were used for all measures. To account for multiple comparisons, a more stringent threshold of $P < 0.01$ was used to assess statistical significance. Results with $0.01 < P < 0.05$ are reported as trends.

We computed effect sizes according to Cohen’s $d$. Effect size is defined as the difference between the mean change scores of both groups divided by the pooled SD of the change scores. An effect size of 0.2 reflects a small effect, 0.5 a medium effect and $\geq 0.8$ a large effect. Spearman’s Rho coefficients were used to calculate correlations between change in clinical characteristics (Y-BOCS, HAM-A and HAM-D) and change in neuropsychological performance.

5.3 RESULTS

GROUP CHARACTERISTICS
Sixteen patients were included in the DBS group. Two patients of the DBS group were lost to follow-up at eight months of stimulation because they refused further participation in the study. Their results were included in the baseline to three week analyses. The control group consisted of 14 patients with treatment-refractory OCD. Six out of 16 patients of the DBS group and five out of 14 patients of the control group fulfilled the criteria for comorbid major depressive disorder (MDD). A chi-square test did not reveal a statistical significance in distribution of comorbid MDD between both groups ($\chi^2(1)= 0.01; \ p=0.92$). There were no significant differences between patients in both groups with respect to mean age, education, intelligence quotient, age of onset, duration of illness, and baseline Y-BOCS, HAM-A and HAM-D scores (table 1).

CLINICAL SYMPTOMS
Three weeks post-operatively, the DBS group and control group showed no statistically significant difference in OCD-, anxiety- and depressive symptoms. The DBS group scored
### Table 1 Demographic and clinical characteristics of the DBS group and control group at baseline.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Age of onset (years)</th>
<th>Duration of illness (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean; ± SD)</td>
<td>42.56 (11.4)</td>
<td>38.00 (9.8)</td>
<td>1.18</td>
<td>0.25</td>
</tr>
<tr>
<td>Gender (male/ female)</td>
<td>9/ 7</td>
<td>5/ 9</td>
<td>χ² = 1.27</td>
<td>0.26</td>
</tr>
<tr>
<td>DART- IQ (mean; ± SD)</td>
<td>92.4 (9.2)</td>
<td>94.4 (9.0)</td>
<td>-0.62</td>
<td>0.54</td>
</tr>
<tr>
<td>Age at onset (mean; ± SD)</td>
<td>14.2 (7.4)</td>
<td>16.3 (6.8)</td>
<td>-0.81</td>
<td>0.43</td>
</tr>
<tr>
<td>Duration of illness (mean; ± SD)</td>
<td>29.0 (12.5)</td>
<td>23.7 (8.4)</td>
<td>1.37</td>
<td>0.18</td>
</tr>
<tr>
<td>Y-BOCS (mean; ± SD)</td>
<td>31.7 (3.6)</td>
<td>32.4 (4.6)</td>
<td>0.87</td>
<td>0.40</td>
</tr>
<tr>
<td>HAM-A (mean; ± SD)</td>
<td>20.9 (5.9)</td>
<td>20.21 (8.3)</td>
<td>0.25</td>
<td>0.80</td>
</tr>
<tr>
<td>HAM-D (mean; ± SD)</td>
<td>19.5 (6.7)</td>
<td>17.6 (8.3)</td>
<td>0.70</td>
<td>0.49</td>
</tr>
</tbody>
</table>

DART-IQ= Dutch Adult Reading Test Intelligence Quotient; HAM-A= Hamilton Anxiety rating scale; HAM-D= Hamilton Depression rating scale; Y-BOCS= Yale-Brown Obsessive-Compulsive Scale

32.6 ± 4.5 points on the Y-BOCS compared to 31.1 ± 4.8 points of the control group. The DBS group scored 15.5 ± 5.4 points on the HAM-A compared to 18.9 ± 8.2 points of the control group. The DBS group scored 16.3 ± 5.8 points on the HAM-D compared to 16.4 ± 6.5 points of the control group. In the DBS group, OCD as well as anxiety and depressive symptoms improved significantly in the open phase of the trial (eight months postoperatively). The Y-BOCS showed a mean decrease of 15.7 ± 10.8 points, the HAM-A showed a mean decrease of 10.7 ± 8.1 points and the HAM-D showed a mean decrease of 9.0 ± 6.2 points. In the control group, OCD, anxiety and depressive symptoms remained unchanged: at the third neuropsychological assessment the Y-BOCS showed a mean decrease of 0.4 ± 3.6 points, the HAM-A showed a mean decrease of 2.7 ± 5.6 points and the HAM-D showed a mean increase of 0.7 ± 4.9 points.

**ADVERSE EVENTS**

Five patients reported forgetfulness. Specifically, patients mentioned short-term memory deficits, possibly related to being less able to follow a conversation. Three patients reported word-finding problems, which were described as a ‘tip of the tongue phenomenon’. All symptoms were rated as mild adverse events.

**NEUROPSYCHOLOGICAL TESTS**

The outcomes on neuropsychological tests for both groups at baseline, three weeks postoperatively, and eight months postoperatively, are shown in table 2. At baseline, the DBS group and control group did not significantly differ in cognition except for a lower score on the Digit Symbol Substitution in the DBS group. Three weeks
Table 2 Raw cognitive test scores at baseline and change scores at 3 weeks and 8 month follow-up for the DBS and control group. P values are corrected for differences at baseline.

<table>
<thead>
<tr>
<th>Test</th>
<th>DBS</th>
<th>Control</th>
<th>Statistics (df)</th>
<th>P-value</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>California Verbal Learning Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total recall in 5 trials</td>
<td>52.9 ± 10.8</td>
<td>57.8 ± 11.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change score 3 weeks</td>
<td>-1.9 ± 6.9</td>
<td>0.5 ± 5.5</td>
<td>T(28)= -1.08</td>
<td>0.28</td>
<td>-0.4</td>
</tr>
<tr>
<td>Change score 8 months</td>
<td>2.5 ± 6.6</td>
<td>4.6 ± 8.9</td>
<td>T(28)= -0.58</td>
<td>0.57</td>
<td>-0.3</td>
</tr>
<tr>
<td>Stability of time</td>
<td></td>
<td></td>
<td>T(27)= 0.10</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td><strong>Digit span</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forwards</td>
<td>9.3 ± 1.9</td>
<td>9.5 ± 2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change score 3 weeks</td>
<td>0.2 ± 1.7</td>
<td>0 ± 2.1</td>
<td>T(27)= 0.17</td>
<td>0.87</td>
<td>0.1</td>
</tr>
<tr>
<td>Change score 8 months</td>
<td>-0.3 ± 1.8</td>
<td>-0.2 ± 2.4</td>
<td>T(27)= -0.14</td>
<td>0.89</td>
<td>-0.1</td>
</tr>
<tr>
<td>Stability of time</td>
<td></td>
<td></td>
<td>T(27)= -0.30</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Backwards</td>
<td>5.7 ± 1.5</td>
<td>6.6 ± 2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change score 3 weeks</td>
<td>1.4 ± 1.6</td>
<td>0.4 ± 1.4</td>
<td>T(27)= 1.14</td>
<td>0.26</td>
<td>0.7</td>
</tr>
<tr>
<td>Change score 8 months</td>
<td>1.0 ± 1.9</td>
<td>0.9 ± 2.0</td>
<td>T(29)= -0.19</td>
<td>0.85</td>
<td>0.1</td>
</tr>
<tr>
<td>Stability of time</td>
<td></td>
<td></td>
<td>T(28)= -1.17</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td><strong>Rey Complex Figure Test</strong></td>
<td></td>
<td></td>
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<tr>
<td>Copy score</td>
<td>31.6 ± 2.7</td>
<td>30.9 ± 4.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change score 3 weeks</td>
<td>-1.7 ± 1.9</td>
<td>1.7 ± 3.7</td>
<td>T(27)= -3.64</td>
<td>0.001**</td>
<td>-1.2</td>
</tr>
<tr>
<td>Change score 8 months</td>
<td>-2.3 ± 3.1</td>
<td>2.6 ± 4.3</td>
<td>T(28)= -3.92</td>
<td>0.001**</td>
<td>-1.3</td>
</tr>
<tr>
<td>Stability of time</td>
<td></td>
<td></td>
<td>T(28)= -1.59</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Immediate recall score</td>
<td>21.6 ± 7.6</td>
<td>19.9 ± 6.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change score 3 weeks</td>
<td>-1.8 ± 5.9</td>
<td>3.1 ± 5.0</td>
<td>T(28)= -2.2</td>
<td>0.03*</td>
<td>-0.9</td>
</tr>
<tr>
<td>Change score 8 months</td>
<td>0.4 ± 4.4</td>
<td>6.4 ± 4.7</td>
<td>T(27)= -3.75</td>
<td>0.001**</td>
<td>-1.3</td>
</tr>
<tr>
<td>Stability of time</td>
<td></td>
<td></td>
<td>T(28)= -0.52</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td><strong>Executive functioning</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroop Color Word Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time card 3 - time card 2 seconds</td>
<td>44.0 ± 22.4</td>
<td>32.9 ± 11.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change score 3 weeks</td>
<td>-6.5 ± 14.1</td>
<td>-3.6 ± 7.9</td>
<td>T(27)= 0.43</td>
<td>0.67</td>
<td>-0.3</td>
</tr>
<tr>
<td>Change score 8 months</td>
<td>-7.6 ± 15.8</td>
<td>-3.2 ± 11.6</td>
<td>T(28)= 0</td>
<td>1.00</td>
<td>-0.3</td>
</tr>
<tr>
<td>Stability of time</td>
<td></td>
<td></td>
<td>T(28)= -0.39</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td><strong>Verbal fluency</strong></td>
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<tr>
<td>Phonemic (A)</td>
<td>11.8 ± 3.8</td>
<td>11.0 ± 4.9</td>
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<td>Change score 3 weeks</td>
<td>-1.8 ± 2.4</td>
<td>-0.2 ± 4.8</td>
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<td>-0.6 ± 3.0</td>
<td>1.9 ± 4.5</td>
<td>T(28)= -1.61</td>
<td>0.11</td>
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<td>T(28)= -0.75</td>
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Table 2 Extended

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<td>Phonemic (N)</td>
<td>11.9 ± 4.2</td>
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<td>T(28)= -0.87</td>
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<tr>
<td>Semantic (animals)</td>
<td>22.3 ± 5.6</td>
<td>23.3 ± 5.5</td>
<td>T(27)= -1.66</td>
<td>0.098</td>
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<td>-1.5 ± 5.2</td>
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<td>Change score 8 months</td>
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<td>0.2 ± 4.2</td>
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<td>0.56</td>
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<td>Stability of time</td>
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<td>Semantic (occupations)</td>
<td>15.6 ± 2.9</td>
<td>14.8 ± 3.5</td>
<td>T(28)= 2.28</td>
<td>0.03*</td>
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<td>-0.9 ± 3.9</td>
<td>2.9 ± 2.5</td>
<td>T(27)= -3.04</td>
<td>0.002**</td>
<td>-1.2</td>
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<tr>
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<td>-0.5 ± 4.0</td>
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<td>0.06</td>
<td>1.0</td>
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<tr>
<td>Stability of time</td>
<td></td>
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<td>T(28)= 1.08</td>
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<tr>
<td>Trail Making Test</td>
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</tr>
<tr>
<td>Time B/ time A</td>
<td>2.0 ± 0.4</td>
<td>2.2 ± 0.7</td>
<td>T(28)= 1.31</td>
<td>0.19</td>
<td>0.7</td>
</tr>
<tr>
<td>Change score 3 weeks</td>
<td>0.6 ± 0.8</td>
<td>0.1 ± 0.7</td>
<td>T(29)= 1.91</td>
<td>0.06</td>
<td>0.8</td>
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<tr>
<td>Change score 8 months</td>
<td>0.8 ± 1.6</td>
<td>-0.2 ± 0.6</td>
<td>T(28)= 1.08</td>
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<td>Stability of time</td>
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<td>Wisconsin Card Sorting Test</td>
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<tr>
<td>Number of categories</td>
<td>4.4 ± 2.1</td>
<td>5.1 ± 1.9</td>
<td>T(28)= -0.45</td>
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<td>Change score 3 weeks</td>
<td>-0.6 ± 2.1</td>
<td>-0.5 ± 1.6</td>
<td>T(28)= -0.34</td>
<td>0.74</td>
<td>0</td>
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<td>0.1 ± 1.7</td>
<td>0.1 ± 1.2</td>
<td>T(28)= 0.12</td>
<td>0.90</td>
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<tr>
<td>Stability of time</td>
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<tr>
<td>% of perseverative errors</td>
<td>19.9 ± 17.8</td>
<td>13.6 ± 11.1</td>
<td>T(28)= -0.38</td>
<td>0.86</td>
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<td>-1.8 ± 12.5</td>
<td>2.4 ± 12.6</td>
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<td>0.59</td>
<td>-0.1</td>
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<tr>
<td>Change score 8 weeks</td>
<td>-4.0 ± 8.4</td>
<td>-2.7 ± 12.0</td>
<td>T(28)= 0.78</td>
<td>0.44</td>
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<tr>
<td>Tower of London</td>
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<tr>
<td>Total number of steps</td>
<td>32.6 ± 5.5</td>
<td>32.2 ± 5.1</td>
<td>T(27)= -1.01</td>
<td>0.31</td>
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<tr>
<td>Change score 3 weeks</td>
<td>-2.1 ± 5.6</td>
<td>0.7 ± 8.0</td>
<td>T(27)= -1.89</td>
<td>0.07</td>
<td>-0.8</td>
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<td>Change score 8 months</td>
<td>-2.0 ± 7.2</td>
<td>3.9 ± 7.7</td>
<td>T(28)= -0.90</td>
<td>0.38</td>
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<td>Stability of time</td>
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<tr>
<td>Raven</td>
<td>9.2 ± 1.7</td>
<td>8.4 ± 3.0</td>
<td>T(27)= -1.97</td>
<td>0.05*</td>
<td>-0.8</td>
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<td>T(28)= -0.74</td>
<td>0.46</td>
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<td>-0.4 ± 2.5</td>
<td>0.5 ± 2.4</td>
<td>T(28)= 0.53</td>
<td>0.60</td>
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Table 2 Extended

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<th>P-value</th>
<th>Cohen’s d</th>
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<td>Continuous Performance Test</td>
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<td>1.7 ± 0.7</td>
<td>1.6 ± 0.7</td>
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<td>-0.1 ± 0.7</td>
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<td>0.1 ± 1.0</td>
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<td>-0.2 ± 1.0</td>
<td>0 ± 1.1</td>
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<td>0.19</td>
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<td><strong>Digit Symbol Substitution</strong></td>
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<td>Number of digits</td>
<td>63.5 ± 11.1</td>
<td>68.7 ± 16.4</td>
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<td>2.9 ± 5.6</td>
<td>1.1 ± 10.1</td>
<td>T(27)= 1.04</td>
<td>0.30</td>
<td>0.2</td>
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<tr>
<td>Change score 8 months</td>
<td>6.5 ± 7.4</td>
<td>2.7 ± 10.0</td>
<td>T(28)= 1.33</td>
<td>0.19</td>
<td>0.4</td>
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<tr>
<td>Stability of time</td>
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<td>T(28)= 0.67</td>
<td>0.52</td>
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<tr>
<td><strong>Motor system</strong></td>
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<td>Purdue Pegboard</td>
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<tr>
<td>Dominant hand</td>
<td>14.1 ± 1.7</td>
<td>13.5 ± 2.3</td>
<td></td>
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<tr>
<td>Change score 3 weeks</td>
<td>-0.2 ± 1.9</td>
<td>0.7 ± 1.9</td>
<td>T(27)= -1.2</td>
<td>0.23</td>
<td>-0.5</td>
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<tr>
<td>Change score 8 months</td>
<td>-0.3 ± 1.4</td>
<td>0.3 ± 1.4</td>
<td>T(27)= -0.63</td>
<td>0.54</td>
<td>-0.4</td>
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<tr>
<td>Stability of time</td>
<td></td>
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<td>T(28)= 0.50</td>
<td>0.62</td>
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<tr>
<td>Non-dominant hand</td>
<td>13.2 ± 2.6</td>
<td>12.8 ± 1.7</td>
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<tr>
<td>Change score 3 weeks</td>
<td>0.4 ± 1.6</td>
<td>0.2 ± 1.6</td>
<td>T(27)= 0.62</td>
<td>0.54</td>
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<td>Change score 8 months</td>
<td>0.5 ± 2.4</td>
<td>1.4 ± 1.9</td>
<td>T(28)= -0.94</td>
<td>0.35</td>
<td>-0.4</td>
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<td></td>
<td></td>
<td>T(28)= -1.30</td>
<td>0.20</td>
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</table>

Values are mean (SD). Change score at 3 weeks was defined as the score at three weeks postoperatively minus baseline score. Change score at eight months postoperatively was defined as the score at eight months postoperatively minus baseline score. Negative change scores indicate decline in performance except for test variables assessing speed and for error scores (Stroop Color Word Test, Trail Making Test, Wisconsin Card Sorting Test - % perseverative errors). A significant p-value at 3 weeks refers to an effect of the intervention at 3 weeks. A significant p-value at stability of time refers to an effect of the intervention at 8 months. A non-significant p-value at stability of time with a significant p-value at 3 weeks refers to an effect from the intervention at 3-weeks that is still present at 8 months. The effect size (Cohen’s d) is negative if the DBS group shows more decline in performance on this variable than the control group, or positive if the DBS group shows more improvement, except for the test variables assessing speed and for error scores.

* P ≤ 0.05, ** P ≤ 0.01.
postoperatively the DBS group had a significant reduced performance compared to the control group on the RCFT- copy score and verbal fluency (category occupations). The RCFT- recall score and RAPM showed a trend toward reduced performance in the DBS group compared to the control group. At eight months follow up, compared to the control group, the reduced performance on RCFT- copy score was still present as well as the trend toward reduced performance in the RCFT- recall score and RAPM. Verbal fluency on the other hand showed an improvement compared to the control group at eight months follow up.

CORRELATIONS
Regarding the question whether clinical changes after DBS treatment are associated with changes in cognitive functioning, exploratory correlational analyses were performed to examine relationships after eight months of stimulation between change in clinical measures and change in neuropsychological performance in the DBS group. We found no significant correlations between change in symptoms and change in cognitive functioning. Reduced performance on the copy score of the Rey Complex Figure Test did not significantly correlate with decrease of OCD symptoms \((r = -0.42, P = 0.14)\), anxiety symptoms \((r = -0.30, P = 0.29)\) and depression symptoms \((r = -0.15, P = 0.61)\). No significant correlation was found between reduced performance on the recall score of the Rey Complex Figure Test and decrease of OCD symptoms \((r = -0.28, P = 0.34)\), anxiety symptoms \((r = 0.42, P = 0.14)\) and depression symptoms \((r = 0.40, P = 0.15)\). Reduced performance of the score on the semantic verbal fluency task did not significantly correlate with decrease of OCD symptoms \((r = 0.10, P = 0.75)\), anxiety symptoms \((r = 0.25, P = 0.40)\) and depression symptoms \((r = 0.27, P = 0.35)\). Consistently, reduced performance on the score on the Raven did not correlate significantly with decrease of OCD symptoms \((r = -0.20, P = 0.52)\), anxiety symptoms \((r = 0.070, P = 0.82)\) and depression symptoms \((r = 0.37, P = 0.20)\).

5.4 DISCUSSION
In this study we investigated cognitive functioning of OCD patients treated with DBS targeted at the NAcc, pre-operatively, three weeks post-operatively and at eight months follow-up. This study is the first longitudinal study on cognitive functioning in DBS that includes a matched control group and thus controls for test-retest effects and natural fluctuations in cognitive functioning. The goals of this study were to establish the cognitive safety of DBS and to investigate whether clinical changes after DBS treatment are associated with changes in cognitive functioning.

With respect to the first goal, our results show that three weeks after surgery, performance was reduced in the DBS group compared to the control group on measures
of visual organization and semantic verbal fluency. We found a trend towards reduced performance in the DBS group on visual memory and abstract reasoning tasks. Cognitive functioning was unaffected on measures of cognitive flexibility, planning and cognitive inhibition and the domains of verbal memory, attention and motor system functioning. Despite substantial improvement in clinical symptoms following eight months of stimulation, the DBS group continued to show a reduced performance on a measure of visual organization and a trend toward reduced performance on measures of visual memory and abstract reasoning compared to the control group. Semantic verbal fluency, on the other hand, improved from three weeks to eight months postoperatively. Cognitive functioning was found to be stable on measures of cognitive flexibility, planning and cognitive inhibition as well as in the domains of verbal memory, attention and motor system functioning.

These findings are consistent with an earlier study of unilateral DBS of the NAcc in treatment-refractory OCD patients, where stable cognitive functioning was found one year after implantation on measures of planning, verbal fluency and sustained attention. However, a recent study of DBS in the anterior limb of the internal capsule/ventral striatum for OCD and MDD found a significant improvement in verbal memory. In addition, a study of DBS of the NAcc in MDD found significant improvements in sustained attention, visual organization, verbal and visual memory and visual perception. Differences in outcome between our study and these studies might be due to the difference in patient group and resulting differences in neuropsychological profile at baseline. For example OCD, contrary to MDD, is not associated with deficits in verbal memory. Besides, the lack of a control group and resulting practice effects (four neuropsychological assessments in one year) in the second study might also have contributed to differences in outcome.

Although the magnitude of the changes on measures of visual organization, visual memory, verbal fluency and abstract reasoning is relatively small compared to total baseline scores, the effect-sizes were large on all measures. Reduced visual memory, as assessed with the recall performance on the RCFT has been related to failures in the employment of appropriate organisational strategies, suggesting that failures on recall performance are secondary to impaired executive functioning. Also the reduced performance in visual organization and verbal fluency and trend toward decline in abstract reasoning hints at reduced executive functioning. Since all reduced performance was already present at the neuropsychological assessment three weeks post-surgery, it may result directly from surgical intervention: i.e. the insertion of electrodes through the frontal lobe. On the other hand, we can not exclude the possibility that the reduced performances are stimulation-related since ventral contact points were directly activated after surgery. The first hypothesis seems more likely because it is supported by the extensive literature on the effects of DBS on cognition in Parkinson’s disease. DBS for Parkinson’s disease seems to result in mild deficits in...
executive functioning, particularly in verbal fluency, that seem to occur immediately after surgery. Comparison of stimulation ‘on’ versus ‘off’ conditions suggest that these deficits could be partly due to electrode implantation through the frontal lobe, resulting in disruption of frontal-striatal-thalamic circuitry. The lack of recovery in visual organization, visual memory and abstract reasoning after eight months of stimulation in our study may be indicative of a persistent effect of surgery. The improvement in semantic verbal fluency and stabilization of abstract reasoning however could be due to several factors: first, a transient effect of surgical intervention, second, a positive effect of stimulation and third, an effect related to improvement in clinical symptoms. As changes in cognition were not correlated with changes in clinical symptoms, our results do not support the latter hypothesis.

To recapitulate, what can be stated about the neuropsychological safety of DBS targeted at the NAcc? Cognitive functioning was unaffected on the majority of neuropsychological measures and the magnitude of the changes on measures of visual organization, visual memory and abstract reasoning was relatively small. A recent study in this same group of patients shows that DBS has a positive impact on patients’ perception of their quality of life. In this study, patients labeled cognitive problems as mild side-effects, which never resulted in a request for discontinuing stimulation. This supports our assumption that the advantages in daily life resulting from the clinical effects of DBS outweigh the reduced cognitive performances. For these reasons we conclude that DBS targeted at the NAcc is a safe treatment in terms of cognition. Nevertheless, we observed some reduced performances on specific measures of executive functioning and found large effect sizes on these measures. This underlines the clinical relevance of these findings. It is likely that these effects result from the surgical intervention, while there seems to be no effect of stimulation. Because of the potential mild reduced performance on cognitive functioning, associated with the surgical intervention, it is important to fully inform patients before surgery about possible side-effects so they can make a deliberate decision for DBS treatment.

The second goal of our study was to investigate whether clinical changes after DBS treatment were associated with changes in cognitive functioning. Various cognitive deficits across several domains have been identified in OCD, including impaired performance on memory tasks as a consequence of strategy failures, deficits in reversal learning and impaired response inhibition. It is proposed that these impairments arise from inhibitory deficits, consistent with lateral orbitofrontal loop dysfunction, particularly in the orbitofrontal cortex. Impaired reversal learning has been identified as a neurocognitive endophenotype in OCD in a study in which patients and their unaffected siblings were compared. Conversely, a prospective study indicates that the neuropsychological deficits in OCD might be state-dependent: effective CBT in OCD patients improved performance on a memory task requiring
organizational strategy (RCFT). Our study provides the opportunity to investigate the relationship between large and rapid changes in symptoms and changes in cognitive functioning. Despite substantial clinical improvement after DBS treatment, patients deteriorated on the RCFT. Furthermore changes in clinical symptoms and changes in cognitive functioning were unrelated. Therefore, our results do not support the hypothesis that neuropsychological deficits in OCD are state-dependent and suggest that OCD symptoms and cognitive functioning may have a distinct neurobiological substrate.

5.5 LIMITATIONS

A limitation of this study is that patients were not randomized to either the DBS group or the control group. Alongside the DBS group and control group of treatment-refractory OCD patients we did not form a third group consisting of healthy subjects. Therefore it remains unclear whether the DBS group showed OCD specific cognitive deficits at baseline and how these are possibly influenced by DBS. Another limitation of this study is the immediate activation of stimulation at the ventral contact points after surgery, whereby discrimination between surgical effects and stimulation effects is hindered. Therefore, we recommend post-surgery neuropsychological assessment with inactive stimulation parameters for future studies. The stimulation of the dorsal contacts at eight months follow up compared to the stimulation of the ventral contacts at three weeks postoperatively could hinder the interpretation of our findings. However, it is unlikely that this was a confounding factor since previous literature showed that ventral stimulation compared to dorsal stimulation did not result in differences in cognitive functioning. Although our DBS patient group is relatively large compared to previous neuropsychological DBS studies, the small sample size is still a limitation of our study. The possible resulting lack of power might explain the discrepancy between the subjective reports of our DBS patients and the objective cognitive results. Mild forgetfulness was reported by five out of 16 patients and word finding problems were reported by three out of 16 patients as permanent side effects of DBS treatment. However, these subjective neuropsychological complaints were not objectified in the present study. On the other hand, this discrepancy might reflect the difference between subjective experiences of side effects and objective cognitive functioning after DBS, emphasizing the importance of objective neuropsychological assessment in DBS research. Interestingly a same discrepancy is recently reported in a study of DBS of the subgenual cingulated gyrus in treatment-resistant depression: short-term memory deficits, paraphasic errors of speech and word finding difficulties were reported while neuropsychological testing revealed general stability of cognitive functioning over
time. It may be that patients with certain characteristics (e.g. older patients) are more prone to cognitive effects of DBS, which level out if group means are investigated. This should be investigated in future studies with a larger sample.

5.6 CONCLUSION

The results of this study show an overall picture of preserved cognition following bilateral DBS targeted at the NAcc in treatment-refractory OCD patients. Consequently, it could be considered as a relatively safe method in terms of cognition. A reduced performance was found on specific tasks measuring executive functioning, likely related to the surgical intervention. The lack of improvement in cognitive functioning with on-going stimulation, in spite of pronounced symptomatic changes, may suggest an independent relation between cognitive functioning and severity of OCD symptoms. Before firm conclusions can be drawn, replication studies should be performed in which we strongly recommend a larger sample of included DBS patients, inclusion of control groups and a comprehensive neuropsychological battery.
REFERENCES


CHAPTER 6

THE LINK BETWEEN OBSESSIVE-COMPULSIVE DISORDER AND COGNITION: LESSONS FROM DEEP BRAIN STIMULATION

Mariska Mantione, Dorien Nieman, Damiaan Denys

Submitted
ABSTRACT

Several cognitive deficits have been associated with obsessive-compulsive disorder. However, the nature of this association remains unclear. Deep brain stimulation is a novel treatment for obsessive-compulsive disorder leading to pronounced improvement in symptoms. The aim of this study was to investigate whether deep brain stimulation affects cognitive functioning. Therefore, we compared neuropsychological performance in an ‘on’ versus ‘off’ stimulation condition. Fourteen patients with treatment-refractory obsessive-compulsive disorder underwent deep brain stimulation targeted at the nucleus accumbens. They were randomly allocated to two groups in a double-blind cross-over phase: the first group (3 females; 3 males; mean age 42.8 ± 13.5) underwent 2 weeks of active stimulation followed by 2 weeks of sham stimulation and the second group (3 females; 5 males; mean age 46.0 ± 7.7) vice versa. Cognitive functioning was assessed at baseline, after two weeks and after four weeks. Despite significant change in obsessive-compulsive symptoms in the ‘on and ‘off’ stimulation conditions, cognitive functioning remained unchanged. Obsessive-compulsive symptoms and cognitive deficits may therefore have different neurobiological substrates that are relatively unrelated. Alternatively, the state-of-the-art neuropsychological tests that were employed may not optimal to objectify changes in cognitive functioning of patients with obsessive-compulsive disorder.
6.1 INTRODUCTION

The daily behaviour of patients with obsessive-compulsive disorder (OCD) suggests a profound cognitive dysfunction. Indeed, this is substantiated by evidence of poorer performance of OCD patients compared to healthy controls across several neuropsychological domains. Deficits in memory and executive functions, in particular set-shifting and response inhibition, have been reported. The largest effect sizes have been found on tests of non-verbal memory. These cognitive deficits are hypothesized to be involved in the aetiology and the maintenance of OCD symptoms. It has been investigated whether cognitive deficits are state dependent i.e. fluctuate with the severity of OCD symptoms or are trait related, i.e. underlie OCD and are independent of the severity of OCD symptoms. Most studies found persistent cognitive deficits after treatment with medication and cognitive behavioural therapy (CBT). Impaired visuo-spatial memory and organisational skills have been suggested as trait features of OCD and impaired reversal learning has been identified as a neurocognitive endophenotype of OCD. However, one study found that cognitive deficits improved after CBT.

Deep brain stimulation (DBS) is a treatment in which chronic, high frequency, electrical stimulation is delivered to specific brain areas via implanted electrodes. Acute and pronounced effects on OCD symptoms have been reported after optimization of stimulation parameters. So far, the effect of these large and rapid changes on cognitive functioning has barely been studied. In a previous study of our group on DBS and cognition in treatment-refractory OCD patients we found a reduced performance on several specific measures of cognitive functioning despite a pronounced effect on clinical symptoms, suggesting that the severity of OCD symptoms is independent of cognitive functioning. The objective of the present study is to extend our previous findings, by evaluating the neuropsychological performance of treatment-refractory OCD patients that underwent DBS targeted at the nucleus accumbens (NAc) in an ‘on’ and ‘off’ stimulation condition. DBS is perfectly suitable for a double-blind experiment since stimulation may be switched on and off without patient nor experimenter knowing.

6.2 MATERIALS AND METHODS

STUDY OVERVIEW

This study was part of a clinical trial, investigating the effectiveness and safety of DBS targeted at the NAc for treatment-refractory OCD. The inclusion and exclusion criteria, study design and surgical procedure have been extensively described by Denys et al. In short, the original clinical trial consisted of 3 sequential treatment phases: an open...
eight-month treatment phase, followed by a double-blind cross over phase of four weeks and an ensuing maintenance phase of one year. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study was approved by the Medical Ethical Committee of the AMC. Informed consent of the patients was obtained after the nature of the procedures had been fully explained.

The present study focuses on the double-blind cross-over phase. Fourteen, treatment-refractory OCD patients were randomly allocated to two groups: group 1 underwent 2 weeks of active stimulation followed by 2 weeks of sham stimulation (on-off group) and group 2 underwent 2 weeks of sham stimulation followed by 2 weeks of active stimulation (off-on group). Block randomization was used with computer-generated random sequence, providing adequate concealment. A comprehensive neuropsychological test battery was administered before patients entered the double-blind cross-over phase, i.e. after eight months of stimulation (T1). The same neuropsychological battery was repeated after the end of the first 2 weeks (active stimulation for group 1 and sham stimulation for group 2) (T2) and last 2 weeks (sham stimulation for group 1 and active stimulation for group 2) (T3). At the start of the cross-over phase, all patients were on monopolar stimulation with active dorsal contacts 2 and 3, a frequency of 130 Hz, a pulse width of 90 microseconds and voltage ranging from 3.5 to 5.0 V. Medication was kept stable during the whole cross-over phase.

NEUROPSYCHOLOGICAL TESTING

The neuropsychological test battery encompassed the cognitive domains of intelligence, memory, visuoconstructional function, executive functions and inhibition, attention and motor system. Specifically, the test battery was composed of the following measures: the Dutch version of the National Adult Reading Test (DART), the short 12-problem version (set I) of the Raven Advanced Progressive Matrices (RAPM), the Dutch version of the California Verbal Learning Test (CVLT), the digit span (forwards and backwards) of the Wechsler Adult Intelligence Scale (WAIS-III), the Rey Complex Figure Task (RCFT), the Stroop Color Word Test, verbal fluency, the Trail Making Test (TMT), the Wisconsin Card Sorting Test (WCST), the Tower of London (ToL), the Continuous Performance Test – identical pairs, the Digit Symbol Substitution of the WAIS-III and the Purdue Pegboard. Further description of these standard neuropsychological measures is not included here, but can be found in Mantione et al.14 Where available, alternated forms of the neuropsychological tests were used in a balanced order across patients to minimize practice effects.

CLINICAL SYMPTOMS

Obsessive-compulsive-, depressive- and anxiety symptoms of the DBS group and control
group were assessed with the Y-BOCS\textsuperscript{15,16}, the Hamilton Anxiety Scale (HAM-A)\textsuperscript{17} and the Hamilton Depression Scale (HAM-D)\textsuperscript{18} respectively.

**STATISTICAL ANALYSIS**

All data were analysed using the SPSS statistical package for Windows (version 20.0; IBM Company Chicago, IL, USA). Differences in age, premorbid intelligence, clinical symptoms and neuropsychological performance between both groups after eight months of stimulation were examined by means of a Mann-Whitney U-test. Gender differences were analysed using a Chi-square test. To assess the effect of stimulation on neuropsychological performance a linear mixed model analysis was conducted with period and treatment as independent variables. Analyses were performed by testing three effects: carry-over effects (the influence of the first treatment carries over when the second treatment is applied), period effects (the effect of stimulation is different in the on-off group than in the off-on group, e.g. because of familiarization with the study situation) and treatment-effects. Considering the small sample sizes in both groups we decided to correct for baseline differences (T1) between both groups on neuropsychological performance in our analysis. Given the relation between IQ and neuropsychological performance and age and neuropsychological performance we also decided to correct for baseline differences in IQ (DART) and age (T1). Neuropsychological performance, IQ and age were included as covariates in the mixed model analysis. To account for multiple comparisons, a more stringent threshold of $P < 0.01$ was used to assess statistical significance. Results with $0.01 < P < 0.05$ are reported as trends. Spearman’s Rho coefficients were used to calculate correlations between change in clinical symptoms (Y-BOCS, HAM-A and HAM-D) and change in neuropsychological performance during the double blind cross-over period.

**6.3 RESULTS**

**CLINICAL CHARACTERISTICS**

Fourteen patients entered the double-blind cross-over period. Six patients were allocated to group 1 (stimulation on – stimulation off) and eight patients were allocated to group 2 (stimulation off – stimulation on). One patient of group 1 was lost to follow-up at the 2-week period of sham stimulation as rebound of symptoms made neuropsychological evaluation impracticable. The results of this patient were included in the baseline to active stimulation analysis. There were no significant differences between patients in both groups with respect to age, gender, premorbid intelligence and Y-BOCS, HAM-A and HAM-D scores before cross-over (Table 1).
Table 1 Comparison of both groups at baseline, before cross-over on clinical symptoms.

<table>
<thead>
<tr>
<th></th>
<th>After 8 months of stimulation</th>
<th>Statistics</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n=6)</td>
<td></td>
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<tr>
<td></td>
<td>Stimulation on</td>
<td></td>
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<tr>
<td></td>
<td>Stimulation off</td>
<td>-0.52</td>
<td>0.60</td>
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<tr>
<td></td>
<td>-Stimulation on</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Group 2 (n=8)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Stimulation off</td>
<td>0.22</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>-Stimulation on</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>42.8 ± 13.5</td>
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<tr>
<td><strong>Gender (f/m)</strong></td>
<td>3/3</td>
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<tr>
<td><strong>Premorbid intelligence (DART)</strong></td>
<td>95.5 ± 10.0</td>
<td>-1.43</td>
<td>0.15</td>
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<tr>
<td></td>
<td>89.0 ± 8.3</td>
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<tr>
<td><strong>y-BOCS</strong></td>
<td>23.3 ± 10.0</td>
<td>-0.71</td>
<td>0.48</td>
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<td></td>
<td>18.8 ± 10.7</td>
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<tr>
<td><strong>HAM-A</strong></td>
<td>12.0 ± 8.0</td>
<td>-1.11</td>
<td>0.27</td>
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<td></td>
<td>14.3 ± 5.8</td>
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<td><strong>HAM-D</strong></td>
<td>10.8 ± 7.1</td>
<td>-1.04</td>
<td>0.30</td>
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<td></td>
<td>14.6 ± 5.8</td>
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</tbody>
</table>

HAM-A= Hamilton Anxiety rating scale; HAM-D= Hamilton Depression rating scale; y-BOCS= Yale-Brown Obsessive-Compulsive Scale

**CLINICAL SYMPTOMS**

Stimulation caused a mean reduction of 8.3 ± 2.3 points (P=.004) on the Y-BOCS, a mean reduction of 12.1 ± 9.1 points (P<.01) on the HAM-A and a mean reduction of 11.3 ± 7.2 points (P<.01) on the HAM-D.

**NEUROPSYCHOLOGICAL OUTCOME**

Before cross-over there was a significant difference between both groups on the percentage of perseverative errors of the WCST (P=.01) and copy score of the RCFT (P=.03). We found one significant carry-over effect (P= 0.047 for treatment × period interaction) on the RAPM and therefore excluded this test from the analysis. For all other neuropsychological measures we assessed the effect of stimulation on cognitive functioning using a mixed-model regression analysis with treatment and period as independent variables. The outcomes on neuropsychological tests for both groups before cross-over, after week 2 (active stimulation for group 1 and sham stimulation for group 2) and week 4 (sham stimulation for group 1 and active stimulation for group 2) are shown in Table 2. After correction for period effects, treatment (stimulation) only showed a trend towards reduced performance on the digit span backwards. The other cognitive tests showed no significant difference under stimulation (stimulation ‘on’ versus stimulation ‘off’). We found no significant correlations between change in symptoms and change in cognitive functioning.
Table 2 Raw cognitive test scores at baseline and change scores at 3 weeks and 8 month follow-up for the DBS and control group. P values are corrected for differences at baseline.

<table>
<thead>
<tr>
<th>Test</th>
<th>Condition</th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Statistics</th>
<th>P-value</th>
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<td><strong>Memory</strong></td>
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<tr>
<td>California Verbal Learning Test</td>
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<tr>
<td>Total recall in 5 trial</td>
<td>Group 1 (on-off)</td>
<td>62.8 ± 12.8</td>
<td>59.7 ± 13.2</td>
<td>66.8 ± 10.1</td>
<td>T = -0.99</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>48.6 ± 12.4</td>
<td>43.5 ± 9.1</td>
<td>56.6 ± 12.9</td>
<td>T = -0.99</td>
<td>0.35</td>
</tr>
<tr>
<td>Digit span</td>
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<tr>
<td>Forwards</td>
<td>Group 1 (on-off)</td>
<td>9.3 ± 1.8</td>
<td>10.7 ± 0.8</td>
<td>9.6 ± 13</td>
<td>T = -0.88</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>8.6 ± 1.7</td>
<td>10.4 ± 2.3</td>
<td>10.3 ± 2.1</td>
<td>T = -0.88</td>
<td>0.40</td>
</tr>
<tr>
<td>Backwards</td>
<td>Group 1 (on-off)</td>
<td>6.8 ± 2.5</td>
<td>7.8 ± 1.7</td>
<td>10.0 ± 1.0</td>
<td>T = 2.55</td>
<td>0.03</td>
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<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>6.3 ± 2.4</td>
<td>7.0 ± 2.2</td>
<td>7.4 ± 2.7</td>
<td>T = 2.55</td>
<td>0.03</td>
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<tr>
<td>Rey Complex Figure Test</td>
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<tr>
<td>Copy score</td>
<td>Group 1 (on-off)</td>
<td>31.8 ± 3.9</td>
<td>32.3 ± 1.8</td>
<td>32.4 ± 2.5</td>
<td>T = 1.08</td>
<td>0.3</td>
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<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>27.3 ± 3.6</td>
<td>29.7 ± 2.4</td>
<td>27.8 ± 3.3</td>
<td>T = 1.08</td>
<td>0.3</td>
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<tr>
<td>Immediate recall score</td>
<td>Group 1 (on-off)</td>
<td>23.3 ± 7.8</td>
<td>27.2 ± 5.7</td>
<td>24.5 ± 6.2</td>
<td>T = -1.76</td>
<td>0.11</td>
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<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>21.2 ± 5.6</td>
<td>17.6 ± 8.5</td>
<td>21.2 ± 8.0</td>
<td>T = -1.76</td>
<td>0.11</td>
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<tr>
<td><strong>Executive functioning</strong></td>
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<td>Stroop Color Word Test</td>
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<tr>
<td>Time card 3 – time card 2 seconds</td>
<td>Group 1 (on-off)</td>
<td>35.8 ± 22.5</td>
<td>31.2 ± 19.5</td>
<td>20.6 ± 10.1</td>
<td>T = -0.83</td>
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<td>Group 2 (off-on)</td>
<td>39.4 ± 17.0</td>
<td>30.5 ± 12.6</td>
<td>28.5 ± 6.4</td>
<td>T = -0.83</td>
<td>0.43</td>
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<tr>
<td>Verbal fluency</td>
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<tr>
<td>Phonemic (A)</td>
<td>Group 1 (on-off)</td>
<td>13.2 ± 4.3</td>
<td>15.2 ± 4.6</td>
<td>14.0 ± 2.9</td>
<td>T = -1.93</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>10.0 ± 3.6</td>
<td>10.4 ± 4.3</td>
<td>12.4 ± 4.8</td>
<td>T = -1.93</td>
<td>0.08</td>
</tr>
<tr>
<td>Phonemic (N)</td>
<td>Group 1 (on-off)</td>
<td>11.3 ± 3.5</td>
<td>10.2 ± 5.7</td>
<td>12.0 ± 2.1</td>
<td>T = 1.01</td>
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<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>12.1 ± 2.7</td>
<td>11.1 ± 4.6</td>
<td>11.0 ± 3.1</td>
<td>T = 1.01</td>
<td>0.34</td>
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<tr>
<td>Semantic (animals)</td>
<td>Group 1 (on-off)</td>
<td>21.0 ± 2.9</td>
<td>23.7 ± 1.8</td>
<td>22.4 ± 3.4</td>
<td>T = -1.74</td>
<td>0.11</td>
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<td>Group 2 (off-on)</td>
<td>22.0 ± 6.7</td>
<td>19.4 ± 6.3</td>
<td>22.5 ± 7.5</td>
<td>T = -1.74</td>
<td>0.11</td>
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<tr>
<td>Semantic (occupations)</td>
<td>Group 1 (on-off)</td>
<td>17.7 ± 2.3</td>
<td>17.3 ± 3.7</td>
<td>16.4 ± 2.8</td>
<td>T = -1.00</td>
<td>0.34</td>
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<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>17.8 ± 5.2</td>
<td>16.4 ± 4.8</td>
<td>17.6 ± 2.9</td>
<td>T = -1.00</td>
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<tr>
<td>Trail Making Test</td>
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<td></td>
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<tr>
<td>Time B/ time A</td>
<td>Group 1 (on-off)</td>
<td>3.2 ± 2.4</td>
<td>1.8 ± 0.2</td>
<td>2.0 ± 0.5</td>
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<td>0.07</td>
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<tr>
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<td>Group 2 (off-on)</td>
<td>2.6 ± 0.8</td>
<td>2.5 ± 0.4</td>
<td>2.1 ± 0.8</td>
<td>T = 1.99</td>
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<tr>
<td>Wisconsin Card Sorting Test</td>
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<tr>
<td>Number of categories</td>
<td>Group 1 (on-off)</td>
<td>5.8 ± 0.4</td>
<td>6.0 ± 0</td>
<td>6.0 ± 0</td>
<td>T = 0.70</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>3.6 ± 2.8</td>
<td>2.8 ± 2.8</td>
<td>3.3 ± 2.6</td>
<td>T = 0.70</td>
<td>0.50</td>
</tr>
<tr>
<td>% of perseverative errors</td>
<td>Group 1 (on-off)</td>
<td>6.9 ± 2.1</td>
<td>7.4 ± 2.6</td>
<td>7.2 ± 1.9</td>
<td>T = 0.90</td>
<td>0.39</td>
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<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>22.4 ± 14.5</td>
<td>20.1 ± 15.2</td>
<td>16.9 ± 13.8</td>
<td>T = 0.90</td>
<td>0.39</td>
</tr>
</tbody>
</table>
**6.4 DISCUSSION**

We investigated the cognitive functioning of treatment-refractory OCD patients after DBS targeted at the NAc in ‘on’ and ‘off’ stimulation. Despite significant change in OCD symptoms, cognitive functioning remained unchanged. In a previous study we found reduced performance on several measures of executive functioning besides overall preserved cognitive functioning after eight months of open stimulation. The present results provide further evidence for the hypothesis that cognitive functioning is independent of the severity of OCD symptoms.

To date, only two other studies reported about the effect of stimulation on cognitive functioning. Comparable to our findings, Abelson et al. (2005) found no consistent patterns of cognitive change with stimulation. Also Mallet et al. (2010) found that neuropsychological performance at the end of active stimulation did not differ significantly from the neuropsychological performance at the end of sham stimulation.

### Table 2 Extended

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Statistics</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tower of London</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total number of steps</td>
<td>Group 1 (on-off)</td>
<td>29.5 ± 6.8</td>
<td>34.0 ± 8.1</td>
<td>31.2 ± 5.3</td>
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<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>30.3 ± 7.9</td>
<td>32.4 ± 7.9</td>
<td>31.6 ± 8.8</td>
<td></td>
</tr>
<tr>
<td><strong>Attention</strong></td>
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<td>Continuous Performance Test</td>
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<tr>
<td>Figures d-prime</td>
<td>Group 1 (on-off)</td>
<td>1.6 ± 1.0</td>
<td>1.8 ± 1.3</td>
<td>2.5 ± 0.6</td>
<td>T= -0.09</td>
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<td>Group 2 (off-on)</td>
<td>1.5 ± 0.7</td>
<td>1.6 ± 1.2</td>
<td>1.9 ± 1.3</td>
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</tr>
<tr>
<td>Figures Log-B</td>
<td>Group 1 (on-off)</td>
<td>0.3 ± 0.5</td>
<td>0.1 ± 0.5</td>
<td>0.5 ± 0.7</td>
<td>T= 1.62</td>
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<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>0.1 ± 0.9</td>
<td>0.2 ± 1.1</td>
<td>-0.7 ± 1.0</td>
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</tr>
<tr>
<td><strong>Digit Symbol Substitution</strong></td>
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<tr>
<td>Number of digits</td>
<td>Group 1 (on-off)</td>
<td>65.2 ± 12.3</td>
<td>68.2 ± 12.8</td>
<td>69.4 ± 11.9</td>
<td>T= -1.54</td>
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<td>Group 2 (off-on)</td>
<td>70.3 ± 16.2</td>
<td>69.4 ± 18.5</td>
<td>75.0 ± 20.7</td>
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<tr>
<td><strong>Purdue Pegboard</strong></td>
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<td>Dominant hand</td>
<td>Group 1 (on-off)</td>
<td>14.2 ± 0.8</td>
<td>14.0 ± 0.9</td>
<td>14.6 ± 1.7</td>
<td>T= 0.08</td>
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<td>Group 2 (off-on)</td>
<td>12.7 ± 2.6</td>
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</tr>
<tr>
<td>Non-dominant hand</td>
<td>Group 1 (on-off)</td>
<td>13.8 ± 1.7</td>
<td>13.8 ± 1.2</td>
<td>14.8 ± 0.8</td>
<td>T= 2.09</td>
</tr>
<tr>
<td></td>
<td>Group 2 (off-on)</td>
<td>13.0 ± 2.6</td>
<td>13.6 ± 1.9</td>
<td>13.9 ± 2.6</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean raw scores (SD). Higher scores indicate better performance except for test variables assessing speed and for error scores (Stroop Color Word Test, Trail Making Test, Wisconsin Card Sorting Test - % perseverative errors, Tower of London).
stimulation. Our findings are also in line with the majority of literature that found no persistent patterns of change after treatment with medication and CBT.4-8

Two hypotheses could explain these findings: first, OCD symptoms and cognitive deficits have different neurobiological substrates that are relatively unrelated, and second, the state-of-the-art neuropsychological tests that were employed are not optimal to objectify changes in cognitive functioning observed in and reported by OCD patients. Regarding the first hypothesis, our results suggest that the effects of DBS can be ascribed to changes in neurobiological substrates underlying OCD symptoms and not cognition. With our research design, we could not investigate if cognitive deficits in OCD are trait markers. It has been shown previously that family members without OCD symptoms of OCD patients suffer the same cognitive deficits as patients.21 If cognitive deficits and OCD symptoms are unrelated, it is of course challenging to know why they both are present. Regarding the second hypothesis, it is plausible that OCD patients show changes in cognitive functioning in daily life after DBS; for example, they are less focused on the object of their OCD (e.g. dirt, symmetry etc), that may suggest a change in attention, and they are more able to dismiss obsessions, that may suggest an improvement in mental flexibility. It may be difficult to investigate idiosyncratic changes in cognition in a scientific research design in which the same test is administered to all patients under controlled conditions in a lab. This situation may be too far removed from real life cognitive functioning.

A shortcoming of this study is that, given the lack of a healthy control group, it is unknown if OCD patients had cognitive deficits at forehand. Also practice effects might have affected the results, since there were three neuropsychological assessments in four weeks following earlier assessments in the open phase of the study. This may have especially influenced the results on tests in the memory domain. Furthermore, even though patients served as their own controls in a cross-over design, the sample size in this study was small, probably resulting in low power. Given the small sample size, group 1 and group 2 showed differences in certain neuropsychological test results before entering the double-blind cross-over phase, despite randomization. Although we corrected for baseline differences in our analysis we can not rule out that this might have influenced our results. Consequently, our findings should be viewed as exploratory.
REFERENCES


PART III

SIDE EFFECTS OF DEEP BRAIN STIMULATION IN OBSESSIVE-COMPULSIVE DISORDER
CHAPTER 7

SMOKING CESSION AND WEIGHT LOSS FOLLOWING CHRONIC DEEP BRAIN STIMULATION OF THE NUCLEUS ACCUMBENS: THERAPEUTIC AND RESEARCH IMPLICATIONS.

Mariska Mantione, Wim van de Brink, P. Richard Schuurman, Damiaan Denys

ABSTRACT

BACKGROUND
Smoking and overeating are compulsory habits that are difficult to stop. Several studies have shown involvement of the nucleus accumbens in these and other addictive behaviours. In this case-report we describe a patient who quit smoking and lost weight without any effort and we review the underlying mechanisms of action.

CLINICAL PRESENTATION
A 47-year old woman presented with chronic, treatment-refractory obsessive-compulsive disorder, nicotine dependence and obesity.

INTERVENTION
The patient was treated with deep brain stimulation of the nucleus accumbens for obsessive-compulsive disorder. Unintended, effortless and simultaneous smoking cessation and weight loss were observed.

CONCLUSION
This study supports the idea of compulsivity with common circuitry in the processing of diverse rewards and suggests that DBS of the nucleus accumbens could be a possible treatment of patients with a dependency not responding to currently available treatments.
7.1 INTRODUCTION

Recent data show that 28.8% of the European population smoke cigarettes on a daily basis. Although most smokers endorse the importance to quit, very few will actually quit smoking without active treatment. Nicotine withdrawal symptoms (insomnia, anxiety, dysphoria, irritability, difficulty concentrating, and restlessness) generally persist for about 3 weeks often leading to early relapse. However, craving can persist for months or even years. As a consequence 90 - 95 % of all spontaneous quitters relapse within one year. Moreover nicotine increases energy expenditure and reduces appetite, and therefore smoking cessation is associated with an average weight gain of 5-10 kg.

Obesity (body mass index > 30) has dramatically increased over the past 30 years and is now afflicting about a third of the adult population in Europe. Interventions based on the promotion of lifestyle changes to decrease excessive food consumption (dieting) and increased physical activity (exercise) are effective and can normalize weight if followed rigorously, but unfortunately they are very difficult to sustain.

In the course of treatment with deep brain stimulation (DBS) of the nucleus accumbens for chronic treatment-refractory obsessive-compulsive disorder, we observed in a 47-year old patient a non-intended, spontaneous stop of smoking and a sustained reduction of food intake resulting in substantial weight loss.

7.2 CASE REPORT

Mrs. D, a 47-year old, married woman was referred for deep brain stimulation (DBS) of the nucleus accumbens to treat a severe refractory obsessive-compulsive disorder (OCD). She had been suffering from OCD for 26 years and reported obsessions concerning fear of dirt, need for symmetry and excessive cleaning and ordering compulsions. She scored a total of 38 points on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS: extremely severe OCD), 17 points on the Hamilton Anxiety Scale (HAM-A: mild anxiety) and 11 points on the Hamilton Depression Scale (HAM-D: mild depression). She used a combination of paroxetine 60 mg and quetiapine 250 mg for her obsessive-compulsive symptoms. She also had a long history of smoking: for 22 years she smoked a packet of cigarettes daily. In the last 2 years she had been smoking 35 cigarettes a day. She tried to quit smoking twice (one spontaneous quitting attempt and one quitting attempt with active treatment) but relapsed both times. She scored a total of 10 points on the Fagerstrom Test for Nicotine Dependence (FTND: very high dependence). At the time of inclusion Mrs. D. was 107 kg with a length of 1.70 cm, corresponding with a BMI of 37 (obesity).
After signing informed consent, Mrs D. was included in the DBS study. With reference to the side effects, the paroxetine was reduced from 60 mg to 20 mg. In November 2006, two electrodes (Model 3389, Medtronic Inc. Minneapolis, MN, USA) were implanted bilaterally in the nucleus accumbens and connected to a Soletra model 7428 DBS stimulator (Medronics, Inc. Minneapolis, MN, USA). The center of the deepest contacts was positioned 3 mm in front of the anterior border of the anterior commissure (AC), 7 mm lateral and 4 mm below the line connecting the anterior and posterior commissure (PC). This was verified by post-operative CT, fused with preoperative MR. The following stimulation-parameters were used directly after implantation: monopolar stimulation with contacts 0 and 1 negative (cathode); pulse width 90 µs; frequency 185 Hz; voltage 3.5 V.

Three weeks after implantation the stimulation of the electrode contacts was changed from contacts 0 and 1 to contacts 2 and 3 (negative); other stimulation parameters remained the same. From this moment, obsessive compulsive symptoms started to improve gradually. Within a period of 5 months Y-BOCS scores dropped from 38 to 2 points (subclinical OCD symptoms). Time spent on obsessions and compulsions declined from 20 hours a day to less than 1 hour a day. The HAM-A gradually declined from 17 to 2 points (subclinical anxiety) and the HAM-D from 11 to 3 points (subclinical depression). Although she was still having obsessions and compulsions for one hour a day, she was not impaired by them in her daily life anymore. The patient enjoyed her new life. In the summer of 2007, she attained the best improvement in OCD and anxiety symptoms. At this moment she reported that she realized that she was not dependent on her compulsions anymore, but that she was still dependent on her cigarettes. This awareness of being a smoker made her feel uncomfortable about herself. With this in mind she started to watch smokers and non-smokers and came to the conclusion that non-smokers looked healthier and more relaxed than smokers. At the same time, the smell and the taste of the cigarettes became unpleasant to her. Therefore, she decided to quit smoking. She told herself that she would be a non-smoker starting the next day. That day she stopped smoking. She did not crave for cigarettes and did not experience withdrawal symptoms. Four days after she stopped smoking, she felt very comfortable with her new lifestyle as a non-smoker. She even did not experience craving while sitting next to her husband, who continued smoking 30 cigarettes a day. In contrast to previous quitting attempts, she now pities smokers instead of envying them. She recently convinced her husband to quit smoking too, although he is having a hard time, experiencing serious withdrawal.

For Mrs. D., the possibility of weight gain after smoking cessation was a serious concern. The first months after DBS surgery she gained 8 kg. She considered losing weight before smoking cessation, but decided to do both at the same time because it would be hard
anyway. Two weeks after she stopped smoking she started to lose weight with support of a dietician. At that point she weighed 115 kg (BMI= 39). Due to her new eating pattern she started to lose 1 kg a week. After losing the first 10 kg she started exercising, starting once a week and building up to 5 times a week. Ten months after she started dieting, she lost 44 kg without any effort and reached her goal: 71 kg (BMI=25).

The 2-year follow-up showed that Mrs. D. maintained her weight of 71 kg. She is still not smoking and there is no wish to start smoking again. At that moment she scored 1 point on the Y-BOCS (subclinical OCD symptoms), 3 points on the HAM-A (subclinical anxiety) and 3 points on the HAM-D (subclinical depression). It should be noticed that Mrs. D. did not stop smoking and did not start to loose weight immediately following DBS. This happened 10 months after DBS surgery when most of her obsessive-compulsive symptoms had disappeared. Mrs. D. describes that before DBS surgery the only thing she could think of and that was important to her was keeping her house clean. As a result she smoked and ate automatically, without thinking. With the improvement of OCD symptoms, she reported having tranquility in her head for the first time since many years. This gave her the possibility to stop her compulsions and subsequently to think about other habits she wanted to change. She feels exactly the same way about smoking cessation and losing weight: she banished them both effortlessly from her life.

Figure 1 Postoperative lead locations superimposed on a preoperative magnetic resonance imaging scan
7.3 DISCUSSION

The case described above is notable for the following reasons. After obsessive-compulsive symptoms had disappeared the patient stopped smoking and remained abstinent without any effort and without craving and withdrawal symptoms. Smoking cessation was not accompanied by the expected but unwanted weight gain, but by an effortless reduction in food intake resulting in a (desired) loss of 28 kg. This case demonstrates that compulsions, smoking and excessive food consumption were perceived as undesirable habits by the patient and that DBS of the nucleus accumbens may alter compulsivity in a range of different psychiatric diseases.

Recent evidence suggests that compulsivity is related to the brain reward system, in which dopamine projections of the ventral tegmental area to the nucleus accumbens and parts of the frontal lobe are involved, regardless of whether the reward is chemical or behavioral. Clinical and preclinical evidence consistently points to a hyperactive dopaminergic circuit in OCD, and suggests increased dopamine activity in the ventral striatum. Similarly, cigarette exposure has been associated with activation of the cortico-striatal circuits with increased dopamine concentrations in the ventral striatum/nucleus accumbens. Moreover, brain mechanisms of overeating leading to obesity appear to be comparable to those that ultimately result in compulsive drug consumption in addictive disorders. Both food consumption and drug use are driven by their rewarding properties, which have been linked to increases in dopaminergic activity in brain reward circuits. The enhanced reward of drugs in addiction and to food in obesity is most frequently associated with changes of the nucleus accumbens, ventral pallidum and hypothalamus.

The precise mechanism of DBS remains uncertain. Imaging studies with high frequency DBS in OCD are few and somewhat contradictory, as they have demonstrated both increases and decreases in orbitofrontal metabolism. In addition results from an in vivo animal study suggest the inhibition of certain subsets of the orbitofrontal neurons.

This case suggests that DBS of the nucleus accumbens affects cortico-striatal circuits regardless of the pathological condition involved, obsessive-compulsive symptoms, smoking or obesity. Our finding corroborates the finding of two previous studies showing efficacy of nucleus accumbens modulation in treatment-refractory addiction. Kuhn et al. described a case of unintended remission of alcohol dependence after deep brain stimulation of the nucleus accumbens in a patient with severe anxiety disorder and secondary depressive disorder and Gao et al. reported sustained abstinence of in 11 of 28 (39%) patients with treatment-refractory opiate dependence after bilateral lesioning of the nucleus accumbens.
7.4 CONCLUSION

Together these findings suggest that DBS of the nucleus accumbens might be able to suppress symptoms of various disorders in which the pathophysiology involves the brain reward circuitry, of which the nucleus accumbens is a critical relay station. Besides OCD both substance abuse and eating disorders might belong to this category of diseases. However, more research is needed to confirm our preliminary findings and to understand the underlying mechanisms of action.
REFERENCES

CHAPTER 8

A CASE OF MUSICAL PREFERENCE FOR JOHNNY CASH FOLLOWING DEEP BRAIN STIMULATION OF THE NUCLEUS ACCUMBENS

Mariska Mantione, Martijn Figee, Damiaan Denys

ABSTRACT

Music is among all cultures an important part of the live of most people. Music has psychological benefits and may generate strong emotional and physiological responses. Recently, neuroscientists have discovered that music influences the reward circuit of the nucleus accumbens, even when no explicit reward is present. In this clinical case study, we describe a 60-year old patient who developed a sudden and distinct musical preference for Johnny Cash following deep brain stimulation (DBS) targeted at the nucleus accumbens. This case report substantiates the assumption that the nucleus accumbens is involved in musical preference, based on the observation of direct stimulation of the accumbens with deep brain stimulation. It also shows that accumbens DBS can change musical preference without habituation of its rewarding properties.
8.1 INTRODUCTION

Mr. B., a 59-year old married man, was referred to the department of Anxiety disorders, suffering from obsessive-compulsive disorder (OCD) for 46 years. He reported obsessions about fear for uncertainty and illogical things, and compulsions about seeking reassurance and hoarding. At the moment of referral, Mr. B. scored a total of 33 points on the Yale-Brown obsessive-compulsive scale (Y-BOCS), corresponding to extremely severe OCD. He scored 18 points on the Hamilton Anxiety Scale (HAM-A), corresponding with moderate anxiety and 14 points on the Hamilton Depression Scale (HAM-D), corresponding with mild depression. In spite of extensive treatment with pharmacotherapy and cognitive behavioral therapy, symptoms were still overpowering and Mr. B. remained extremely hindered in daily living.

Suffering from treatment-refractory OCD, Mr. B., was included for treatment with accumbens DBS. After signing informed consent, Mr. B., was implanted in December 2006 with two four-contact electrodes (Model 3389, Medtronics, Minneapolis). The electrodes were connected via subcutaneous extensions to Soletra stimulators (Medtronic, Minneapolis) placed bilaterally in an infraclavicular pocket under general anesthesia. The center of the deepest contacts was positioned 3 mm in front of the anterior border of the anterior commissure (AC), 7 mm lateral and 4 mm below the line connecting the anterior and posterior commissure (PC). This was verified by post-operative CT, fused with preoperative MR.

After DBS surgery Mr. B. entered an optimization phase in which optimal stimulation parameters were adjusted. Within 6 weeks after surgery Mr. B. experienced a decline in anxiety and obsessions, with stimulation parameters fixed on contacts 2 and 3 set negative and case set positive, a voltage of 5.0 V., a pulse width of 90 microseconds and a frequency of 185 Hz. It was notable that, for the first in years, he was not seized by panic and able to postpone his compulsions. After this initial decrease in obsessive-compulsive symptoms a standardized cognitive behavioral treatment program was added to address his avoidant behavior. Within 6 months his symptoms decreased gradually to a Y-BOCS of 8 points, corresponding with mild OCD. The HAM-A declined to 4 points, corresponding with subclinical anxiety and the HAM-D declined to 2 points, corresponding with subclinical depression. Mr. B. reported he felt very confident, calm and assertive and he started to call himself ’Mr. B. II’, the new and improved version of himself.

Mr. B., had never been a huge music lover. His musical taste was broad, covering Dutch-language songs, the Beatles and the Rolling Stones, with a preference for the last
named. While music did not occupy an important position in his live, his taste in music had always been very fixed and his preferences stayed the same throughout decades. On average, a half year after DBS surgery, Mr. B. stated that he was turning into a Johnny Cash fan. He had been listening to the radio, when he coincidentally heard ‘Ring of Fire’ of the Country & Western singer and experienced that he was deeply affected by the song. Mr. B. started to listen to more songs of Johnny Cash and noticed that he was deeply moved by the raw and low-pitched voice of the singer. Moreover, he experienced that he preferred the performance of the songs in the Seventies and Eighties, due to the fullness of the voice of the older Johnny Cash in that period. His favourite songs, ‘Folsom prison blues’, ‘Ring of fire’ and ‘Sunday morning coming down’ had a certain rhythm with a fast tempo in common that moved him. Mr. B. reported that he felt good following treatment with DBS and that the songs of Johnny Cash made him feel even better. From this moment on, Mr. B. kept listening simply and solely to Johnny Cash and bought all his CD’s and DVD’s. When listening to his favourite songs he walks back and forth through the room and feels like he finds himself in a movie in which he plays the hero’s part. He reports that there is a Johnny Cash song for every emotion and every situation, feeling happy or feeling sad and although Mr. B. played almost simply and solely Johnny Cash songs for the following years, the music never starts to annoy him. From the first time Mr. B. heard a Johnny Cash song, the Dutch-language songs, the Beatles and the Rolling Stones have been banned. Except when the stimulators run down or accidentally go out. Then, Johnny Cash is unconsciously ignored and his old favourites are played once again, just as it was for the past 40 years.

8.2 BACKGROUND

Most people find music to be an important part of their lives, whatever culture they may be from. Research on how the brain processes music is emerging. It appears that the auditory cortical regions contain specializations for analyzing and encoding pitch-based (melodic) relations and time-based (rhythmic) relations in music. Interactions between auditory areas and the frontal cortices, via ventral and dorsal routes, are crucial in allowing working memory to bring these elements of music together in abstract representations. These representations produce tonal and temporal expectancies based on structural regularities found in music. There appears to be an implicit and generalized knowledge of musical rules and regularities due to exposure to music of a given genre. Additionally, there is more explicit knowledge when listeners are familiar with a specific piece of music and anticipation arises because they know that a particular event is followed by another. Depending on whether expectancies are violated or confirmed, listeners can experience tension and suspense or relaxation. The
resulting moments of anticipation and resolution are believed to be a basis for emotions and rewarding experiences in response to music. Since the pleasurable aspects of music differ from the functional characteristics of other reward stimuli, it has been suggested that the rewarding properties of music are realized indirectly by influencing these emotions. Musical taste, i.e. whether a particular piece of music is experienced as rewarding, may thus depend on individually defined cortical representations of the structure of this music, in interaction with brain systems involved in emotions and rewards. Indeed, our favourite songs may evoke strong rewarding emotions, and even when music is unfamiliar to us and heard without a conscious goal, it can elicit strongly positive feelings accompanied by physical responses and this may depend on interactions of the cortical system with the striatal dopaminergic system.

However, favourite songs and musical styles vary widely among people and various individual factors, such as personality, self-esteem, age, sex and income have been addressed to a greater or lesser extent as sources of variation in musical taste. As of yet, no anatomical or biological substrate has been identified that is explicitly related to musical preference. The current case report may provide important insights into the neural correlates of musical preference, by suggesting a relationship between neural stimulation and taste of music.

8.3 DISCUSSION

This exceptional case shows a patient who developed a distinct and entirely novel musical preference for Johnny Cash accompanied by powerful positive feelings, that was present during stimulation of the accumbens but absent during off stimulation. There are two remarkable aspects in this clinical observation that may suggest an association between DBS and changed musical preference. Firstly, preference for musical styles usually develops during late adolescence and early adulthood, and tends to prevail for the rest of people’s lives. The patient, on the contrary, developed a sudden change in musical taste at 60 years of age. Moreover, his former musical taste reoccurred immediately when stimulation was interrupted due to battery depletion, suggesting a direct causal link between musical preference and stimulation of the accumbens. Secondly, while music formerly did not play an important role in his life, following stimulation music became suddenly extremely rewarding to the patient. Contrary to our normal experiences where repetitive listening to the same music or song eventually results in a habituation to its rewarding properties, in this case, the Johnny Cash songs never started to annoy the patient and kept the enduring capacities of pleasure and reward.
Our case appears to substantiate the idea that the NAcc plays a fundamental role in the rewarding properties of music. It has been proved that the ventral striatum and in particular the NAcc is a central region for processing reward and pleasure information. Increases in NAcc neuron activity and dopamine release are observed during expectations and experience of rewards. Even behavioral addictions that are non-drug related turn out to alter the reward circuit, consisting of dopamine projections linking the ventral tegmental area, NAcc, and part of the frontal lobe. Increases in ventral striatal activity have been associated with the rewarding properties of food consumption, cocaine-induced euphoria, monetary reward and nicotine addiction. Even when no explicit reward is present, as may be the case with listening to pleasant music, brain reward structures appear to be involved. For example, have shown that passive listening to music results in a significant activation of subcortical structures including the NAcc. Salimpoor et al. have demonstrated that intense pleasure in response to music was associated with dopamine release in the ventral striatum. It is likely that musical NAcc activation directly increases hypothalamic and insula regions, which are thought to regulate physiological responses to rewarding stimuli.

We recently showed that DBS of the ventral striatum in OCD restores neural processing of rewarding stimuli explaining how NAcc DBS may influence the sensitivity to natural rewards such as music. Moreover, NAcc DBS in the current case was also associated with the kind of music that was preferred. In agreement, Salimpoor et al. demonstrated that the NAcc was activated when listeners heard their selected pleasurable music. Notably, it has been suggested that musical preference is encoded by the NAcc through interaction with cortical regions as a function of previous experiences with musical sounds. The current observations may imply however, that the NAcc could encode musical preference by itself and without any previous experience with the particular type of music. Alternatively, DBS may alter musical preference by modulation of corticostriatal networks. The frontostriatal reward circuitry is activated during highly pleasurable experience of music, especially during affective processing of music and when music is personally preferred and familiar. Recently, our group demonstrated that DBS is able to down-regulate excessive functional network connectivity in OCD, whereas listening to music increases functional network connectivity. Although highly speculative, listening to music may serve as a new and healthier way to engage brain networks following DBS-induced remission of compulsive behaviours. It has been suggested that the cortical system is able to predict tonal or rhythmic relationships in music, which are experienced as pleasurable via interaction with the ventral striatum. Our patient reported that after DBS he was grasped in particular by the rhythm of Johnny Cash songs and by the tone of his voice. Hence, DBS may have changed musical preference by modulating frontostriatal decoding of tonal and rhythmic relationships.
One may, of course, argue that during stimulation the patient developed a new kind of obsession and compulsion while his former obsessions of fear for uncertainty and illogical things declined. His preference for Johnny Cash, however, does not match the definition of obsessions or compulsions. Listening to Johnny Cash is pleasurable and not preceded by anxiety, nor is discomfort provoked when the patient is prevented from listening. The patient does not feel obsessed with Johnny Cash, nor compelled to listen and his behavior does not result in reduction of anxiety or tension. Alternatively, DBS may have changed musical preference by influencing self-confidence. In contrast with the patients’ life before surgery, having far less obsessive-compulsive-, anxiety and depressive symptoms, he felt highly confident after DBS, characterizing himself as ‘Mr. B. II’. It could be suggested that the image he creates when listening to songs of Johnny Cash seems to match his ‘new’ confident self. Like Mr. B. states: ‘it seems as if Johnny Cash goes together with DBS’. Eventually, the strong feelings of pleasure that this self-created image elicits, implies that the associated behavior is rewarding and is likely to be repeated.7,31 It has been shown that self-esteem influences musical preference, although it does not explain the largest part of the relationship between individual factors and musical taste. Besides, it appears that one of the reasons for listening to a favorite musical style for men is to use imagination and to create an image of oneself.10 Together with the aspect that music is rewarding due to the emotions it enhances,32 both prefacing factors may have influenced the development of a distinct musical preference for Johnny Cash in our patient.

CONCLUDING REMARKS
Together these findings demonstrates involvement of the NAcc in the rewarding properties of music and suggests that DBS may alter musical preference by modulation of broader networks. Besides, it shows that accumbens DBS may change musical preference without habituation of its rewarding properties. However, more research is needed to confirm our preliminary findings and to understand the underlying mechanisms of action.
REFERENCES


PART IV

DISCUSSION AND SUMMARY
CHAPTER 9

GENERAL DISCUSSION
9.1 OVERVIEW

The aim of this thesis was to add to the knowledge about DBS for treatment-refractory OCD, in particular concerning its effectiveness, cognitive safety and mechanism of action. To this aim, a clinical trial was designed to study the effectiveness and safety of DBS of the NAc in treatment-refractory OCD patients. This turned to be a journey of discovery. Along the way we questioned the effectiveness of DBS as a stand-alone treatment, leading to the addition of CBT to DBS. Subjective reports about cognitive dysfunction by DBS patients instigated us to investigate the effect of DBS on cognition. Specific side effects of the treatment resulted in a careful examination of the role of the NAc and its mechanism of action.

We addressed the following research questions:
- Is DBS of the NAc an effective treatment for treatment-refractory OCD patients?
- Do we need additional CBT to improve the effect of DBS of the NAc?
- Is DBS of the NAc a safe treatment in terms of cognition?
- Is there a relation between changes in clinical symptoms and changes in cognition?
- What can we learn from the specific side effects of DBS of the NAc?

Every journey comes to an end. This final chapter will discuss the findings of previous chapters. It will provide a summary of the main findings of the studies and will address these findings in light of the current literature. In addition, the relevance of the findings will be discussed. The chapter concludes with the implications of the results for clinical practice and recommendations for future research.

9.2 MAIN FINDINGS

Is DBS of the NAc an effective treatment for treatment-refractory OCD patients?
We conclude that bilateral DBS of the NAc is an effective treatment for treatment-refractory OCD patients based on three results: first, we found a significant improvement of OCD symptoms in the open phase of the trial, second, we found a significant difference between active and sham stimulation on OCD symptoms in the cross-over phase of the trial and finally, the majority of patients responded to treatment.

Do we need additional CBT to improve the effect of DBS of the NAc?
In the efficacy trail, DBS of the NAc resulted in a partial response in most patients. Our explorative study on the augmentation of CBT to DBS suggests that this partial response can be enhanced and the number of responders increased by the addition of CBT.
Is DBS of the NAc a safe treatment in terms of cognition?
Neuropsychological assessment before implantation, after the surgical intervention and after eight months of open stimulation suggests that DBS of the NAc may be considered a safe method in terms of cognition since we found that cognitive functioning was unaffected on the majority of measures. However, we found a reduced performance on several measures of executive functioning in the DBS group, possibly related to surgical intervention.

Is there a relation between changes in clinical symptoms and changes in cognition?
In the open phase of the study, we found pronounced improvement in clinical symptoms despite reduced performance on some measures of executive functioning. In the cross-over phase, we found no differences in neuropsychological measures between the ‘on’ and the ‘off’ stimulation condition, despite a complete relapse of symptoms in the ‘off’ stimulation condition. Two hypotheses could explain our results: first, OCD symptoms and cognitive deficits have different neurobiological substrates that are relatively unrelated. Second, the state of the art neuropsychological tests that were employed are not optimal to objectify changes in cognitive functioning observed in and reported by OCD patients, because these tests are assessed under controlled conditions in the lab; a situation that is too far removed from real life cognitive functioning.

What can we learn from the specific side effects of DBS of the NAc?
A case report shows that DBS of the NAc might be able to suppress symptoms of various disorders if at least its pathophysiology involves the brain reward circuitry. A second case report shows the involvement of the NAc in the rewarding properties of music and suggests that DBS of the NAc can change musical preference without habituation of its rewarding properties.

9.3 RELEVANCE OF THE FINDINGS

EFFICACY AND SAFETY OF DBS
At present, 200 patients have been treated with DBS for treatment-refractory OCD worldwide. The results of approximately 80 patients have been reported in open (case) studies and controlled studies. Different brain targets have been the subject of study. Besides the anterior limb of the internal capsule (ALIC), the nucleus subthalamicus (STN) and NAc, also the ventral capsule/ventral striatum (VC/VS) and inferior thalamic peduncle (ITP) have now been studied. Overall, DBS in treatment-refractory OCD results on average in a 40 to 60% improvement of OCD symptoms in half of the patients. DBS of the VC/VS region seems to improve mood, obsessions and compulsions whereas DBS
of the STN particularly improved compulsions. Our results of 72% improvement in OCD symptoms in the 56% of responding patients after DBS of the NAc is one the largest follow-up improvement reported to date. So far, we are the only center that studied the augmentation of CBT to DBS. The large improvement in our study compared to other studies suggests that the combination of DBS and CBT could be optimal for substantial symptom improvement in treatment-refractory OCD.

Serious, procedure-related side effects of DBS are rare and most side effects of stimulation are transient and could be reversed by adjustment of stimulation parameters. Therewith, DBS could be considered a relatively safe treatment. Cognitive safety of DBS in treatment-refractory OCD has been reported in several studies. However, small sample sizes, lack of a control group and the use of a limited range of tests hinder the interpretation of the results of these studies. In our study, we used a matched control group longitudinally and a wide range of neuropsychological tests. The results of our study suggest reduced performances on some measures of executive functioning, possibly related to the surgical intervention.

DBS AND ITS MECHANISM OF ACTION
This thesis, above all, shows that DBS is an effective and safe approach for treatment-refractory OCD patients. But, what does it learn us about its mechanism of action? Several findings in this thesis may be of importance. First, the lack of a relation between improvement in clinical symptoms an changes in cognition, second, the pronounced increase in self-confidence after DBS and third the need of CBT to further decrease clinical symptoms after DBS.

First, in our studies on DBS and cognition, we found on the one hand, a reduced performance on several tasks of executive functioning despite a pronounced improvement in clinical symptoms and we found on the other hand, no differences in neuropsychological test results between the ‘on’ and the ‘off’ stimulation condition of the cross-over phase, despite a complete relapse of symptoms in the ‘off’ stimulation condition. Previous research has studied whether the cognitive deficits in OCD are state-dependent (e.g. improve after treatment in OCD symptoms) or trait-related (e.g. independent of the severity of OCD symptoms and persistent after treatment). Most research showed that OCD patients have persistent cognitive deficits after successful treatment. This thesis supports the assumption that OCD symptoms and cognitive deficits have different neurobiological substrates that are relatively unrelated and suggests that the clinical improvement after DBS is not accomplished by improvement in cognitive functioning.

Second, in our study on the effectiveness of DBS we observed that the effect of stimulation started with an acute improvement in mood and subsequent decrease in anxiety symptoms. Subsequently, obsessions decreased and finally compulsions. The
acute improvement in mood and decrease in anxiety symptoms was very pronounced. It resulted in half of the patients in a short and transient period of hypomania. However, also after normalization of the hypomanic symptoms, a strong feeling of self-confidence persisted. Patients described feeling more assertive and equal instead of inferior to other people. The case study of Mr. B. serves as a good illustration. After all, Mr. B. clearly described that he felt very confident, calm and assertive after DBS. He even started to call himself ‘Mr. B. II’, the new and improved version of himself. Might the effect of DBS be accomplished by increasing self-confidence?

Before DBS, assessing an interview for personality disorders, patients frequently described having low self-esteem and mentioned this as a central theme in their life. One patient fulfilled the criteria for avoidant personality disorder but seven other patients fulfilled the criteria for features of avoidant personality disorder and eleven patients stated that they had been preoccupied with criticism and rejection in social situations all of their life. Avoidant personality disorder has been found to be the second most prevalent personality disorder in OCD. One of the criteria of avoidant personality disorder, low self-esteem, has been identified as a symptom that precedes the onset of OCD. Research has shown that OCD patients base their self-esteem on other people’s opinions and that they are pre-occupied by the possibility of causing others harm, resulting in a negative judgement by others. This suggests a sensitivity to blame and criticism by other people. In addition, there is some evidence that self-esteem and obsessions may be linked. Possibly, the increase of self-confidence after DBS results in a reduced preoccupation with critical judgements of others. In this sense, it could have influenced the intensity of obsessions and thereby improve OCD.

Third and last, an important finding of our study on the effectiveness of DBS was, that after initial improvement of DBS, CBT was needed to accomplish further reduction of symptoms. This finding is comparable to the combination of medication and CBT, in which the average effect of medication leaves patients in general with significant clinical symptoms, and CBT may be used to augment the benefit of medication. The mechanism of action of the combined treatment of medication and CBT is still relatively unknown. Regarding the combination of DBS and CBT, we hypothesize that DBS lays a foundation for CBT in these treatment-refractory patients, by decreasing affective symptoms and subsequently decreasing the intensity of obsessions. This allows patients to regain control of their own behaviour: by exposing themselves to fearful situations while refraining from compulsions, they experience that they can manage anxiety, are able to dismiss obsessions and thereby are able to stop their compulsions.

The other side of this mechanism of action is that patients do have to regain this control to improve their quality of life. We have several examples of patients that experienced an initial improvement in symptoms, but still avoided fearful situations and still performed compulsions. The best illustration is the patient with
complete ego-syntonic OCD that experienced a decrease in obsessions after DBS and sometimes ‘forgot’ to perform his compulsions. This made him so anxious, as he still wanted to do everything perfect, that he paid more attention to perform all his compulsions and refused to participate in CBT. Despite the initial reduction in symptoms, eventually his OCD did not significantly improve. It is our impression that patients who set themselves the most strict goals in CBT, benefit the most from DBS treatment. This shows that DBS is not optimal as a stand-alone treatment and that a combination of two complementary treatments, DBS as a neurosurgical treatment and CBT as a psychiatric/ psychological treatment, may be more effective in reducing OCD symptoms. As DBS, that is currently the most invasive treatment in OCD, is insufficient to accomplish remission in OCD, it can be concluded that sole biological treatments in OCD are suboptimal and treatment of OCD should consists of a combination of both biological and psychological interventions.

In summary, this thesis learns that DBS is suboptimal as a stand-alone biological treatment. Its clinical effect is not mediated by improving cognition. On the other hand, clinical experience shows that the increase of self-confidence may play an important role, that has not yet been investigated.

THE CONCEPT OF OCD
What can we learn from DBS with respect to the concept of OCD? In DSM-5, OCD shifted from the category of anxiety disorders to the stand-alone category ‘obsessive-compulsive and related disorders’. This has been the result of a long-lasting debate. The main reason for the shift has been the research of past decades, that suggests that OCD and obsessive-compulsive spectrum disorders are behaviourally and phenomenologically distinct from anxiety disorders. A defining feature of anxiety disorders for example is the presence of psychological and somatic manifestations of anxiety. In OCD and obsessive-compulsive spectrum disorders, anxiety symptoms, although frequently present, are more variable and heterogeneous in nature. It is stated that this makes anxiety a less stable feature of these diagnoses. In addition, distinct anxiety symptoms may dominate at different stages of OCD: obsessions result initially in anxiety but with time, extensive compulsions and avoidance may decrease the occurrence of anxiety. It is not known to what extent the anxiety associated with OCD arises in response to obsessions and compulsions or generates obsessions and compulsions. The finding that OCD symptoms tend to worsen under stress supports the last assumption. The acute and profound decrease in anxiety after DBS and the subsequent improvement in OCD symptoms suggest that anxiety does have a significant role in the maintenance of OCD symptoms, even in a progressive and severe stage of the disorder. The spontaneous reports of patients that anxiety during exposure after DBS is not as intolerable as in previous CBT treatment attempts, supports
the assumption that anxiety in OCD arises in response to obsessions.

However, the mechanism of action of DBS shows another defining feature of OCD. After initial improvement of OCD symptoms in response to DBS, CBT was needed to decrease long-standing compulsions that had a habitual nature. It is stated that compulsions can be seen as a rewarding experience due to their capacity to reduce distress generated by obsessions. In the course of longstanding OCD, patients may then develop dependency upon compulsive behaviour. In this perspective, it is possible to conceptualize the course of OCD as a progression from an anxiety disorder to a disorder of behavioural addiction. The case report of Mrs. D. describes that she perceived her compulsions as well as her smoking and excessive food consumption as undesirable habits. In addition, patients in our trial described that, even though they do not feel anxious anymore and are convinced of the uselessness of their compulsions, they continue to perform their compulsions, just because it feels so good. This illustrates that OCD may start as an anxiety disorder and may progress in the course of the disease into a disorder of reward processing. In neuroanatomic perspective, our observation of acute improvement of affective symptoms after DBS of the NAc and the reported specific effect on compulsions after DBS of the STN hints at the involvement of two different anatomical circuits in OCD. One circuit might be associated with a mood and anxiety spectrum responding to stimulation of the NAc, and another circuit could be related to a compulsive habit spectrum responding to STN stimulation.

9.4 CLINICAL IMPLICATIONS

Our studies add substantial evidence to the effectiveness of DBS for treatment-refractory OCD and therewith to the acceptance of DBS as a last resort treatment for OCD. Additional CBT is now an important part of DBS all over the world and other centers copy our treatment program. In our center, the profound improvement in mood that we observed during the trial, laid the foundation for the application of DBS for major depressive disorder. In addition, the assumption that DBS might alter compulsivity in a range of psychiatric diseases initiated the application of DBS for addiction and eating disorders.

We have now a decade of experience in DBS for treatment-refractory OCD patients. In ten years 50 patients underwent DBS in our center. Worldwide, so far 200 patients have been treated with DBS in multicenter studies, comparing different targets. The limited number of patients and the distribution of patients over different centers and countries makes it difficult to gain clinical expertise in the treatment. Therefore, one of the main challenges for the future will be the translation of clinical research into clinical practice. Herein, the optimization of the post-operative management will play an important role.
The findings of this thesis suggest that CBT could fulfill a part of this role, by further improving symptoms and learning patients to regain control of their own behaviour. In addition to CBT, another part of this role could be fulfilled by further psychological treatment. It is our experience that with the reduction of longstanding OCD symptoms other problems may come to expression. First, personality problems, that were less pronounced when patients experienced severe OCD symptoms, may hinder patients in their daily life after effective DBS. For example, OCD may have had a role in the regulation of emotions in patients having a borderline personality disorder (BPS). This leaves them after effective DBS, with no coping mechanisms at their disposal in periods of stress. Sometimes, although there is still improvement in anxiety and obsessions, patients start to perform again compulsions that initially were vanished after DBS and additional CBT. This does not make comorbid BPS an exclusion criterion for DBS but underlines the importance of accurate diagnostics and formulation of a treatment plan in the inclusion phase of DBS. Second, after patients experience a reduction of OCD symptoms, sometimes after decades of severe symptoms, mourning can be an unforeseen problem. Patients can mourn about all their fruitless efforts to overcome OCD and their lost chances in life. Treatment may be necessary to come to terms with this loss and support patients to built up a new life. Third, relationship problems may develop following effective DBS. Normally, in the course of the disease, patient and partner have found an equilibrium in their relationship. Reduction in symptoms may lead to a change of roles and disturbance of this equilibrium. Relationship therapy then might be an outcome.

In this perspective, DBS for treatment-refractory OCD patients might be seen as part of a three-step approach to improve OCD as well as quality of life: (1) DBS, (2) additional CBT, (3) further psychological treatment. It is of importance that DBS centres have the expertise to offer the required treatment or have the possibilities to refer patients to specialized centres for further treatment in close collaboration.

The findings of this thesis further underline the importance of a baseline neuropsychological assessment in the inclusion phase of DBS. Several patients in our trial complained about word-finding problems and forgetfulness as side effects of the treatment. With a neuropsychological investigation at baseline, the results of a second neuropsychological investigation can be compared to objectify the subjective reports of patients and their implications for daily life.

9.5 Future Directions

First of all, the addition of CBT to DBS is promising, but the evidence is still limited since our study had an explorative nature. Therefore, a larger randomized controlled
trial should be performed comparing one group of stand-alone DBS and one group of DBS and additional CBT. Hereafter, also the best treatment protocol of additional CBT, regarding frequency, length and individual or group therapy, has to be studied. In addition, the influence of DBS on personality traits is scarcely studied and could be an interesting topic for future research. Herein, the concept of self-esteem could be considered as an important factor.

Furthermore, considering the substantial number of patients that do not respond after DBS, predictors of outcome are an important topic for further research. Predictors of outcome have not yet been identified but some studies have reported preliminary observations. The provocation of a smell, laugh, flushing, relief of anxiety, feeling of warmth, happy feeling and beneficial effects of ERP directly after adjustment of stimulation, have been suggested as candidates for predictors of good outcome in the long term. In addition, the onset of laughter during the surgical procedure and optimization of parameters has been mentioned as a predictor of response. Baseline severity of OCD symptoms did not predict outcome. In our trial, we observed a clear relation between non-response and type of obsessive-compulsive symptoms. Patients with perfectionism, hoarding or symmetry who believed in the worthiness and soundness of their obsessions did not respond well to DBS. For this reason, we have excluded this type of OCD for some time from treatment. However, one patient with perfectionism that we excluded from DBS, committed suicide shortly thereafter. Another patient with perfectionism that we eventually included for DBS because of her young age, disabling condition, lack of alternative treatment options and the suicide of the earlier patient, responded well to DBS. Alternatively, we have included patients that we considered good candidates for DBS and did not respond to treatment. This illustrates that patient selection for DBS should be a careful consideration and prudence is in order when predictors of outcome are considered. Therefore, in future research, predictors of outcome should be studied in larger groups. Possible predictors of outcome that may be considered are type of OCD, soundness of the obsessions, IQ, personality disorders and cognitive deficits at baseline.

Finally, the findings of reduced performance in measures of executive functioning can cover new ground for the investigation of cognitive safety in DBS for OCD. So far, there has been evidence that the clinical effectiveness of DBS is achieved with stable and even improved cognitive functioning. However, studies are seriously hampered by methodological limitations: most reports on cognitive functioning in psychiatric patients following DBS are case studies and also in larger studies practice effects cannot be ruled out since none of the studies included a control group. Besides, the subjective reports of patients hint at cognitive deterioration after DBS. This raises the question whether neuropsychological tests might be not sensitive enough or studies lack power to detect possible decline in performance. For these reasons, an important
challenge for future research is to carefully establish the cognitive safety of DBS for OCD. In addition, it would be interesting to investigate if patients with cognitive deficits at forehand might be more prone to cognitive deterioration after DBS, as is done in DBS research in Parkinson’s disease. This could lead to the determination of cut-off scores on the basis of which patients have to be excluded from treatment. The following considerations have to be made: first, patients must have a cognitive status that makes them able to understand the procedure and make a deliberate decision for DBS. Second, they must have a cognitive status that enables them to collaborate during treatment, and third, it has to be assured that DBS is expected to help patients and not harm them.26

It could be expected that drawing safe selection boundaries with regard to cognition will be a difficult task, due to the small number of patients in studies to date, the difficulty to form a control group, the possible influence of medication and the multiple comparisons in neuropsychological research. A large multicenter study could overcome these issues and is therefore recommended. Furthermore, it may be interesting to investigate new, ecologically valid cognitive tests that can capture the cognitive changes sometimes observed in and reported by patients after DBS.
REFERENCES


SUMMARY
Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder with an estimated life-time prevalence of 2%. OCD is characterized by persistent thoughts (obsessions) that are frequently recognized as irrational, and repetitive ritualistic behaviors (compulsions) that usually represent attempts to minimize distress caused by obsessions. Severe OCD leads to pronounced suffering and has a major impact on family relationships, social life and the capacity to function at work. At present, clinical management of OCD consists of pharmacological treatment, in particular selective serotonin reuptake inhibitors, and cognitive behavioural therapy (CBT). Although often effective, both treatments have their limitations and even when the best available treatments are applied, approximately 10% of patients remain severely affected and suffer from treatment-refractory OCD. This thesis is about a new and last-resort treatment option for this group of treatment-refractory patients: deep brain stimulation (DBS). The overall objective of the thesis was to add to the knowledge about DBS for treatment-refractory OCD. It describes a 10-year journey of research in which we learned about its effectiveness, cognitive safety and mechanism of action.

TO BEGIN WITH - INTRODUCTION
The introduction of this thesis (Chapter 1) provides a short background of DBS for treatment-refractory OCD. It gives an overview of the knowledge about DBS for OCD in 2005 and describes our journey of pioneering research in DBS.

TARGETS FOR DEEP BRAIN STIMULATION
Chapter 2 encompasses an overview of the effects of five different targets of stimulation in DBS for treatment-refractory OCD. It describes that since the introduction of DBS as a treatment for treatment-refractory OCD in 1998, the results of approximately 80 OCD patients have been reported worldwide. Our review indicates that, when these results are combined, DBS results in a 40 to 60% symptom decrease in at least half of the patients. The efficacy, the time to response and the type of symptoms that improve, depend on the target of stimulation. Although side effects occur, most of these are transitory and linked to specific stimulation parameters that can be changed. We concluded that DBS research has opened up the opportunity to investigate how various symptom layers of OCD, such as anxiety, obsessions, compulsions, and depressed mood are related to brain activity within the cortico-striato-thalamo-cortical network.

SEARCH FOR EFFICACY -
DBS OF THE NAC FOR TREATMENT-REFRACTORY OCD
Chapter 3 describes our search for efficacy. We developed a trial to investigate the effectiveness and safety of bilateral DBS of the NAc in an open eight-month treatment phase, double-blind four week cross-over phase and open twelve months maintenance
Sixteen patients with OCD according to DSM-IV criteria, meeting stringent criteria for treatment refractoriness, were included in the study. We assessed efficacy of DBS by evaluating change in OCD symptoms, anxiety symptoms and depressive symptoms and we defined the number of responders. In the open phase of the study, OCD symptom severity decreased with 46% after eight months. Nine out of 16 patients were responders with a mean decrease of 72% in OCD symptoms. In the double-blind, sham-controlled phase, the mean difference between active and sham stimulation on OCD symptoms was 25%. Also depression and anxiety decreased significantly. Except for mild subjectively reported forgetfulness and word-finding problems, we found no permanent adverse events. We concluded that our results suggest that bilateral DBS of the NAc may be an effective and safe treatment for treatment-refractory OCD.

**ADDITIONAL TREATMENT - CBT AUGMENTS THE EFFECTS OF DBS IN OCD**

Chapter 4 focuses on the augmentation of CBT to DBS of the NAc and aims to evaluate its efficacy. It describes an explorative study that was part of the trial on the effectiveness and safety of bilateral DBS of the NAc for treatment-refractory OCD. After stabilization of improvement in OCD symptoms, we added a standardized 24-week CBT treatment program to DBS in the open treatment phase. We evaluated change in OCD symptoms, anxiety symptoms and depressive symptoms. Following addition of CBT to DBS, we observed an additional significant decrease in OCD symptoms, but not in anxiety and depressive symptoms. Furthermore, the number of responders increased from 6 patients to 9 patients. In a subsequent double-blind phase, in which stimulation was discontinued, OCD symptoms returned to baseline (relapse) and anxiety and depressive symptoms worsened (rebound) compared to baseline. With stimulation on again, OCD symptoms improved to the post-CBT level instead of the post-optimization level, which suggests that learned CBT techniques were preserved (but not active) during off-stimulation. This explorative study suggests that a combined treatment of nucleus accumbens DBS and CBT may be optimal for improving obsessive-compulsive symptoms in treatment-refractory OCD and emphasizes the complementariness of both treatments. We concluded that DBS seems to result in affective changes that may be required to enable response prevention during CBT. However, we also conclude that a subsequent RCT is necessary to draw firm conclusions.

**DBS AND COGNITION - COGNITIVE EFFECTS OF DBS IN OCD**

Chapter 5 aims to objectify the subjective reports of cognitive problems of our patients during the treatment. We investigated the cognitive safety of DBS for treatment-refractory OCD and the relation between clinical changes and cognitive functioning.
We compared sixteen patients with treatment-refractory OCD, treated with DBS of the NAc, with a control group of fourteen patients with treatment-refractory OCD, treated with care as usual. Cognitive functioning was assessed at baseline, three weeks postoperatively and following eight months of stimulation. The association between change in clinical symptoms and change in cognitive functioning was investigated. We concluded from this study that DBS of the NAc may be considered as a safe method in terms of cognition since cognitive functioning was unaffected on the majority of neuropsychological measures. Nevertheless, we observed reduced performance on some specific measures of executive functioning, possibly related to the surgical intervention. The lack of association between changes in clinical symptoms and cognitive test results suggests that the clinical effect of DBS is not mediated by improving cognition.

**DBS AND COGNITION -**
**THE LINK BETWEEN OCD AND COGNITION: LESSONS FROM DBS**

Chapter 6 aims to investigate whether deep brain stimulation affects cognitive functioning. We compared neuropsychological performance in an ‘on’ versus ‘off’ stimulation condition in fourteen patients with treatment-refractory obsessive-compulsive disorder that underwent deep brain stimulation targeted at the NAc. They were randomly allocated to two groups in a double-blind cross-over phase: the first group underwent 2 weeks of active stimulation followed by 2 weeks of sham stimulation and the second group vice versa. Cognitive functioning was assessed at baseline, after two weeks and after four weeks. Despite significant change in obsessive-compulsive symptoms in the ‘on and ‘off’ stimulation conditions, cognitive functioning remained unchanged. Obsessive-compulsive symptoms and cognitive deficits may therefore have different neurobiological substrates that are relatively unrelated. Alternatively, the state-of-the-art neuropsychological tests that were employed may not optimal to objectify changes in cognitive functioning of patients with obsessive-compulsive disorder.

**SPECIFIC SIDE EFFECTS -**
**SMOKING CESSATION AND WEIGHT LOSS FOLLOWING DBS**

Chapter 7 presents a patient with treatment-refractory OCD, nicotine dependence and obesity in which we observed unintended, effortless and simultaneous smoking cessation and weight loss after DBS of the NAc. This case study supports the idea of compulsivity with common circuitry in the processing of diverse rewards and suggests that DBS of the NAc could be a possible intervention for patients with a dependency not responding to currently available treatments.
Chapter 8 presents a 60-year old patient who developed a sudden and distinct musical preference for Johnny Cash following DBS targeted at the NAc. This case report substantiates the assumption that the NAc is involved in musical preference, based on the observation of direct stimulation of the accumbens with DBS. It also shows that accumbens DBS can change musical preference without habituation of its rewarding properties.

**DISCUSSION**

In Chapter 9 we discuss the results of our research and describe the implications for clinical practice. We conclude that DBS is an effective and safe approach for treatment-refractory OCD patients. We discuss that, regarding its mechanism of action, DBS is suboptimal as a stand-alone biological treatment and that CBT can lead to an additional significant decrease of OCD symptoms and an increase in number of responders. Its clinical effect is not mediated by improving cognition but the increase of self-confidence may play an important role. We discuss that DBS has the potential to enhance our knowledge of OCD. It learns us that anxiety has a role in the maintenance of OCD symptoms and that OCD, in the course of the disease, may progress into a disorder of reward processing. The findings of this thesis add substantial evidence to the effectiveness of DBS for treatment-refractory OCD and therewith to the acceptance of DBS as a last resort treatment for OCD. A future challenge will be the translation of clinical research into clinical practice. Herein, psychological treatment may contribute to the optimization of the post-operative management. Considering the substantial number of patients that do not respond after DBS, we suggest that future research should investigate predictors of outcome. Finally, considering the inconsistent findings so far, we state that important challenges for future research are to carefully establish the cognitive safety of DBS for OCD and to investigate new, ecologically valid cognitive tests that can capture the cognitive changes sometimes observed in and reported by patients after DBS.
APPENDIX
NEDERLANDSE SAMENVATTING
Obsessieve-compulsieve stoornis (OCS) of dwangstoornis, is een psychiatrische stoornis die wordt gekenmerkt door aanhoudende gedachten (obsessies), die als onzinnig worden beschouwd, en repeterende handelingen (compulsies), die worden uitgevoerd om de angst en de onrust die obsessies oproepen te verminderen. OCS heeft een lifetime prevalentie van 2%. Als de stoornis ernstig is, heeft ze significant lijden tot gevolg, een grote impact op sociale relaties, en de mogelijkheid tot werken. De behandeling van OCS bestaat uit medicamenteuze behandeling, met name selectieve serotonineropnameremmers (SSRI’s), cognitieve gedragstherapie (CGT) en de combinatie van beiden. Hoewel behandeling vaak effectief is, hebben beide behandelmethoden hun beperkingen. Ten eerste hebben beide methoden maar een beperkte respons. Daarnaast kan medicatie bijwerkingen hebben, en de exposure en responspreventie zo’n intense angst bij patiënten oproepen dat 25% uitvalt in behandeling. Zelfs wanneer de best mogelijke behandeling wordt toegepast, houdt ongeveer 10% van de patiënten ernstige klachten: zij lijden aan therapie-resistente OCS.

Dit proefschrift gaat over een nieuwe behandeling als laatste redmiddel voor deze specifieke groep van OCS patiënten: diepe hersenstimulatie (DBS). Diepe hersenstimulatie is een behandeling waarbij operatief twee elektroden in de hersenen worden ingebracht die met een neurostimulator, een soort pacemaker, worden gestimuleerd. De techniek wordt al langer toegepast bij de ziekte van Parkinson en sinds 1998 bij OCS als eerste psychiatrische stoornis. In 2005 begon ons onderzoek naar de effectiviteit en veiligheid van DBS in de nucleus accumbens (NAc), een hersenkern die wordt geassocieerd met de verwerking van beloning, motivatie en verslaving. In 2005 was er naast een aantal casusbeschrijvingen vrijwel niets bekend over de toepassing van DBS bij OCS. Dit proefschrift beschrijft onze zoektocht en bevindingen van de afgelopen de 10 jaar op het gebied van de effectiviteit, veiligheid en het werkingsmechanisme van DBS. Het heeft daarmee als belangrijkste doel de kennis over DBS voor therapie-resistente OCS te vergroten en legt de nadruk op de psychologische kant van DBS, zowel wat betreft de psychotherapeutische benadering als de neuropsychologische effecten.

**OM TE BEGINNEN – INLEIDING**
De inleiding van dit proefschrift (hoofdstuk 1) schets in het kort de achtergrond van DBS voor therapie-resistente OCS. Ze geeft een overzicht van de stand van zaken in 2005 en beschrijft het eerste pionieren en onze zoektocht naar de werkzaamheid van DBS.

**TARGETS VOOR DBS**
Hoofdstuk 2 geeft een overzicht van vijf verschillende stimulatiegebieden die bij DBS voor therapie-resistente OCS worden gebruikt. We laten in dit hoofdstuk zien dat
sinds de start van DBS als behandeling voor therapie-resistente OCS, over de resultaten van ongeveer 80 OCS patiënten wereldwijd is gerapporteerd. Wanneer de resultaten worden gecombineerd, resulteert DBS in 40 tot 60% symptoomafname bij ten minste de helft van de patiënten. De effectiviteit, tijd tot respons en het type symptomen dat verbetert, is daarbij afhankelijk van het stimulatiegebied dat gestimuleerd wordt. Hoewel bijwerkingen optreden, zijn ze meestal van voorbijgaande aard en gerelateerd aan specifieke stimulatieparameters die kunnen worden aangepast. We concluderen in dit hoofdstuk dat onderzoek naar DBS het mogelijk maakt om te onderzoeken hoe de verschillende symptoomdimensies van OCS, zoals angst, obsessies, compulsies en depressie, zijn gekoppeld aan hersenactiviteit in het cortico-striato-thalamo-corticale circuit.

**DE ZOEKTOCHT NAAR EFFECT**
**DBS VAN DE NUCLEUS ACCUMBENS VOOR THERAPIE-RESISTENTE OCS**

Hoofdstuk 3 beschrijft onze zoektocht naar de werkzaamheid van DBS. Hiertoe zetten we een behandelstudie op waarin we de effectiviteit en veiligheid van bilaterale DBS van de NAc onderzochten in een open behandelfase van acht maanden, een dubbelblinde cross-over fase van vier weken, en een opvolgfase van 12 maanden. We includeerden 16 patiënten met OCS volgens de DSM-IV criteria in de studie, die aan strikte criteria voor therapie-resistente OCS voldeden. De effectiviteit van DBS werd vastgesteld door de verandering in OCS symptomen, angstsymptomen en depressieve symptomen te meten evenals het aantal patiënten dat respondeerde. In de open fase van de studie daalde de ernst van de OCS symptomen met gemiddeld 46% na acht maanden. Negen van de 16 patiënten respondeerden op de behandeling, met een gemiddelde afname van 72% in OCS symptomen. In de dubbelblinde placebo-gecontroleerde fase van de studie was het verschil tussen placebo en actieve stimulatie 25%. Tevens namen angst- en depressieve symptomen significant af. Behoudens milde en subjectief gerapporteerde klachten van vergeetachtigheid en woordvindings-problemen, vonden we geen permanente bijwerkingen van de behandeling. We concluderen dan ook dat bilaterale DBS van de NAc een effectieve en veilige behandeling is voor therapie-resistente OCS.

**AANVULLENDE BEHANDELING**
**CGT VERSTERKT HET EFFECT VAN DBS IN OCS.**

Hoofdstuk 4 richt zich op de toevoeging van CGT aan DBS. Het heeft als doel de effectiviteit van deze gecombineerde behandeling te evalueren. Dit hoofdstuk beschrijft een exploratieve studie die onderdeel was van de eerder beschreven studie naar de effectiviteit en veiligheid van bilaterale DBS van de NAc. In de open behandelfase van de studie werd na stabilisatie van de initiële verbetering in OCS symptomen na optimalisatie van DBS, een gestandaardiseerde CGT van 24 weken gestart. Hierbij evaluerden we de verandering in OCS symptomen, angst en stemming. Na het toevoegen van CGT
aan DBS trad er nogmaals een significante verbetering in OCS symptomen op, hoewel angst- en depressieve symptomen hetzelfde bleven. Het aantal patiënten dat op de behandeling respondeerde nam toe van zes patiënten naar negen patiënten. In de fase die volgde, werd de stimulatie uitgezet (terwijl patiënten en onderzoekers niet wisten of de stimulatie uit of aan stond) en verslechterden de OCS symptomen opnieuw naar het zelfde niveau van voor de DBS therapie (relapse). De angst- en depressieve symptomen daarentegen verslechterden naar een niveau dat ernstiger was dan voor DBS (rebound). Met het opnieuw aanzetten van de stimulatie, verbeterden de OCS symptomen weer naar het niveau van na het afronden van de CGT in plaats van naar het niveau van na de optimalisatie van DBS. Dit suggereert dat de geleerde CGT technieken behouden bleven (alhoewel ze niet actief gebruikt werden) gedurende de periode dat de stimulatie uit stond. Deze exploratieve studie laat zien dat een gecombineerde behandeling van DBS en CGT mogelijk het meest optimaal is om OCS symptomen in therapie-resistente OCS te verbeteren en benadrukt dat beide behandelingen elkaar aanvullen. We concluderen dat DBS lijkt te resulteren in affectieve veranderingen (waaronder vermindering van angst) die mogelijk nodig zijn om de exposure en responspreventie in CGT aan te kunnen. Een randomized controlled trial (een onderzoek waarin door het toeval bepaald wordt welke DBS patiënt de CGT krijgt en welke niet) zou deze voorlopige conclusies kunnen bevestigen.

**DBS EN COGNITIE - COGNITIEVE EFFECTEN VAN DBS IN OCS**

Hoofdstuk 5 heeft als doel de subjectief gerapporteerde cognitieve problemen (geheugenklachten en woordvindings-problemen) van patiënten na DBS te objectiveren. Hiertoe zetten we een studie op waarin we de cognitieve status van therapie-resistente patiënten onderzochten en de relatie tussen klinische veranderingen en veranderingen in cognitief functioneren. We vergeleken 16 patiënten met therapie-resistente OCS die werden behandeld met DBS van de NAc met een controlegroep van 14 patiënten met therapie-resistente OCS, die werden behandeld met care-as-usual. Er werd neuropsychologisch onderzoek afgenomen voor de operatieve ingreep, drie weken na de operatieve ingreep en na acht maanden van chronische stimulatie. Het cognitief functioneren was onveranderd op de meerderheid van de neuropsychologische taken, waardoor we konden concluderen dat DBS geen significante invloed heeft op het cognitief functioneren van patiënten. Desondanks vonden we hiernaast een verminderde prestatie op een aantal specifieke taken die het executief functioneren meten, mogelijk gerelateerd aan de operatieve ingreep. Executief functioneren omvat de hogere controle functies van de hersenen, die van belang zijn bij doelgerichte acties. Het ontbreken van een relatie tussen verandering in klinische symptomen en verandering in cognitief functioneren suggereert dat het klinisch effect van DBS niet wordt gemedieerd door het verbeteren van cognitie.

NEDERLANDSE SAMENVATTING
**DBS EN COGNITIE -**

**DE RELATIE TUSSEN OCS EN COGNITIE: WAT KUNNEN WE LEREN VAN DBS?**

Op het eerste gezicht suggereren de klinische eigenschappen van OCS ernstige cognitieve tekorten. Compulsief controleren bijvoorbeeld zou te maken kunnen hebben met een tekort in visueel geheugen. De moeite die patiënten hebben om obsessies van zich af te zetten, zou het gevolg kunnen zijn van een tekort in mentale flexibiliteit. Echter, de literatuur over de aanwezigheid van cognitieve tekorten bij OCS is niet eenduidig, evenals de bevindingen over de invloed van verbetering van symptomen op het cognitief functioneren.

In **hoofdstuk 6** was ons doel om te onderzoeken of de stimulatie zelf het cognitief functioneren in OCS beïnvloedt. We vergeleken het cognitief functioneren van 14 therapie-resistente OCS patiënten die werden behandeld met DBS in een dubbelblinde cross-over fase. Patiënten werden random toegewezen aan twee groepen: de eerste groep kreeg 2 weken actieve stimulatie gevolgd door 2 weken placebo stimulatie en de tweede groep vice versa. Er werd neuropsychologisch onderzoek afgenomen bij baseline, na 2 weken en na 4 weken. Ondanks een significant verschil in OCS symptomen tussen de actieve en placebo conditie bleef het cognitief functioneren onveranderd. Dit suggereert dat OCS symptomen en cognitieve tekorten in OCS mogelijk verschillende neurobiologische substraten hebben die niet met elkaar zijn gekoppeld. Een mogelijke andere verklaring is dat de neuropsychologische testen niet optimaal zijn om veranderingen in het cognitief functioneren van OCS patiënten adequaat te objectiveren. De individuele cognitieve veranderingen die patiënten bemerken in het dagelijks leven worden mogelijk onvoldoende gevangen door de standaard neuropsychologische tests die in een gecontroleerde omgeving worden afgenomen.

**SPECIFIEKE BIJWERKINGEN -**

**STOPPEN MET ROKEN EN AFVALLEN NA DBS.**

**Hoofdstuk 7** is een case report over één van de patiënten in de studie met therapie-resistente OCS, nicotine afhankelijkheid en overgewicht. Patiënte werd succesvol behandeld met DBS. Tevens stopte zij na DBS spontaan en zonder moeite met roken en viel gelijktijdig 44 kilo af. Ook op de lange termijn begon zij nooit meer met roken en raakte nog meer gewicht kwijt. Deze casusbeschrijving suggereert dat compulsies, en verslaving aan roken en eten een gedeelde basis van compulsiviteit (dwangmatigheid) hebben die kan worden beïnvloed met DBS. Het laat tevens zien dat DBS van de NAc een mogelijke behandeling kan zijn voor patiënten met (middelen)afhankelijkheid die niet goed reageren op de huidige beschikbare behandelmethode.
SPECIFIEKE BIJWERKINGEN -
EEN CASUS OVER MUZIKALE VOORKEUR VOOR JOHNNY CASH.

Hoofdstuk 8 beschrijft de casus van een 60-jarige patiënt die een plotse en specifieke muzikale voorkeur voor Johnny Cash ontwikkelde na DBS. Patiënt had in zijn leven nooit een sterke muzikale voorkeur maar luisterde na DBS alleen nog maar naar muziek van Johnny Cash. Hij kocht al zijn CD's en DVD's en beschreef dat er voor elke situatie of gemoedstoestand wel een passend nummer is. Ondanks dat hij na DBS jarenlang naar Johnny Cash luisterde, begon de muziek hem nooit te vervelen. Behalve als de DBS per ongeluk uitging: dan verviel hij weer in zijn oude muzieksmaak. Deze casusbeschrijving onderschrijft de aannemer dat de NAc een rol speelt in muzikale voorkeur. Het laat ook zien dat accumbens DBS muzikale voorkeur kan veranderen zonder dat de belonende aspecten van muziek verloren gaan.

DISCUSSIE

In hoofdstuk 9 bespreken we de resultaten van ons onderzoek zoals in de vorige hoofdstukken beschreven en bespreken we de implicaties voor de klinische praktijk. Onze belangrijkste conclusie is dat DBS een effectieve en veilige behandelmethode is voor therapie-resistente OCS patiënten. DBS lijkt suboptimaal als een op zichzelf staande biologische behandeling. Het toevoegen van CGT leidt tot een afname van OCS symptomen als ook tot een toename van het aantal responders. Het klinisch effect van de behandeling lijkt niet te worden gemedieerd door het verbeteren van cognitief functioneren. Verder bespreken we dat DBS de potentie heeft om ons kennis over OCS te vergroten. Het leert ons dat angst een rol speelt bij het in stand houden van OCS symptomen en dat OCS, in het beloop van de stoornis, kan uitgroeien tot een ‘behavioral addiction’.

De bevindingen van dit proefschrift tonen aan dat DBS een effectieve behandeling kan zijn voor patiënten met therapie-resistente OCS, en dragen daarmee bij aan de acceptatie en implementatie van DBS als een laatste redmiddel voor patiënten die niet reageren op beschikbare reguliere behandelingen. Een uitdaging voor de toekomst is de vertaling van DBS als behandelstudie naar DBS als klinische behandeling. De psychologische behandeling zou hierbij een grote rol kunnen spelen. Gegeven het substantiële deel van de patiënten dat onvoldoende op DBS reageert, zal toekomstig onderzoek zich moeten richten op voorspellers voor respons. De rol die het verbeteren van zelfvertrouwen speelt in de verbetering van klinische symptomen na DBS is een onontgonnen gebied dat het leent om verder onderzocht te worden. Tot slot zal, gezien de huidige inconsistentie bevindingen, het vaststellen van de veiligheid van DBS op cognitief vlak een belangrijke uitdaging voor toekomstig onderzoek zijn. Daarbij zullen er valide cognitieve tests moeten worden ontwikkeld die in staat zijn de cognitieve veranderingen te meten die soms geobserveerd en gerapporteerd worden door patiënten na DBS.
LIST OF PUBLICATIONS
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Spitzer U, Figee M, Mantione M, Denys D. To feel free or to be free? To the psychology of experience of patients with obsessive-compulsive disorder under deep brain stimulation. *Nervenheilkunde* 2009;28:634-42.

DANKWOORD
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