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. 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. 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. First, patients usually have only a partial response to medication and CBT. Across all pharmacological treatments, the percentage of responders in placebo-controlled studies is around 40%. Approximately 60% of patients have a partial response to CBT and only 25% of patients are in full remission following CBT. 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. Even when the best available treatments are applied, approximately 10% of patients remain severely affected and suffer from treatment-refractory OCD. 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. 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. 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 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. 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. Two case studies had underlined the possible effectiveness of DBS of the STN in treatment-refractory OCD. Mallet et al. had reported an average decrease of 82% in OCD symptoms in 2002 and Fontaine et al. 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
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.² 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 x 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