Introduction
Chapter 1

Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease which is clinically characterized by bradykinesia, tremor, rigidity and postural imbalance. Lately, the non-motor deficits of the disease such as autonomic disorders, sleep disorders, and neuropsychological and neuropsychiatric features are receiving more and more attention. The disease is associated with advancing age, but disease onset at a younger age is not uncommon.

Neuropsychological impairments and behavioral changes

Neuropsychological impairments can be present in PD at the earliest stages. Many studies claim that cognitive impairments such as mental slowness, encoding problems, attention deficits, and impairments of working memory can all be explained as a consequence of executive dysfunction.1,2 Recently, however, researchers have stated that cognitive impairments in PD are more heterogeneous.3,4 Impairments were found on a wide range of tests measuring psychomotor speed, language, attention and executive functions, memory, and visuospatial abilities. It was concluded that memory and/or visuospatial functions were affected independently of executive dysfunction. With disease progression, dementia becomes a common feature of the disease with a prevalence of 24-31%.5 Patients and relatives often report mild behavior changes in an early stage of the disease. These concern among others decrease in interest and/or initiative, emotional flattening or increased compulsiveness. Later in the disease these behavioral changes can progress to neuropsychiatric disorders with hallucinations, obsessive-compulsive disorder, pathological gambling, hypersexuality and depression or apathy. Minor depressive symptoms are common in PD, but only 3-8% of the patients fulfill the DSM criteria for a depressive disorder.6 Depression shares symptoms with apathy such as loss of interest, which occurs in PD also in absence of depression. Apathy includes a primary lack of motivation which can negatively influence effort and productivity. Flattened affect and lack of response are also associated with apathy.7

Pathophysiology of Parkinson's disease and the role of the basal ganglia

The development of cognitive and behavioral changes in PD is related to dysfunction of the basal ganglia and other subcortical and striatofrontal networks. Neuronal losses occur in the dopaminergic nigrostriatal loop, noradrenergic and
serotonergic systems, cholinergic forebrain system and in specific nuclei of the amygdalae and the limbic system. Moreover, limbic and/or cortical Lewy body and Alzheimer type pathologies play a role in the development of cognitive and behavioral alterations.  

The functional circuitry of the basal ganglia is described by different models. An early model by Albin et al (1989) refers to a direct pathway in which striatal information goes through the internal globus pallidus (GPI) and the substantia nigra pars reticulata (SNR) and then to the thalamus and from there to the frontal cortex. The indirect pathway comprises the external pallidum (GPe), the nucleus subthalamicus (STN), and the internal pallidum (GPI) and SNR. The model of Alexander (1990) is more complex and consists of five parallel, segregated circuits: motor, oculomotor, dorsolateral prefrontal and lateral orbitofrontal and limbic circuits. There are many problems with both models because several experimental findings are not accounted for. According to Yelnik (2002), the functional anatomy of the basal ganglia is nowadays subdivided into three functional territories: the sensorimotor territory (the putamen) projecting back to motor cortices (prefrontal motor cortex, SMA, premotor cortex), the associative territory (dorsal caudate nucleus) projecting to the prefrontal cortex, and the limbic territory (ventral striatum) projecting to anterior cingulate cortex and medial orbitofrontal cortex. Yelnik explains that some researchers believe that the operation of these territories is mostly segregated. This way, pathways for movement are independent from pathways for cognitive and emotional functioning. On the other hand some researchers state that these pathways are not completely segregated and exchange of information between the territories takes place. Finally, Yelnik mentions basal ganglia models that use both convergence and segregation alternatively according to the task/environmental conditions. Lately, neural network models have been proposed to describe the function of the basal ganglia. One model replaced the insufficient dichotomy of direct/indirect pathways by proposing a primary role for the hyperdirect pathway (cortex – STN – GPI – thalamus –STN) next to the direct pathway (cortex – striatum – GPI – thalamus – cortex). Cortical activity targets the STN which hyperdirectly excites the GPI, bypassing the striatum. Competition between those loops provides the basal ganglia – cortex system with the ability to select motor programs. Cognitive function is not integrated in this model, but has been in another biologically based, neurocomputational model proposed by Frank. This model is based on the standard basal ganglia model with the direct and indirect pathways (Figure 1). Frank’s model is particularly relevant to the present
thesis, because in a later version it incorporates the role of the subthalamic nucleus. According to Frank, the basal ganglia provide a selective dynamic mechanism for the gating of information and support trial-and-error learning. Positive and negative feedback have opposing effects on dopamine release. Positive feedback leads to a dopamine burst which provides the direct pathway with a go signal for the execution of a response and at the same time inhibits the no-go signal in the indirect pathway. Negative feedback leads to a dopamine dip and releases the no-go signal from inhibition. Consequently, the execution of the response will stop. This theory was tested in a network model which learned to select one or two responses to different input stimuli. In probabilistic classification tasks, the network learned to respond concordantly with the performance of healthy volunteers. When PD was introduced in the network model by deleting 75% of the units in the Substantia Nigra, the simulated decrease of dopamine levels led to less efficient probabilistic learning. The hypothesis that this is due to impaired Go learning which depends on DA bursts was supported by research in unmedicated PD patients, who learned more from avoiding negative outcome than from the positive outcomes of their choices.

Figure 1 The corticostriato-thamocortical loops

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direct loop (cortex – striatum – GPi – thalamus – cortex)
indirect loop (GPe- STN- GPi- SNR- thalamus)
hyperdirect loop (cortex – STN – GPi – thalamus –STN)
Simulated supplementation with dopaminergic medication resulted in continuously elevated levels of dopamine and blocked the dips in dopamine needed for negative feedback, leading to impaired No-Go learning. This was also found in PD patients taking their regular dopaminergic medication. Moreover, simulated dopamine overdose in the model led to impairment in reversal learning just as in medicated PD patients in the early stages when dopaminergic damage is restricted to the dorsal striatum and the ventral striatum is relatively intact.

In a refined model, Frank integrated the STN, because the STN is part of the hyperdirect pathway and has diffuse reciprocal connections with the GPe. Dopamine depletion is associated with increased STN, GPe and GPi activity. Moreover, dopamine depletion leads to oscillatory activity in these nuclei. This pathological activity is related to the motor impairments in PD. The refined network model was able to simulate that lesions of the STN eliminated the network oscillations in the basal ganglia, but suggests that this is at the cost of impairment in decision making. Frank reasons as follows: When there are many potential concurrent responses to a stimulus and conflict load increases, the STN is activated by the cortex and gives a “global no-go response” to the GPe. This results in a delay in the execution of the response giving the basal ganglia more time to choose the most adaptive response. This way the STN prevents a premature response, which could be less adequate. He tested his theory in the network model. The concept of conflict was introduced in the model. The network had to learn one out of four responses for each of the four cues instead of the maximum of two responses in the previous version. The network received feedback by increasing or decreasing dopamine levels. The network learned to select the response most associated with positive reinforcement based on go/no-go learning. When response conflict was increased because of higher number of alternatives, the network model with intact STN became slower because of the global no-go signal. In models with simulated STN lesions response time was not associated with conflict load. Furthermore, it did not always choose the best among two positively associated responses. The global no-go response, which is only activated in cases of high response conflict, ensures that accuracy does not always go at the cost of speed of the system. When a decision is easy, the information process is fast. When the decision is complicated and more accuracy is needed, the process is delayed.

According to Frank it shows “that by modulating when a response is executed, the STN reduces premature responding and therefore has substantial effects on which
response is ultimately selected, particularly when there are multiple competing responses. Interesting and heuristically useful as these theoretical models may be, one needs to realize that they are still gross simplifications of the anatomical and functional reality. See for example a review by Saint-Cyr on the same subject, which does much more justice to the complexity of the basal ganglia.

**Treatment of Parkinson's disease**

In the early stages of the disease motor symptoms can often be treated adequately by means of dopaminergic replacement medications, levodopa with a decarboxylase inhibitor and/or a dopamine agonist. In some patients anticholinergics are used, especially in case of tremor. The effects of the anti-Parkinson medication on cognition and behavior differ widely. In de novo patients levodopa replacement therapy can initially lead to a nonspecific arousal effect, which facilitates cognitive processes that require effort. In a later stage when patients experience on-off response fluctuations on medication, levodopa can have different effects on different tests of executive functions. Patient in the 'off' phase have poorer results on verbal fluency, spatial working memory and visual attention tasks compared to the 'on' phase. On the other hand, lower scores on other executive tests such as card sorting, conditional associative learning and memory scanning were found when patients were in the 'on' phase. The negative effect of levodopa on card sorting tests and conditional associative learning can be explained by the model of Frank that states that learning is impaired because medicated patients have difficulties in suppressing highly activated responses, that were previously relevant.

Dopamine agonists have recently received bad publicity, because of their relation with hypersexuality, pathological gambling and compulsive medication use. Effects of dopamine agonists on cognition are not well understood, but executive dysfunction after taking pramipexol has been described. Anticholinergics are notorious for their negative effect on cognition such as hallucinations, memory impairments or full blown dementia. With advancing disease patients often develop side effects of medication, including wearing off, when Parkinson symptoms return in a shorter period of time after taking medication, and ‘on-off’ response fluctuations in which periods of good effect of levodopa medication (although often with dyskinesias) alternate with the sudden, unpredictable appearance of parkinsonian symptoms. When these response fluctuations appear, other drugs may
be added, such as MAO-B inhibitors, amantadine, COMT inhibitors, anticholinergics, and/or atypical neuroleptics, to suppress parkinsonian symptomatology, or side effects of other medications. Finally, all dopaminergic medications, amantadine, and anticholinergics may cause hallucinations, and/or delusions.

When medication no longer improves sufficiently the motor symptoms of PD, or when side effects prevent an adequate dosage of anti-Parkinson medication, stereotactic surgery may be considered.

**Stereotactic surgery**

In 1948 stereotactic neurosurgery was introduced for treatment of Parkinson’s disease, and ablative procedures such as pallidotomy and thalamotomy were regularly performed in the fifties and sixties. After the introduction of levodopa in 1967, surgery was temporarily restricted to single cases. Improvements in surgical techniques, the introduction of deep brain stimulation, and shortcomings of the pharmacotherapy, led to a revival of stereotactic neurosurgery for patients with advanced PD.

Nowadays, several nuclei are possible targets for stereotactic surgery, but for the research described in this thesis we restricted ourselves to unilateral pallidotomy and bilateral STN stimulation. Unilateral pallidotomy is a procedure whereby an electrode is introduced in the sensorimotor part of the globus pallidus, the posteroventral part of the inner segment of the globus pallidus (GPi). By radiofrequency stimulation a small area of brain cells and nerve fibres is destroyed by coagulation. Posteroventral pallidotomy of the GPi improves motor symptoms and reduces levodopa induced dyskinesias on the contralateral side to the surgical lesion. An alternative for ablative surgery is deep brain stimulation (DBS), in which chronic high frequency electrical stimulation improves Parkinson symptoms bilaterally. DBS has several advantages compared to lesioning. Firstly, the procedure can be applied bilaterally without major side effects. Next, the stimulator can be switched off making the treatment reversible. Moreover, DBS permits adjustment of the contacts and stimulation parameters after surgery. Bilateral DBS of the subthalamic nucleus (STN) is more effective than unilateral pallidotomy. The precise function of the STN is unknown, but as described
above, current theories hypothesize that the STN is a control system which may perform action selection. The STN has strong reciprocal connections with the external pallidum. STN DBS ameliorates the major motor symptoms of PD, possibly because of inhibition of STN output.\textsuperscript{25} Unilateral pallidotomy seems relatively safe with respect to cognition and behavior.\textsuperscript{26} In most studies only a negative effect on verbal fluency was found in patients who underwent left-sided treatment.\textsuperscript{27} However, most studies were comprised of few patients.

In 1999 the first study on neuropsychological effects of STN DBS was published by Ardouin et al.\textsuperscript{28} They concluded that STN DBS did not affect memory or executive functions, although they observed deterioration in verbal fluency and an improvement on the Trailmaking test. However, relatively young patients were selected and the scope of the neuropsychological test battery was limited. Another study by Saint Cyr et al (2000),\textsuperscript{29} which included older patients, was less positive. They found a decline in working memory, psychomotor speed, set switching, phonemic fluency and long term consolidation of verbal information. The cognitive decline was attributed to a decline of executive functions and was most obvious in patients of 69 years and older. Moreover, a decline was also seen on a scale measuring behavioral control. A depression scale only showed a temporary improvement in mood for the older patient group. The number of patients was limited. Disease progression might explain the decline because a control group was lacking. A case study from another group reported a patient who suffered from a major, reversible depression when stimulation was switched on, but one of the contacts of the electrode was placed in the substantia nigra instead of the STN. Transient behavioral changes have also been mentioned after other stereotactic procedures.\textsuperscript{30,31}

From these early studies on the cognitive effects of STN DBS the general assumption arose that bilateral STN DBS was just as safe as unilateral pallidotomy as long as the electrodes were properly positioned, but this assumption was not evidence-based. These early studies had the following limitations: 1) the patient groups were not large enough, 2) only limited test batteries were used, 3) no comparisons were made with a control group, and 4) individual decline was not always examined or only in a superficial manner. Moreover, the case studies showed that behavior could be influenced by stimulation.
Our approach

The main question: “Does STN DBS in patients with PD lead to cognitive decline and behavioral changes?” had not been answered properly by the studies cited above. With our approach we tried to overcome the limitations of the early studies.

Comprehensive evaluation
We used a comprehensive neuropsychological battery because we were interested in a broad spectrum of neuropsychological modalities. However, we laid an emphasis on the executive functions, because the early studies suggested implications in this modality, and also because the executive functions are already affected in many PD patients long before stereotactic surgery is considered. Next, we included several behavioral scales to monitor possible neuropsychiatric and dysexecutive symptoms common in Parkinson's disease. With mood scales we observed mood from the patient’s view but also from the proxy’s and the psychologist’s view. We evaluated the patients before surgery and six and twelve months after surgery.

Control group
Repeated assessment with tests and questionnaires is subject to retest effects. Patients perform better on tests with which they are accustomed. The use of parallel forms cannot completely prevent this. Consequently, a possible decline after bilateral STN stimulation could be obscured because of this retest effect. Conversely, an apparent decline after surgery might be due not to the procedure itself, but to disease progression. A randomized trial would have been the best approach to control for these confounding effects. However, because of the impressive motor benefits of STN DBS without severe mental side effects, it was considered ethically unacceptable to place patients on a waiting list for a year to complete the neuropsychological study. Therefore we formed a control group of PD patients with disease duration of at least six years.

Accent on neuropsychological profile
As is the case in our clinical practice, we were interested in the neuropsychological profile of the patients. However, the study of profiles entails intricate statistical problems. For example, a statistically significant change on one particular test out of a larger battery of tests may be a chance finding. On the other hand, slight
decline on several tests, although each separate decline might be statistically insignificant, could be indicative of cognitive problems in daily life. In order to deal with these problems, a new statistical method was developed. This method, termed multivariate normative comparisons, compares the test profile of each patient with the profile of the control group.

Predictors
Finally, we wanted to find out if we could predict which patients would decline after STN DBS in order to improve selection criteria of patients for this treatment. Therefore, we needed to include a sufficiently large patient group.

Outline of the thesis

Chapter 2
In the first study we evaluated the differential cognitive and behavioral effects six and twelve months after unilateral pallidotomy and STN DBS. This study was part of a randomized, single blind, multicentre trial which compared the effects of these procedures on motor functioning. This study was powered to compare the motor functioning; its sample size was too small to detect subtle neuropsychological changes which could still be clinically relevant. Subsequently, the 22 STN patients from this trial formed the start for a study in which we evaluated the neuropsychological effects of STN DBS in a larger patient group.

Chapters 3 and 4
We compared the changes in cognition and behavior six months after surgery with a control group of PD patients. Eventually, we enrolled 105 STN patients and 40 control subjects. At the twelve month follow-up we looked again at the group changes, but this time we also examined the individual changes with the new statistical method referred to above, the multivariate normative comparisons. Moreover, we assessed predictors of cognitive and psychosocial outcome of STN DBS.
Introduction

Chapters 5, 6 and 7
In the group of STN patients there were some patients who suffered severe neuropsychological side-effects of the procedure. Three of them were the subjects of in-depth case studies, which form the remainder of this thesis. We describe a patient who developed pathological gambling shortly after STN DBS (chapter five). We evaluated his neuropsychological profile including his ability for decision making at different stimulation and medication parameters. Next, in chapter 6 we describe a patient who had reversible cognitive decline after STN DBS, probably as a result of postoperative electrode displacement. In chapter 7, we describe a patient who developed a dysexecutive syndrome after STN DBS.

Chapter 8
In the final chapter the main findings are discussed. The thesis ends with a summary in English and Dutch.
References
