Neuropsychological effects of subthalamic nucleus stimulation in Parkinson's disease

Smeding, H.M.M.

Citation for published version (APA):
General discussion
Main findings

The main question of this thesis was “Does STN DBS in patients with PD lead to cognitive decline and/or behavioral changes?”. We found that about one third of the patients showed cognitive decline after STN DBS. The STN patients as a group performed worse than the control group on a cognitive screening task, on all verbal fluency measures, on verbal memory and on selective attention (chapter 3). Furthermore, we found that STN DBS led to slightly more decline than unilateral pallidotomy (chapter 2). Quality of life increased in one out of three patients after STN DBS. Worsening and improvement of mood were seen in equal proportions of patients (15% each). Relatives of STN DBS patients reported an increase in dysexecutive symptoms on questionnaires. Moreover, they reported more cognitive complaints and an increase in lability/irritability for the STN group at 6 months after surgery (chapter 3).

A subsidiary question of the thesis was “Can we predict which patients will suffer cognitive decline after surgery?”. Our results showed that patients with advanced age, a low levodopa response or impairments in attention have a higher chance of cognitive decline after surgery than young patients with a high levodopa response without attention disorders (chapter 4).

Comparison to earlier research

Discrepancies in cognitive decline

The most conspicuous result of our study is that the percentage of cognitive decline is higher than previously described. There are several reasons for this discrepancy. Firstly, we assessed patients in a more comprehensive way than anterior studies. Previous studies used shorter batteries or used tests with poor psychometric qualities that are not sensitive to change. Thus, our study was more sensitive to subtle changes after STN DBS. Secondly, although some studies reported no changes at all after STN DBS, in other papers changes in cognition and behavior were trivialized. For example, Funkiewiez et al. concluded that STN DBS does not lead to global cognitive deterioration. After scrutinizing this paper, I counted 10% of the patients with global cognitive deterioration after STN DBS in this study. Behavioral changes were interpreted as “rare”, although there was an
increase in apathy and several psychiatric events after surgery, adding up to 24% of this patient sample. The study of Dujardin et al. concluded that “in some patients it (STN DBS) can induce overall cognitive decline or behavioral changes”. Because cognitive decline was found in 3 out of the 9 patients, this “some” was absolutely interpreted instead of relatively. Several other authors seem to have jumped on the bandwagon and concluded that STN DBS is safe from a cognitive point of view, while in their results they also mention decline on specific tests, mostly verbal fluency but also in reverse digit span and in delayed recall of verbal memory. Cognitive decline seems to be considered relevant only if it is severe and takes the form of a dementia syndrome. However, to inform patients properly before the operation, and for postoperative management, it is important to assess all cognitive effects or other side effects of STN DBS without regard to severity. Therefore, we looked at individual cognitive decline. The third reason for discrepancy with earlier research is probably that we used a new, more comprehensive method of statistical testing. Usually, individual cognitive decline is simply measured as the percentage of patients that improved or declined more than one standard deviation on single tests. One disadvantage of this method is that when a patient has declined on four tests out of 10 and improved on one test, there is no criterion to decide if this should be considered cognitive decline. Next, the risk of finding at least one significant deviation by chance when in reality there is none becomes very high because of the sheer number of comparisons in the univariate technique. In addition, clinicians miss relevant information about the cognitive functioning of the patients if they only look at single tests instead of the profile of neuropsychological changes. A profile of mental slowing has other implications than a significant change on a constructive task. Furthermore, slight declines on several tests can be just as important as a large decline on a single test. We therefore used a new statistical method of multivariate normative comparisons that examined the profile of test performances of each of the STN patients and compared it to the controls. Slight declines are easily missed by the old method but are detected by the new method. This way, we determined that 30% of the patients had a profile of cognitive decline after STN DBS not seen in the control group.

**Comparable improvement in quality of life**

Other results of our study are less discrepant. For example, one out of three patients showed an improvement in quality of life after STN DBS. Actually, this seems rather low for a procedure that has such impressive motor results. However, our
group results of 16% improvement in quality of life for the STN group is fairly comparable to a recent RCT \(^{10}\) that found improvements in quality of life of 22% for the STN group. This study did not report individual improvement. An explanation for the low number of patients that report improvement in quality of life may reside in the phenomenon of response shift, which refers to changes over time in internal standards, values, and the definition of quality of life.\(^{11}\) Patients start thinking differently about their quality of life because of adaptation or due to becoming accustomed to better (or worse) functioning. A year after STN DBS life seems to have taken its usual course, and patients may judge their level of quality of life according to the new standard of motor functioning. The same phenomenon could also explain why relatives of the STN patients not longer notice cognitive decline at 12 months, while they had at 6 months, and psychometric tests still measure cognitive decline. After a year relatives may have become accustomed to the new situation of decreased cognitive functioning.

**Possible explanations**

*Does postoperative reduction of medication explain cognitive decline?*

How can we explain the executive decline and behavioral changes after STN DBS? Postoperative reduction of dopaminergic medication has often been suggested as a cause of postoperative changes in cognition and behavior. STN DBS is said to mimic the effects of levodopa medication on motor functioning, but without the mood enhancing effects.\(^{12}\) After surgery dopaminergic medication can often be reduced, and sometimes discontinued completely.\(^{12}\) In some patients this leads to apathy, which resolves after adding levodopa medication.\(^{13}\) However, we did not find a relationship between the reduction of medication and executive decline or mood changes in our study. Therefore, cognitive decline and behavior changes cannot exclusively be due to reduction of medication.

Nevertheless, it could be possible that patients become more sensitive to dopamine agonists, a class of anti-parkinsonian drugs with a different pharmacological mechanism. We suggested this possibility in chapter 6 about the patient who developed pathological gambling shortly after STN DBS although dopamine agonists were halved. This problem behavior resolved when dopamine agonists were stopped (*chapter 6*). Unlike levodopa and related substances, the cognitive
side effects of dopamine agonists have not yet been extensively studied. One study attributed executive dysfunction, i.e. decline in verbal fluency, verbal memory and attention to pramipexole, one of the dopamine agonists. These side effects are fairly comparable to the side effects of STN DBS. Recently, it has become standard management to stop dopamine agonists after surgery.

**Do mood changes explain cognitive decline?**
Both depression and hypomania after STN DBS have been offered as explanations for executive decline. Depression is associated with cognitive impairments, mostly in the executive domain. The same applies to mania. There are obvious similarities between the executive dysfunctions of PD and the cognitive concomitants of depression or mania, because usually both are relatively modest and both involve effortful processing. However, only 4% of the variance of the cognitive decline in our sample could be explained by mood changes. Moreover, although there were 16 STN patients who showed worsening of mood 12 months after surgery, only one patient fulfilled DSM-IV criteria for a major depressive episode. Sixteen patients showed improved mood at 12 months, but only one patient fulfilled DSM-IV criteria for mania.

**Do surgical side effects explain cognitive decline?**
Cognitive decline has also been attributed to surgical side effects. Some state that cognitive decline is caused by faulty placement of the electrode. This can indeed be the case as we described in our study about the reversible dementia after STN DBS (*Chapter 5*). We cannot completely rule out the possibility of some displacement of the electrodes in the other patients, because we could not obtain postoperative MRI verification of the electrode placement due to the restrictions of Dutch radiological departments. Nevertheless, evident motor improvement suggested proper placement. When there were any doubts about motor functioning or side effects, the preoperative MRI scan was co-registered with the CT scan to verify the position of the electrodes. Other authors stated that cognitive decline is transient, caused by surgical effects such as microlesioning or edema. In our study we did not find improvement at twelve months postsurgery, by which time microlesions and/or edema would have completely resolved. To the contrary, the effect sizes of most cognitive measures were larger at 12 months compared to six months after surgery. Thus, cognitive decline did not resolve over time. Absolute decline of cognitive measures in the
STN group did not increase, but the control group had a larger retest effect (i.e. those patients improved due to practice and familiarity). Absence of such an effect may be interpreted as decline.

**STN stimulation explains cognitive decline**

The remaining, and most probable explanation is that the stimulation itself causes the cognitive and behavioral changes. Some authors argue against a direct stimulation effect causing cognitive decline because of the small effect that has been found in studies that compared cognition and mood in PD patients while they were on and off stimulation.\(^ {17,18}\) However, in these stimulation challenge studies the interval between on and off stimulation was restricted, sometimes only to an hour. Motor symptoms reappear sequentially when STN DBS is switched off with worsening of axial signs within 3 to 4 hours.\(^ {19}\) Possibly, effects on mood or cognition take even longer to emerge. In our case studies we switched stimulation off for a week and we assessed notable stimulation effects on cognition and behavior.

There are two possible mechanisms of stimulation effects. The first is spread of electrical current to neighboring structures; the second is the direct effect on the target structure itself. The second mechanism will be discussed under the next heading. The first mechanism contains that cognitive decline might be caused by the spread of electrical current to surrounding areas. The STN is surrounded by several structures that have indirect connections with the cortex. In chapter 7, we described a case study of a patient who developed executive dysfunction and personality change after STN DBS. In this patient, the highest contacts of the electrode were dorsal to the STN. Although they were more effective for motor functioning, they induced the most notable neuropsychological side-effects. In this case, stimulation probably involved the fields of Forel, and the zone incerta, perhaps spreading posteriorly into the meso-diencephalic reticular formation. The pallidothalamic projections pass through these areas\(^ {20,21}\) and stimulating these structures may in turn negatively influence thalamic relays to the the orbitofrontal cortex, the anterior cingulate cortex, and the dorsolateral prefrontal cortex.\(^ {22,23}\) However, stimulation of the three contacts of the electrode gave different effects on motor status and behavior while they are only millimeters apart from each other. This suggests that the current does not spread very far and that there are various pathways that influence motor and cognitive functioning differently.\(^ {24}\) Thus,
spread of electrical current to neighboring structures does not seem to explain all cognitive and behavioral effects.

**Influences of STN on cognition**

Here I come to the second mechanism that may explain how stimulation of the STN itself causes cognitive decline and behavior changes. It is not clear how STN DBS works. At first, it was suggested that DBS blocks neuronal activity in the STN, thereby indirectly normalizing the activity of the GPi. Recently, also an excitatory effect on the STN’s target structures has been proposed. To make it even more complicated, an experimental study showed that DBS can have inhibitory as well as excitatory effects on multiple parts of the same neurons.

**Figure 1** The corticostriato-thalamocortical loops

![Diagram of the corticostriato-thalamocortical loops](image)

The neurocomputational network model of Frank, that was proposed for explanatory reasons in the introduction of this thesis, assumes that the STN is blocked by the stimulation. In an intact system, the STN is part of the hyperdirect pathway in which supplementary and premotor areas directly project to the STN which then directly excites the GPi, bypassing the striatum (see figure 1). Because of the diffuse reciprocal connections between the STN and the GPe, Frank assumes that the STN is probably not well suited to suppress specific responses. Instead, he
posits a modulatory function of the STN. When there are many concurring responses to a stimulus, the STN is activated more by the cortex than when there is no response conflict. Subsequently, with conflicting responses the STN activates the GPi more strongly. Subsequently, the GPi inhibits the thalamus and a response is not facilitated. Frank calls this a “global no-go response” of the STN to the GPi. This results in a delay in the execution of the response (response inhibition) giving the basal ganglia more time to choose the most adaptive response. In this way the STN prevents a premature response, which could be less adequate. After stimulation, the STN cannot give this global no-go response to the GPi in conditions of high demand, and the system will tend to respond prematurely with more mistakes or less adaptive responses. In addition, inhibiting a response that has a high probability of occurrence becomes more difficult. Frank tested his hypothesis in patients after STN DBS and found that STN patients did not slow down during a high conflict choice on a probabilistic selection task while reaction times increased normally in PD patients who were treated with dopaminergic medication only.28 Increased responding after STN DBS was only seen when high conflict was due to options with high probabilities of occurrence, and not when both options had low probabilities.

In relating this neurocomputational model to the neuropsychological test results of the present studies, it becomes clear that suppressing an automated response, such as in the Stroop task, indeed showed decline after STN DBS (chapter 3 and 4). The lower score for the recall in the verbal memory task and decreased verbal fluency can be explained because in these tasks words, which already have been recalled, have to be suppressed to enable new words to appear. After STN DBS the recall of new words becomes more difficult, because the STN usually helps to overcome the last response, which inherently has a high probability. Moreover, the reports of increased impulsivity and increased crying after STN DBS are compatible with the theory of Frank that predicts disinhibition of the system, assuming that the system does not distinguish between cognition and other forms of behavior. On the other hand, the findings of loss of initiative and loss of spontaneity are both discordant with the model of Frank, because they presume inhibition of the frontal areas after STN DBS.

A study that demonstrated shorter reaction time with stimulation switched on compared to stimulation switched off29 supports the theory of Frank, because Frank predicts that after STN DBS the system will work faster. More importantly, response inhibition was impaired when tasks in that study became more
demanding, consistent with Frank’s hypothesis.\textsuperscript{29} Witt et al\textsuperscript{30} also concluded that STN DBS impaired response inhibition, i.e. slightly more errors on the Stroop color word card. However, suppression of habitual responses on a random number generation test improved after STN DBS. The latter finding is not expected on from the theory of Frank. Conflicting with the Frank model also was a study that used the Hayling task, which requires patients to complete sentences first with a habitual response, and subsequently with a semantically unrelated response. In the first part of this task, only one response is correct (e.g. “One eats soup with a ….”), in the second part there are many correct responses as long as it is not the habitual response (any word is correct as long as it is not related to eating soup).\textsuperscript{31} This study found that STN DBS improved reaction times on this second half of the task even though it requires suppression of a habitual response. The shorter reaction times after STN DBS that Van den Wildenberg et al\textsuperscript{32} found on a stop task are consistent with the Frank model but the unchanged accuracy rate is not. The authors of this study did not relate the improvement to STN function but to improved motor functioning because it was also seen after thalamic stimulation. These studies cited above show that results in response inhibition depend on different task requirements. Moreover, the dopaminergic medication that patients used in all these studies could have confounded the results on response inhibition. Taken together, it seems that responding after STN DBS becomes faster on tasks in which patients have to inhibit a habitual response and can choose from many alternatives of which several are correct. In the studies with tasks in which the choice is between many competing alternatives with only one correct response, more errors are made because of impaired response inhibition. This interpretation can reconcile these seemingly conflicting findings with the theory of Frank. STN DBS leads to faster responding because the STN does not give the usual global no-go response and does not slow the process when there are multiple competing responses, but under circumstances where a precise response is required, the responses will be less adequate and sometimes even wrong. Thus, after STN DBS, the system responds faster but less accurately.

\textbf{Does imaging show what happens after STN DBS?}

A PET study found increased blood flow after STN DBS in the STN, globus pallidus and thalamus, and reduced blood flow in frontal, parietal and temporal cortex, which suggests that DBS does not block the STN but increases firing. As a result, activity of the frontal systems is inhibited.\textsuperscript{33} Frontal inhibition could
probably explain the decline in verbal fluency, the decrease in memory functioning and the decrease in mental speed we found in our study. This explanation is endorsed by imaging studies that showed that decrements in cortical activation were related to decreased verbal fluency and decreased cognitive control after STN DBS.\textsuperscript{23,29,34} Probably, the mechanism of STN DBS is more complex than this, because another PET study found that cerebral blood flow was increased in the supplementary motor area during the execution of a motor task.\textsuperscript{35} Just as in the other studies, this study found that STN DBS decreased the activity at rest in prefrontal areas and in the temporal lobes. The authors suggested that the DBS effect consisted of ultimately normalizing overactivity, because in a control group of patients in whom DBS was programmed at ineffective parameters, the same regions were overactive compared to healthy controls.

The results from the imaging studies seem far from conclusive. Interpretation of the results is difficult because of different research designs. The patient groups in the studies are quite small. The problem is that STN DBS will probably have variable effects on blood flow in patients, due to variability in electrode location, stimulation parameters, and individual physiological differences.

\section*{Limitations}

\textit{No randomization}

Our study was not a randomized trial. Randomization between surgery and a waiting list control condition is not considered ethical because of the proven efficacy of the DBS procedure on motor functioning. Differences between the groups in cognitive decline could be due to differences in demographic or disease characteristics. The STN group was slightly younger than the control group, used more dopaminergic medication and had longer disease duration. When we covaried for baseline group differences, results showed the same pattern. Nevertheless, we cannot totally rule out the possibility that the cognitive reserve of the STN patients had already been more affected because of longer disease duration and higher amounts of medication, making them more prone to sudden cognitive decline. On the other hand, the control group was older and cognitive reserve also decreases with age.\textsuperscript{36}
No evaluation of dementia
We did not evaluate our patients in such a way that we were able to apply consensus criteria to diagnose dementia. Therefore, we could not ascertain that the cognitive decline after STN DBS was not, in some cases, compatible with a dementia syndrome. In the STN group, there were patients with moderate to severe decline. Scores on neuropsychological tests transferred from the unimpaired to the impaired range, but we could not definitely exclude dementia at baseline. A recent study found that 9% of the patients developed dementia within 6 months after surgery. The follow-up after 3 years revealed an incidence of dementia similar to the incidence reported in medically treated patients.9 However, there was no direct control group and the study used a limited neuropsychological battery.

No control group of general surgery
The control group of our study consisted of PD patients who did not undergo surgery. To find out if cognitive decline is specific to STN DBS, or if it is a more general finding after surgery, we should have added a control group of patients: preferably Parkinson patients, undergoing a general surgical procedure.

Sample size
Another limitation was the sample size of our study. Although the present study had the largest number of patients compared to other studies on neuropsychological aspects of DBS, this number is still quite small for establishing stable predictive models. What is needed is a study with a sample of at least 200 patients to establish predictors of outcome with more certainty37. This is only feasible with an international multicentre trial. It remains essential that a comprehensive set of neuropsychological variables are studied, because subtle but clinically relevant changes will not be detected with coarse measures. Moreover, cognitive change was not restricted to verbal fluency or psychomotor speed, but was also seen on several other measures, i.e. tests of memory and attention.

Sensitivity of the questionnaires
We designed our study protocol to assess neuropsychiatric changes but perhaps our protocol was not sensitive enough to catch more subtle behavioral changes. After surgery, patients and their relatives complained often about loss of interest or loss of spontaneity. Many patients said they cried much more often, and some were
more easily annoyed. Restlessness and impulsivity were also mentioned. We related these behavior changes to executive dysfunction. Although we found an increase of dysexecutive symptoms rated on a questionnaire by relatives of STN patients, the association between the score on this questionnaire and the cognitive decline was weak. Patients, whose relatives reported an increase in dysexecutive symptoms, did not match the patients showing cognitive decline. Perhaps, the behavior changes already existed before surgery as these are common in PD. After surgery, behavioral changes could have been mis-attributed to the surgical procedure. A more likely possibility is that the DEX is not sensitive enough to detect these changes because of poor psychometric properties. Therefore, we need to improve clinimetrics for PD with questionnaires on neuropsychological functioning imbued with proper psychometric qualities, especially designed for PD or other basal ganglia diseases characterized by executive dysfunction. The phenomenon of response shift should be taken into account as well.

**Clinical implications**

What do the cognitive decline and/or behavior changes after STN DBS mean for patients in their daily life? When cognitively intact patients develop a dementia syndrome after surgery, it is obvious what the change means for their daily life. However, what are the practical implications of mild cognitive decline?

**Four considerations concerning mild cognitive decline**

1) **Reduction of cognitive dissonance obscures complaints of cognitive decline**
Most patients state that the motor improvement after STN DBS outweighs the costs of cognitive decline. This seems a good reason to disregard mild cognitive decline after STN DBS. Nevertheless, we should be prepared for the phenomenon of cognitive dissonance. People do not like a discrepancy between their beliefs or opinions and their actual behavior. Usually they attempt to address this discrepancy by rationalizing their choices (i.e. reducing cognitive dissonance). STN DBS is an invasive procedure patients see as a last resort. The surgical procedure itself presents a heavy burden for patients. After such an investment, most individuals will tend to say “yes” when asked if surgery was worthwhile Negative consequences of surgery will be ignored.
2) **Cognitive decline is only precipitated**

Another reason to disregard mild cognitive decline is the suggestion of Aybek et al. that STN DBS only has a precipitating effect on executive decline in PD, because also in medically treated patients cognitive decline belongs to the natural course of the disease. Even though this latter part of their statement is true, patients still have to be properly informed about the possible negative influence of STN DBS on their cognitive functioning.

3) **Patients have cognitive complaints**

A reason not to disregard mild cognitive decline after STN DBS is that when asked properly STN patients and/or their relatives have complaints about cognitive functioning and behavior. Most of them probably link those complaints to the surgical procedure. STN patients complained about “leaving drawers ajar” or “no longer being able to recall answers to a quiz within the beep (time limit)” or “not being as witty anymore in a conversation”. Relatives complained more often about loss of interest. Neuropsychologists assume a relationship between the complaints of patients and the neuropsychological findings. The decline on the Stroop color-word task after STN DBS implies a worsening of selective attention, which is compatible with the complaints of the STN patients about absentmindedness or forgetfulness. The decline in verbal fluency and/or verbal memory after STN DBS implies that patients need more time to recall relevant information. Recall of information when there is a time limit, as happens in a conversation or a quiz, is less efficient than before, leading to the aforementioned complaints. These changes in executive functions often do not manifest themselves in the outpatient clinic because of the structured situation that is well known to the patient. However, they appear more frequently in novel situations of everyday life.

4) **Social adjustment is not successful**

The last reason to take cognitive decline after STN DBS seriously is that mild executive decline and/or behavior changes cause problems in social functioning after STN DBS. The study of Schüpbach et al. entitled “A distressed mind in a repaired body” reported that, despite an unchanged group score on the social adjustment scale, difficulties were commonly seen in relationships with 70% marital problems and in a disappointing 56% of patients who resumed their jobs after successful STN DBS. According to the authors, the unsuccessful social
adjustment could not be explained by neuropsychiatric changes because mood and anxiety improved notably. They stated that the problems with social adjustment could also not be attributed to neuropsychological changes. This seems to be a premature judgment because no sensitive tests were used. Moreover, as an aside they mention that unstructured interviews with patients revealed difficulties with planning ahead, ordering complex thoughts and distractibility, impatience, and irritable behavior. These difficulties seem indicative of the executive dysfunction that we demonstrated in our study.

Oddly enough, in the same year the same centers published another paper on social adaptation. After careful reading, it appeared that they were reporting on a subgroup from the Schüpbach study. The Schüpbach study pursued the individual changes in social adaptation in great depth, whereas the paper from Houeto et al. accentuated the positive outcome on group level of STN DBS on mood, anxiety and quality of life. On the issue of social adaptation they reported just as Schüpbach had, that the group scores unexpectedly did not ameliorate, but incidences of marital problems or job return were not mentioned. These two papers show that reporting on group scores only does not reveal unfavorable individual changes in social adaptation after STN DBS. Despite the stable group scores, the individual changes in social adaptation after STN DBS are alarming and could be related to cognitive decline.

In our study 23 percent of the 65 STN DBS patients who had a long lasting relationship reported an increase in marital problems within the first year after surgery. This increase is much higher than the three percent increase in marital problems of the control patients (p=0.02, one-tailed. Unlike Schüpbach et al. we did not explicitly ask about marital problems.

**How to improve outcome after STN DBS**

Given the results of the present studies, which show that cognitive decline occurs fairly often after STN DBS and has implications for daily life; we need to ask how STN DBS outcome can be improved. Our best prospect is a better, more stringent, selection of patients. Until now, cognitive exclusion criteria have been far from uniform. Most centers agree that patients with dementia should be excluded for STN DBS. Dementia has often been defined as a score lower than 24 on the Mini Mental State Examination. The Mattis’ Dementia Rating scale is also a widely used cognitive screening instrument for which in DBS screening a cut-off score of 120 is used as well as a cut-off of 130. Because age and educational level
have an influence on the results of these instruments, normative scores should be used corrected for age and education.43 Besides, Parkinson patients can still have cognitive disorders, despite a score above the cut-off on a dementia screening instrument, because of the relative insensitivity of these instruments for executive disorders typical of Parkinson disease. In our study we identified baseline predictors of cognitive decline and baseline predictors of improvement in quality of life. We found that a low levodopa response, advanced age and attention impairments at baseline predicted cognitive decline after STN DBS (Chapter 4). A high levodopa response predicted improvement of quality life. We calculated postoperative probability on cognitive decline or improvement in quality of life based on the predictive factors of our study. Some examples based on the tables from chapter 4 will be discussed.

A Parkinson patient with a good levodopa response of 70% has an almost 50% probability of improvement in quality of life. When he is 55 and has no cognitive impairment, he has a probability at cognitive decline of 20%. This probability increases to 50% when he scores two standard deviations below his norm group on the Stroop card 3 and on the Trailmaking part B. Another example: a 65 year-old patient with a low levodopa response of 30% has a probability of improvement in quality of life of only 15%. When he scores at an average level on the attention tasks, his probability of cognitive decline is about 30%, but when his score falls two standard deviations below his norm group the probability of cognitive decline rises to 90%. This latter patient is probably not the best candidate for STN DBS. We cannot base an absolute exclusion criterion on these predictors, because even the worst candidate has still a probability of improvement in quality of life. In addition, as we mentioned before in the limitations section, the predictors are based on models that need larger patient groups to become more reliable. When group size increases, it could be possible that not only impairment in attention but also other cognitive impairments will be identified as valid predictors of cognitive decline after STN DBS. Probably, the smaller the cognitive reserve, the higher the chances of cognitive decline.

**Informed decision making**

Patients and their relatives have to be informed about the chances of improvement and the risks of STN DBS. This way, they will be enabled to make an informed decision. However, this process is hindered by the impairments that patients with Parkinson disease can have in decision making.44 PD patients have more difficulty
predicting the consequences of their behavior and judging risks and chances than healthy people. Even healthy people do not make choices by rationally calculating their risks and chances. From economic psychology we know that when a decision has to be made between a certain loss now and a chance on a even larger future loss balanced against comparatively weighted winnings, people are inclined to take large risks. The choice for no surgery can be seen as a certain loss because there is no chance for improvement of motor functioning and patients have to keep on living with the motor disorder. Even if the probabilities of cognitive decline or absence of motor improvement after surgery are large, patients will overrate the chance of a positive outcome because people generally have a bias for optimism and they feel that they have nothing to lose. Another problematic aspect of decision making when risks are involved, is the experiential awareness of the consequences of the decision. When people have knowledge about or experience with the risky outcome, they tend to estimate the risk as higher than when they cannot easily imagine the outcome. This means that patients and their relatives will probably overestimate the chance on cognitive decline and emotional changes when they experienced these before and will underestimate the risk when they cannot imagine the consequences of cognitive decline and emotional changes. Doctors should know about these issues around decision making because they have to decide too about surgery and advise their patients. There is no reason to believe doctors will not be subjected to the same psychological processes that influence human decision making.

**Concluding remarks**

STN DBS is one of the marvels of modern neurosurgery. The effects are almost immediate and highly visible. In some cases, the change after surgery is miraculous. Patients, who shook from their chair before surgery because of dyskinesias, sit perfectly still after surgery. Patients who did not go out anymore, because they attracted unwanted attention, are able to socialize normally again after surgery. Patients, who depended on their spouse to get out of bed, live independently after surgery. Hardly surprising, many patients feel reborn. Because of the successes of DBS, the application possibilities to other neurological and even neuropsychiatric conditions will be actively promoted. The spectacular effects
in some patients could lead to unrealistic expectations in future patients and doctors too. To improve the quality of the treatment, we should look beyond motor improvement. Therefore, we looked carefully at the cognitive and behavioral effects and more generally at the outcomes in terms of quality of life.

The present series of experiments proves that cognitive decline occurs often after STN DBS, as does improvement in quality of life. A high levodopa response predicts improvement in quality of life. Cognitive decline ranges from slight decline to dementia. A poor levodopa response, advanced age and impairments in attention at baseline predict cognitive decline. Consequently, doctors who select Parkinson patients for DBS should not rely on the MMSE or on the Mattis’ Dementia rating scale scores as an exclusion criterion, because these are not sensitive enough instruments. A thorough neuropsychological examination should be standard before stereotactic surgery to assess possible cognitive impairments and emotional problems. Patients with a low levodopa response and cognitive impairments should not be implanted with STN DBS, because of the low probability of improvement and a high risk of cognitive decline. Refraining from surgery in these cases is not the same as ‘doing nothing’. Moreover, because the decision about surgery is always complex, it should be taken by a multidisciplinary team that includes a neurologist, a neurosurgeon, a Parkinson nurse, a psychiatrist and a neuropsychologist. Finally, a neuropsychological examination should also be standard after STN DBS to assess side effects on cognition and behavior, because in some patients it is possible to influence these side effects positively by adaptation of stimulation parameters. Moreover, information about these side effects generally improves acceptance and management.

I hope that this thesis will stimulate doctors to take the possible cognitive and behavioral costs of STN DBS into account in balance with the anticipated motor improvement that is often wonderful.
References


General discussion


Summary

This thesis concerns the neuropsychological effects of bilateral deep brain stimulation of the subthalamic nucleus (STN DBS) in Parkinson’s disease (PD).

Chapter 1 provides an introduction in the aspects of Parkinson’s disease that are relevant for this thesis: the pathophysiology of PD, the pharmacological treatment, the neuropsychological impairments and behavioral changes that occur in PD, and the different neurosurgical treatments. An overview of the neuropsychological effects of pallidotomy and the early studies on STN DBS is given including the shortcomings of those studies.

In chapter 2 we investigated the differential cognitive and behavioral effects of unilateral pallidotomy and STN DBS six and twelve months after surgery. This study was part of a randomized clinical trial. We compared 14 pallidotomy patients with 20 STN patients on neuropsychological tests of language, memory, visuospatial function, mental speed and executive functions. Also a depression rating scale, and self and proxy ratings of memory and dysexecutive symptoms were administered. Although group sizes were rather small, this study suggests that STN DBS has slightly more negative effects on executive functioning than unilateral pallidotomy.

In chapter 3 we describe a study in which we compared patients after STN DBS with a nonsurgical control group of PD patients. Six months after surgery STN DBS leads to a decline on measures of verbal fluency, color naming, selective attention, and verbal memory. Moreover, a decrease in positive affect, and an increase in emotional responsivity and cognitive complaints is seen. On the other hand, the STN group shows an increase in quality of life and a slight decrease in depressive symptoms. Nine percent of the subthalamic patients had psychiatric complications. We conclude that STN DBS leads to executive decline in a subgroup of patients with implications for daily life of these patients and their relatives.

With a new statistical method, the Multivariate Normative Comparisons, we show in chapter 4 that STN DBS improves quality of life in about one third of the patients at the cost of cognitive decline in a similar proportion of patients.
Levodopa response, age and performance on attention tests at baseline are predictors of cognitive and psychosocial outcome. Postoperative decrease in dopaminergic medication was not related to cognitive decline.

In chapter 5 a patient is presented who suffered from severe cognitive decline after STN DBS. Cognitive decline resolved after switching off DBS. Adjustment of stimulation settings to the dorsal contacts led to a minor setback in cognition. The electrodes were probably displaced as a result of brain shift caused by CSF leakage during surgery and subsequent unfolding of the brain in the postoperative period.

Chapter 6 describes a patient with advanced Parkinson’s disease who developed pathological gambling within a month after successful STN DBS. Slight cognitive decline was evident a year after surgery. Performances on decision-making tests became worse with stimulation of the most dorsal contact compared to the more ventral contact. Pathological gambling disappeared after discontinuation of pergolide and changing the stimulation parameters. In this patient pathological gambling does not seem to be related to decision-making but appears to be related to a combination of bilateral STN stimulation and treatment with dopamine agonists.

Chapter 7 presents a patient who became increasingly irritable, distractible and forgetful after subthalamic stimulation. His manners were lost and he used aggressive vocabulary. Patient had a history of a left pallidotomy. Switching off the stimulators led to a remarkable recovery of behavior. When we adapted the stimulator to a lower contact point, the behavioral changes and executive dysfunction were less severe than at the higher contact point but motor functioning was not satisfactory. After returning to the higher contact point, the mental problems reappeared again, although less severe than immediately after surgery.

Chapter 8 is a discussion about the neuropsychological results of our studies on STN DBS in Parkinson’s disease. The percentage of 30% cognitive decline seems rather high compared to other studies, but our results are based on more sensitive tests, a better statistical method that looks at the profile of neuropsychological changes. Moreover, we looked at all cognitive decline instead of only considering dementia to be relevant. The improvement in quality of life in 30% of the patients is comparable to other studies. As an explanation for the low number of patients
that report improvement in quality of life I propose the phenomenon of response shift, which refers to changes over time in internal standards, values, and the definition of life quality. Subsequently, I discuss several explanations for cognitive decline after STN DBS such as postoperative reduction of medication, the use of dopamine agonists, mood changes, surgical side effects and the STN DBS itself. Our neuropsychological findings could not be completely explained by a neurocomputational theory of the STN which was coined by Frank (2006, 2007). I furthermore discuss the limitations of our studies of which the most important ones are that the studies were not randomized, and that we did not include an extra patient group to control for general effects of surgery. With respect to the clinical implications of this thesis, I give four reasons to take mild cognitive decline seriously. I describe that older patients with a low levodopa response and impairments in attention have a lower chance at improvement in quality of life and a higher risk of cognitive decline than young patients with a high levodopa response and no cognitive impairments. These baseline predictors should be used for a more stringent selection of candidates for subthalamic stimulation. I end the thesis with some concluding remarks on the importance of neuropsychological examination for the STN DBS treatment of PD. Although the motor effects of the treatment are often spectacular, the neuropsychological costs should be taken into account.