Deep brain stimulation of the subthalamic nucleus and globus pallidus internus for advanced Parkinson's disease

Vincent Odekerken

DEEP BRAIN STIMULATION OF THE SUBTHALAMIC NUCLEUS AND GLOBUS PALLIDUS INTERNUS FOR ADVANCED PARKINSON'S DISEASE

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Colofon:
Printed by: Ridderprint BV – www.ridderprint.nl
Layout by: Remco Wetzels | Ridderprint BV
Cover design: Friso Elzinga

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Agnietenkapel

op vrijdag 14 oktober 2016, te 14:00 uur

door Vincentius Jozef Johannes Odekerken

geboren te Naarden

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Introduction: Deep brain stimulation for advanced Parkinson's disease

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Adapted from
Odekerken V.J., van den Munckhof P., Schuurman P.R., de Bie R.M. Dubbelzijdige diepe hersenstimulatie bij de ziekte van Parkinson. Tijdschr Neurol Neurochir 2013;114:143-8.

SUMMARY

Deep Brain Stimulation (DBS) for Parkinson's disease is a treatment option in patients with medication-induced motor response fluctuations, when medication schedule adjustments are no longer able to sustain optimal functioning in daily life. DBS mainly improves motor symptoms that initially responded well to dopaminergic treatment, such as tremor, bradykinesia and rigidity. DBS also reduces the time spent in off-drug phase, dyskinesias, and medication use. The most important complications of surgery are intracerebral hematoma (rarely encountered), infection, hardware complications, and cognitive impairment and behavioral changes. Both globus pallidus parts interna (GPi) DBS and subthalamic nucleus (STN) DBS improve motor symptoms, but it is unclear which nucleus improves symptoms more. Moreover, STN DBS might be associated with more side-effects on cognition, mood, and behavior. The Netherlands SubThalamic And Pallidal Study (NSTAPS) is a randomized controlled trials that compares outcome after GPi DBS and STN DBS up to three years after surgery. Functioning, cognition, mood, behavior, motor symptoms, quality of life and complications of surgery are evaluated. The results are discussed in this thesis.

INTRODUCTION

Patients who have advanced Parkinson's disease (PD) are often hindered by medication-induced response fluctuations (henceforth called response fluctuations).[1] They experience sudden and unpredictable transitions between periods of relatively little hypokinetic-rigid symptoms (the 'on-drug' phase) and periods of much of these symptoms (the 'off-drug' phase). In addition, they may experience bothersome dyskinesias. When adapting the medication scheme does not satisfactorily improve motor symptoms and response fluctuations, deep brain stimulation (DBS) becomes a treatment option.[2] DBS is a technique that has been used since the early 1990's in the treatment of advanced PD.[3]

How is DBS performed?

The large part of the surgery is commonly performed under local anesthesia. On the morning of the surgery, a stereotactic frame is placed on the head of the patient and tightened to the skull using four screws for stabilization (figure 1). Subsequently, an MRI of the brain is made to determine the three-dimensional target coordinates in relation to the reference marks on the frame. After determination of the coordinates of the left and right targets in the basal ganglia and the trajectory towards these targets, the patient is transferred to the operating theater. Two burr holes are made in the skull and a test electrode is inserted into the brain. Once the electrode approaches the target, electrical stimulation is applied to evaluate the clinical effect of stimulation on the motor symptoms and possible side-effects. Some centers also use micro-electrode recordings to assess the local neuronal firing patterns as an additional verification of the target. Once consensus is reached on the optimal position of the electrode, the test electrode is replaced by the permanent electrode. The patient then undergoes general anesthesia and the electrode is attached to a subclavicular neurostimulator by a subcutaneous connection cable. In the weeks and months following surgery, the stimulation settings and the medication scheme will be adjusted to reach an optimal effect on symptom reduction.

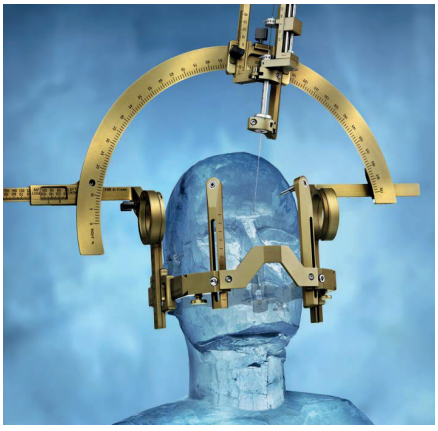

Figure 1. *The stereotactic frame (Leksell Stereotactic System©)*

To evaluate the indication for DBS, a 2-day admission of the patient takes place a few months before surgery. During this admission, the extent of symptoms in on-phase and off-phase, the medication side-effects, and cognitive and psychiatric symptoms are evaluated. An MRI of the brain, laboratory investigations, electrocardiogram and evaluation by an anesthetist are performed to assess the safety of possible surgery. It is of the utmost importance to evaluate the expected effect and side-effects in individual patients before deciding to perform the surgery, since over 30% of the non-successful surgeries are due to incorrect patient selection.[4] Six centers in the Netherlands perform DBS: the Academic Medical Center in Amsterdam, University Medical Center Groningen, the Maastricht Universitair Medisch Centrum, Haga Hospital in the Hague, St. Elisabeth Hospital in Tilburg, and Medisch Spectrum Twente in Enschede. A movement disorders DBS team usually consists of a neurologist specialized in movement disorders, a DBS neurosurgeon, a psychiatrist, neuropsychologist, and a PD nurse.

What is improved by DBS?

Extensive research has been performed to investigate the effectiveness of DBS in advanced PD. The motor symptoms, health-related functioning and quality of life are greatly improved.[3, 5-9] These positive effects are mainly due to the improvement of motor symptoms in off-phase. This leads to fewer fluctuations in symptoms and functioning. Dyskinesias are also vastly improved.[3, 5-9] Time per day spent in off-phase or time with troublesome dyskinesias is diminished.[5, 6] This implies that patients who are impaired by off-periods or dyskinesias but function well during on-phases benefit most from DBS. Figure 2 is a schematical representation of daily functioning before and after DBS. It shows that it is crucial to evaluate the duration of off- and on-phases during the DBS screening process.

Figure 2.

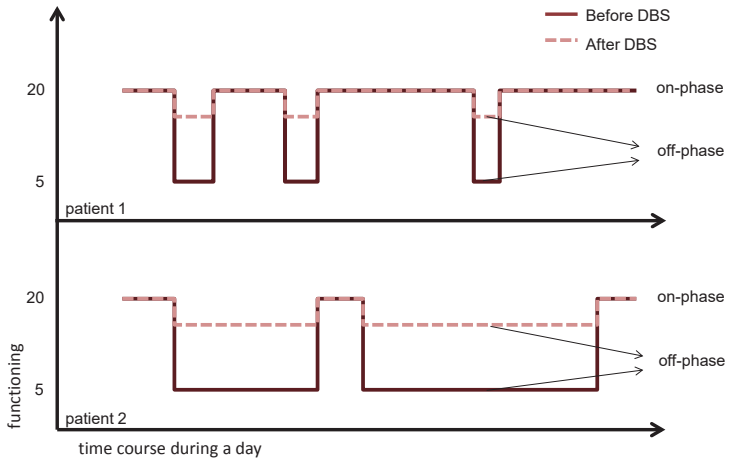

Figure 2. *The x-axis shows the time course of a day of two PD patients.* The y-axis displays level of functioning, with higher scores representing better functioning. The scores on this scale in off- and on-phase are the same for both patients. However, since patient 2 spends much more time of the day in off-phase pre-operatively, the gain of functioning is much higher after DBS than in patient 1.

Some symptoms improve more than others after DBS. Tremor, rigidity, and bradykinesia in the limbs usually improve most.[7] Walking and balance can marginally improve, but freezing usually does not.[7] Dysarthria and hypophonia do not improve. Dysarthria can also be a side-effect of DBS, especially with more current.[10] As a rule of thumb, patients that experience much symptom relief by dopaminergic medication, but are hindered by response fluctuations or dyskinesias, are good DBS candidates.[11]

What are the risks?

The most relevant complications of DBS are intracerebral hematoma (1-2%) and infections (2-3%).[5, 6, 8] Hardware-related complications like lead fractures or electrode migration are reported in 0-19% of the surgeries. Skin erosion and battery discomfort can also occur.[12] Reported mortality rates vary between 0 and 4.4%,[5, 6, 8, 12] of which the upper limit does not appear to be representative of daily practice. In over 700 patients operated in the Academic Medical Center since 1995, one patient has died due to surgery. There is more risk of suicide (0.45% successful suicide, 0.90% attempt at suicide) compared to a control population. Dysarthria can also be a complication of DBS.[5] Verbal fluency diminishes slightly after DBS.[8] As stated before, walking and balance can improve slightly after DBS, but an increased frequency of falls has also been described.[8]

Compared to non-surgical treatment of PD there is a higher chance of the complications mentioned above, but also a decrease of other treatment complications (e.g., response fluctuations, dyskinesia) that can also lead to admission or hospital care.[5]

When should DBS be considered?

DBS has been proven to be an effective treatment for advanced PD since its introduction in the 1990s. The average duration of dopaminergic drug use before surgery is 12 years.[5, 6, 8] A more recent large study also showed that DBS can be effective at improving quality of life earlier on in the disease course.[13] This study randomized patients, that were experiencing response fluctuations, to STN DBS or best medical treatment after an average of 7.5 years disease duration. Subsequently, DBS patients had a better quality of life, health-related functioning, and less dyskinesias. However, because DBS may be associated with serious morbidity, it should only be considered for patients that at least experience a decrease of health-related functioning due to symptoms that are expected to be relieved by DBS.

There is no set age limit, but a higher age is associated with more co-morbidity and cognitive dysfunction, which increases the risks of DBS.[14] Figure 3 shows a schematic representation of the disease phases and an outline of the therapeutic options throughout the disease course.

Figure 3.

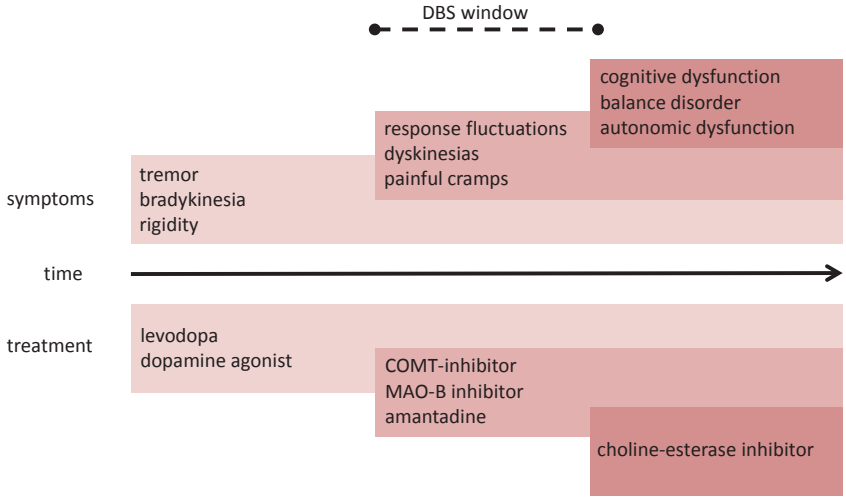

Figure 3. *Schematic representation of the disease course and treatment options in Parkinson's disease.* Every stage has a different combination of symptoms that determine daily functioning. COMT = catechol-O-methyl transferase, MAO-B= monoamineoxidase-B, DBS = deep brain stimulation.

When to refrain from DBS?

The indication for DBS is somewhat paradoxical. A good response to dopaminergic drugs is an important factor for success, while the main indication for DBS is an insufficient effect of dopaminergic drugs on maintaining daily health-related functioning.

The maximum benefit on motor symptoms that is to be expected from DBS is reducing off-phase symptoms to a level that is close to the motor symptoms in on-drug phase, but with less dyskinesias. That implies that poor improvement of motor symptoms with optimal medication is an important reason to refrain from resorting to DBS. Patients who are mainly hindered by symptoms that respond poorly to DBS, such as gait problems, autonomic dysfunction, or dysarthria, constitute another group of patients in which DBS should not be considered because the expected health-related functional improvement is small.

Recent psychiatric disorders such as depression or psychosis, as well as cognitive dysfunction, can worsen after DBS, and this should therefore be carefully evaluated when considering DBS.[15-17] Other reasons to refrain from DBS are factors that make surgery less likely to succeed, such as severe brain atrophy or extensive co-morbidity. A hypokinetic-rigid syndrome with another etiology than PD usually does not respond well to DBS.[18]

The current question: Globus pallidus pars internus (GPi) or nucleus subthalamicus (STN)?

The era of DBS for PD began with the efforts of Benabid and his team in thalamic stimulation

for patients with tremor dominant PD.[19] The great advantage of DBS over lesioning was that it could more readily be applied bilaterally. In the following years, stimulation other nuclei in the basal ganglia also showed to improve bradykinesia and rigidity.[3,20] Subsequent non-randomized comparative studies were performed showing that GPi DBS might be less effective than STN DBS for PD motor symptoms and equally effective for dyskinesias.[21-24] In 2005 one small blinded randomized controlled trial comparing STN with GPi DBS was published which suggested that the procedures are equally effective for PD motor symptoms and dyskinesias.[25] However, STN DBS seemed to be associated with more problems in cognition, mood, and behavior.[25,26] A large randomized trial was needed to compare both the effect on motor symptoms and the effect on cognition, mood, and behavior, to determine which nucleus is the preferred target in bilateral DBS for advanced PD. At the time, two large trials were initiated, the Netherlands SubThalamic And Pallidal Study (NSTAPS) trial and the Veterans Affairs trial.[6,8]

This thesis will discuss the results of the NSTAPS trial: a randomized controlled trial comparing GPi DBS and STN DBS.

AIM AND OUTLINE

The NSTAPS trial compares the outcome after GPi DBS and STN DBS in a randomized controlled fashion. The aim of the study is to evaluate whether patients with advanced PD and an indication for DBS should undergo bilateral GPi DBS or bilateral STN DBS.

Part I: results one year after surgery

Measuring outcome of two different surgical interventions in patients with advanced PD is complex. GPi DBS and STN DBS are known to have different action mechanisms and thus the effects and side-effects may also differ.[27] The symptoms of PD vary over the course of the day and are different from person to person.[1,2] Comparing efficacy of GPi DBS and STN DBS in a single measure is thus a challenging task. We chose health-related functioning (disability) as our primary outcome measure, using the AMC Linear Disability Scale (ALDS) score in off-drug and on-drug phase.[28] Both scores were recalculated into *one* score representing functioning over the entire day by using a diary of time spent in off-drug and on-drug of individual patients. Since aforementioned concerns were raised on the cognitive, mood, and behavioral side-effects of STN DBS, a composite score was chosen as the second primary outcome that evaluates these domains. *Chapter 2* discusses the primary and secondary outcomes: functioning, cognition, mood, behavior, motor symptoms, quality of life, and complications of surgery. *Chapter 3* more extensively explores the neuropsychological effects after GPi DBS and STN DBS. The correlation between neuropsychological decline and quality of life is analyzed. *Chapter 4* describes the psychiatric effects, with specific attention to psychiatric diagnoses, mood, anxiety, depression and mania. Affect, personality changes, and social function are also evaluated.

Part II: results three years after surgery

Due to the chronicity of PD and the changing symptoms over time, patient follow-up until three years after surgery is discussed. *Chapter 5* comprises the primary and secondary outcomes three years after surgery. A linear mixed model for repeated measures was used to analyze the change in effect over different points in time. In *chapter 6* the neuropsychological and psychiatric effects three years after surgery are described. Cognitive outcome was measured with the Mattis Dementia Rating Scale and a selected neuropsychological battery.[29] The changes in effect over time on all neuropsychological tests are presented as well as changes in depression, anxiety and mania scales. Descriptive statistics on psychiatric diagnoses, suicidal ideation, and social functioning are presented.

Part III: Influence of re-operation and active contact localization

In some cases DBS does not provide satisfactory results. Little is known about the clinical effect of re-operation to a different target. We investigate this effect of re-operation to a different target after failure of initial DBS in advanced PD (*chapter 7*). The baseline characteristics, the effect of initial surgery and re-operation of NSTAPS patients and previously published cases that underwent re-operation to a different target due to unsatisfactory results of the initial surgery were descriptively analyzed.

The precision of implantation is an important factor for a successful outcome, especially in a small nucleus such as the STN.[30] However, multiple studies did not find any difference in mean implantation coordinates between patients that do or do not improve well after DBS.[31-33] In *chapter 8* we hypothesize that random deviations from the ideal target are the cause of suboptimal effect, not per se structural targeting errors. This would not be caught in analyses of mean coordinates. Therefore we investigate the effect on clinical outcome of the distance from individual active contacts to the mean of all active contacts .
Finally, *chapter 9* is a general discussion of the NSTAPS results, its place in current literature and offers recommendations for future research.

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PART I

Results one year after surgery

2 |

Clinical outcome one year after subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease

Authors

Vincent J.J. Odekerken, Teus van Laar, Michiel J. Staal, Arne Mosch, Carel F.E. Hoffmann, Peter C.G. Nijssen, Guus N. Beute, Jeroen P.P. van Vugt, Mathieu W.P.M. Lenders, M. Fiorella Contarino, Marieke S.J. Mink, Lo J. Bour, Pepijn van den Munckhof, Ben A. Schmand, Rob J. de Haan, P. Richard Schuurman, Rob M.A. de Bie, for the NSTAPS study group.

Adapted from

Odekerken V.J., van Laar T., Staal M.J. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. Lancet Neurol. 2013 Jan;12(1):37-44.

ABSTRACT

Trial design: We performed a randomized, controlled, blinded trial comparing bilateral globus pallidus pars interna (GPi) deep brain stimulation (DBS) with bilateral subthalamic nucleus (STN) DBS.

Methods: Participants: Inclusion criteria were idiopathic PD and despite optimal pharmacological treatment at least one of the following symptoms: severe response fluctuations, dyskinesias, painful dystonias, or bradykinesia. Exclusion criteria were age below 18 years, previous functional stereotactic neurosurgery, H&Y stage 5 at the best moment during the day, a MATTIS dementia rating scale score of 120 or less (out of 144), currently active psychosis, and contraindications for the neurosurgical procedure.

Intervention: Either bilateral GPi DBS or bilateral STN DBS was performed depending on randomization.

Hypothesis: GPi DBS produces greater functional improvement than STN DBS because of a lower rate of cognitive, mood, and behavioral complications with similar improvement of motor symptoms.

Outcome: The primary outcome measures were (1) the off-on drug phases weigthed AMC Linear Disability Scale (ALDS, functional health) and (2) a composite score for cognitive, mood, and behavioral effects up to one year after surgery. Secondary outcomes consisted of symptom scales, activities of daily living scales, a quality of life questionnaire, adverse effects and medication use.

Randomization: Patients were randomized to GPi DBS or STN DBS in a 1:1 ratio.

Blinding: Patients and assessors were blinded to treatment allocation.

Results: Numbers randomized: Recruitment was completed after enrolling 128 patients (65 GPi, 63 STN). Numbers Analyzed: Weighted ALDS change scores were obtained in 90 patients, the composite score in 127 patients, and the secondary outcome measures in 125 patients.

Outcome: The off-on drug phases weighted ALDS mean change score (GPi 3.0±14.5, STN 7.7±23.2) and the number of patients with cognitive, mood, and behavioral effects (GPi 58%, STN 56%) were not significantly different between the two groups. Secondary outcomes showed that without PD medication, the Unified Parkinson's Disease Rating Scale motor examination mean change score (GPi 11.4±16.1, STN 20.3±16.3, p=0.03) and ALDS mean change score (GPi 11.8±18.9 and STN 0.3±27.1, p=0.04) were improved significantly more in the STN group compared to the GPi group.

Harms: The rate of the adverse effects was similar in both groups.

Conclusions: No significant difference was seen between the groups concerning cognitive, mood and behavioural effects. The better effects on disability and on motor symptoms in off phase indicate that the STN is the preferred target for DBS in PD.

Trial registration: www.controlled-trials.com, number, ISRCTN85542074

Funding: Funded by Stichting Internationaal Parkinson Fonds, Prinses Beatrix Fonds, Parkinson Vereniging.

INTRODUCTION

Patients with advanced Parkinson's disease (PD) often show rapid, seemingly unpredictable swings between mobility (the on phase), usually with dyskinesias, and immobility (the off phase). Many of these patients respond unsatisfactorily to adjustments in pharmacological treatment.[1] Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) for advanced PD was first used in the 1990s.[2, 3] The results of subsequent studies by different groups suggested that bilateral STN DBS reduces both PD motor symptoms and dyskinesias by about 50%.[4,5 6] The effectiveness of bilateral DBS of the globus pallidus pars interna (GPi) was also explored.[7,8] The results of non-randomized comparative studies suggested that bilateral GPi DBS was slightly less effective than STN DBS for the treatment of PD motor symptoms and was equally effective for the treatment of dyskinesias.[4,9] However, the STN was already thought by many to be the better target for DBS in patients with PD, which might have caused a major bias in these series.[10, 11] The results of two randomized controlled trials that compared bilateral STN with GPi DBS suggested that the procedures were equally effective for PD motor symptoms and dyskinesias.[12,13] DBS-associated problems in cognitive, mood, and behavioral features seemed to occur more often in the STN groups.[10,12,14]

The Netherlands SubThalamic and Pallidal Stimulation (NSTAPS) study was initiated in 2007 to test the hypothesis that bilateral GPi DBS would produce greater improvement in disability than would bilateral STN DBS, assuming a lower rate of cognitive, mood, and behavioral complications, with similar improvement of motor symptoms.

By contrast with previous studies that investigated the effectiveness of DBS, we chose a generic disability scale as a primary outcome measure. This was because GPi DBS and STN DBS might have different effects on the various motor symptoms and because both procedures might be accompanied by cognitive and psychiatric adverse effects.[14,15] Cognitive status and mood might have an effect on self-reported quality of life, which could lead to interpretation issues with these scales.

METHODS

Study design and participants

We recruited patients from five centers in the Netherlands that were experienced in doing DBS for PD. We included patients aged 18 years or older who had idiopathic PD and, despite optimum pharmacological treatment, at least one of the following symptoms: severe response fluctuations, dyskinesias, painful dystonias, or bradykinesia. We excluded patients if they had previous functional stereotactic neurosurgery, Hoehn and Yahr stage 5 at the best moment during the day, a Mattis dementia rating scale score of 120 or lower (out of 144), active psychosis, or contraindications for the neurosurgical procedure. Each site's medical ethics committee approved the study and patients provided written informed consent.

Randomization and masking

By use of a computer-generated randomization sequence, patients were randomly assigned to receive either GPi DBS or STN DBS in a one-to-one ratio at the clinical trial office of the Department of Neurology, Academic Medical Center (AMC, Amsterdam, Netherlands). Randomization was done by trial nurses who had no further involvement in the study. We applied a minimization procedure according to drug use (levodopa equivalent dose <1000 mg *vs* ≥1000 mg) and treatment center. Patients and the clinical, neuropsychological, and psychiatric assessors were masked to treatment allocation. Patients regularly visited a non-masked neurologist at the outpatient clinic to adjust DBS settings together with adjustment of medication.

Procedures

All centers were experienced in DBS surgery (all surgeons were performing DBS surgery for at least 3 years at the start of the trial). The DBS surgery was done according to each center's standard protocol. The final position of the electrode was determined on the basis of MRI, macro-electrode stimulation effects, and, in three of five centers, semi-micro-electrode recordings. During the course of the study, changes in drug treatment and DBS settings were allowed in both groups. Baseline and 12-month assessments were done during standardized off-drug and on-drug phases. The off phase was defined as the condition of the patient after withholding antiparkinsonian drugs for 12 h overnight. The on phase was a patient's condition 1 h after a supra-threshold levodopa dose. Identical doses were used at baseline and the follow-up assessment. To analyze changes in medication and to calculate the supra-threshold levodopa dose, the different drugs were pooled in levodopa equivalent doses according to the following conversion formula:

(regular levodopa dose × 1)+(slow-release levodopa
× 0.75) + (bromocriptine × 10) + (apomorphine × 10) +
(ropinirole × 20) +(pergolide × 100) + (pramipexole × 100) and, if taking entacapone,
+ 0.2 × (regular levodopa dose + [slow-release levodopa × 0.75]).[16]

The 12-month assessment was done with the stimulators turned on. No changes in outcome measures were made after the start of the trial.

The primary outcomes were disability and the number of patients with a negative composite score of cognitive, mood, and behavioural effects. We assessed disability using a 26-item version of the AMC linear disability scale (ALDS). The ALDS is a linear and generic health scale to quantify functional status in terms of the ability to do basic (eg, self-care, eating, transfer) and complex (eg, household tasks, travelling, walking long distances) activities of daily living. ALDS scores range from 0 points to 100 points, with lower scores indicating more disability. The psychometric properties (reliability, validity, responsiveness, absence of ceiling effects) of the ALDS item

databank have been extensively assessed and shown to be good.[17-21]The items chosen for this study fit the expected range of disability of the PD population. Because the ALDS is a continuous measure of disability, it is possible to recalculate the scores obtained in standardised off and on phases into a weighted score for time in either phases, which then represents disability throughout the day, instead of exclusively during episodes with or without medication.

At baseline and 12 months after surgery, patients completed a diary in which they rated every period of 30 min from 06.00 to 00.00 for 3 days. Patients were instructed to rate periods under the following categories: asleep, parkinsonism, on without dyskinesias, or on with dyskinesias. We calculated patients' ALDS, weighted by time spent in either on phase or off phase, according to the following formula:

weighted ALDS = off phase ALDS × (h in off phase/[h in on phase + h in off phase]) + on phase ALDS × (h in on phase/[h in on phase + h in off phase])

For the composite score of cognitive, mood, and behavioral effects at 12 months, we assessed the following items: a clinically significant worsening on three or more cognitive tests based on the reliable change index (RCI, appendix);[22] the loss of professional activity, work, or job; the loss of an important relationship (e.g., marriage); or psychosis, depression, or anxiety for 3 months or longer as defined by the mini-international neuropsychiatric interview (MINI) psychiatric assessment.[23] Death of a partner was not counted as a loss of an important relationship. If the patient fulfilled at least one of these items, we regarded the composite score to be negative.

In the off-drug phase, we recorded the following scales at baseline and at 12 months: unified Parkinson's disease rating scale (UPDRS) motor examination section (ME),[24] clinical dyskinesia rating scale (CDRS),[25] ALDS, UPDRS activities of daily living section (ADL), [24] and the Schwab and England score.[24]

We also recorded the same scales during the on-drug phase. Additionally, the Parkinson's disease sleep scale (PDSS)[26] and the PD quality of life questionnaire (PDQL)[27] were recorded in the on phase. Drugs used were recorded at baseline and follow-up. DBS settings and adverse events were also recorded during follow-up. We added the following post-hoc endpoints: hours spent in off-drug and on-drug phase, and gait and postural stability (using UPDRS ME items 27 arising from chair, 28 posture, 29 gait, 30 postural stability).

Neurologists at each treatment center (who were aware of treatment allocation) examined the patients and recorded adverse events directly after surgery, 1 week after surgery, and 3 months, 6 months, and 12 months after surgery. Structured questionnaires, with space for events that were not specified, were used for the registration of adverse events. An independent data and safety monitoring board (DSMB), consisting of a neurologist, a neurosurgeon, and a clinical statistician, monitored the trial.

Statistical analysis

For the off-on phase weighted ALDS, we used the effect size *d* (difference between mean scores of the intervention groups divided by the pooled standard deviation [SD]) as a benchmark for assessing the relative magnitude of differences between both strategies. In the Co-morbidity and Aging in Rehabilitation Patients (CARPA) study, the SD of the ALDS scores for PD was 10.[19] The results of this study suggest that over a 3-year period the increase in disability was equivalent to a decrease of five points on the ALDS. Although an effect size of 0.50 is defined as moderate,[28] such a difference in disability scores might be clinically important. On the basis of these data, a sample size of 64 patients in each intervention group (128 in total) was required to have 80% power to detect a moderate effect size of d=0.50 in favor of GPi DBS, using a two group *t* test with a 0.05 two-sided significance level. Assuming that the rate of cognitive, mood, and behavioral effects would be 25% in the STN DBS group,[14] we estimated that at least 110 patients (55 patients in each treatment group) would be needed to detect a difference of 20% (25% STN *vs* 5% GPi) using a χ^2 test with α=0.05 and β=0.20.

We used the intention-to-treat principle for all analyses. We summarized baseline characteristics and outcome parameters using descriptive statistics. The main analyses of this trial consisted of a comparison between the mean change in off-on phase weighted ALDS scores from baseline to follow-up at 12 months with the two-group *t* test, and the proportion of patients with a negative composite score for cognitive, mood, and behavioral effects with the χ^2 test. We also analyzed the 12-month ALDS scores using linear regression, including the baseline ALDS scores and the stratification variables (levodopa equivalent dose and treatment center) into the model. With regard to the 12-month composite scores, we also did logistic regression, using the stratification variables as covariates. The differences between treatment groups for the secondary outcomes were analyzed with χ^2, Fisher's exact test, *t* test, or Mann-Whitney *U* tests, as appropriate. Also, we created imputation models to assess possible differences in outcome due to incomplete diary data. One model used age, Schwab and England baseline off-drug scores, the MDRS at baseline, and the available diary data as predictors for missing values. The second model used type of intervention, available diary data, and outcome on the UPDRS ME as predictors to impute any missing diary data.

p values of less than 0.05 were considered statistically significant. Because the ALDS has been developed within the framework of item response theory (IRT), the calculated p values for this scale were based on the original units of measurements (logits). We did no interim analyses.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, and writing of the report. Two authors (VJJO and RMAdB) guaranteed the veracity and completeness of the data analyses. VJJO and RMAdB had full access to all the data in the study and the final responsibility for the decision to submit for publication.

RESULTS

Between Feb 1, 2007, and March 29, 2011, we enrolled 128 patients; 65 were randomly assigned to GPi DBS and 63 to STN DBS (figure 1). Baseline demographic and clinical characteristics are described in table 1. Three patients in the GPi group withdrew from follow-up (one patient wanted a second operation elsewhere and two considered follow-up to be too onerous). The calculations for the weighted ALDS were based on data for 90 patients that filled in the diaries at baseline and at 12-month follow-up (GPi n=44, STN n=46; see the appendix for details of missing diary data). Semi-micro-electrode recordings were used to determine the optimal location for the DBS electrodes in 88% (112 of 128) of the surgeries. We recorded no difference in mean off-on phase-weighted ALDS change score between the groups (table 2). Additional multivariable linear regression analysis showed no effect of intervention type on the 12-month ALDS scores (p=0.68).

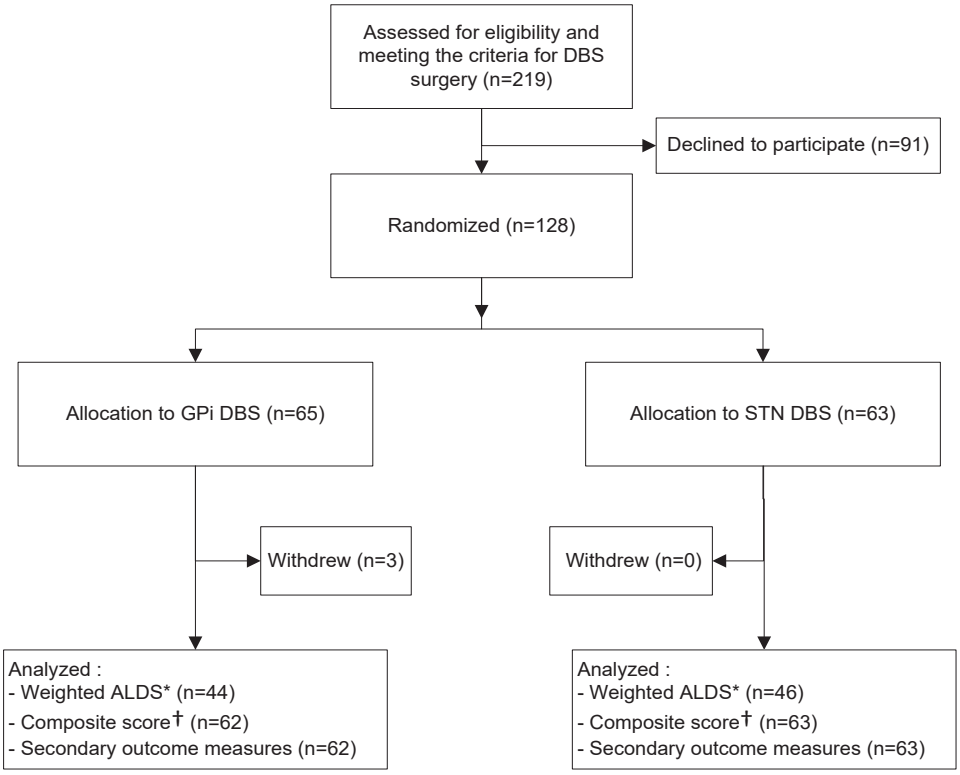

Figure 1. *Enrolment and Outcomes.** For the off and on drug phase weighted AMC linear Disability Scale (ALDS) 9 diaries in the GPi group and 6 in the STN group were not available at baseline; at 12 months, 15 were not available in the GPi group and 12 in the STN group. Forty-four patients in the GPI group and 46 in the STN group completed both diaries which could be used for calculating the weighted ALDS change score.
† Composite score for cognitive, mood and behavioral effects.

Table 1. *Baseline characteristics.*

	GPi DBS (n=65)	STN DBS (n=63)
Age (mean±SD) – yr	59.1±7.8	60.9±7.6
Age of onset PD (mean±SD) – yr	48.5±7.6	48.6±9.4
Male sex – no. (%)	44 (68)	44 (70)
Duration of PD (mean±SD) – yr	10.8±4.2	12.0±5.3
Duration of use of medication for PD (mean±SD) – yr	9.0±3.9	9.5±5.6
Hours per day spent in on drug phase* (mean±SD) – h	9.2±3.0	9.1±3.3
On drug phase Hoehn & Yahr stage† (median [range])	2.5 [0-4]	2.5 [0-4]
Levodopa equivalent dose‡ ≥1000 mg/d – no. (%)	43 (69)	43 (68)
Treatment Center – no.		
Academic Medical Center, Amsterdam	37	39
University Medical Center, Groningen	12	9
Haga Hospital, The Hague	7	8
St. Elisabeth Hospital, Tilburg‖	6	4
Medisch Spectrum Twente, Enschede‖	3	3
Mattis Dementia Rating Scale § (mean±SD, range, 0-144)	138.7±4.0	138.1±5.1

* *Calculated using a 3-day diary.*
† *Five patients (three GPi, two STN) had a Hoehn & Yahr stage of four in on drug phase.*
‡ *Levodopa equivalent dose = regular levodopa dose x 1 + slow release levodopa x 0.75 + bromocriptine x 10 + apomorphine x 10 + ropinirole x 20 + pergolide x 100 + pramipexole x 100 + (regular levodopa dose + [slow release levodopa x 0.75]) x 0.2 if taking entacapone.*
§ *Seven patients (two GPi, five STN), who had a score of 125-129, none had a score <125.*
‖ *These centers did not use peri-operative micro-electrode recordings. Microrecordings were performed in 88% of the patients.*

We recorded no between-group difference in the number of patients with a negative composite score for cognitive, mood, and behavioral effects (table 2). Additional multivariate logistic regression analysis showed no between-group difference in outcome (OR 0.97, 95% CI 0.48–1.98; p=0.94). Analysis of separate components of the composite score also showed no between-group differences (table 2).

Table 2. *Primary outcomes.*

	Baseline		12 Months		Mean change at 12 months from baseline*			
	GPi DBS	STN DBS	GPi DBS	STN DBS	GPi DBS	STN DBS	p-value†	effect size
Weighted ALDS‡ (disability, range 0-100, n=90, mean±SD)	73.8±13.9	68.0±19.0	76.8±13.3	75.8±19.3	3.0±14.5	7.7±23.2	0.28	0.24
Score for cognitive, mood, and behavioural adverse effects ≥1 (n=127) – no. (%)			36 (58%)	35 (56%)			0.94	
Parts of composite score – no. (%):								
Decline on neuropsychological exam§			17 (27)	22 (35)				
Loss of professional activity/ work/job			1 (2)	0 (0)				
Loss of an important relationship Psychosis‖			11 (17)	5 (8)				
Depression‖			4 (6)	4 (7)				
Anxiety‖			7 (11)	11 (18)				
			9 (14)	6 (10)				

* *A positive difference score indicates clinical improvement and a negative score clinical deterioration.*
† *Using two-group t-test for weighted ALDS, χ^2 test for the composite score.*
‡ *AMC Linear disability scale (ALDS).*
§ *Decline on neuropsychological exam is defined as a significant worsening on three or more cognitive tests based on the reliable change index (RCI).*
‖ *Psychosis, depression, or anxiety for a period of 3 months or longer.*

In secondary analyses, the mean change in UPDRS ME score during the off phase was lower in the GPi DBS group than in the STN DBS group (table 3). The improvement in ALDS during the off phase in the STN group was larger than in the GPi group (table 3). We found no statistically significant differences between the two groups when assessing CDRS and UPDRS ADL scores. The Schwab and England scores during the off phase improved more in the STN group than in the GPi DBS group (table 3).

In the on-drug phase, dyskinesias measured by the CDRS were reduced more in the GPi DBS group than they were in the STN DBS group (table 3). We found no differences between the groups with regard to changes in UPDRS ME, PDSS, ALDS, UPDRS ADL, Schwab and England, and PDQL scores.

The mean levodopa equivalent dose reduction between baseline and 12 months was larger in the STN DBS group than in the GPi DBS group (table 3). For DBS settings, the mean amplitude and pulse width were both larger in the GPi group than in the STN group; the mean frequency settings were similar between the two groups (table 3).

Table 3a. *Secondary outcomes*.	Baseline		12 Months*		Mean change at 12 months from baseline†			
	GPi DBS	STN DBS	GPi DBS	STN DBS	GPi DBS	STN DBS	P-value‡	effect size
Off phase (n=125)								
UPDRS Motor Examination (range 0-108, mean±SD)	43.8±13.5	44.4±15.5	32.4±12.6	24.1±14.4	11.4±16.1	20.3±16.3	0.03	0.55
Clinical Dyskinesia Rating Scale (range 0-28, mean±SD)	0.6±1.2	1.0±2.0	0.5±1.6	0.8±2.0	0.1±1.5	0.2±2.8	0.87	0.04
ALDS (disability, range 0-100, mean±SD)	53.1±21.8	48.8±23.8	64.9±22.0	69.1±21.8	11.8±18.9	20.3±27.1	0.04	0.36
UPDRS Activities of Daily Living (range 0-52, mean±SD)	17.9±6.2	18.2±6.5	14.0±6.6	12.3±7.9	3.9±6.2	5.8±6.2	0.09	0.30
Schwab and England Scale (range 0-100, median [range])	50 [10-90]	40 [10-90]	60 [10-100]	70 [10-90]	10 [-50-70]	20 [-50-80]	0.02	
On phase (n=125)								
UPDRS Motor Examination (range 0-108, mean±SD)	16.0±8.0	17.0±9.9	16.0±9.4	14.4±11.1	0.0±11.2	3.4±12.2	0.17	0.13
Clinical Dyskinesia Rating Scale (range 0-28, mean±SD)	5.3±3.8	4.8±3.7	2.3±3.2	3.8±4.5	3.0±3.7	1.1±4.5	0.01	-0.46
Parkinson's Disease Sleep Scale (range 0-150, mean±SD)	83.6±18.7	81.3±17.1	90.8±18.3	94.7±16.8	7.2±20.4	13.5±16.7	0.07	0.35
ALDS (disability, range 0-100, mean±SD)	84.2±7.9	81.1±13.0	83.4±8.9	80.5±13.8	-0.7±9.1	-0.7±15.2	0.98	-
UPDRS Activities of Daily Living (range 0-52, mean±SD)	6.0±4.9	7.9±5.1	7.5±5.4	8.0±6.3	-1.4±5.8	0.0±5.0	0.16	0.11
Schwab and England Scale (range 0-100, median [range])	80 [40-100]	80 [30-100]	80 [30-100]	80 [20-100]	0 [-60-30]	0 [-60-50]	0.16	
PD quality of life questionnaire (range 0-185, mean±SD)	86.3±17.8	85.4±22.3	96.9±19.1	102.0±20.6	10.6±19.1	16.5±20.6	0.10	0.36
Medication and DBS settings (n=125)								
Levodopa equivalent dose**§ (**mean±SD)	1331±637	1254±473	1122±604	708±423	-208±521	-546±561	0.01	0.30
Voltage (mean±SD) – V			2.9±0.5	2.6±0.6			0.004	
Frequency (mean±SD) – Hz			137.5±20.0	135.0±20.8			0.52	
Pulse width (mean±SD) – µs			73.0±23.8	63.9±9.6			0.008	

Table 3b. *Secondary outcomes.*	Baseline		12 Months*		Mean change at 12 months from baseline†			
	GPi DBS	STN DBS	GPi DBS	STN DBS	GPi DBS	STN DBS	P-value‡	effect size
Post–hoc analyses:								
3-Day diaries (n=90)								
Time in off drug phase (mean±SD) – h/day	6.0±3.2	6.2±3.5	4.8±3.6	4.5±4.4	-1.3±3.4	-1.5±3.6	0.71	0.06
Time in on drug phase without dyskinesias (mean±SD) – h/day	6.5±3.6	6.3±4.4	9.5±3.7	9.4±4.6	3.0±4.2	3.1±3.9	0.92	0.02
Time in on drug phase with dyskinesias (mean±SD) – h/day	2.5±2.5	2.9±2.8	0.5±1.2	0.8±1.3	-2.0±2.5	-2.1±2.8	0.85	0.04
Posture and Gait (n=125)								
UPDRS Motor Examination items 27, 28, 29, 30 (range 0-16, mean±SD), off phase	6.11±2.8	7.35±3.7	5.41±2.6	4.6±3.3	0.70±3.0	2.73±3.3	0.007	0.64
UPDRS Motor Examination items 27, 28, 29, 30 (range 0-16, mean±SD), on phase	2.93±1.5	3.27±2.6	3.48±2.1	3.89±3.6	-0.54±1.8	-0.61±3.3	0.71	0.03

* *Assessments with DBS on.*
† *A positive difference score indicates clinical improvement and a negative score clinical deterioration.*
‡ *Using two group t-test, or Mann-Whitney U test in case of Schwab and England Scale,*
§ *Levodopa equivalent dose = regular levodopa dose x 1 + slow release levodopa x 0.75 + bromocriptine x 10 + apomorphine x 10 ropinirole x 20 + pergolide x 100 + pramipexole x 100 + (regular levodopa dose + [slow release levodopa x 0.75]) x 0.2 if taking entacapone.*

In post-hoc analyses, both groups showed a similar reduction in time in off-drug phase and time in on-drug phase with dyskinesias (table 3). Gait and postural stability items improved more in the STN group than in the GPi group (table 3). The imputation models showed no changes in outcomes on the weighted ALDS (data not shown).

23 (3%) of 768 adverse-events questionnaires were not completed. There were 290 adverse events in the GPi group and 303 in the STN group; we found no statistically significant differences between the two groups in the occurrence of any adverse events (table 4). In one patient, who was allocated to STN DBS, the surgery was aborted because of a low threshold for oculomotor side-effects during macro-stimulation in the STN. The patient underwent surgery for GPi DBS 41 weeks later, but had a deep intracerebral hemorrhage during that surgery with a resultant hemiparesis. Two patients (both in the STN group) had small postoperative hemorrhages near the electrode tip that were detected by planned postoperative CT scans, without any accompanying symptoms. Semi-micro-electrode recordings were used in two of the three patients with a peri-operative hemorrhage. 64 (22%) of 290 adverse events in the GPi group and 76 (25%) of 303 in the STN group were judged to be related to active stimulation. Of all adverse events, 22 (2%) were present at one or more subsequent visits.

Table 4. *Adverse events.*

	GPi DBS (N=65) No. (%)	STN DBS (N=63)	P-value*
Cerebral infarction (peri-operative)	0 (0)	0 (0)	-
Cerebral hemorrhage† (peri-operative)	0 (0)	3 (5)†	0.08
Epilepsy (peri-operative)	0 (0)	1 (2)	0.31
Epilepsy (post-operatively)	2 (3)	1 (2)	0.67
Implantation-site infection	2 (3)	2 (3)	0.89
Facial palsy	2 (3)	4 (6)	0.34
Dysphasia	7 (11)	8 (13)	0.60
Dysarthria	19 (29)	25 (40)	0.21
Dysphagia	13 (20)	7 (11)	0.34
Hiccups	10 (15)	2 (3)	0.06
Apraxia of eyelid opening	11 (17)	14 (22)	0.37
Oculomotor or visual field disturbance	6 (9)	4 (6)	0.70
Sensory disturbance	5 (8)	9 (14)	0.20
Balance disorder	23 (35)	30 (47)	0.19
Hypersalivation	14 (22)	14 (22)	0.72
Emotional lability	47 (72)	53 (84)	0.29
Paresis	1 (2)	1 (2)	0.92
Dyskinesias	17 (26)	24 (38)	0.16
Delirium	14 (22)	15 (24)	0.59
Other‡	97	87	-

* χ^2 or Fisher's exact test when appropriate.

† Including one patient in which surgery was aborted because of oculomotor problems during macro-stimulation in the STN. The patient underwent surgery for GPI DBS 41 weeks later and suffered from a deep intracerebral hemorrhage during that surgery.

Including one report of hypomania (STN), 10 reports of dysphoria or depression (3 GPi and 7 STN), and 3 hematomas at the battery implantation site (1 GPi and 2 STN).

PANEL: RESEARCH IN CONTEXT

Systematic review

We searched PubMed with the terms "DBS" and "deep brain stimulation" for randomized controlled trials. We also searched PubMed with the terms "DBS" and "subthalamic nucleus" and "globus pallidus internus" for reports published before Sept 11, 2012, with no language restriction. We identified three randomized controlled trials[12, 13, 15, 30, 31] that compared GPi DBS with STN DBS. All three trials found improvement of motor symptoms with both GPi DBS and STN DBS in the off-drug phase. The magnitude of the improvements differed between these trials.

Interpretation

To our knowledge, our study is the second largest randomized controlled trial comparing bilateral globus pallidus pars interna (GPi) deep brain stimulation (DBS) and subthalamic nucleus (STN) DBS. Also, our use of both disability and cognition, mood, and behavior as primary outcomes answers important questions about the effectiveness and side-effects of GPi and STN DBS that were raised by previous trials. Although the primary outcomes did not show a difference between GPi and STN DBS on the weighted ALDS and composite score for cognition, mood and behavior, important differences were seen on the secondary outcomes. By contrast with the Veterans Administration Cooperative DBS Study group findings, our study shows an improvement of motor symptoms of 45% in off-drug phase in the STN group, which lends support to findings from previous studies investigating STN DBS.[3, 4, 12, 32, 33]

DISCUSSION

We detected no difference between GPi and STN DBS in drug-phase-weighted ALDS, which was one of our primary outcomes. In the off -drug phase, however, the difference in improvement on the ALDS scores between the GPi and STN DBS group was very large. We suggest three main reasons for this discrepancy. First, the fact that only 70% of patients completed the diaries at both baseline and follow-up resulted in a loss of power in our analysis of the weighted ALDS. Scheduled surgeries were not cancelled if patients had not completed the diary for logistical reasons and because such cancellation would prevent patients from receiving an effective treatment. Second, the standard deviation for the ALDS score was larger than we had anticipated: up to 23.2 points instead of the anticipated 10. The third reason concerns the weighting of the scores. The effects of treatment on the ALDS scores in on-drug phase were much the same for both procedures, and at 12-month follow-up, patients spent 70% of the time in the on phase. Hence, the large difference between the two groups in off -drug phase scores contributes only 30% to the weighted ALDS.

Nevertheless, for the off -drug phase, the difference in disability between the two groups is clinically relevant. For example, a typical patient who scored 50 on the ALDS in off phase preoperatively would only just be able to have a shower independently. With an improvement of about 12 points (GPi group) the patient would be able to walk down a flight of stairs. However, with an improvement of 20 points (STN group), this patient would be able to visit a restaurant independently.

This study is an active control: both groups receive a treatment (instead of one group receiving placebo)—an average yearly decline of the ALDS in patients with Parkinson's disease who did not receive DBS is 1.3 points.[19]

The second primary outcome, the composite score for cognitive, mood, and behavioral effects, also did not support the hypothesis of superiority of GPi DBS over STN DBS. The high number of patients with a negative composite score in both groups warrants clarification.

First, previous DBS studies describe the neuropsychological tests as mean scores and SDs; our outcome measure is a dichotomous composite measure and thus cannot directly be compared with these studies. Second, if a patient had a negative score because of the loss of an important relationship, this does not necessarily imply worsening (or improvement for that matter) of disability or perceived quality of life. We chose to include this parameter because such issues might be a result of subtle cognitive or behavioral problems that have an effect on daily life but are not detected by standard psychiatric questionnaires. However, the results of the composite scores do not suggest that GPi DBS led to fewer issues regarding cognition, mood, and behavior in direct comparison with STN DBS.

The findings of our study with respect to the effect of STN DBS on motor symptoms in the off phase are in agreement with the results of a meta -analysis of cohort studies that showed a

reduction of 52% on the UPDRS ME with STN DBS.29 Of the three previous randomized trials[13,30,31] that compared GPi DBS with STN DBS (panel) the largest was by the Veterans Administration Cooperative DBS Study group (2010, n=299), which followed patients up to 36 months postoperatively.[13,30] The primary outcome was the change in motor function (UPDRS ME). The study did not show a difference in effect on motor symptoms between GPi and STN DBS.

By contrast with our findings, this trial showed an improvement in off phase motor symptoms of only 26% with STN DBS, 6 months and 24 months after surgery. A possible explanation for this discrepancy could be the fact that the physicians responsible for managing postoperative DBS settings and concurrent drug schedule adjustments in Follett and colleagues' study[13] did not know if patients had received GPi or STN DBS. Because each target needs a different approach during postoperative management, this approach might have led to a suboptimum clinical improvement in the STN group.

For example, optimum benefit from STN DBS often requires much medication reduction because of the synergistic effect of medication and STN DBS in the short term. Also, characteristics of patients and differences in targeting might account for the difference in outcome. In the Veterans Administration Cooperative DBS study,[13,30] medication use was reduced more in the STN group than in the GPi group. The level of depression worsened after STN DBS and improved after GPI DBS (p=0.02).[13,30] After 36 months, motor function was still better than it was at baseline in the off phase. Mattis dementia rating scale scores decreased faster in the STN group than in the GPi group (p=0.01); other neurocognitive measures showed a gradual decrease overall.

The COMPARE trial investigated unilateral GPi or STN DBS in 45 patients.[15,31] It showed a similar improvement of motor function and mood in both groups. However,

quality of life improved more in the GPi group than it did in the STN group (38% vs 14%, respectively; p=0.03).[15,31]

The third study, by Anderson and colleagues[12] (n=23), showed an improvement of motor scores in the off phase after 12 months of both GPi and STN stimulation (39% vs 48%). Dyskinesia was reduced by stimulation with both GPi and STN (89% vs 62%). Cognitive and behavioral complications were seen only in combination with STN stimulation.

Compared with STN DBS, GPi DBS reduced dyskinesias more effectively during the standardized assessments in the on phase at 12 months. Patients received the same amount of levodopa to induce an on-phase during the standardized assessment at 12 months as at baseline. However, because patients with STN DBS use less medication in daily life, they might have less severe dyskinesias than indicated by our measurements during the standardized assessments. In this respect, diaries showed similar reductions in off time as well as time that dyskinesias were present for GPi and STN DBS.

Post-hoc analysis of gait and postural stability showed superiority of STN DBS in the off phase. DBS amplitude and pulse widths were on average lower in the STN group, which is consistent with

previous findings and leads to longer intervals between replacement of pulse generators.[3]

The inclusion criteria for the trial were similar to the criteria used in regular clinical practice when counselling patients with Parkinson's disease for DBS treatment. In this respect, the only extra exclusion criterion for the trial was previous stereotactic functional neurosurgery. Also, the inclusion and exclusion criteria did not contain an upper age limit and the minimum MDRS score required for inclusion was low. Five of the six hospitals in the Netherlands that did DBS participated in the trial. All these factors contributed to the external validity of the study.

When taking all these factors into consideration, our data suggest that the STN is the preferred target for DBS in PD, because of more substantial improvement of symptoms and disability in off phase, in combination with the need for fewer drugs and lower battery consumption.

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APPENDIX 1. NEUROPSYCHOLOGICAL TEST AREAS.

A Reliability Change index (RCI) of ≤ -1.645 on at least one subtest per area would lead to the conclusion of deterioration in this area. Deterioration on 3 areas or more would lead to assigning a point for cognition on the composite endpoint of cognitive, mood, and behavioral adverse effects.

1. Verbal Fluency (subtests: letter, category)
2. Auditory Verbal Learning Test, Dutch version (15 word test (subtests: total, recall))
3. Stroop Color-word Task (subtests: reading color words, naming colored patches, color-word interference condition)
4. Trail Making Test (subtests: A, B)
5. Boston Naming Test
6. Wechsler Adult Intelligence Scale (subtests: digit span, letter-number sequencing)
7. Wechsler Adult Intelligence Scale (subtest: similarities)
8. Wechsler Adult Intelligence Scale (subtest: matrix reasoning)
9. Rivermead Behavioral Memory Test (subtests: direct, delayed recall)
10. Wisconsin Card Sorting Test
11. Facial Expression of Emotion: Stimuli and Test

APPENDIX 2. DESCRIPTION OF MISSING DIARY DATA.

The following table displays the number of missing values of the parameters involved in calculating the change scores for the weighted ALDS according to the formula in the methods section (h represents hours):

Patients in total	GPi (n=65)	STN (n=63)
Patients missing the baseline diary (n=9)	5	4
Patients missing the 12-month diary (n=20)	11	9
Patients missing both diaries (n=9, baseline and 12-month)	5	4
Total missing (n=38)	21	17

- Three patients withdrew from the GPi group. All missing values for the baseline diaries were due the fact that surgery was not postponed if patients had not completed their diaries. We did not specifically record why patients did not complete their diaries at 12 months, but this was either due to incomplete/ incorrect use of the diary or due to not feeling well enough to fill in these diaries.
- These diaries had to be completed at home, requiring the patients to monitor their clinical state per half hour for three consecutive days. The ALDS was obtained during the hospital visits, at which nearly all the patients were able to attend.

3 |

Neuropsychological outcome one year after subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease

Authors

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Adapted from

Odekerken V.J., Boel J.A., Geurtsen G.J. et al. Neuropsychological outcome after deep brain stimulation for Parkinson's disease. Neurology. 2015 Mar 31;84(13):1355-61.

ABSTRACT

Objective: To assess the neuropsychological outcome 12 months after bilateral deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) or subthalamic nucleus (STN) for advanced Parkinson's disease. Methods: We randomly assigned patients to receive either GPi DBS or STN DBS. Standardized neuropsychological tests were performed at baseline and after 12 months. Patients and study assessors were masked to treatment allocation. Results: Univariate analysis of change scores indicated group differences on Stroop word reading and Stroop color naming (CI 1.9 – 10.0 and 2.1 – 8.8), on Trail Making Test B (CI 0.5 – 10.3), and on WAIS similarities (CI -0.01 – 1.5), with STN DBS showing greater negative change than GPi DBS. No differences were found between GPi DBS and STN DBS on the other neuropsychological tests. Older age and better semantic fluency at baseline predicted cognitive decline after DBS.

Conclusions: We found no clinically significant differences in neuropsychological outcome between GPi DBS and STN DBS. No satisfactory explanation is available for the predictive value of baseline semantic fluency for cognitive decline.

Classification of evidence: This study provides Class I evidence that there is no large difference in neuropsychological outcome between GPi DBS and STN DBS after 12 months. The study lacks the precision to exclude a moderate difference in outcomes.

INTRODUCTION

Patients with advanced Parkinson's disease (PD) often respond unsatisfactorily to adjustments of pharmacological treatment.[1] In this advanced stage, motor symptoms and dyskinesias are effectively treated by deep brain stimulation (DBS). Both bilateral DBS of the globus pallidus pars interna (GPi) and bilateral DBS of the subthalamic nucleus (STN) are effective procedures in PD.[2-4] Two randomized controlled trials comparing bilateral DBS of the GPi and bilateral DBS of the STN reported equal efficacy on PD motor symptoms and dyskinesias.[2,3] The Netherlands SubThalamic And Pallidal Stimulation (NSTAPS) trial, the third randomized controlled multicenter study comparing bilateral GPi DBS and bilateral STN DBS, indicated greater functional improvement during the medication off-drug phase in STN DBS.[4] This study also showed no difference between the groups on a composite score for cognition, mood, and behavior. Conversely, previous studies have reported more cognitive problems in the STN group compared to GPI DBS [2,5] and controls with PD.[6] A decline in cognition as well as negative changes in mood and other behavioral features have a negative effect on quality of life.[7] Thus, the impact of GPi DBS and STN DBS on cognition, mood, and behavior are important aspects of the outcome after surgery. Establishing baseline parameters that can predict cognitive deterioration might help in patient selection for DBS. Only one previous randomized controlled trial comparing neuropsychological outcome after GPi DBS and STN DBS is available. This trial found less motor improvement in off-drug phase after STN DBS than the NSTAPS trial. In this article we will 1) examine the neuropsychological outcomes after GPi DBS and STN DBS of the NSTAPS trial, and 2) investigate the predictive value of baseline parameters on cognitive decline after DBS.

METHODS

Primary outcomes of the initial study were (1) functional health and (2) the number of patients with a negative composite score of cognitive, mood, and behavioral effects. These primary outcomes were published previously. This article describes the results of the neuropsychological tests used for the cognitive evaluation. Classification of Evidence: This study provides Class I evidence on neuropsychological outcome 12 months after GPi DBS and STN. The study lacks the precision to exclude a moderate difference in outcomes.

PATIENTS

Between January 2007 and March 2011, five participating centers in the Netherlands enrolled a total of 128 patients. Enrollment criteria, study design, and study procedures have been elaborately reported previously. [4] Patients were included in the study if they were aged 18 years or older, had idiopathic PD, and, despite optimal pharmacological treatment, experienced at least one of the following symptoms: severe response fluctuations, dyskinesias, painful dystonias, or bradykinesia. Exclusion criteria consisted of: previous stereotactic surgery, Hoehn and Yahr

stage 5 at the best moment of the day ,[8] a Mattis dementia rating scale (MDRS) score of 120 or lower (out of 144),[9] active psychosis, or contraindications for the neurosurgical procedure.

STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND PATIENT CONSENTS

The medical ethics committee of each of the participating centers approved the study protocol and patients provided written informed consent. This trial is registered with www.controlled-trials.com, number ISRCTN85542074.

PROCEDURES

Based on a computer-generated sequence, patients were randomly assigned to receive either GPI DBS or STN DBS in a one-to-one ratio, applying a minimization procedure according to drug use (levodopa equivalent dose <1000 mg vs ≥1000 mg) and treatment center. Patients as well as clinical, neuropsychological, and psychiatric assessors were blinded for treatment allocation. Patients regularly visited a non-blinded neurologist at the outpatient clinic to adjust DBS settings together with adjustment of PD medication. Adjustments were allowed in both groups. The DBS surgery was performed according to each center's standard protocol, and the final position of the electrode was determined on the basis of MRI, macro-electrode stimulation effects, and, in three of five centers, semi-micro-electrode recordings. Baseline and 12-month motor assessments were done during standardized off-drug and on-drug phases (off phase, withholding antiparkisonian drugs for 12 h overnight; on phase, 1 h after a suprathreshold levodopa dose). Patients performed the neuropsychological tests and questionnaires during the on-drug phase at baseline and 12 months, with the stimulators turned on at 12 months.

NEUROPSYCHOLOGICAL TESTS

Neuropsychologists assessed an extensive battery of standardized neuropsychological tests. *Pre-morbid intelligence* was assessed using the Dutch Adult Reading Test,[10] which is the Dutch version of the National Adult Reading Test. *Attention and working memory* was assessed using the Stroop color-word test,[11] Trail Making Test parts A and B (TMTA/ TMTB),[12] the subtest Letter and Number Sequencing of the Wechsler Adult Intelligence Scale III (WAIS-III),[13] the subtest Digit Span of the WAIS-III, and the Vienna Test System simple and choice reaction speed tests (VTS S1 and S3).[14] *Executive functions* were assessed using the Wisconsin Card Sorting Test (WCST),[15] the Controlled Oral Word Association Test (COWAT) referred to as phonemic fluency,[16] and category fluency, referred to as semantic fluency.[16] *Language* was assessed using the Boston Naming Test (BNT),[17] and the subtest Similarities of the WAIS-III.[13] *Memory* was assessed by the Dutch version of Rey's Auditory Verbal Learning Test (AVLT),[18] logical memory of the Rivermead Behavioral Memory Test (RBMT).[19] *Spatial reasoning* was assessed by the subtest Matrix Reasoning of the

WAIS-III.[13] Where possible, parallel test versions were used at 12-month assessments to avoid retest effects (see appendix e-1 for additional explanation on the neuropsychological tests).

QUALITY OF LIFE

Quality of life (QoL) was assessed using the PD quality of life questionnaire (PDQL).[20] Scores range from 0 points to 185 points, with higher scores indicating better QoL.

STATISTICAL ANALYSIS

Group differences

Statistical analyses of neuropsychological data were performed on normative scores corrected for age, gender, and/or education where appropriate. Change scores for neuropsychological tests were calculated by subtracting baseline scores from 12-month scores. Change scores were checked for normality of distribution, and either t tests or Mann-Whitney U tests were used to compare groups. The 95% CI was reported. The effect sizes of changes were expressed as Cohen's *d*. These were calculated by taking the difference in mean change score of both groups divided by the pooled standard deviations of the baseline scores. An effect of 0.20 to 0.49 reflects a small effect, 0.50 to 0.79 a medium effect, and ≥ 0.80 a large effect.[21] We did not correct the level of significance to reduce the probability of type I error due to multiple comparisons because we were mainly interested in detecting adverse effects of the surgical interventions. Under this circumstance, type II error (failing to detect an effect when it actually exists) is more serious than type I error (considering an effect to be real when it actually is not).[22]

Predictors of cognitive decline

Apart from between-group differences, a secondary aim was to predict cognitive decline after DBS using baseline parameters. Cognitive decline at 12 months was defined as a significant worsening on three or more cognitive tests based on the reliable change index (RCI)[23]. A decline in three scores means a decline on at least three out of 12 different neuropsychological tests. In addition, a test that yields multiple scores is combined into one score. Example: the Stroop test resulted in three scores which made up the overall Stroop score. If a patient failed one Stroop subtest or more, the overall score was scored as 'fail'. The TMT, AVLT, RBMT, and fluency tests were scored similarly. The other neuropsychological tests yielded only one score. The RCI index was calculated according to: $RCI = (X_2 - X_1)/S_{diff,}$ where X_1 is the patient's baseline score, X_2 is the patient's 12-month score, and S_{diff} is the standard error of the difference between both test scores. A score of RCI ≤ -1.645 was considered a significant worsening on a test.

Neuropsychological tests were averaged to form composite scores to reduce the amount of variables and, consequently, to increase the power of the analysis. Tests measuring a similar

construct were combined. This was based on literature[24] and in accordance with a previous study investigating predictors of cognitive decline after DBS.[6] The composite score 'mental speed' consisted of Stroop word reading, Stroop color naming, and TMTA; 'attention' consisted of Stroop color-word interference and TMTB; 'immediate memory' consisted of the immediate recall conditions of the AVLT and RMBT; and 'delayed memory' consisted of the delayed recall conditions of the AVLT and RBMT.

First, we investigated if there were differences in the groups in cognitive decline after DBS by the use of a chi square test. Then, we evaluated which available baseline variables that might influence change in cognition (age, sex, education, disease duration, MDRS, UPDRS-III off score, levodopa equivalent dose (LED), [25] amount of dopamine agonist expressed in LED, levodopa response, the composite baseline neuropsychological scores and remaining standardized neuropsychological test scores) had a 'significant' (p <0.20) association with cognitive decline. We included all parameters mentioned above as an exploratory analysis since no stable predictors are available from literature.

These measures were then entered as independent variables into a multivariable logistic regression model using a stepwise forward approach. Effect sizes were expressed in odds ratios (OR) with their 95% CI. The Hosmer-Lemeshow test was used to determine the goodness of fit of the model. Multicollinearity of the independent variables was assessed using variance inflation factors.

Impact of cognitive decline on QoL

We compared QoL in patients that cognitively declined (decliners) based on the RCI with patients that did not decline (non-decliners). We calculated a change score by subtracting the baseline score from the 12-month score. The change score was checked for normality of distribution, and either a t test or Mann-Whitney U test was used to compare groups.

Missing data

If missing values occurred on a test that a patient did not complete due to fatigue or time constraints, the missing score was replaced by the mean score in that specific group. If missing values were due to the inability of the patient to perform the task, the minimum score in that specific group replaced this missing value. Most missing data points were due to fatigue or time constraints, only a small amount of data points were missing due to inability. A total of 7.2% of the neuropsychological data points were missing (4.8% at baseline, 8.8% at 12 months). In the GPi group, 7.0% of the neuropsychological data points were missing: 4.8% at baseline on 18 variables across 16 patients and 9.1% at 12 months on 22 variables across 30 patients. In the STN group, 6.6% of the data points were missing: 4.7% at baseline on 20 variables across 17 patients and 8.5% at 12 months on 16 variables across 25 patients. Analyses with and without missing data yielded comparable results (data available on request). The presented results are based on the imputed dataset.

RESULTS

Characteristics

A total of 128 patients were randomly assigned to either GPi DBS (65 patients) or STN DBS (63 patients). Fourteen patients, 7 GPi DBS and 7 STN DBS patients, did not complete neuropsychological assessment at 12 months for the following reasons: some patients refused, some kept cancelling appointments, some without a specified reason. These patients showed no significant differences on baseline measures (age, MDRS, disease duration) and improvement at 12 months on the Unified Parkinson's Disease Rating Scale (UPDRS) motor section in off-drug phase when compared to the patients with a complete neuropsychological follow-up assessment. Data from 58 GPI DBS patients and 56 STN DBS patients were analyzed. Baseline demographic and clinical characteristics of the two groups are shown in table 1.

Table 1. *Demographic and clinical characteristics at baseline.*

Baseline characteristics	GPi (n=58)	STN (n=56)
Age, years	59.2 (7.7)	60.3 (7.4)
Male sex, no. (%)	40 (69%)	42 (75%)
Education, years	11.5 (2.8)	12.4 (3.4)
Dutch Adult Reading Test, IQ	107.1 (12.5)	103.3 (13.6)
Mattis Dementia Rating Scale	138.5 (3.8)	138.3 (5.3)
Age of onset, years	49.0 (7.6)	48.6 (9.5)
Disease duration at inclusion, years	10.9 (4.0)	12.3 (5.5)
PD medication use, years *	8 (6.5-12)	9 (6-12.75)
Levodopa Equivalent Dose (LED), mg/day *	1226 (892.5-1655)	1200 (900-1428.8)

Values are mean (SD), except for variables with an * = median (interquartile range). GPi=globus pallidus pars interna. STN=subthalamic nucleus.

Between group comparisons

Baseline neuropsychological test variables were equally distributed between treatment groups (table 2, raw scores are provided in table e-1). Analyses of change scores showed between-group differences on Stroop word reading (GPi mean (SD) -1.1(10.4), STN -7.0 (11.3), CI 1.9 – 10.0) and Stroop color naming (GPi -2.6 (9.6), STN -8.1 (8.1), CI 2.1 – 8.8), on TMTB (GPi -0.7 (12.0), STN -6.1 (14.2), CI 0.5 – 10.3), and borderline significance on the WAIS similarities (GPI -0.1 (2.3), STN -0.8 (1.7), CI -0.01 – 1.5) with STN DBS showing greater negative change than GPi DBS. Effect sizes of these differences were small to medium.

Table 2. *Standardized neuropsychological test scores: baseline scores and change scores at 12-months in relation to type of intervention*

Test	GPI (n=58)	STN (n=56)	95% CI	Cohen's d *
Attention and working memory				
Stroop word reading	40.9 (9.5)	43.4 (12.0)		
Change score	-1.1 (10.4)	-7.0 (11.3)	1.9 – 10.0	0.55
Stroop color naming	44.2 (9.8)	46.0 (11.4)		
Change score	-2.6 (9.6)	-8.1 (8.1)	2.1 – 8.8	0.51
Stroop color-word interference	44.0 (9.7)	45.5 (10.4)		
Change score	-3.6 (7.5)	-4.9 (7.7)	-1.5 – 4.1	0.13
TMT A	39.3 (10.5)	43.0 (11.9)		
Change score	-1.1 (9.6)	-1.5 (10.4)	-3.3 – 4.2	0.04
TMT B	40.3 (12.9)	43.0 (15.6)		
Change score	-0.7 (12.0)	-6.1 (14.2)	0.5 – 10.3	0.38
WAIS letters and numbers	9.9 (3.3)	9.1 (3.6)		
Change score	-1.4 (3.4)	-0.5 (2.7)	-2.1 – 0.2	-0.28
WAIS digit span	10.8 (3.2)	10.2 (3.1)		
Change score	-0.9 (2.7)	-0.5 (2.4)	-1.4 – 0.5	-0.13
VTS1 reaction	48.8 (6.8)	49.2 (9.0)		
Change score	-0.8 (6.6)	-2.5 (7.2)	-0.8 – 4.3	0.22
VTS1 motoric	46.9 (7.0)	49.4 (8.2)		
Change score	2.2 (6.8)	0.9 (8.3)	-1.5 – 4.1	0.17
VTS3 reaction	42.0 (9.5)	41.1 (9.5)		
Change score	-2.0 (10.6)	-2.6 (8.5)	-3.0 – 4.1	0.06
VTS3 motoric	38.5 (8.7)	39.2 (7.7)		
Change score	0.9 (8.9)	3.1 (7.7)	-5.3 – 0.8	-0.27
Executive function				
WCST categories (completed categories)	3.6 (2.1)	3.9 (2.1)		
Change score	-0.3 (2.2)	-0.3 (2.5)	-1.0 – 0.8	-0.05
WCST # of errors	38.9 (7.3)	41.9 (6.9)		
Change score	0.4 (8.1)	0.1 (7.2)	-2.5 – 3.1	0.04
WCST # of perservative errors	42.9 (6.4)	46.6 (7.6)		
Change score	1.3 (6.7)	-0.1 (8.9)	-1.6 – 4.2	0.19
Phonemic fluency	49.9 (9.6)	50.0 (12.2)		
Change score	-6.1 (8.2)	-6.9 (9.6)	-2.5 – 4.1	0.07
Semantic fluency	50.3 (7.9)	50.2 (9.0)		
Change score	-5.1 (7.4)	-7.2 (8.5)	-0.9 – 5.0	0.25
Language				
BNT	50.44 (6.1)	52.0 (7.6)		
Change score	-0.4 (5.4)	-1.9 (7.0)	-0.8 – 3.8	0.17
WAIS similarities	10.6 (2.9)	10.6 (3.4)		
Change score	-0.1 (2.3)	-0.8 (1.7)	-0.01 – 1.5	0.24
Memory				
RAVLT immediate recall	48.6 (10.2)	49.3 (12.0)		
Change score	-3.1 (11.3)	-3.1 (9.6)	-3.9 – 3.9	0.001
RAVLT delayed recall	50.7 (10.9)	48.5 (12.4)		
Change score	-3.7 (10.6)	-1.7 (10.5)	-5.9 – 1.9	-0.17
RBMT immediate recall	41.2 (11.0)	41.5 (10.2)		
Change score	-2.7 (8.3)	-2.0 (9.4)	-4.0 – 2.6	-0.07
RBMT delayed recall	43.1 (11.0)	41.7 (10.6)		
Change score	-3.0 (8.7)	-2.4 (8.1)	-3.8 – 2.5	-0.06
RBMT % recall	50.0 (13.1)	46.5 (13.6)		
Change score	-2.8 (15.8)	-0.1 (10.1)	-9.4 – 4.0	-0.16
Spatial functioning				
WAIS matrix reasoning	8.8 (2.9)	9.2 (2.8)		
Change score	-0.1 (2.8)	-0.6 (2.8)	-0.5 – 1.5	0.17

Values are mean (SD) based on T-scores, except for WAIS subtests, which are Scaled Scores. WCST categories is given as the number of categories completed.
* Positive Cohen's d scores show a relative better performance in GPi DBS compared with STN DBS. GPi=globus pallidus pars interna. STN=subthalamic nucleus.

Prediction of cognitive decline

There was no significant difference between the two groups on cognitive decline based on the composite score after DBS. In GPi DBS 17 patients (29.3%) experienced cognitive decline, in STN DBS 22 patients (39.3%) experienced cognitive decline (p=0.26, X^2 test). Six patients had a MDRS below 130 at baseline (1 GPi patient and 5 STN patients). Two STN patients showed significant cognitive decline at 12 months based on the criterion of at least three significant RCIs, which is similar to the percentage of patients with cognitive decline in the entire group. The following independent variables were identified as potential predictors for cognitive decline and entered into the logistic regression model based on p<0.20: age, disease duration, MDRS, agonist LED dose, digit span, semantic fluency (table 3, see table e-2 for the association analyses of all baseline parameters). The stepwise forward regression model showed age at baseline (OR 1.10, 95% CI 1.03 to 1.18, p=0.003) and semantic fluency at baseline (OR 1.06, 95% CI 1.01 to 1.12, p=0.032) as independent predictors (table 3). The regression model appeared to fit the data (Hosmer-Lemeshow test: p=0.70). Variance inflation factors indicated that multicollinearity was low (<1.30).

Table 3. *Impact of baseline parameters on cognitive decline 12 months after DBS.*

Baseline predictors	No cognitive decline (n=75)	Cognitive decline (n=39)	P Values*	OR
Age	58.4 (7.7)	62.4 (6.4)	0.007	1.10
Disease duration, years	10 (8-14)	12 (9-17)	0.18	**
MDRS total score	140 (138-142)	138 (134-141)	0.04	**
Agonist LED score	200 (0-400)	300 (0-500)	0.09	**
WAIS digit span	10.2 (2.9)	11.2 (3.6)	0.12	**
Semantic fluency	49.4 (7.9)	51.9 (9.2)	0.14	1.06
			Hosmer-Lemeshow	0.70

Values are mean (SD) or median (interquartile range). * p Values were calculated using the Mann-Whitney U test or two-group T-test, when appropriate. ** Variables were not significant in the stepwise forward regression model. OR=odds ratio.

Impact of cognitive decline on QoL

Results on the PDQL show no significant differences on change scores between decliners and non-decliners (mean improvement of decliners: 9.9 ± 19.6, non-decliners: 15.8 ± 17.9, CI -1.5 – 13.3).

DISCUSSION

This in-depth analysis of the neuropsychological data of the NSTAPS trial shows only small differences between GPi DBS and STN DBS at 12 months after DBS. We found significant differences on Stroop word reading, Stroop color naming, TMTB, and WAIS similarities with STN DBS showing greater negative change than GPi DBS. These results suggest a larger decline in mental speed (Stroop word reading and Stroop color naming), attention (TMTB) and possibly language (WAIS similarities) after STN DBS. However, this effect was not reproduced on the TMTA and Stroop color-word interference, respectively. These differences in cognitive change are similar to previous randomized controlled trials comparing GPi DBS and STN DBS. Follet et al. only found a significant difference between the groups on a task measuring processing speed and working memory (WAIS-III digit symbol test), with the decline being greater for STN DBS after 24-months.[3] Although different cognitive tasks were used, the differences between GPi DBS and STN DBS seem to occur mainly on tasks measuring components of speed.[3,4] One must interpret the statistically significant findings with care since we did not correct for multiple comparisons.
The rate of cognitive decline in our study appears high compared to a recent publication by Rothlind et al.[26] The amount of patients showing cognitive decline based on the RCI's was about three times as high (NSTAPS: GPi 29.3%,STN DBS 39.3% compared to Rothlind: 10.9% for DBS in general) in our study. However, the Rothlind study uses a different strategy for calculating a composite RCI for overall decline, which makes comparison of how many patients show cognitive decline between the two studies difficult. Results are actually very similar when comparing percentual decline on individual neuropsychological tests (mean decline on all matching tests of the two studies: 9.0% in the Rothlind study and 6.5% in our study on matching tests).
In contrast to the Rothlind study, we did find an improvement of QoL in both the decliners and non-decliners. The difference in improvement between these groups was not statistically significant. This could be a power issue.
In the smaller study by Anderson and colleagues, cognitive complications were only observed in the STN group.[2] A recently published review concluded that there might be a possible advantage of uni- and bilateral GPi DBS over STN DBS when comparing cognitive outcomes.[27] However, the clinical relevance of this difference is unknown, since functional outcome scores and quality of life scores do not differ between these groups.[2,4] Additionally, no difference was found in our study between GPi DBS and STN DBS when using a composite score for neuropsychological examination.
STN DBS might even be superior to GPi DBS when evaluating functional improvement during the medication off-drug phase.[4]
The predictive model from the multivariate logistic regression indicated higher age and better semantic fluency at baseline as independent predictors for cognitive decline at 12 months. Age is a plausible predictor for cognitive outcome. Better baseline semantic fluency, on the other

hand, was not expected to predict cognitive decline. We have no satisfactory explanation for this finding.

To our knowledge, only two other studies have reported on predictive modeling of cognitive decline after DBS. Smeding et al. reported age, attention, and levodopa response at baseline to be predictors for cognitive decline at 12 months in STN DBS.[6] The statistical evaluation and method of assessment of cognitive decline was different in our study. Cognitive decline in our study is based on RCI derived from the test manuals, whereas in the study by Smeding et al. it was based on multivariate normative comparison with the PD control group.

The other study indicated that baseline list learning and IQ were the best predictors for post DBS immediate story recall, the variable that was most affected after STN DBS in their sample.[28] This study did not asses predictors of decline of cognition on a composite score.

The results from our regression analysis, as well as the variation in predictors between different studies thus far, suggest these models for predicting cognitive outcome are unstable. Small sample sizes and differences in study protocols might contribute to this variation. A stable predictive model would be very useful for clinicians in daily practice. Since new randomized controlled trials between GPi DBS and STN DBS are less likely to be performed, a meta-analysis using individual patient data of previous studies might be the preferred strategy to obtain a more reliable prediction model for cognitive outcome after DBS.

No large differences in neuropsychological outcome between GPi DBS and STN DBS have been found in randomized clinical trials. The choice for either GPi DBS or STN DBS cannot be reliably based on baseline patient characteristics with the models that are currently available.

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SUPPLEMENTAL DATA TABLE E-1, NSTAPS NEUROPSYCHOLOGICAL EXAMINATION

Table e-1. *Unstandardized neuropsychological test scores at baseline and change scores at 12-months.*

Test	GPI (n=58)	STN (n=56)
Attention and working memory		
Stroop word reading (s)	49.0 (8.7)	47.5 (9.6)
Change score	1.7 (9.2)	7.7 (12.6)
Stroop color naming (s)	65.1 (11.2)	64.9 (16.4)
Change score	5.7 (17.8)	12.3 (14.9)
Stroop color-word interference (s)	120.8 (43.4)	124.3 (80.2)
Change score	17.0 (44.3)	23.3 (53.2)
TMT A (s)	48.0 (16.2)	45.1 (24.3)
Change score	4.4 (22.5)	2.3 (18.3)
TMT B (s)	129.4 (73.4)	128.6 (111.6)
Change score	11.1 (78.6)	44.4 (139.0)
WAIS letters and numbers	9.5 (2.6)	8.8 (3.1)
Change score	-1.2 (2.5)	-0.4 (2.3)
WAIS digit span	15.1 (3.5)	14.3 (3.2)
Change score	-1.1 (2.9)	-0.5 (2.3)
VTS1 reaction (ms)	368.8 (61.5)	386.6 (115.1)
Change score	19.2 (81.1)	23.1 (96.5)
VTS1 motoric (ms)	262.6 (64.5)	243.4 (60.8)
Change score	-7.12 (63.4)	-7.2 (68.2)
VTS3 reaction (ms)	525.5 (102.2)	530.6 (128.8)
Change score	20.3 (117.7)	40.3 (112.5)
VTS3 motoric (ms)	268.3 (71.4)	257.1 (66.5)
Change score	1.6 (78.0)	-15.3 (61.8)
Executive function		
WCST categories	3.6 (2.1)	3.9 (2.1)
Change score	-0.3 (2.2)	-0.3 (2.5)
WCST # of errors	43.8 (23.7)	41.8 (21.2)
Change score	5.5 (23.7)	3.1 (22.7)
WCST # of perservative errors	22.6 (15.5)	22.6 (14.3)
Change score	2.1 (14.0)	0.7 (14.2)
Phonemic fluency	37.1 (10.6)	37.8 (13.9)
Change score	-6.1 (8.3)	-7.0 (9.8)
Semantic fluency	20.5 (4.0)	20.6 (4.8)
Change score	-2.5 (3.5)	-3.4 (4.0)
Language		
BNT	54.9 (2.9)	55.4 (3.3)
Change score	-0.2 (2.5)	-0.8 (2.6)
WAIS similarities	25.0 (4.7)	25.0 (5.3)
Change score	-0.1 (3.6)	-1.5 (2.9)
Memory		
RAVLT immediate recall	40.3 (9.1)	41.0 (10.3)
Change score	-2.8 (8.9)	-2.8 (7.6)
RAVLT delayed recall	8.5 (3.0)	8.0 (3.4)
Change score	-1.0 (2.7)	-0.5 (2.7)
RBMT immediate recall	16.9 (5.9)	16.9 (5.6)
Change score	-1.6 (4.4)	-1.2 (5.0)
RBMT delayed recall	13.5 (5.5)	13.1 (5.8)
Change score	-1.7 (4.6)	-1.4 (4.3)
RBMT % recall	78.2 (18.3)	75.3 (17.5)
Change score	-3.5 (22.6)	-0.1 (25.6)
Spatial functioning		
WAIS matrix reasoning	13.6 (5.3)	14.5 (5.3)
Change score	-0.2 (4.4)	-1.2 (4.6)

Values are mean (SD) based on raw scores. Positive change scores indicate improvement except for timed variables and error scores. GPi=globus pallidus pars interna. STN=subthalamic nucleus. n=number of patients.

SUPPLEMENTAL DATA TABLE E-2

Table e-2. *Impact of baseline parameters on cognitive decline 12 months after DBS.*

Baseline predictors	**No cognitive decline (n= 75)**	**Cognitive decline (n= 39)**	**P**
Age	58.4 (7.7)	62.4 (6.4)	**0.007**
Male sex, no. (%)	52 (69.3)	30 (76.9)	0.39
Education	11.9 (3)	12.1 (3.5)	0.66
Disease duration, years	10 (8-14)	12 (9-17)	**0.18**
MDRS total score	140 (138-142)	138 (134-141)	**0.04**
UPDRS-III off	43 (32.5-54)	41 (31-55)	0.87
LED total dose	1200 (900-1522)	1195 (907.5-1680)	0.54
Agonist LED	200 (0-400)	300 (0-500)	**0.09**
Levodopa response	0.4 (0.20)	0.4 (0.18)	0.90
Attention and working memory			
Mental speed	42.8 (9.0)	42.8 (7.7)	0.99
Attention	43.3 (10.5)	43.0 (10.8)	0.90
WAIS letters and numbers	9.6 (3.2)	9.4 (4.0)	0.80
WAIS digit span	10.2 (2.9)	11.2 (3.6)	**0.12**
VTS1 reaction	48.6 (7.4)	49.9 (8.9)	0.41
VTS1 motoric	46.9 (43-51)	47 (43-51)	0.61
VTS3 reaction	41.1 (38-43)	42 (35-46)	0.50
VTS3 motoric	38.5 (34-43)	39 (35-42)	0.77
Executive function			
WCST # of errors	40.8 (6.6)	39.4 (8.2)	0.32
WCST # of perservative errors	45.3 (6.1)	43.6 (9.1)	0.23
Phonemic fluency	49.6 (10.6)	50.6 (11.6)	0.64
Semantic fluency	49.4 (7.9)	51.9 (9.2)	**0.14**
Language			
BNT	50.8 (7.5)	52.1 (5.5)	0.33
WAIS similarities	10.4 (3.2)	11.0 (3.1)	0.34
Memory			
Immediate recall	45.2 (9.3)	45.2 (8.0)	0.99
Delayed recall	45.7 (10.5)	46.7 (7.9)	0.54
Spatial functioning			
WAIS Matrix reasoning	9.2 (2.9)	8.7 (2.7)	0.43

Values are mean (SD) or median (interquartile range). * p Values were calculated using the Mann-Whitney U test or two-group T-test, when appropriate.

SUPPLEMENTAL DATA APPENDIX E-1, NSTAPS NEUROPSYCHOLOGICAL EXAMINATION

Attention and working memory

The Stroop color-word test[11] consisted of three conditions: Stroop word reading: read words, red, yellow, blue, green, while printed in black ink, Stroop color naming: name colors printed in small rectangles, Stroop color-word interference: name colors of printed words, while the words are printed in non-matching ink. The score for each condition is the time in seconds to complete 100 items. In the TMTA numbers had to be connected, and in the TMTB numbers and letters had to be connected while alternating.[12] Score for each condition represents the time in seconds needed for completion. The score for the subtest Letter and Number Sequencing of the WAIS-III represents the number of trails correctly completed.[13] Forward and backward digit span were combined into one total score, which represents the number of items correctly answered.[13] The Vienna Test System simple and choice reaction speed test (VTS S1 and S3) is a computerized test.[19] The score for VTS S1reaction is the time it took a patient to remove his finger from a sensor when a yellow circle displayed on the screen. The score for VTS S1motoric, is the time it took a patient to press a button when his finger was already removed from to the sensor. VTS S3reaction and VTS S3motoric were measured similarly with the note that in addition to the yellow circle a beep had to be present as well. The score for each sub measure represents time in milliseconds.

Executive functions

A computerized version of the WCST was used.[15] Cards had to be sorted according to one of the possible rules (by color, number, or form) without prior knowledge of these rules. Feedback was given after each sort. Scores are the number of completed categories, the number of errors, and the number of perseverative errors. The COWAT, letter fluency, consisted of three trails with different letters, each during one minute.[16] Total score is the number of correct items in 3 minutes, referred to as phonemic fluency. Category fluency consisted of two trails, animals and occupation, each during one minute.[16] Total score is the number of correct items for both categories, referred to as semantic fluency.

Language

An abbreviated 30-item version of the BNT was used; scores of the original version were estimated by extrapolation.[17] During the subtest Similarities of the WAIS-III a common aspect in objects or concepts had to be identified.[13] Score is the number of trails correctly completed.

Memory

For the AVLT, the sum of items recalled during trail 1 to 5 is the immediate recall score.[18] The number of items recalled after 20 minutes is the delayed recall score. The immediate recall score for the RBMT is the number of elements correctly recalled, the delayed recall score is the number of elements recalled after a 15-minute interval.[19]

Spatial functioning

During the subtest Matrix Reasoning of the WAIS-III a series of incomplete gridded patterns had to be completed by choosing from five possible options.[13] Score is the number of trails correctly completed.

4 |

Psychiatric and social outcome one year after subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease

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Adapted from

Psychiatric and social outcome after deep brain stimulation for advanced Parkinson's disease. Boel J.A., Odekerken V.J., Geurtsen G.J., Schmand B.A., Cath D.C., Figee M., van den Munckhof P., de Haan R.J., Schuurman P.R., de Bie R.M.; NSTAPS study group. Mov Disord. 2016 Mar;31(3):409-13.

ABSTRACT

Background: The aim of this study was to assess psychiatric and social outcome 12 months after bilateral DBS of the GPi and STN for advanced PD.

Methods: We randomly assigned patients to receive GPi DBS (n=65) or STN DBS (n=63). Standardized psychiatric and social questionnaires were assessed at baseline and after 12 months.

Results: No differences were found between GPi DBS and STN DBS on psychiatric evaluation. Within-group comparisons showed small but statistically significant changes on several measures in both groups. Descriptive statistics indicated slight changes in social functioning. Marital satisfaction of patients and partners remained relatively stable after GPi and STN DBS.

Conclusions: We found neither differences in psychiatric and social outcome between GPi DBS and STN DBS, nor any relevant within-group differences. The decision for GPi DBS or STN DBS cannot be based on expected psychiatric or social effects.

INTRODUCTION

Deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) or the subthalamic nucleus (STN) are treatment options in advanced Parkinson's disease (PD). Concerns have been raised regarding the psychiatric side effects of DBS, especially of STN DBS.[1-5] Additionally, STN DBS patients would experience difficulties in several aspects regarding social adaption after surgery.[1] Possible psychiatric side effects are important because they greatly impact quality of life in PD.[6-8]

For these reasons, scales assessing psychiatric symptoms and social functioning were added to the protocol of the Netherlands SubThalamic And Pallidal Stimulation (NSTAPS) trial, in which the effects of bilateral GPi DBS and STN DBS are compared.[9] Here we report the psychiatric outcome 12 months after DBS (between-group and within-group analyses). Furthermore, we report descriptive statistics on psychiatric diagnoses and social functioning before and after GPi DBS and STN DBS.

METHODS

This article presents secondary outcomes on psychiatric and social measures from the NSTAPS trial. The study design and primary outcomes have been reported previously.[9] This trial was registered with www.controlled-trials.com, number ISRCTN85542074.

PATIENTS AND PROCEDURES

We enrolled a total of 128 patients between January 2007 and March 2011. Information on in- and exclusion criteria as well as stereotactic surgery is described elsewhere.[9] Psychiatric and social questionnaires were assessed in the on-medication phase at baseline and at 12 months, with the stimulators turned on at 12 months. The medical ethics committee approved the study protocol. Patients provided written informed consent.

OUTCOME MEASURES

Extensive standardized psychiatric evaluation, performed at baseline and at 12 months, consisted of interviews and self-report questionnaires based on Diagnostic and Statistical Manual of Mental Disorders (DSM IV) classified psychiatric disorders, and quantitative self-reports on characteristics and severity of psychopathology, personality, mood and affect, and social functioning.[10]

Between-group and within-group analyses were performed for the following four psychiatric scales. The Young Mania Rating Scale (YMRS) was used to assess the severity of manic symptoms.[11] Mood was assessed with the Hospital Anxiety and Depression Scale (HADS).[12] The Positive and Negative Affect Schedule (PANAS-X) was used to measure affect.[13] The Five Factor Personality Inventory-II (FFPI) was used to assess the 'Big Five' factors of personality.[14]

Descriptive analyses were performed on data from the following questionnaires. We measured

psychopathology with the Mini-International Neuropsychiatric Interview (MINI).[15] To obtain a quantitative measure of suicidal ideation, a short interview was used from the Netherlands Study on Depression and Anxiety (NESDA).[16] Social functioning was assessed using a social participation- and a network questionnaire(NESDA).[16] The current work situation was evaluated[17], as well as sexual functioning of patients.[18] Marital satisfaction was assessed by interview (NESDA). Both patients and their partners rated personal characteristics of their significant other (supplement I).

STATISTICAL ANALYSES

Analyses were based on the intention-to-treat principle. We performed linear regression to compare GPi DBS and STN DBS on the psychiatric scales (the YMRS, HADS, PANAS, and FFPI). Within-group differences of GPi DBS and STN DBS before and 12 months after surgery were assessed using paired t-tests or Wilcoxon signed rank tests.

We created imputation models to assess possible differences in outcome due to incomplete data on the YMRS, HADS, FFPI, and PANAS. The significance level was set at 0.05 (two-sided test). In view of the explorative nature of this study, we did not correct for multiple testing.[19] Statistical analyses were performed with SPSS software V.20.0.0.1.

With regard to the descriptive analyses on psychiatric diagnoses and social functioning before and after GPi DBS and STN DBS, we calculated frequencies of dysfunctions, without the use of formal statistical tests. For all statistical analyses, patients who completed the specific scales at both assessments were included.

RESULTS

A total of 128 patients were randomly assigned to either GPi DBS (65 patients) or STN DBS (63 patients). Baseline characteristics are displayed in table 1.[9] Three patients withdrew from the GPi group, and none from the STN group. Patterns of missing data of the YMRS, HADS, FFPI, and PANAS were analyzed. On average 18.3% of the data points were missing. Missing data did not significantly differ between GPi DBS and STN DBS. The presented results are based on the non-imputed dataset (imputed data yielded similar outcomes and are available on request).

BETWEEN-GROUP COMPARISON (GPI DBS VS. STN DBS)

The four psychiatric questionnaires, the YMRS, HADS, PANAS, and FFPI, indicated no significant differences between GPi DBS and STN DBS (Table 2).

Table 1. Demographic and clinical characteristics at baseline.

	GPi DBS (n=65)	STN DBS (n=63)
Age (mean±SD) – yr	59.1±7.8	60.9±7.6
Age of onset PD (mean±SD) – yr	48.5±7.6	48.6±9.4
Male sex – no. (%)	44 (68)	44 (70)
Duration of PD (mean±SD) – yr	10.8±4.2	12.0±5.3
Duration of use of medication for PD (mean±SD) – yr	9.0±3.9	9.5±5.6
Hours per day spent in on drug phase* (mean±SD) – h	6.5±3.6	6.3±4.4
On drug phase Hoehn & Yahr stage (median [range])	2.5 [0-4]	2.5 [0-4]
Levodopa equivalent dose† ≥1000 mg/d – no. (%)	43 (69)	43 (68)
Mattis Dementia Rating Scale (mean±SD, range, 0-144)	138.7±4.0	138.1±5.1

* Calculated using a 3-day diary. † Levodopa equivalent dose = regular levodopa dose x 1 + slow release levodopa x 0·75 + bromocriptine x 10 + apomorphine x 10 + ropinirole x 20 + pergolide x 100 + pramipexole x 100 + (regular levodopa dose + [slow release levodopa x 0·75]) x 0.2 if taking entacapone. GPi= globus pallidus pars interna. STN= subthalamic nucleus.

Table 2. Between-group and within-group analyses of the YMRS, HADS, PANAS, and FFPI.

	Baseline		12 months		***p*** **beween-group**	***p*** **within-group**	
	GPi	STN	GPi	STN	GPi vs. STN	GPi	STN
YMRS							
Total score*	2 (1-4)	1 (0-4)	1 (1-3)	2 (1-3)	0.77	0.04	0.42
HADS							
Total score	12.2 (4.4)	11.3 (6.3)	12.0 (6.5)	11.6 (6.3)	0.75	0.81	0.62
Anxiety	6.1 (2.7)	5.8 (3.4)	5.9 (2.9)	5.4 (3.3)	0.54	0.51	0.31
Depression	6.0 (2.8)	5.5 (3.4)	6.1 (4.5)	6.2 (3.8)	0.41	0.90	0.07
PANAS							
Positive affect	32.8 (5.7)	33.0 (6.5)	30.1 (6.0)	31.4 (6.3)	0.41	0.01	0.02
Negative affect	19.3 (6.0)	18.8 (5.9)	18.7 (5.9)	19.0 (6.7)	0.73	0.63	0.86
FFPI							
Extraversion	-0.2 (1.0)	-0.1 (1.1)	-0.5 (1.1)	-0.1 (1.1)	0.07	0.01	0.67
Agreeableness	2.8 (1.1)	2.8 (1.1)	2.6 (1.0)	2.5 (1.2)	0.89	0.02	0.13
Conscientiousness	0.8 (1.1)	0.7 (1.3)	0.7 (1.1)	0.7 (1.0)	0.74	0.48	0.99
Emotional Stability	1.0 (0.9)	1.2 (1.0)	0.9 (0.9)	1.0 (1.0)	0.92	0.45	0.13
Autonomy	0.9 (1.1)	1.2 (0.8)	0.6(0.80)	0.9 (0.8)	0.66	0.06	0.03

All values are mean (SD), except for those marked with an * these are median (inter quartile range). *p* between-group was calculated using linear regression to adjust for baseline scores. The 12-month score was entered as the dependent variable, while the baseline score and treatment-group were entered as independent variables. Prior to linear regression, the YMRS scores were log transformed due to skewness of the data. *p* within-group was calculated using paired t-tests or Wilcoxon signed rank tests, when appropriate. YMRS= Young Mania Rating Scale, GPi n = 49, STN n = 53. HADS= Hospital Anxiety and Depression Scale, total score: GPi n = 53, STN n= 54. PANAS= Positive and Negative Affect Schedule, GPi n=38, STN n=40. FFPI= Five Factor Personality Inventory-II, GPi n=51, STN n=51. GPi= globus pallidus pars interna. STN= subthalamic nucleus.

WITHIN-GROUP COMPARISON

GPi DBS

The YMRS scores were statistically significantly lower at 12 months (-1.1 from a baseline score of 3.2 out of 60, p=0.04). No significant differences were found on the HADS. The PANAS positive affect score was significantly lower (p=0.01) at 12 months, but the absolute difference was small (-2.7 from a baseline score of 32.8 out of 50). The 12-month FFPI showed significantly lower scores on extraversion (p=0.01) and agreeableness (p=0.02).

STN DBS

At 12 months, no significant differences were found on the YMRS and the HADS. The PANAS positive affect score was significantly lower (p=0.02) at 12 months, but the absolute difference was small (-1.6 from a baseline score of 33.0 out of 50.0). The 12-month FFPI showed significantly lower scores on autonomy (p=0.03). See table 2.

DESCRIPTIVE COMPARISON OF PSYCHIATRIC AND SOCIAL FUNCTIONING

Psychiatric evaluation using the MINI showed similar presence of dysthymia (both 0), (hypo-) manic episode (GPi 0, STN 1), panic disorder (GPi 1, STN 0), alcohol abuse and dependence (both 0), and psychotic disorder (GPi 5, STN 4), in the 12 months after surgery. Depressive disorders were reported more after STN DBS (GPi 7, STN 11), agoraphobia was reported more after GPi DBS (GPi 9, STN 4: supplement II). Suicidal ideation in the week prior to the psychiatric evaluation was present in none of the GPi DBS patients and one DBS STN patient at baseline, and in one GPi DBS patient and two STN DBS patients in the week prior to the 12-month evaluation.

Regarding societal participation, more than 80% of patients in both DBS groups were a member of an organization, which remained stable over time. Most patients who were a member also attended meetings of their organizations. Most patients were members of a PD patient organization, sport and/or religious organization (supplement III). Regarding networking, the number of friends a patient thought to have remained stable (GPi DBS: four friends at baseline and at 12 months, STN DBS: five friends at both assessment). Most patients were unfit for work (GPi n= 23, STN n=22) or were already retired (GPi n=19, STN =17) at baseline (supplement IV). Sexual desire seems slightly diminished after both GPi DBS (n=56) and STN DBS (n=56). Sexual satisfaction remained relatively stable as well as the number of times sexual intercourse was initiated (supplement V). Two patients in the GPi group ended a relationship in the year after surgery, and none in the STN group. Marital satisfaction of both patients and partners remained stable after both DBS procedures (supplement VI).

DISCUSSION

This study provides evidence of no difference in psychiatric outcome between GPi DBS and STN DBS for PD. In addition, descriptive analyses show stable social functioning after DBS in both targets.

The choice between GPi DBS or STN DBS in advanced PD is still a source of controversy.[20] A trial by Anderson et al. reported more cognitive and behavioral adverse effects after STN DBS.[5] This was an RCT with a small sample size (GPi 10, STN 10). Our between group-comparison showed no evidence that psychiatric effects are different after GPi or STN DBS, which is in line with findings from a trial comparing DBS with best medical treatment,[21] and findings from a comparison of unilateral GPi DBS and STN DBS.[22]

Within-group comparisons showed little change 12 months after surgery. Overall, the mania rating scores were very low at both points in time and thus not indicative for mania. The results on the HADS indicated slightly higher subscale scores for anxiety than for depression, as has been reported before in 177 PD patients without DBS.[6] We found no change in scores after 12 months, suggesting a stable mood profile regarding anxiety and depression.

The positive affect scores also showed significant but small decreases in both groups, which can be considered negligible since scores at baseline and 12 months are within one standard deviation of healthy adults. Absolute changes on the character traits on the FFPI were also small, for example 0.2 standard deviation for GPi DBS on extraversion, and therefore do not seem clinically relevant.

There is no observed increase in psychiatric disorders after DBS in either target (MINI-interviews). This is an important confirmation that DBS is a safe procedure in PD from a psychiatric point of view.[21] The psychotic disorders observed in the 12 months after DBS were transient and mostly due to medication. In our study suicidal ideation seems not to differ between GPi and STN DBS, which has been reported before.[23] There were no suicide attempts in our trial 12 months after surgery.

Sexual desire seems to be lower 12 months after both GPi DBS and STN DBS. Sexual satisfaction and number of monthly initiations of sexual intercourse seemed not to change after surgery. Based on this data it is not possible to establish an origin of the decline of sexual desire, but a decrease in dopaminergic medication could play a role. While a negative effect of DBS on societal participation has been described,[1] our data shows stable participation and a stable number of friends. Especially the stable marital satisfaction is a reassuring finding, since case reports have been published about relational issues after DBS.[1]

A caveat of this study is the missing data. The NSTAPS protocol was exhaustive for patients. Importantly, there was no difference in the amount of missing data between the groups, and the imputation analyses resulted in similar outcomes.

In conclusion, we did not find large differences in psychiatric and social effects between GPi DBS

and STN DBS. Moreover, there was little deterioration over time. Thus, DBS in both the STN and the GPi seems a safe procedure for PD patients with respect to psychiatric and social outcome. Consequently, the decision for GPi DBS or STN DBS in individual patients cannot be based on expected psychiatric or social effects of these interventions.

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SUPPLEMENTAL DATA

Supplement I. Assessment of marital satisfaction.

Please rate how satisfied or dissatisfied you are regarding the relationship with your partner based on the following aspects.

Answer options:

1. Very dissatisfied
2. Dissatisfied
3. Not dissatisfied, not satisfied
4. Satisfied
5. Very satisfied

Questions:

1. Daily support and encouragement my partner gives me
2. The way my partner motivates me
3. My partners overall personality
4. The way my partner considers my wishes
5. My sexual relationship with my partner
6. The level of intimacy in my relationship with my partner
7. The way disagreements are solved
8. The extent to which issues, that I think are important, are discussed
9. The way decisions are made in this relationship

Supplement II. Mini International Neuropsychiatric Interview (MINI).

	Baseline		**12 months***	
Depressive episode	**GPi**	**STN**	**GPi**	**STN**
Depressive disorder current	0	1	1	1
Depressive disorder past	10	2	4	8
Due to somatic condition current	0	0	2	1
Due to somatic condition past	2	0	2	0
Substance induced current	0	0	0	0
Substance induced past	0	1	1	3
Including melancholic features	0	0	1	1
Dysthymia				
Dysthymia disorder current	0	0	0	0
Dysthymia disorder now	0	0	0	0
Suicidality				
Suicide risk current	4	4	4	5
Risk: low	3	1	2	1
Risk: medium	1	3	2	4
Risk: high	0	0	0	0

	Baseline		12 months*	
	GPi	STN	GPi	STN
(Hypo-) manic episode				
Hypomanic current	0	0	0	0
Hypomanic past	2	1	0	0
Manic current	0	0	0	0
Manic past	1	0	0	0
Due to somatic condition current	0	0	0	0
Due to somatic condition past	0	0	0	0
Substance induced current	0	0	0	0
Substance induced past	1	1	0	1
Panic disorder				
Panic disorder lifetime	1	0	1	0
Limited symptom attacks lifetime	3	0	1	0
Panic disorder current	0	0	0	0
Anxiety disorder due to somatic condition	0	0	0	0
Substance induced anxiety disorder with panic attacks	0	1	0	0
Agoraphobia				
Agoraphobia current	3	5	9	3
Agoraphobia lifetime	5	5	9	4
Panic disorder without agoraphobia	0	0	0	0
Panic disorder with agoraphobia	0	0	0	0
Agoraphobia without history of panic disorder	3	4	7	3
Agoraphobia with history of panic disorder	0	0	1	0
Agoraphobia without history of limited symptoms	0	1	0	1
Social phobia				
Social phobia current	2	0	4	3
Simple phobia	0	1	1	3
Obsessive compulsive disorder				
OCD current	1	0	1	0
Due to somatic condition	1	0	0	0
Substance induced	0	0	1	0
Posttraumatic stress disorder				
PTSD current	0	0	0	0
Alcohol abuse and dependence				
Alcohol dependence current	0	0	1	0
Alcohol dependence past	0	1	0	0
Alcohol abuse current	0	0	0	0
Alcohol abuse past	3	3	0	0
Drug(s) dependence current	0	0	0	0
Drug(s) dependence past	0	0	0	0
Drug(s) abuse current	0	0	0	0
Psychotic disorders				
Psychotic syndrome current	0	0	1	0
Psychotic syndrome past	0	1	1	1
Due to somatic condition current	0	0	1	0
Due to somatic condition past	0	0	1	1
Substance induced current	4	2	1	1
Substance induced past	4	5	3	2
Anorexia nervosa				
Anorexia nervosa current	0	0	0	0
Bulimia nervosa				
Bulimia nervosa current	0	0	0	0
Generalized anxiety disorder				
Generalized anxiety disorder current	0	0	0	1
Due to somatic condition current	0	0	0	0
Substance induced current	0	0	0	0
Antisocial personality disorder				
Antisocial personality disorder current	0	0	0	0
Somatic disorder				
Somatic disorder current	0	0	0	0
Somatic disorder past	0	0	0	0
Adjustment disorder				
Adjustment disorder	1	0	0	0
Mixed anxiety/depression disorder				
Mixed anxiety/depression disorder	2	1	0	0

*At baseline the categories 'disorders past' reflect all lifetime disorders. At 12 months the categories 'disorders past' reflect disorders that were present in the past year, but not at the time of the assessment anymore. GPi n=57, STN n=57. GPi=globus pallidus pars interna. STN=subthalamic nucleus.

Supplement III. Membership of organizations and attendance of meetings.

	Baseline		12 month	
	GPi	STN	GPi	STN
Member of an organization	45	49	44	47
Attend meetings*	37 (82%)	37 (75%)	38 (86%)	34 (72%)
Organizations:**				
Organization for elderly	0	1	3	1
Work union	2	5	5	1
Political party/ organization	3	1	4	3
Religious organization/ church	13	9	12	13
Local/ neighborhood committee	6	1	3	0
Organization for women	2	0	0	0
Organization helping elderly	3	1	0	4
Action committee	4	4	5	2
Patient organization	30	33	32	34
Music/ drama organization	5	3	3	4
Hobby organization	9	7	8	12
Sports organization	19	12	17	10
Other	4	9	4	8

* Number of patients out of those who mentioned to be a member of an organization (percentage of patients out of those mentioned to be a member of an organization).

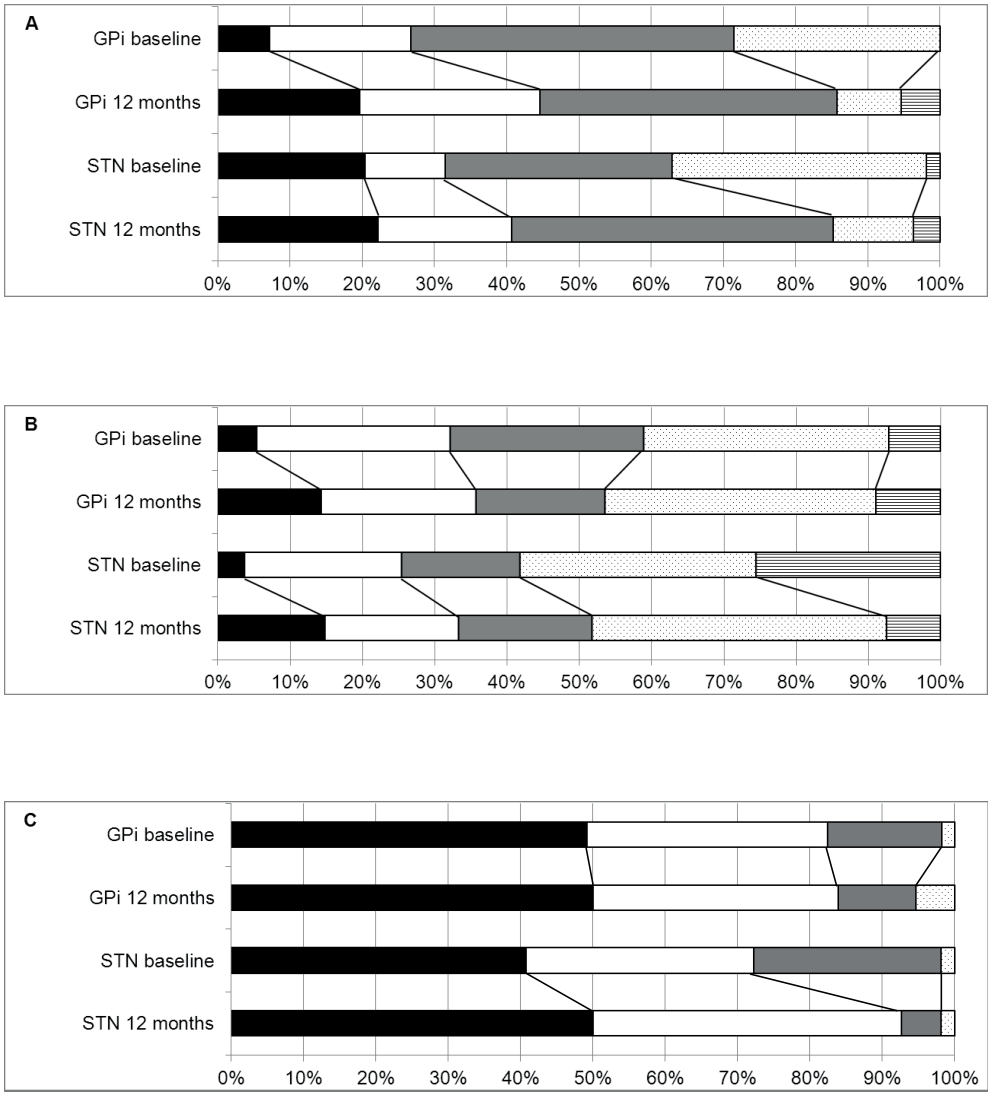
** A patient can be a member of more than one organization. GPI n=55, STN n=56. GPi=globus pallidus pars interna. STN=subthalamic nucleus.

Supplement IV. Work situation.

	Baseline		**12 months**		**Change**	
	GPi	**STN**	**GPi**	**STN**	**GPi**	**STN**
Wage labor	9	5	8	2	-1	-3
Self-employed	0	2	1	3	1	1
Unfit for work	23	22	23	25	0	3
Sickness benefits	1	2	0	0	-1	-2
Retired/ early retirement	19	17	21	19	2	2
Not working	4	7	3	5	-1	-2
Other	0	0	0	1*	0	1

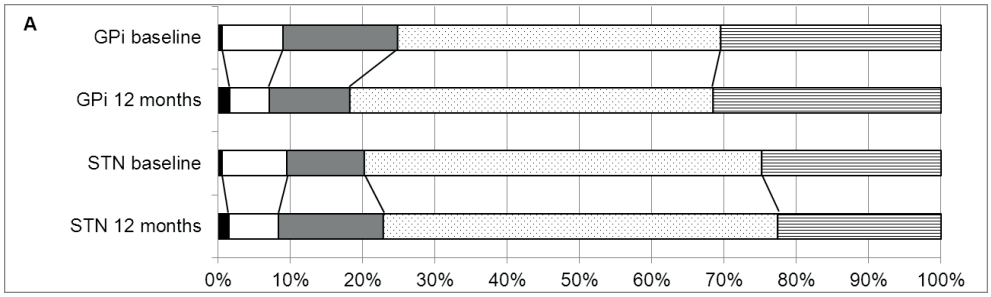
*Social enterprise for individuals with a disability. GPi n=56, STN n=55. GPi=globus pallidus pars interna. STN=subthalamic nucleus.

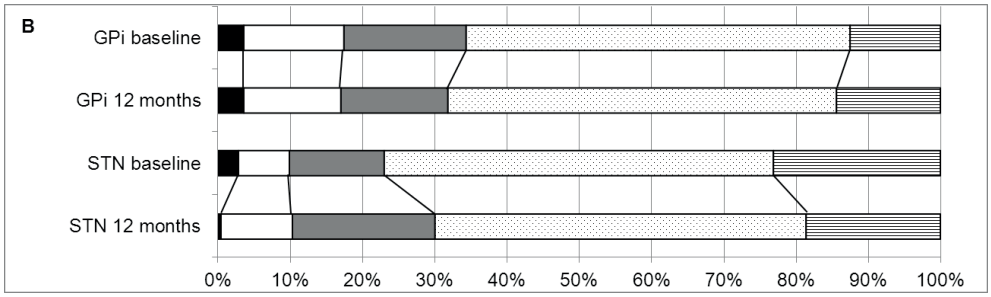
Supplement V. Sexual desire, sexual satisfaction, and monthly initiations at sexual intercourse.



A. Sexual desire was rated as very low (black), low (white), average (grey), high (dashed), and very high (solid line).
B. Sexual satisfaction was rated as very unsatisfied (black), unsatisfied (white), average (grey), satisfied (dashed), and very satisfied (solid line).
C. Monthly initiations at sexual intercourse: No (0) initiations are displayed as black, 1-4 initiations as white, 5-10 initiations as grey, and 11 or more initiations as dashed. Percentages are displayed of all completed questionnaires of patients before and 12 months after GPi DBS and STN DBS. GPi n=56, STN n=54. GPi= globus pallidus pars interna. STN= subthalamic nucleus.

Supplement VI. Marital satisfaction of patients and partners.





A. Marital satisfaction of patients was scored as very dissatisfied (black), dissatisfied (white), average (grey), satisfied (dashed), and very satisfied (solid line). GPi n=43, STN n=47. Percentages are displayed of all completed questionnaires of patients before and 12 months after GPi DBS and STN DBS.
B. Marital satisfaction of the partners was scored as very dissatisfied (black), dissatisfied (white), average (grey), satisfied (dashed), and very satisfied (solid line). GPi n=25, STN n=27. Percentages are displayed of all completed questionnaires of partners before and 12 months after GPi DBS and STN DBS of their significant other. GPi= globus pallidus pars interna. STN= subthalamic nucleus.

Supplement VII. Patients showing decline on multiple measures in multiple domains.

We investigated whether patients showed decline on multiple measures assessing work status, social relationships, psychosis, depression, and anxiety. Table 2 (below) indicates that most patients showed decline on one measures only. In the GPi group, four patients showed decline on 2 measures and one patient on 3 measures. In the STN group, one patient showed decline on 2 measures, one patient on 3 measures, and one patient on 4 measures.

Table 1. *Number of patients showing a negative outcome after 12 months.*

	GPi DBS (n=62)	STN DBS (n=63)
Loss of professional activity, work, or job	1 (2%)	0 (0%)
Loss of an important relationship	11 (18%)	5 (8%)
Psychosis*	4 (6%)	4 (6%)
Depression*	7 (11%)	11 (17%)
Anxiety*	9 (15%)	6 (10%)

*: Psychosis, depression, or anxiety for a period of 3 months or longer.
These scores have been reported in Odekerken et al., 2013 (The Lancet Neurology)

Table 2. *Number of measures on which patients showed decline.*

		GPi DBS (n=62)	STN DBS (n=63)
Decline on:	1 measure	21	17
	2 measures	4	4
	3 measures	1	1
	4 measures		1

PART II

Results three years after surgery

5 |

Clinical outcome three years after subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease

Authors

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Adapted from

GPi vs STN deep brain stimulation for Parkinson's disease: 3-year follow-up. Vincent J.J. Odekerken, Judith A. Boel, Ben A. Schmand, et al. Neurology. 2016 Feb 23;86(8):755-61.

ABSTRACT

Objective: To compare motor symptoms, cognition, mood, and behavior 3 years after deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) and subthalamic nucleus (STN) in advanced Parkinson disease (PD).

Methods: Patients with PD eligible for DBS were randomized to bilateral GPi DBS and bilateral STN DBS (1:1). The primary outcome measures were (1) improvement in motor symptoms in off-drug phase measured with the Unified Parkinson Disease Rating Scale (UPDRS) and (2) a composite score for cognitive, mood, and behavioral effects, and inability to complete follow-up at 36 months after surgery.

Results: Of the 128 patients enrolled, 90 were able to complete the 3-year follow-up. We found significantly more improvement of motor symptoms after STN DBS (median [interquartile range (IQR)] at 3 years, GPi 33 [23–41], STN 28 [20–36], $p = 0.04$). No between-group differences were observed on the composite score (GPi 83%, STN 86%). Secondary outcomes showed larger improvement in off-drug functioning in the AMC Linear Disability Scale score after STN DBS (mean ± SD, GPi 65.2 ± 20.1, STN 72.6 ± 18.0, $p = 0.05$). Medication was reduced more after STN DBS (median levodopa equivalent dose [IQR] at 3 years, GPi 1,060 [657–1,860], STN 605 [411–875], $p < 0.001$). No differences in adverse effects were recorded, apart from more reoperations to a different target after GPi DBS (GPi n = 8, STN n = 1).

Conclusions: Off-drug phase motor symptoms and functioning improve more after STN DBS than after GPi DBS. No between-group differences were observed on a composite score for cognition, mood, and behavior, and the inability to participate in follow-up.

Classification of evidence: This study provides Class II evidence that STN DBS provides more off-phase motor improvement than GPi DBS, but with a similar risk for cognitive, mood, and behavioral complications.

FUNDING

Funded by Stichting Parkinson Fonds, Prinses Beatrix Fonds, and Parkinson Vereniging. (www.controlled-trials.com, number, ISRCTN85542074)

INTRODUCTION

Patients with advanced Parkinson's disease (PD) are often hindered by unpredictable fluctuations between mobility with dyskinesias (the on-drug phase), and immobility (the off-drug phase).[1,2] Deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) and subthalamic nucleus (STN) are both treatment options for levodopa responsive symptoms in advanced PD. Two previous randomized trials reported a similar improvement after GPi DBS and STN DBS.[3,4] Due to concerns about the effects of STN DBS on cognition, mood, and behavior, GPi DBS became a more attractive option.[5] These concerns are primarily based on case-reports and trials that suggest STN DBS is associated with cognitive, mood and behavioral side effects.[2,3,6-8] One randomized trial showed similar effects of GPi and STN DBS on motor symptoms but a faster decline of Mattis Dementia Rating scale (MDRS) scores 3 years after STN DBS.[9]

In contrast to these studies, the 12-month results of our multicenter randomized trial (Netherlands SubThalamic And Pallidal Stimulation, NSTAPS) found a larger improvement of motor symptoms and functioning in off-drug phase after STN DBS compared to GPi DBS.[2] Moreover, we found no differences between GPi DBS and STN DBS for cognition, mood, and behavior.[2] The study objective is to compare the 3-year outcome of GPi DBS and STN DBS regarding motor function and cognitive, mood, and behavioral effects.

MATERIALS AND METHODS

PATIENTS

The study design of the Netherlands SubThalamic And Pallidal Stimulation (NSTAPS) trial has been reported previously.[2] In brief, five participating centers in the Netherlands enrolled a total of 128 patients between January 2007 and March 2011. Patients were included in the study if they were aged 18 years or older, had idiopathic PD, and, despite optimal pharmacological treatment, experienced at least one of the following symptoms: severe response fluctuations, bradykinesia, dyskinesias, or painful dystonias.[2] Exclusion criteria consisted of: Hoehn and Yahr stage 5 at the best moment of the day,[10] previous stereotactic surgery, a Mattis Dementia Rating Scale (MDRS) score of 120 or lower (out of 144),[11] active psychosis, or contraindications for the neurosurgical procedure.

STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND PATIENT CONSENTS

The medical ethics committee of each of the participating centers approved the study protocol and patients provided written informed consent for the additional follow-up after three years. The trial is registered with www.controlled-trials.com, number ISRCTN85542074. Classification of evidence: This study provides Class II evidence, comparing GPi DBS and STN DBS for off-drug phase motor symptoms and cognitive, mood, and behavioral complications.

PROCEDURES

Patients were randomly assigned to receive either GPi DBS or STN DBS (1:1 ratio), applying a minimization procedure according to drug use (levodopa equivalent dose <1000 mg vs. ≥1000 mg) and treatment center. This technique was used to minimize imbalance within distributions of treatment numbers within the various values of each individual possible prognostic factor.[12,13] Patients as well as assessors were blinded for treatment allocation. A non-blinded neurologist saw the patient regularly at the outpatient clinic to adjust DBS settings and PD medication, based on the clinical response of the patient and according to each centers individual protocol.[2] Surgery was performed according to each center's standard protocol. The final position of the electrode was determined on the basis of MRI, macro-electrode stimulation, and, in three of five centers, micro-electrode recordings.[2]

OUTCOME MEASURES

In line with the 12-month outcome assessments, the 3-year outcomes were registered during standardized off- and on-drug phases.[2] The off-drug phase was defined as the condition of the patient after withholding PD medication for 12 hours overnight.[2] The on-drug phase was the condition one hour after a supra-threshold levodopa dose.[2] The doses at follow-up were identical to the individual baseline doses. PD drugs were converted in levodopa equivalent doses for analysis.[14] The 12-month and 3-year outcomes were assessed with the stimulators turned on. The two primary outcomes were (1) the Unified Parkinson's Disease Rating Scale (UPDRS) Motor Examination (ME) in off-drug phase and (2) the number of patients with a negative composite score of cognitive, mood, and behavioral effects, and inability to participate in follow-up.[2,15]For the 3-year composite score of cognitive, mood, and behavioral effects the following items were assessed: *(a)* a significant worsening on two or more out of five cognitive tests based on the reliable change index (RCI),[16] *(b)* the loss of professional activity/work/job, *(c)* the loss of an important relationship (*e.g.*, marriage), *(d)* psychosis, depression, or anxiety for a period of three months or longer as defined by the M.I.N.I. psychiatric evaluation, [17] or (e) missing the 3-year follow-up assessments (*e.g.*, inability to participate, death).[2] If the patient fulfilled at least one of these items, the outcome on the composite score was considered negative.[2] To assess part (*a)* of the composite score, the following cognitive tests were administered: Stroop color-word test, Trail making tests A and B, Letter and Number Sequencing, letter fluency and category fluency, and the Dutch version of the Rey Auditory verbal learning test.[2,18-22] The subsequent secondary outcome measures were used. In off-drug phase the following scales were recorded at baseline and follow-up: UPDRS ME[15] sum score of items 27-30 (arising from chair, posture, gait, postural stability), Clinical Dyskinesia Rating Scale (CDRS),[23] ALDS, UPDRS activities of daily life section (ADL),[15] and the Schwab and England score (S&E).[2,24] The same scales were also recorded in on-drug phase. In addition, the Parkinson's Disease Sleep Scale (PDSS)[25] and the PD quality of life questionnaire (PDQL)[26] were recorded in on-drug phase.[2] We also registered medication, DBS settings, self-report off/on-drug phase diaries, and adverse events.

STATISTICAL ANALYSIS

Analyses were based on the intention-to-treat principle. An additional per-protocol analysis (excluding patients who were re-operated to a different target) was performed for the primary outcome measures due to crossover surgery during follow-up. We used a linear mixed model for repeated measures for statistical analysis of the first primary outcome (UPDRS ME in off-drug) as well as for the secondary outcome measures (off-drug phase CDRS, ALDS, UPDRS ADL, S&E, and on-drug phase UPDRS ME, CDRS, ALDS, UPDRS ADL, S&E, PDSS, and PDQL). First, normal distribution of the outcome variables was investigated. Statistical analyses were then performed on appropriately transformed data (square root or log transformations) in case of non-normal distribution of the data. The first mixed models included group (GPi DBS vs. STN DBS), time (baseline, 12 months, and 3 years), and interaction between these two, as well as the stratifying variables treatment center and drug dosage as fixed variables. Dependency of repeated measures was taken into account by including a random-intercept for each patient. Maximum likelihood was used as the estimation method. Because the stratifying variables treatment center and drug dosage were non-significant in the model, we also built mixed models with only group, time, and interaction between group and time. This resulted in a better model fit, assessed using Akaike Information Criteria (AIC). Therefore, the final mixed model included group, time, and interaction between these two as fixed variables, while leaving the random-intercept and estimation method unchanged. Assumptions of linear mixed model analyses were analyzed by investigating the residual versus predicted values, as well as the residuals of the outcome variables.

The second primary outcome (a negative composite score) was evaluated using Chi-square tests. Adverse events were compared using Chi-square with Yates' correction or Fisher's exact test when appropriate. DBS settings were only reported descriptively.

The significance level was set at 0.05 (two-sided test). Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software (release V.20.0.0.1). Graphs illustrating the fitted values resulting from the mixed models were produced using the R open statistical package (release V.3.0.3).

ADVERSE EVENTS

The neurologist at the treatment center (aware of treatment allocation) examined the patients and registered the adverse events up to 12 months.[2] The 3-year follow-up registration of adverse events was performed by a blinded assessor. Adverse events were assessed using structured questionnaires.

ROLE OF THE FUNDING SOURCE

The sponsors had no role in study design, data collection, analysis, and interpretation. The report was written independently of the sponsors and without the use of ghost-writers. The completeness and veracity of the analyses is guaranteed by authors VJJO and RMAdB.[2]

RESULTS

A total of 128 patients were randomized to GPi DBS (65 patients) or STN DBS (63 patients) between January 2007 and March 2011 (Figure 1).[2] The baseline demographic and clinical characteristics were balanced (table 1). Assessment of the primary outcomes was available in 90 patients (GPi 47, STN 43) after 3 years. The reasons for loss to follow-up were as follows: participation too strenuous (n=22), patient cannot be reached (n=3), deceased (n=8), and not available (n=5).

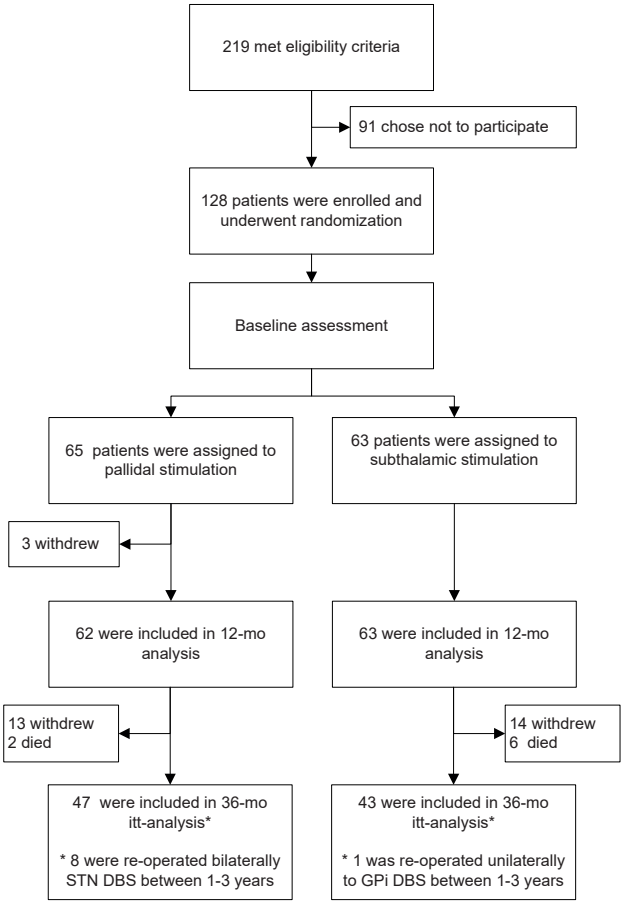


Figure 1. *Enrolment and follow-up*
- numbers of patients included in analysis based on completed motor examinations.
- itt = intention-to-treat

The following baseline parameters were compared between patients that were lost or not lost to follow-up: operation type (GPi vs. STN), treatment center, MDRS score, age at disease onset, disease duration, and UPDRS ME score in off-drug phase. The patients that were lost to follow-up were not different at baseline, except for mean disease duration (lost to follow-up 9.4 years vs. not lost to follow-up 12.0 years, *p*=0.02). Eight patients were re-operated from bilateral GPi DBS to bilateral STN DBS. In one patient with bilateral STN DBS the right electrode was changed to GPi DBS.

Table 1. *Baseline characteristics.*

	GPi DBS (n=65)	**STN DBS (n=63)**
Age (mean±SD) – yr	59.1±7.8	60.9±7.6
Age of onset PD (mean±SD) – yr	48.5±7.6	48.6±9.4
Male sex – no. (%)	44 (68)	44 (70)
Duration of PD (mean±SD) – yr	10.8±4.2	12.0±5.3
Duration of use of medication for PD (mean±SD) – yr	9.0±3.9	9.5±5.6
Hours per day spent in on-drug phase* (mean±SD) – h	6.5±3.6	6.3±4.4
On-drug phase Hoehn & Yahr stage (median [range])	2.5 [0-4]	2.5 [0-4]
Levodopa equivalent dose† ≥1000 mg/d – no. (%)	43 (69)	43 (68)
Mattis Dementia Rating Scale (mean±SD, range, 0-144)	138.7±4.0	138.1±5.1

* Calculated using a 3-day diary.

† Levodopa equivalent dose = regular levodopa dose x 1 + slow release levodopa x 0.75 + bro mocriptine x 10 + apomorphine x 10 + ropinirole x 20 + pergolide x 100 + pramipexole x 100 + (regular levodopa dose + [slow release levodopa x 0.75]) x 0.2 if taking entacapone.

PRIMARY OUTCOME MEASURES

Results are summarized in table 2. Intention-to-treat analysis showed more improvement of the off-drug phase UPDRS ME score after 3 years in the STN group (median [IQR], GPi 33 [23-41], STN 28 [20-36], *p*=0.04, *figure 2a*). At 3 years there was no between-group difference on the composite score for cognitive, mood, or behavioral effects, and missing the 3-year follow-up assessments (GPI n=39 [83%], STN n=37 [86%], *p*=0.69).

Per protocol analysis showed similar results, indicating more improvement of the UPDRS ME score off-drug phase after STN DBS at 3 years (median [IQR], GPi 33 [21.5-41], STN 28 [20-36], *p*=0.04). Per protocol analysis of the composite score showed no difference between the groups (GPi n=32 [80%], STN n= 37 [86%], *p*=0.46).

Table 2. *Primary outcome measures* intention to treat analyses	Baseline		12 Months		36 Months		***P* value* GPi DBS vs STN DBS**
Baseline n=128, 12 months n=125, 3 years n=90	GPi DBS	STN DBS	GPi DBS	STN DBS	GPi DBS	STN DBS	
UPDRS Motor Examination (range 0-108, median[I-QR]), off-drug phase	43[32.5-53]	41[33.8-55]	33[21.5-41]	21[15-32]	33[23-41]	28[20-36]	0.04
Composite score for cognitive, mood, behavioral adverse effects and inability to participate ≥1 (n, %)	-	-	36 (58%)	35 (56%)	39 (83%)	37(86%)	0.69
Parts of composite score							
- Decline on neuropsychological exam†	-	-	17 (22%)	22 (35%)	32 (68%)	36 (84%)	-
- Loss of professional activity, work, or job	-	-	1 (2%)	0 (0%)	2 (3%)	3 (5%)	-
- Loss of an important relationship	-	-	11 (17%)	5 (8%)	8 (12%)	7 (11%)	-
- Psychosis‡	-	-	4 (6%)	4 (7%)	5 (8%)	3 (5%)	-
- Depression‡	-	-	7 (11%)	11 (18%)	2 (3%)	4 (6%)	-
- Anxiety‡	-	-	9 (14%)	6 (10%)	4 (6%)	2 (3%)	-
- Inability to participate §	-	-	3 (5%)	0 (0%)	13 (20%)	14(22%)	-
- Death	-	-	0 (0%)	0 (0%)	2 (3%)	6 (10%)	-

* Using mixed model analysis or chi-square tests at 36 months when appropriate. P values reported in the table and text represent the interaction effect between group and time comparing baseline to 3 years. Mean or median outcome values in text and tables were based on the original data since back transformation result in non-matching values.

† Decline on neuropsychological exam is defined as a significant worsening on three out of 12 (12 months) or two out of five (36 months) cognitive tests based on the reliable change index (RCI).

§ Defined as not having completed the UPDRS Motor examination at 36 months. UPDRS: Unified Parkinson's Disease Rating Scale.

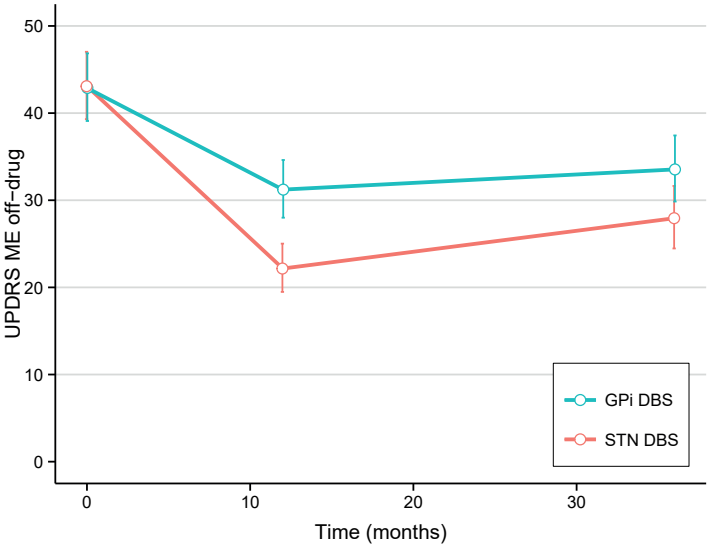
‡ Psychosis, depression, or anxiety for a period of 3 months or longer.

SECONDARY OUTCOME MEASURES

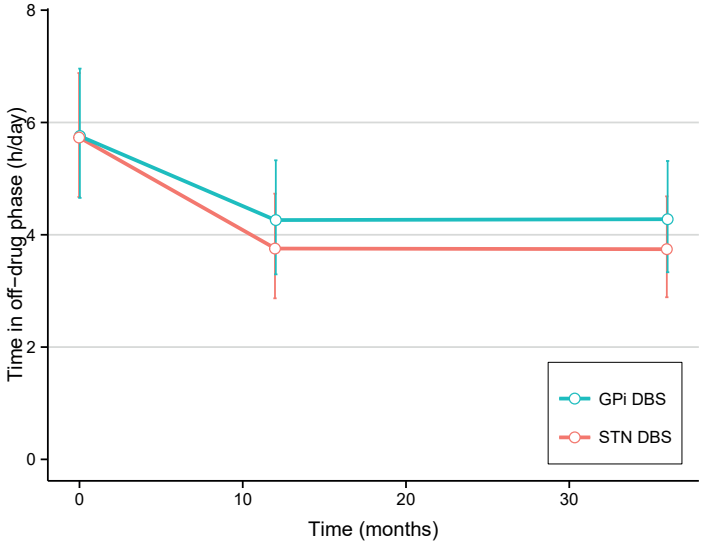
Results are summarized in table 3. No between-group differences at 3 years were detected on the UPDRS sum score of items 27-30, CDRS, UPDRS ADL, and S&E in off-drug phase. The off-drug phase improvement in functioning on the ALDS tended to be higher in the STN group at 3 years (GPi 65.2±20.1, STN 72.6±18.0, p=0.05). In on-drug phase no between-group differences were detected on the UPDRS ME, PDSS, ALDS, UPDRS ADL, S&E, and PDQL. The CDRS in on-drug improved more after GPi DBS at 3 years (GPi 2.2±2.7, STN 3.3±4.1, p=0.02).

MEDICATION, AND DBS SETTINGS, AND DIARIES

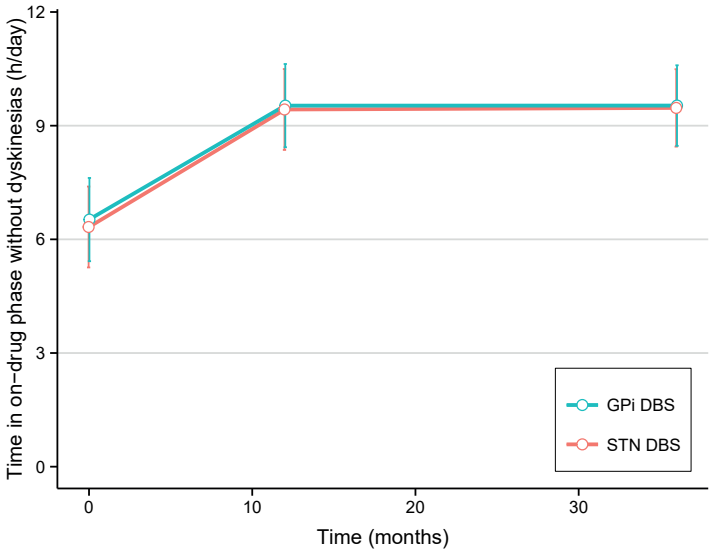
The median levodopa equivalent dose was 1060 mg [657-1860] in the GPi group and 605 mg [411-875] in the STN group (p<0.001). For DBS settings, the GPi group used mean amplitude of 3.0±0.6 V and the STN group 2.8±0.6 V at 36 months. The settings for frequency were similar for both groups (GPi 134±22 Hz, STN 138±18 Hz), whereas pulse width was slightly larger in the GPi group (GPi 70±17 µs, STN 63±11 µs). No between-group differences were seen in the diaries on time spent in different drug states (table 3, figure 2).


50
40
30
20
10
0
UPDRS ME off–drug
0
10
20
30
Time (months)
GPi DBS
STN DBS

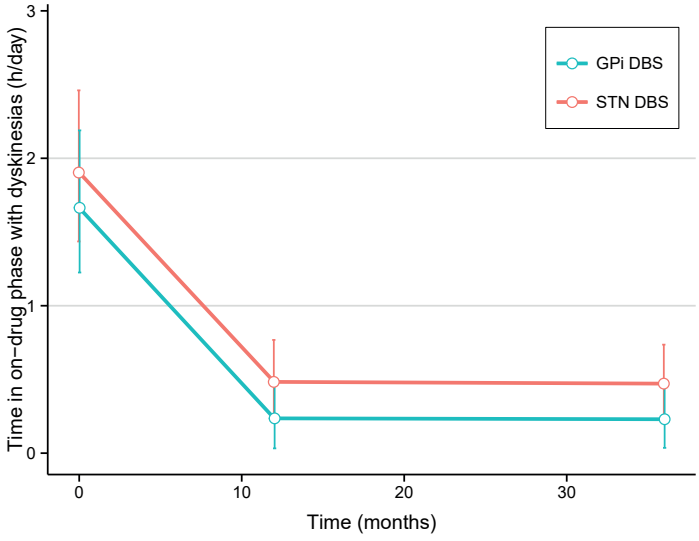
a


8
6
4
2
0
Time in off–drug phase (h/day)
0
10
20
30
Time (months)
GPi DBS
STN DBS

b



c



d

Figure 2. *Fitted values of UPDRS ME off-drug scores (a) and time spent in different clinical states over time (b-d).* Plotted are the fitted values resulting from the mixed model analysis: circles represent mean UPDRS ME off-drug scores and error bars represent 95% confidence intervals. UPDRS ME: Unified Parkinson's Disease Rating Scale Motor Examination part, GPi: globus pallidus pars interna, STN: subthalamic nucleus, DBS: Deep Brain Stimulation.

Table 3a. *Secondary outcome measures* intention to treat analyses	**Baseline**		**12 Months**		**36 Months**		***P* values**
Baseline n=128, 12 months n=125, 3 years n=90	GPi DBS	STN DBS	GPi DBS	STN DBS	GPi DBS	STN DBS	GPi vs STN
Off-drug phase							
UPDRS Motor Examination items 27-30 (arising from chair, posture, gait, postural stability, mean±SD)	6.1±2.8	7.3±3.7	5.4±2.6	4.6±3.3	5.3±2.4	5.3±2.9	0.10
Clinical Dyskinesia Rating Scale (range 0-28, mean±SD)	0.6±1.2	1.0±2.0	0.5±1.6	0.8±2.0	0.7±1.1	0.8±1.7	0.71
ALDS (functional health, range 0-100, mean±SD)	53.1±21.8	48.8±23.8	64.9±22.0	69.1±21.8	65.2±20.1	72.6±18.0	0.05
UPDRS Activities of Daily Living (range 0-52, mean±SD)	17.9±6.2	18.2±6.5	14.0±6.6	12.3±7.9	14.8±6.4	13.8±7.5	0.88
Schwab and England Scale (range 0-100, median [range])	50 [10-90]	40 [10-90]	60 [10-100]	70 [10-90]	60 [20-90]	60 [10-90]	0.12
On-drug phase							
UPDRS Motor Examination (range 0-108, median[IQR])	16 [10-20]	17[10.5-23]	13[8.5-24.5]	14[7-19.5]	19[13-28]	19[9-28.3]	0.19
UPDRS Motor Examination items 27-30 (arising from chair, posture, gait, postural stability, median[IQR])	2[2-3]	3[2-4]	3[1-4]	3[1-5]	3[2-5]	3[2-5]	0.93
Clinical Dyskinesia Rating Scale (range 0-28, mean±SD)	5.3±3.8	4.8±3.7	2.3±3.2	3.8±4.5	2.2±2.7	3.3±4.1	0.02
Parkinson's Disease Sleep Scale (range 0-150, mean±SD)	83.6±18.7	81.3±17.1	90.8±18.3	94.7±16.8	95.7±16.6	96.7±18.8	0.79
ALDS (functional health, range 0-100, median [IQR])	87.6 [83.5-89.5]	86.3 [78.1-89.5]	88.1 [82.9-89.5]	85.4 [78.1-89.5]	84.9 [76.4-89.5]	86.6 [72.7-89.5]	0.62
UPDRS Activities of Daily Living (range 0-52, median [IQR])	5 [2-10]	7 [4-11]	6 [3-12]	6 [3-10]	9·5 [5-13.5]	10.5 [5-14]	0.49
Schwab and England Scale (range 0-100, median [range])	80 [40-100]	80 [30-100]	80 [30-100]	80 [20-100]	80 [20-100]	80 [20-100]	0.39
PD quality of life questionnaire (range 0-185, mean±SD)	86.3±17.8	85.4±22.3	96.9±19.1	102.0±20.6	88.8±19.7	84.9±18.8	0.60

Table 3b. *Secondary outcome measures* intention to treat analyses	**Baseline**		**12 Months**		**36 Months**		***P* values**
Baseline n=128, 12 months n=125, 3 years n=90	GPi DBS	STN DBS	GPi DBS	STN DBS	GPi DBS	STN DBS	GPi vs STN
Medication and DBS settings							
Levodopa equivalent dose§ (median [IQR])	1250 [893-665]	1200 [900-1370]	935 [655-1550]	590 [430-930]	1060 [657-1860]	605 [411-875]	<0.001
Voltage (mean±SD) – V	-	-	2.9±0.5	2.6±0.6	3.0±0.6	2.8±0.6	-
Frequency (mean±SD) – Hz	-	-	137.5±20	135.0±21	134±22	138±18	-
Pulse width (mean±SD) – µs	-	-	73.0±24	63.·9±10	70.4±17	63±11	-
3-Day diaries							
Time in off-drug phase (median [IQR]) – h/day)	5.7 [4.1-7.1]	6.0 [3.5-7.8]	4.2 [1.9-6.5]	3.8 [0.5-6.2]	4.2 [1.9-6.4]	3.5 [0.7-6.8]	0.35
Time in on-drug phase without dyskinesias (mean±SD) – h/day	6.5±3.6	6.3±4.4	9.5±3.7	9.4±4.6	9.5±3.7	9.5±4.5	0.84
Time in on-drug phase with dyskinesias (mean±SD) – h/day median±IQR	2.5±2.5 2.3[0-4.0]	2.9±2.8 2·5[0-4.7]	0.5±1.2 0[0-0.2]	0.8±1.3 0[0-1.4]	0.4±1.1 0[0-0.2]	0.7±1.2 0[0-1.3]	0.51

*Using mixed model analysis comparing 3 years with baseline. P values reported in the table and text represent the interaction effect between group and time comparing baseline to 3 years. Mean or median outcome values in text and tables were based on the original data since back transformation result in non-matching values. UPDRS: Unified Parkinson's Disease Rating Scale, ALDS: AMC Linear Disability Scale. Although the distribution of the Clinical Dyskinesia Rating Scale is skewed, means instead of medians are reported since medians would appear as either 0 or 1.

ADVERSE EVENTS

Eight patients in the GPi group underwent STN DBS due to lack of benefit from GPi DBS. In five out of these eight patients both electrodes were on target. Seven of the eight patients experienced good results shortly after the first operation, but the clinical benefit gradually deteriorated. One patient from the STN group underwent unilateral GPi DBS due to unilateral lack of benefit from STN DBS (p=0.03 for between groups comparison). One case of lead migration was observed in the STN group, which required a second surgery for replacement of the electrode. No other serious events were observed in this period (table 3).

Table 4. *Adverse events*	**No. between 0-12 months**		**No. between 1-3 years**		***P* values***
	GPi DBS (N=65)	STN DBS (N=63)	GPi DBS (N=47)	STN DBS (N=43)	
Cerebral infarction or haemorrhage	0	0	0	0	-
Re-operation to other target due to lack of effect†	0	0	8	1	0.03
Epilepsy	2	2	0	0	-
Implantation-site infection	2	1	0	0	-
Facial palsy	2	4	0	0	-
Dysphasia or dysarthria	26	32	0	0	-
Dysphagia	13	7	1	2	0.60
Hiccups	10	2	0	0	-
Apraxia of eyelid opening	11	14	0	0	-
Oculomotor disturbance	6	4	1	0	0.48
Sensory disturbance	5	9	0	1	0.48
Balance disorder	23	30	1	1	1.00
Hypersalivation	14	14	1	2	0.60
Emotional lability	47	53	0	4	0.48
Paresis	1	1	0	0	-
Dyskinesias	17	24	1	1	1.00
Delirium	14	15	0	0	-
Other‡	97	87	8	10	0.63

* Comparing adverse effects between 12 and 3 years x^2 with Yates' correction or Fisher's exact test when appropriate.

† Eight patients were converted from bilateral GPi DBS to bilateral STN DBS. One patient was conver ted from bilateral STN DBS to unilateral (left sided) STN and unilateral (right sided) GPi DBS.

‡ Serious other complications were: 1 lead migration (STN).

DISCUSSION

These results of the NSTAPS trial show that the larger improvement of motor symptoms after STN DBS seen after 12 months persists up to 3 years. We found no difference on the composite measure for cognitive, mood, and behavioral adverse effects.

Since the publication of the long-term effects of the cooperative Veteran Affairs trial, GPi DBS became a more attractive option due to the similar effect on motor symptoms and the suggestion of worsening cognition after STN DBS.[5,9] Leading clinicians, however, still debate whether GPi DBS or STN DBS is superior in advanced PD.[27] Our findings demonstrate a long-term superior off-drug phase motor improvement after STN DBS without more side effects concerning cognition, mood, and behavior. The STN group off drug UPDRS ME score worsens by several points between one and three years, while the GPi group score is stable. This might be due to a waning effect, regression to the mean or the reduction of long-acting dopaminergic medication in the STN group. There are insufficient data to support one of these hypotheses.

In contrast to the initial 12-month analysis, we chose the UPDRS ME in off-drug phase as a primary outcome instead of the time-weighted AMC Linear Disability Scale (ALDS) due to the loss of follow-up and the incomplete diary data which has been discussed previously.[2]

The high rate of negative outcomes on the composite score warrants an explanation. The number of tests in the 3-year neuropsychological exam was reduced from twelve to five, which makes within-group comparison of the rate of fails over time difficult. Also, failure to participate in the study and death were added to the composite score, increasing the chance of negative outcome on this endpoint compared to 12 months. The strict composite endpoint was designed for between-group comparison.

The secondary endpoint of off-drug phase functioning, as measured with the ALDS, improved more after STN DBS. This is in line with the larger improvement in UPDRS ME score after STN DBS and confirms its relevance for daily functioning. The fact that this does not translate to better quality of life can be attributed to several factors. First, motor symptoms and functioning in on-drug phase did not differ between the two groups. Quality of life was measured in on-drug phase and reflects the patients' perception of quality of life, unrelated to off- or on-drug phases. Second, many other factors may influence quality of life that may not improve after DBS, such as mood and cognition.[28,29] Dyskinesias were reduced more in the GPi group at 36 months during on-drug standardized assessment. However, this 36-month evaluation is performed with the same amount of levodopa as the patient received at baseline. Since STN DBS patients use far less medication 3 years after surgery, this finding is an artefact of the study design and does not per se reflect dyskinesias in daily life. Indeed, the reduction of time with dyskinesias was similar in both groups.

Adverse events were observed less frequently between 12 months and 3 years than in the first year after surgery, suggesting long-term safety of the procedure after an initial period of peri- and

post-operative risks.[2,4,9,30-34] Especially the incidence of dysarthria and postural instability was lower than we had anticipated. There may be several explanations for this. Firstly, stimulation parameters were only marginally changed after 12 months of follow-up. Secondly, patients may have got used to these symptoms over the years and might not judge them to be surgery related. Eight out of the 65 patients in the GPi DBS group were re-operated to STN DBS. In five of these patients, the electrode position of the initial surgery was considered optimal. The need for re-operations from GPi to STN DBS due to waning effect has been reported. Houeto et al. published a case series of successful re-operation to STN DBS after long-term failure of GPi DBS.[35] In 2004, Volkmann et al. described four patients with good initial response to GPi DBS but waning effect that required conversion to STN DBS.[36]

This study has several limitations. Since we anticipated increased loss to follow-up compared to 12 months, one primary outcome was changed to the UPDRS ME motor score two years before the last patient had his last assessment. The patient diaries needed for the initial primary outcome at 12 months after surgery (AMC Linear Disability Scale [ALDS] weighted for time in off- and on-phase) were frequently not completed fully, which led to a missing score on the weighted ALDS. Furthermore, the UPDRS ME is also a more frequently used and an internationally recognized primary outcome measure after DBS.[3,4,30,32] The sample at 3 years was 70% of the baseline cohort, but the sample size was large enough to detect a difference between two groups on the primary motor endpoint. The dropout was lower than in the VA study, which had a similar design and follow-up period.[9]

The 3-year analyses of the NSTAPS trial show that improvement in motor symptoms persists in the long term after DBS of both targets. Off-drug phase motor symptoms and functioning improve more after STN DBS than after GPi DBS. No between-group differences were observed on a composite score for cognition, mood, and behavior, and the inability to participate in follow-up. Medication was reduced far more after STN DBS and more re-operations were performed after GPi DBS.

Acknowledgements

Funded by Stichting Parkinson Fonds, Prinses Beatrix Fonds, Parkinson Vereniging.
We thank K.L. Leenders, D.A. Bosch, and A.H. Zwindermann for participating in the data monitoring and safety committee. We thank Michiel Staal for his contribution to the study.

NSTAPS study group

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Neuropsychological, psychiatric, and social outcome three years after subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease

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Submitted

ABSTRACT

Background: Effects on non-motor symptoms, mainly cognitive and psychiatric side effects, could influence the decision for either globus pallidus pars interna (GPi) or subthalamic nucleus (STN) deep brain stimulation (DBS) for patients with advanced Parkinson's disease (PD).

Objective: 1) Comparing cognitive and psychiatric outcome 3 years after GPi DBS and STN DBS, and 2) descriptive reporting of suicidal ideation, psychiatric diagnoses, social functioning, and marital satisfaction 3 years after DBS.

Methods: Patients were randomized to receive GPi DBS (n=65) or STN DBS (n=63). Standardized assessment was performed at baseline, 1 year, and 3 years. We used linear mixed model analyses to investigate between-group differences on the Mattis Dementia Rating Scale (MDRS), neuropsychological tests, and psychiatric questionnaires 3 years after DBS.

Results: A total of 87 patients (68%) completed at least one neuropsychological test after 3 years. No significant between-group differences were found on the MDRS ($p = 0.61$), neuropsychological tests (p-values between 0.16 and 0.87), and psychiatric questionnaires (p-values between 0.29 and 0.88) 3 years after DBS. No suicidal ideations were reported. Substance induced psychiatric disorders seem to occur more often after GPi DBS. Social functioning and marital satisfaction seem comparable 3 years after GPi DBS and STN DBS.

Conclusions: Confirming the 1-year results from our trial, 3 years after GPi DBS and STN DBS there are no pronounced between-group differences on measures of cognitive and psychiatric functioning. The substance-induced psychiatric disorders in GPi DBS may be influenced by higher medication dosages in that group.

INTRODUCTION

Deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) or the subthalamic nucleus (STN) are effective treatments for patients with advanced Parkinson's disease (PD), though a consensus has not been reached regarding the optimal target.[1] Deciding on the optimal target involves a combination of factors, including improvement of motor symptoms and the effect on non-motor symptoms, such as the risks of cognitive and psychiatric side effects.

Motor function after GPi DBS and STN DBS has been investigated intensively and two randomized trials reported no significant difference between the two surgical targets up to 3 years after surgery.[2,3] We recently reported persistent better off-drug phase motor improvement 3 years after STN DBS.[4] Considering these contrasting results, non-motor effects of DBS may play a pivotal role in the decision towards a specific target.

Various degrees of cognitive decline and psychiatric side effects have been reported after DBS,[5-7] but elaborate systematic long term reports are limited. The VA study, a randomized controlled trial, indicated superiority of GPi DBS on two cognitive measures 3 years after surgery.[8] The current study is only the second randomized trial to report on neuropsychological and psychiatric outcome 3 years after DBS. We have reported no clinically relevant differences on neuropsychological, psychiatric, and social functioning 1 year after GPi DBS and STN DBS,[9,10] and we anticipate that these previous findings will persist 3 years after DBS.

In the current prospective cohort study we present detailed neuropsychological and psychiatric data of patients included in the Netherlands SubThalamic And Pallidal Stimulation (NSTAPS) trial, 3 years after DBS. We compared GPi DBS and STN DBS on cognitive and psychiatric outcomes 3 years after surgery and we descriptively report suicidal ideation, psychiatric diagnoses, social functioning.

MATERIALS AND METHODS

The study design has been reported previously.[11] This multicenter trial was registered with www.controlled-trials.com, number ISRCTN85542074. In brief, a total of 128 patients were enrolled between January 2007 and March 2011. Patients were included in the study if they were aged 18 years or older, had idiopathic PD, and, despite optimal pharmacological treatment, experienced at least one of the following symptoms: severe response fluctuations, dyskinesias, painful dystonias, or bradykinesia. Exclusion criteria consisted of: previous stereotactic surgery, Hoehn and Yahr stage 5 at the best moment of the day,[12] a Mattis dementia rating scale (MDRS) score of 120 or lower (out of 144),[13] active psychosis, or contraindications for the neurosurgical procedure. The medical ethics committee of each of the participating centers approved the study protocol. Patients provided written informed consent.

Patients were randomly assigned to receive either GPi DBS or STN DBS in a one-to-one ratio, applying a minimization procedure according to drug use (levodopa equivalent dose <1000

mg vs ≥1000 mg) and treatment center. Patients as well as clinical, neuropsychological, and psychiatric assessors were blinded for treatment allocation.

Neuropsychological tests and psychiatric questionnaires

Patients performed the neuropsychological tests and psychiatric test assessment during the on-drug phase at baseline, 1 year, and 3 years, with the stimulators turned on at 1 year and 3 years. The following neuropsychological tests were included in the baseline, 1 year, and 3 years assessment. The MDRS was included to assess global cognitive abilities.[13] Attention and working memory was assessed using the Stroop Color-Word test (Stroop word reading, Stroop color reading, and Stroop interference: naming ink colors of incongruent words),[14] the Trail-Making Test (TMT A: connecting numbers, TMT B: connecting numbers and letters while alternating),[15] and the subtest Letter-Number Sequencing of the Wechsler Adult Intelligence Scale III (WAIS-III LN).[16] Executive functions were assessed using the Controlled Oral Word Association Test (COWAT, naming of words starting with a specific letter in 60 seconds, 3 trials) referred to as phonemic fluency,[17] and category fluency (naming of words in a specific category in 60 seconds, 2 categories) referred to as semantic fluency.[17] The Dutch version of Rey's Auditory Verbal Learning Test was used to assess immediate and delayed memory (AVLT immediate recall is the sum score after 5 trials of a list of 15 unrelated words, referred to as AVLT total, and AVLT delayed recall is the score of one trial 20 minutes after the last trial, referred to as AVLT recall).[18] Raw scores were normed appropriately by age, gender and/or education. Reported in this article are raw scores for the MDRS, scaled scores for the WAIS-III LN subtest, and t-scores for all other neuropsychological tests. The following psychiatric questionnaires were assessed at baseline, 1 year, and after 3 years. The Young Mania Rating Scale (YMRS) was used to assess the severity of manic symptoms and higher scores indicate more manic symptoms.[19] The Hospital Anxiety and Depression Scale (HADS) was used to assess mood, higher scores indicate more distress.[20] Scores include subscale scores for anxiety and depression and a combined total HADS score. Suicidal ideation was assessed using a short interview from the Netherlands Study on Depression and Anxiety (NESDA).[21] Psychiatric diagnoses were assessed according to the Mini-International Neuropsychiatric Interview (MINI).[22] Social functioning was assessed using a network questionnaire in which membership of organizations was assessed (NESDA).[21] Additionally, marital satisfaction was assessed by rating nine relational aspects, such as the partner's motivation, personality, level of intimacy and decision making, on a scale from 1 (very dissatisfied) to 5 (very satisfied). Both patients and partners completed this questionnaire (appendix table A.2).

Statistical analyses

Demographic and clinical characteristics at baseline and data on neuropsychological and psychiatric measures at baseline, 1 year, and 3 years were summarized using descriptive statistics.

We performed linear mixed model analyses for repeated measures to assess between-group differences on cognitive and psychiatric measures 3 years after DBS. Linear mixed model analyses were chosen to fully use the available data. Included in the linear mixed models were the following fixed variables: treatment (GPi DBS vs STN DBS), time (baseline, 1 year, and 3 years), and an interaction between these two. We also built linear mixed models adding the stratifying variables levodopa equivalent dose and treatment center, but these were non-significant when included in the model and did not result in a better model fit using Akaike information Criterion. The former, simpler, model is the final model used in the analyses. Dependency of repeated measures was taken into account by including a random intercept for each patient. Maximum likelihood was used as the estimation method. Assumptions of linear mixed model analyses were analyzed by investigating plots of the residual vs predicted values, as well as the residuals of the outcome variables. Linear mixed model analyses are relatively robust to missing data. However, we did investigate baseline characteristics of patients lost to follow up by 3 years. Descriptive statistics are reported for the NESDA questionnaire on suicidal ideation, the MINI, the NESDA network questionnaire regarding social functioning, and the questionnaire on marital satisfaction. No statistical tests were performed on these data.

Analyses were based on the intention-to-treat principle. The significance level was set at 0.05 (two-sided test). We did not correct for multiple comparisons. We were interested in detecting adverse effects of the surgical interventions and, under this circumstance, a type II error (failing to detect an effect when it actually exists) is more serious than a type I error (considering an effect to be real when it actually is not).[23] Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software (release V.22.0.0.2). Figures presenting fitted mean values resulting from mixed models analyses were made using R open statistical package (V3.2.0).

RESULTS

At baseline, 128 patients were randomly assigned to either GPi DBS (65 patients) or STN DBS (63 patients). Baseline demographic and clinical characteristics are shown in table 1. A total of 87 patients (68%) completed at least one neuropsychological test after 3 years and a total of 78 patients (GPi n=39, STN n=39) completed all neuropsychological tests. Patients who were lost to follow-up at three years had a shorter mean disease duration (lost to follow-up 10.4 years and not lost to follow-up 12.3 years, $p = 0.04$), but were not different regarding surgical target (GPi DBS or STN DBS), MDRS score, age at disease onset, and the Unified Parkinson's Disease Rating Scale Motor Examination score in off-drug phase.

Some patients declined follow-up because participation was too strenuous (n=22). Other patients could not be reached (n=3), were deceased (n=8), were not available (n=5), or the reason was unknown (n=3). Nine patients were re-operated, 8 patients from bilateral GPi DBS to bilateral TN DBS and in one patient with bilateral STN DBS the right electrode was changed to GPi DBS.

Table 1. *Baseline characteristics.*

	GPi DBS (n=65)	**STN DBS (n=63)**
Age (mean±SD) – yr	59.1±7.8	60.9±7.6
Age of onset PD (mean±SD) – yr	48.5±7.6	48.6±9.4
Male sex – no. (%)	44 (68)	44 (70)
Duration of PD (mean±SD) – yr	10.8±4.2	12.0±5.3
Duration of use of medication for PD (mean±SD) – yr	9.0±3.9	9.5±5.6
Hours per day spent in on-drug phase* (mean±SD) – h	6.5±3.6	6.3±4.4
On-drug phase Hoehn & Yahr stage (median [range])	2.5 [0-4]	2.5 [0-4]
Levodopa equivalent dose† ≥1000 mg/d – no. (%)	43 (69)	43 (68)

* Calculated using a 3-day diary.

† Levodopa equivalent dose = regular levodopa dose x 1 + slow release levodopa x 0.75 + bromocriptine x 10 + apomorphine x 10 + ropinirole x 20 + pergolide x 100 + pramipexole x 100 + (regular levodopa dose + [slow release levodopa x 0.75]) x 0.2 if taking entacapone.

GPi DBS vs STN DBS 3 years after surgery

Cognitive outcome

No significant between-group difference was found on the MDRS 3 years after GPi DBS and STN DBS (p=0.61). At 3-year assessment four GPi DBS patients and five STN DBS patients scored below 120. Three years after DBS there was no between-group difference on any of the neuropsychological tests: Stroop test, TMT, WAIS-III LN test, AVLT, and word fluency tests (p-values range between 0.17 and 0.87). Figure 1 visually presents the fitted mean values resulting from the mixed model analyses. Normed scores based on the original data are presented in table 2.

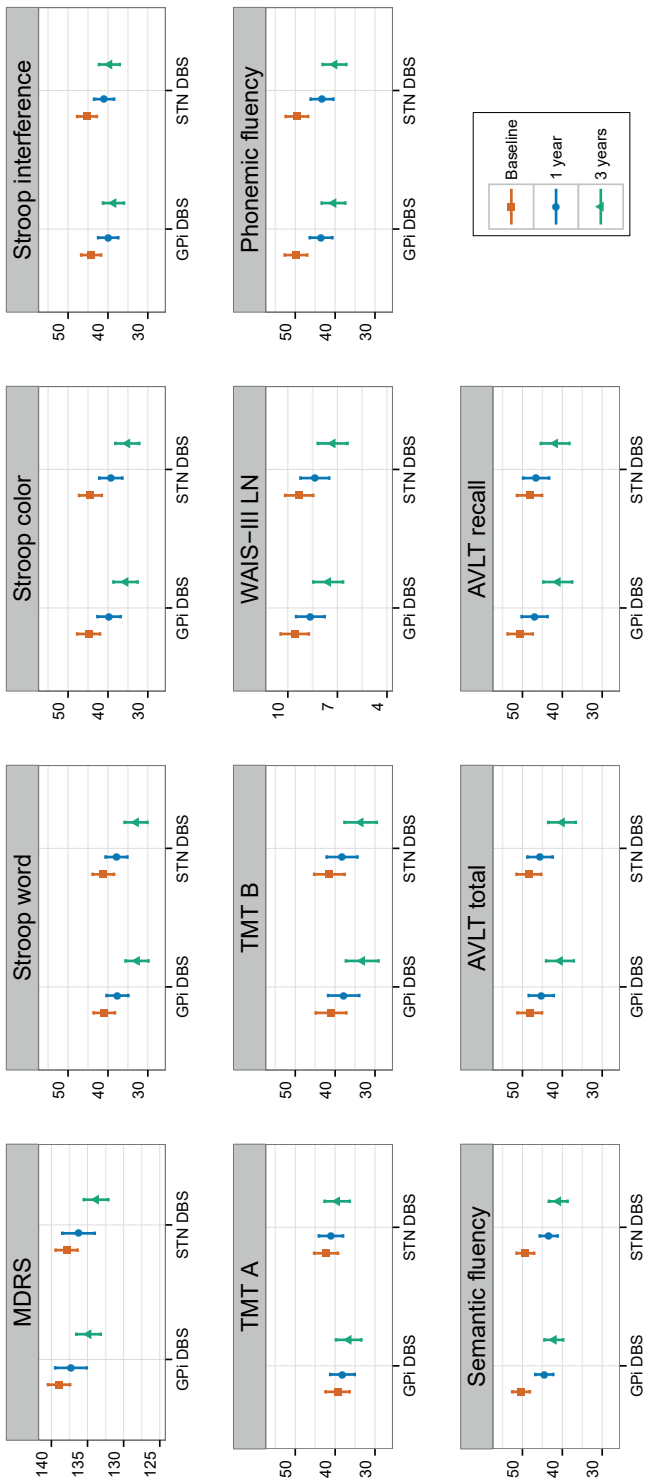

Figure 1. *Fitted mean values resulting from the mixed model analyses for all neuropsychological tests by type of DBS.*
Presented on the Y-axis are t-scores (mean of 50 ± 10), except for MDRS which are raw scores (range 0-144) and for WAIS-III LN which are scaled scores (mean of 10 ± 3). MDRS: Mattis Dementia Rating Scale, TMT: Trail-making test, WAIS-III LN: subtest Letter-Number Sequencing of the Wechsler Adult Intelligence Scale III, AVLT: Dutch version of Rey's Auditory Verbal Learning Test, GPi DBS: globus pallidus pars interna deep brain stimulation, STN DBS: subthalamic nucleus deep brain stimulation.

Table 2. *Normed neuropsychological test scores for GPi DBS and STN DBS.*

	Baseline		**1 year**		**3 years**		***P* value***
	GPi DBS	STN DBS	GPi DBS	STN DBS	GPi DBS	STN DBS	GPi vs STN
MDRS	138.7 (4.0)	138.1 (5.1)	137.3 (6.1)	136.5 (7.4)	135.2 (9.9)	133.8 (7.7)	0.61
Stroop word	39.9 (10.4)	42.3 (10.3)	39.7 (11.0)	36.5 (11.2)	33.7 (14.0)	34.3 (11.8)	0.51
Stroop color	43.6 (10.6)	45.8 (11.8)	41.5 (12.4)	38.0 (11.2)	37.6 (12.9)	36.0 (12.3)	0.17
Stroop interference	43.8 (9.7)	45.6 (10.8)	40.3 (9.3)	40.8 (11.0)	39.3 (10.0)	40.7 (11.1)	0.70
TMT A	39.0 (10.6)	42.6 (12.8)	38.4 (11.1)	41.5 (11.7)	39.1 (14.4)	39.5 (15.1)	0.18
TMT B	39.8 (13.4)	42.6 (16.2)	39.6 (14.6)	38.0 (16.1)	35.5 (18.7)	37.0 (15.6)	0.27
WAIS-III LN	9.8 (3.3)	9.1 (3.8)	8.5 (3.3)	8.7 (3.9)	7.8 (3.9)	7.6 (3.4)	0.87
Phonemic fluency	49.6 (10.1)	50.0 (12.0)	43.9 (11.2)	43.1 (11.7)	41.2 (12.8)	41.2 (13.9)	0.35
Semantic fluency	50.0 (8.1)	49.8 (9.0)	45.3 (8.7)	43.0 (10.0)	42.7 (10.7)	41.4 (10.5)	0.28
AVLT total	48.2 (10.9)	48.4 (12.5)	45.6 (11.7)	46.2 (12.9)	41.2 (12.5)	41.1 (13.2)	0.75
AVLT recall	50.6 (11.6)	48.2 (12.6)	47.0 (11.4)	46.8 (11.9)	41.4 (14.7)	42.0 (14.4)	0.23

Values are mean (SD) from normed data without imputation of missing values. *P values reported in the table resulted from the linear mixed model analyses and represent the interaction effect between treatment group and time at 3 years using baseline as reference. Baseline: GPi DBS n=62, STN DBS n=62, 1 year: GPi DBS n=58, STN DBS n=56 (MDRS, GPi =21, STN =17), 3 year: GPi <=39, STN<=39. MDRS: Mattis Dementia Rating Scale, TMT: Trail-making test, WAIS-III LN: subtest Letter-Number Sequencing of the Wechsler Adult Intelligence Scale III, AVLT: Dutch version of Rey's Auditory Verbal Learning Test, GPi DBS: globus pallidus pars interna deep brain stimulation, STN DBS: subthalamic nucleus deep brain stimulation.

Psychiatric outcome

Results indicated no between-group difference on the YMRS (p=0.88) and HADS (total score: p=0.23, anxiety subscale: p=0.39, depression subscale: p=0.33) after 3 years. Table 3 presents scores on the YMRS and HADS.

Table 3. *Scores on the YMRS and HADS for GPi DBS and STN DBS.*

	Baseline		1 year		3 year		*p* **between-group**
	GPi DBS	STN DBS	GPi DBS	STN DBS	GPi DBS	STN DBS	GPi vs. STN
YMRS total score	2 (1-4)	1 (0-4)	1 (1-3)	2 (1-3)	2 (1-4)	1 (0-3)	0.88
HADS total score	12.2 (4.4)	11.3 (6.3)	12.0 (6.5)	11.6 (6.3)	12.9 (7.1)	11.7 (6.1)	0.23
HADS anxiety	6.1 (2.7)	5.8 (3.4)	5.9 (2.9)	5.4 (3.3)	5.9 (3.4)	5.5 (3.3)	0.39
HADS depression	6.0 (2.8)	5.5 (3.4)	6.1 (4.5)	6.2 (3.8)	6.9 (4.5)	6.2 (3.4)	0.33

YMRS values are median (inter quartile range), HADS values are mean (SD). *p* between-group results from the linear mixed models analyses, representing interaction between treatment group and time (3 years), using baseline as reference. YMRS scores were transformed prior to linear mixed model analysis. YMRS= Young Mania Rating Scale (at baseline and at 1 year: GPi n=49, STN n=53, at 3 years: GPi n=42, STN n=45). HADS= Hospital Anxiety and Depression Scale (at baseline and at 1 year: GPi n=53, STN n=54, at 3 years: GPi n=38, STN n=41). GPi=globus pallidus pars interna. STN=subthalamic nucleus.

Descriptive statistics of suicidal ideations, psychiatric diagnoses, and social functioning 3 years after GPi DBS and STN DBS

Based on the NESDA interview, none of the patients reported suicidal ideations during the week prior to the 3-year assessment (GPi n=41, STN n=43). None of the patients who died (n= 8) committed suicide. One patient asked for euthanasia because of disability due to disease progression.

A total of 87 patients completed the MINI (GPI n=42, STN n=45) at the 3-year assessment. Regarding frequencies of diagnoses, two GPi DBS patients and four STN DBS patient experienced a depressive disorder, four GPi DBS patients experienced agoraphobia currently (*i.e.*, for a period of at least two weeks since the 1-year assessment). Five GPi DBS patients and two STN DBS patients experienced substance induced psychotic disorders currently, and two STN DBS patients experienced substance induced psychotic disorders in the 2 years prior to 3-year assessment. Complete frequencies of the MINI can be found in appendix table A.1.

Three years after surgery, the majority of patients in both DBS groups were a member of an organization (38 out of 42 GPi DBS patients and 40 out of 45 STN DBS patients). Most patients

were a member of a PD patient organization (GPi n=31, STN n=28), or of an organization related to sports (GPi n=17, STN n=9), hobbies (GPi n=9, STN n=10), or religion (GPi n=9, STN n=28). On average 26 GPi DBS patients out of 32 (81%) were satisfied or very satisfied regarding the various aspects assessed in the marital satisfaction questionnaire. An average of 21 out of 30 partners (70%) also rated the aspects as satisfied or higher. In the STN DBS group, 32 out of 37 patients (86%) rated the aspects as satisfied or very satisfied, and 24 out of 31 partners did so (77%). Frequencies are displayed in appendix table A.2.

DISCUSSION

The current study confirms results from our previous publication: there are no clinically relevant differences on cognitive and psychiatric measures between GPi DBS and STN DBS 3 years after surgery. In contrast to the 3-year results from the VA study, we did not find superiority of GPi DBS for MDRS and memory (immediate recall) 3 years after DBS.[8] A recent meta-analysis by Combs et al. suggests that GPi DBS may be a safer alternative to STN DBS in terms of cognition, but these findings are derived from a relatively small literature base (regarding findings for GPi DBS) and may therefore be less likely representative of the true effect.[24] Our negative findings are therefore an important addition to the existing literature.

Regarding overall cognitive decline 3 years after DBS, the VA study reported declines close to 0.5 SD on several measures in both groups. Decline seems to be larger in our study, because overall cognitive decline ranges between 0.3 and 1.0 SD compared to baseline. Scores on cognitive measures at baseline seem to be higher in our study, but match the scores 3 years after DBS as in the VA study. One exception is the lower score on list learning in STN DBS patients in the VA study, hence the reported superiority of GPi DBS on this cognitive test. This was not replicated in our study. Overall, a decline up to 1.0 SD falls within the expected range of cognitive decline after DBS.

When visually inspecting figure 1, there seems to be a steeper decline for both fluency tests in the first year after surgery compared to the decline between 1 year and 3 years. Larger declines on fluency tests in comparison to other neuropsychological tests is a common finding reported after DBS.[7,24] A randomized controlled trial comparing unilateral GPi DBS and STN DBS showed persistence of impairment in verbal letter fluency also during off stimulation.[25] The authors suggested a specific operation or lesion effect, which may also have led to more rapid decline in the first year in our study. Scores from the Stroop interference condition seem to follow a similar pattern but this finding was not replicated on the TMT B, a test assessing comparative cognitive functions.

Confirming our 1-year results,[10] psychiatric outcome measures did not indicate a significant difference between GPi DBS and STN DBS 3 years after surgery. Additionally, scores for mania (YMRS) and scores for anxiety and depression (HADS) remained stable over time. Similar results

on depression scores 3 years after GPi DBS and STN DBS have been reported before.[8]
Results on the MINI did not indicate a substantial number of psychiatric diagnoses after 3 years. However, substance-induced psychiatric disorders seem to occur more often after GPi DBS, which may be due to higher medication dosages compared to STN DBS. Descriptive statistics on social functioning showed that both GPi DBS and STN DBS patients are active members of various organizations 3 years after DBS. Assessment of marital satisfaction does not indicate substantial discrepancies between the ratings of patients and their partners, nor does it indicate large differences between GPi DBS and STN DBS 3 years after surgery.
Drop out can be of concern when interpreting the above results. However, with 32% the dropout after 3 years was relatively low. Additionally, a comparison between those still included after 3 years and those who dropped out did not reveal relevant differences. Though only reporting descriptive statistics on suicidal ideation, psychiatric diagnoses, social functioning, and marital satisfaction may limit interpretation, these findings match our previous report as well as our clinical experience.

CONCLUSION

No differences on neuropsychological and psychiatric outcome were found three years after GPi DBS and STN DBS. Descriptive analyses indicated a higher number of substance-induced psychiatric disorders in GPi DBS, likely influenced by higher medication dosages. Marital satisfaction and social functioning seem comparable 3 years after GPi DBS and STN DBS. Overall, neuropsychological and psychiatric outcome 3 years after DBS do not provide a clear direction for clinicians when considering a surgical target.

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APPENDIX NSTAPS 3-YEAR NEUROPSYCHOLOGICAL AND PSYCHIATRIC OUTCOME

Table A.1. *Mini International Neuropsychiatric Interview (MINI).*

	Baseline*		1 year*		3 years*	
Depressive episode	GPi	STN	GPi	STN	GPi	STN
Depressive disorder current	0	1	1	1	0	0
Depressive disorder past	10	2	4	8	2	1
Due to somatic condition current	0	0	2	1	0	0
Due to somatic condition past	2	0	2	0	0	0
Substance induced current	0	0	0	0	0	0
Substance induced past	0	1	1	3	0	3
Including melancholic features	0	0	1	1	0	0
Dysthymia						
Dysthymia disorder current	0	0	0	0	0	1
Dysthymia disorder past	0	0	0	0	0	0
Suicidality						
Suicide risk current	4	4	4	5	1	0
Risk: low	3	1	2	1	0	0
Risk: medium	1	3	2	4	0	0
Risk: high	0	0	0	0	1	0
(Hypo-) manic episode						
Hypomanic current	0	0	0	0	0	0
Hypomanic past	2	1	0	0	0	1
Manic current	0	0	0	0	0	0
Manic past	1	0	0	0	0	0
Due to somatic condition current	0	0	0	0	0	0
Due to somatic condition past	0	0	0	0	1	0
Substance induced current	0	0	0	0	0	1
Substance induced past	1	1	0	1	0	0
Panic disorder						
Panic disorder lifetime	1	0	1	0	0	0
Limited symptom attacks lifetime	3	0	1	0	0	0
Panic disorder current	0	0	0	0	0	0
Anxiety disorder due to somatic condition	0	0	0	0	0	1
Substance induced anxiety disorder with panic attacks	0	1	0	0	0	1
Agoraphobia						
Agoraphobia current	3	5	9	3	4	0
Agoraphobia lifetime	5	5	9	4	4	0
Panic disorder without agoraphobia	0	0	0	0	1	0
Panic disorder with agoraphobia	0	0	0	0	0	0
Agoraphobia without history of panic disorder	3	4	7	3	3	0
Agoraphobia with history of panic disorder	0	0	1	0	0	0
Agoraphobia without history of limited symptoms	0	1	0	1	0	0

	Baseline*		1 year*		3 years*	
Social phobia						
Social phobia current	2	0	4	3	1	1
Simple phobia	0	1	1	3	1	1
Obsessive compulsive disorder						
OCD current	1	0	1	0	0	1
Due to somatic condition	1	0	0	0	0	1
Substance induced	0	0	1	0	0	0
Posttraumatic stress disorder						
PTSD current	0	0	0	0	0	0
Alcohol abuse and dependence						
Alcohol dependence current	0	0	1	0	1	1
Alcohol dependence past	0	1	0	0	0	1
Alcohol abuse current	0	0	0	0	0	0
Alcohol abuse past	3	3	0	0	0	0
Drug(s) dependence current	0	0	0	0	0	0
Drug(s) dependence past	0	0	0	0	0	0
Drug(s) abuse current	0	0	0	0	0	0
Psychotic disorders						
Psychotic syndrome current	0	0	1	0	0	0
Psychotic syndrome past	0	1	1	1	0	0
Due to somatic condition current	0	0	1	0	0	1
Due to somatic condition past	0	0	1	1	0	1
Substance induced current	4	2	1	1	5	2
Substance induced past	4	5	3	2	1	2
Anorexia nervosa						
Anorexia nervosa current	0	0	0	0	0	0
Bulimia nervosa						
Bulimia nervosa current	0	0	0	0	0	0
Generalized anxiety disorder						
Generalized anxiety disorder current	0	0	0	1	0	0
Due to somatic condition current	0	0	0	0	0	0
Substance induced current	0	0	0	0	0	0
Antisocial personality disorder						
Antisocial personality disorder current	0	0	0	0	0	0
Somatic disorder						
Somatic disorder current	0	0	0	0	0	0
Somatic disorder past	0	0	0	0	0	0
Adjustment disorder						
Adjustment disorder	1	0	0	0	0	0
Mixed anxiety/depression disorder						
Mixed anxiety/depression disorder	2	1	0	0	0	0

*At baseline the categories 'disorders past' reflect all lifetime disorders. At 1 year the categories 'disorders past' reflect disorders that were present in the past year, but not at the time of the assessment anymore. At 3 years the categories 'disorders past' reflect disorders that were present in the past two years, but not at the time of the assessment anymore. At baseline and at 1 year: GPi n=57, STN n=57, at 3 years: GPi n=42, STN n=45. GPi=globus pallidus pars interna. STN=subthalamic nucleus.

Table A.2. *Marital satisfaction of patients and partners.*

3 years after DBS	Very dissatisfied		Dissatisfied		Not dissatisfied, not satisfied		Satisfied		Very satisfied	
GPi DBS	Pt	Part	Pt	Part	Pt	Part	Pt	Part	Pt	Part
Support/ encouragement	0	0	1	0	3	8	10	16	18	5
Motivation	0	0	3	3	4	6	10	13	15	7
Overall personality partner	0	1	1	1	2	7	11	10	18	10
Considers partner wishes	0	0	1	2	3	5	12	15	16	7
Sexual relationship	1	1	4	3	6	8	13	14	8	3
Intimacy	1	0	3	2	4	7	13	15	11	5
Solution for disagreements	1	0	4	3	3	5	18	16	6	5
Discussing important issues	0	0	1	5	2	3	22	16	7	5
Decision making	0	0	1	1	4	2	20	21	7	5
STN DBS										
Support/ encouragement	0	0	0	0	2	9	19	15	16	7
Motivation	0	0	0	0	2	4	22	20	13	7
Overall personality partner	0	0	0	2	0	3	25	19	12	7
Considers partner wishes	0	0	1	2	4	7	14	18	18	4
Sexual relationship	1	0	3	1	8	4	21	24	4	2
Intimacy	0	0	3	3	4	2	25	23	5	3
Solution for disagreements	0	0	2	5	5	5	24	17	6	4
Discussing important issues	0	0	1	3	6	6	27	19	3	3
Decision making	0	0	2	1	3	5	27	21	5	4

GPi patients n = 32, GPi partners n = 30. STN patients n = 37, STN partners n = 31. Pt: patient, Part: partner. GPi=globus pallidus pars interna. STN=subthalamic nucleus.

Note:

The following marital aspects were rated on a scale from 1 (very dissatisfied) to 5 (very satisfied):

1. Daily support and encouragement my partner gives me
2. The way my partner motivates me
3. My partners overall personality
4. The way my partner considers my wishes
5. My sexual relationship with my partner
6. The level of intimacy in my relationship with my partner
7. The way disagreements are solved
8. The extent to which issues, that I think are important, are discussed
9. The way decisions are made in this relationship

PART III

Influence of re-operation and active contact localization

7 |

Changing the target after unsatisfactory outcome of deep brain stimulation for advanced Parkinson's disease: cases from the NSTAPS trial and review of literature

Authors

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Submitted

ABSTRACT

Objectives

To evaluate the clinical effect of re-operation to another target after failure of initial deep brain stimulation (DBS) for Parkinson's disease (PD).

Methods

We descriptively analyzed the baseline characteristics, the effect of initial surgery and re-operation of NSTAPS (Netherlands SubThalamic and Pallidal Stimulation) patients and previously published cases that underwent re-operation to a different target.

Results

A total of 14 patients were identified in the NSTAPS (n=8) study and literature review (n=6). Five out of 11 patients that were re-operated from GPi DBS to STN DBS showed more than 30% improvement of off-drug motor symptoms. Of the three patients re-operated from STN DBS to GPi DBS, none showed more than 30% off-drug motor improvement.

Conclusions

Re-operation to the STN is worth considering if GPi DBS fails. There is insufficient data to evaluate re-operation from STN DBS to GPi DBS.

INTRODUCTION

Deep Brain Stimulation (DBS) has been a treatment option for advanced Parkinson's disease (PD) since the 1990's.[1] The two most frequently used targets for PD are the globus pallidus pars interna (GPi) and the subthalamic nucleus (STN).[2,3] Data from various randomized controlled trials supports that both targets are effective treatment options in severe PD.[4-6] However, there are cases of insufficient response to DBS despite optimal patient selection, electrode placement, and programming.[7,8] In these cases, re-operation to another target is a treatment option, but publications on the effectiveness of re-operation are scarce. There have been case reports of waning GPi-DBS efficacy, where re-operation to the STN provided a satisfactory clinical outcome.[9,10] One case report describes symptom improvement from additional pallidal stimulation after insufficient response to bilateral STN DBS.[11]

In this article we report nine patients of the Netherlands SubThalamic and Pallidal Stimulation (NSTAPS) trial and previously published cases that underwent re-operation to a different target due to unsatisfactory results of the initial surgery.[6] The goal of this report is to describe the clinical characteristics of these patients and to evaluate the effects of re-operation.

METHODS

The NSTAPS study protocol and results have been published previously.[6] In brief, PD patients eligible for DBS were recruited from five centers in the Netherlands. Exclusion criteria were: previous stereotactic neurosurgery, Hoehn and Yahr stage[12] 5 at the best moment during the day, Mattis dementia rating scale score[13] of 120 or below, active psychosis, or contraindications for the neurosurgical procedure. Patients were randomly assigned to receive either GPi or STN DBS surgery. For this article, patients from the NSTAPS study who underwent re-operation to another target were assessed. Information from the NSTAPS database, clinical records, and medical correspondence was obtained from all patients who underwent re-operation. We evaluated motor symptoms using the Unified Parkinson's Disease Rating Scale motor examination (UPDRS-III).[14] The evaluation included motor symptoms at baseline (off-drug and on-drug), after initial DBS surgery (on-stimulation, off-drug), before re-operation (on-stimulation, off-drug), and after re-operation (on-stimulation, off-drug). Blinded assessments were available at 12 and 36 months after the initial surgery. We dichotomized motor outcome: an off-drug UPDRS-III score improvement of 30% or more one year after DBS compared to baseline is considered a treatment success and less than 30% is considered unsuccessful. Perceived improvement after re-operation, if noted in the patient's charts, was evaluated as a subjective outcome. Any bothersome non-motor complications were also retrieved from the charts. When available, MR-CT fusion images were used to ascertain whether leads were correctly placed after the first surgery.

Additionally, we performed a systematic review to identify case reports or case series where PD

patients have been re-operated from STN to GPi or vice-versa. We searched articles in English on PubMed using the following terms (MeSH): deep brain stimulation, OR DBS, AND nucleus subthalamicus, OR subthalamic nucleus, OR STN, OR globus pallidus internus, OR globus pallidus interna, OR globus pallidus pars interna, OR GPi, AND Parkinson's disease, OR Parkinson, OR PD. We report the following parameters to evaluate the success of the initial surgery and re-operation: (1) baseline levodopa response, (2) motor improvement (UPDRS-III % and dichotomous) after initial DBS surgery, (3) motor improvement after re-operation (UPDRS-III %) and perceived success by patient after re-operation (dichotomous), and (4) non-motor/ balance symptoms contributing to impairment. All analyses are descriptive due to the small sample size.

RESULTS

Cases from the NSTAPS trial

A total of 128 patients with severe PD were included in the NSTAPS trial between 2007 and 2011. These patients were randomized to either STN DBS (63 patients) or GPi DBS (65 patients). Of the included 128 patients, nine were re-operated to the other target: eight patients went from bilateral GPi to bilateral STN DBS. A detailed case description is available in Supplement 2. In one patient, the choice was made to relocate only the right electrode to the GPi after 26 months, leaving the left electrode in the STN. Baseline characteristics of the other 8 NSTAPS cases and the 6 literature cases are displayed in Supplement 1.

The mean on-drug UPDRS-III before the first surgery (baseline) was 45 (range 24-88), and the mean percentage of improvement with levodopa was 71% (range 49-82%).

The off-drug UPDRS-III scores at different points in time are displayed in Table 1. The available data from the NSTAPS cases on change in UPDRS-III scores in off-medication phase is also summarized in figure 1.

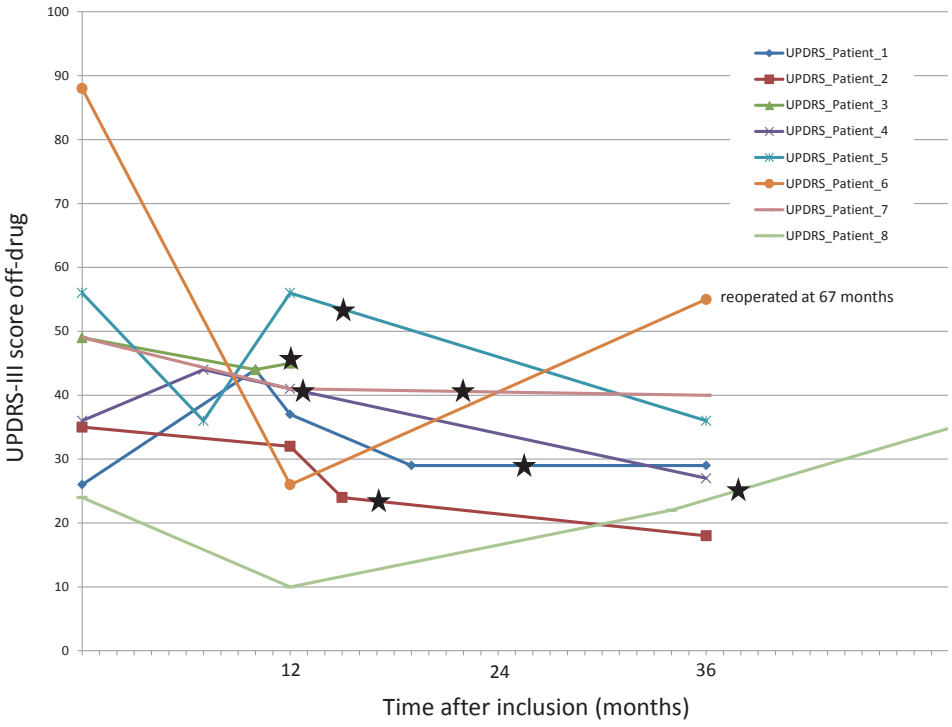

Figure 1. *Unified Parkinson Disease Rating Scale (UPDRS) part III scores in off-drug phase of the eight patients from the Netherlands SubThalamic And Pallidal Stimulation (NSTAPS) trial over time.* The stars indicate the time at which re-operation was performed.

In three patients at least one electrode was found to be off-target (varying between 1.5 and 4 mm, supplement 2). Two of the eight initial GPi DBS treatments were considered successful after one year (30% or more off-drug UPDRS-III improvement), but showed loss of effectiveness of GPi stimulation after several years. Seven of the eight patients subjectively experienced good results shortly after the first operation, with their clinical benefit gradually deteriorating.

Re-operation occurred between 12 and 67 months after start of DBS therapy. The mean pre-re-operation off-drug UPDRS-III score was 39 (range 22-56) and the mean score after re-operation was 31 (range 18-40), with two postoperative scores missing. In quantitative terms, two of the eight re-operations were considered a success, that is, a UPDRS-III improvement greater than 30%. Subjectively, five of the eight patients considered their re-operation a success.

Before the initial surgery, two patients had minor balance problems and three had slight autonomic dysfunction. One of the patients had a history of psychosis prior to initial surgery and one year after re-operation, he was admitted because of recurrent psychosis. After full recovery and discharge from the psychiatry ward, the patient was unable to bear the disease burden and opted for physician-assisted death.

Table 1. *Results*

Patient number	Baseline UPDRS-III off-drug score	Improvement on levodopa (%)	Change in target	1 year UPDRS-III off-drug on-stim score	Success at 1 year?*	Number of months between operation and re-operation	pre-re-operation UPDRS-III off-drug on stim score	post-re-operation UPDRS-III off-drug on-stim score	Success re-operation?*	Additional UPDRS-III improvement after re-operation off-drug, on stim (objective)	Patient perceptive improvement (subjective)
NSTAPS											
1	26	77%	GPi→ STN	37	(-)	26	29	29	(-)	0%	(+)
2	35	49%	GPi→ STN	32	(-)	17	24	18	(-)	25%	(+)
3	49	61%	GPi→ STN	45	(-)	12	44	N/A	N/A	N/A	(-)
4	36	81%	GPi→ STN	41	(-)	12	41	27	(+)	34%	(+)
5	56	70%	GPi→ STN	56	(-)	21	56	36	(+)	36%	(+)
6	88	82%	GPi→ STN	26	(+)	67	55	N/A	N/A	N/A	(-)
7	49	71%	GPi→ STN	41	(-)	23	41	40	(-)	2%	(+)
8	24	75%	GPi→ STN	10	(+)	38	22	38	(-)	-73%	(-)
Minafra											
1	(i)	n/a	STN→ GPi	n/a	N/A	8 years	36	37(iii)	(-)	-3%(iii)	(+)
2	(i)	n/a	STN→ GPi	n/a	N/A	8 years	36	40(iii)	(-)	-11%(iii)	(+/-) (iv)
3	(i)	n/a	STN→ GPi	n/a	N/A	8 years	25	32(iii)	(-)	-22%(iii)	(+)
Houeto											
1	53	57%	GPi→ STN	(ii)	(ii)	27	43	27	(+)	37%	(+)
2	52	81%	GPi→ STN	missing	missing	39	39	16	(+)	59%	(+)
Allert											
1	65	74%	GPi→ STN	23	(+)	10	76	27	(+)	64%	(+)

* Success defined as >30% improvement of pre-operative UPDRS OFF-medication score

Table 1. *Overview of follow-up from patients re-operated from bilateral GPi DBS to bilateral STN DBS.*
Abbreviations: DBS = Deep Brain Stimulation, UPDRS = Unified Parkinson's Disease Rating Scale, Mattis = Mattis Dementia Rating Scale, n/a = not available

1. Only UDPRS scores before re-operation are described, no baseline scores are available.
2. Twelve months after surgery, GPi stimulation (without medication) improved motor disability by 45%, motor fluctuations by 25%, and levodopainduced dyskinesias by 40% (data not shown).
3. Two years after re-operation.
4. Patient 2 improved only marginally still presenting persistent right foot dystonia, freezing, severe bradykinesia and postural instability. Dopaminergic therapy was increased, leading to a mild improvement of gait and bradykinesia, without worsening of dyskinesias.

Cases from the systematic review

The initial search strategy identified 324 articles on February 2nd 2015. Relevant articles were selected by title and abstract screening, resulting in three articles in which re-operations from STN to GPi or vice-versa are reported and individual case descriptions are available.[9, 15, 16] These three articles describe a total of six cases, of which three patients initially received bilateral GPi DBS and three received STN DBS (supplement 1 and table 1).

The mean off-drug UPDRS-III score at baseline was not available in most patients and the mean percentage of improvement on levodopa was available in three patients only (57%, 81%, 74%). None of the patients that were re-operated from STN to GPi had improvement of their off-drug UPDRS-III scores (-3%, -11%, -22%), but two of them reported subjective improvement.

All patients that were re-operated from GPi to STN had a post-operative improvement of the off-drug UPDRS-III (37%, 59%, 64%) and also subjectively experienced improvement. None of the patients had balance problems or autonomic dysfunction at inclusion.

DISCUSSION

The GPi and STN are both still widely used targets for DBS in PD. Very few published case descriptions of re-operations to a different target are available, making this the largest series of patients that have been re-operated to a different target after unsatisfactory results of bilateral GPi or STN DBS. It is remarkable that in the NSTAPS cohort, eight patients were re-operated from bilateral GPi to bilateral STN DBS. In five of these eight patients the choice to re-operate to bilateral STN DBS was made before the results of the NSTAPS trial (more improvement in OFF-drug phase after STN DBS) were available. In the other three patients the knowledge of the trial's primary results might have made clinicians more prone to re-operate from GPi to STN. One might question the adequate selection of patients since this plays an important role in obtaining satisfactory outcome.[8] All 14 cases appear to be adequately selected for DBS when considering the following parameters: all patients showed good baseline levodopa response (between 49-82%, missing in three literature cases) and mainly complained about motor response fluctuations without bothersome cognitive impairments, balance disorder or autonomic symptoms. After surgery, DBS programming and medication optimization were extensively tried by experienced clinicians. In three of the eight NSTAPS cases, post-operative imaging showed that at least one of the electrodes was off target (supplement 2). It is not known if repositioning of these electrodes would have led to satisfactory results because of the decision to immediately convert to STN DBS. In conclusion, half the patients re-operated to STN DBS showed objective clinical improvement of more than 30% on the off-drug UPDRS-III score. However, three out of five of these improved cases were from the systematic review, so this finding is prone to a publication bias. None of the three patients re-operated to GPi DBS showed objective improvement. If insufficient clinical improvement is obtained after GPi DBS and patients selection and electrode placement were correct, re-operation to the STN is worth considering. Currently, there are insufficient data that indicate if re-operating from STN to GPi has a comparable effect.

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Supplement 1. Baseline characteristics

Patient number	Gender	Age at inclusion/DBS operation	Disease duration (years)	UPDRS-III off-drug	UPDRS-III on-drug	Baseline on-drug improvement compared to off-drug (%)	Mattis score	Balance problems	Autonomic problems
NSTAPS									
1	male	46	11	26	6	77%	143	(-)	(+) intermittent erectile dysfunction
2	male	62	9	35	9	74%	139	(+)	(+) increased miction frequency and constipation
3	male	50	14	49	20	59%	139	(-)	(-)
4	female	56	8	36	5	86%	142	(-)	(-)
5	male	36	7	56	14	75%	142	(-)	(-)
6	male	59	15	88	16	82%	141	(-)	(-)
7	male	56	10	49	14	71%	137	(+)	(-)
8	female	42	3	24	6	75%	139	(-)	(+) light autonomic dysfunction
Minafra									
1	Male	54	10	(i)	(i)	n/a	missing	(-)	(-)
2	Female	59	15	(i)	(i)	n/a	missing	(-)	(-)
3	Female	50	7	(i)	(i)	n/a	missing	(-)	(-)
Houeto									
1	Female	64	18	53	23	57%	missing	(-)	(-)
2	Male	46	12	52	10	81%	missing	(-)	(-)
Allert									
1	Female	38	8	65	17	74%	missing	(-)	(-)

Supplement 1. *Overview of baseline characteristics from patients re-operated from bilateral GPi DBS to bilateral STN DBS.* Abbreviations: DBS = Deep Brain Stimulation, UPDRS = Unified Parkinson's Disease Rating Scale, Mattis = Mattis Dementia Rating Scale. (i) Only UDPRS scores before re-operation are described, no baseline scores are available.

Supplement 2. Individual patient description

Center A

Patient 1: 46-year-old male diagnosed with PD 11 since years, had been treated with levodopa for 10 years. This patient presented with a history of unpredictable ON/OFF phases, gait and freezing problems and dyskinesia. He received bilateral GPi DBS treatment, which initially yielded good results. After a few months the patient presented with balance problems, gait initiation failure, freezing and hypersexuality. Medication and stimulation parameters were adjusted, with no clinical improvement. Fusion images showed both electrodes were on target. 26 months after bilateral GPi DBS implantation the patient was re-operated to bilateral STN. OFF-medication motor symptoms remained the same 10 months after the conversion to STN DBS. Cognitive problems gradually arose, it remains unclear if this is due to DBS or PD disease progression.

Patient 2: 62-year-old male diagnosed with PD since nine years, had been treated with levodopa for eight years. This patient presented with a history of medication induced response fluctuations and difficulty walking during the OFF phase, stiffness and balance problems. During the ON phase the patient complained about nausea and dyskinesia in arms, trunk and neck. He received bilateral GPi treatment. The first year the treatment had good results, although the patient had complaints of hypertonia and cramps on the left side of the body. After a year there was a decline in effect, with stiffness being the major complaint. Medication and stimulation parameters were adjusted, with no clinical improvement. Fusion imaging confirmed both electrodes were on target. 17 months after bilateral GPi DBS implantation the patient was re-operated to bilateral STN. Off-medication motor symptoms were improved by 25% 19 months after the conversion to STN DBS. However, bothersome stiffness, bradykinesia and balance problems persisted.

Patient 3: 50-year old male diagnosed with PD since 14 years, had been treated with levodopa since 14 years. This patient presented with a history of severe dyskinesias and rigidity, predominantly on the right side. There were no tremor or coordination problems. The patient had been treated with intrajejunal levodopa infusion for three years before inclusion, with little effect on response fluctuations and medication-induced dyskinesias. He received bilateral GPi DBS. The first months there was a good response to DBS, after which intrajejunal levodopa infusion was stopped. After six months the patient increasingly developed bradykinesia and stiffness. There were complaints of trembling in the right hand and stiffness of the right leg. Medication and stimulation parameters were adjusted, with no clinical improvement. Fusion images showed both electrodes were off target: left electrode 4mm above target, right electrode 2mm above target. An operation with reposition of the leads was suggested, but the patient wanted to be re-operated to the other target. 12 months after bilateral GPi DBS implantation the patient was re-operated to bilateral STN. There is no UPDRS-III data after starting bilateral STN DBS. Postoperatively there were complaints of balance problems and severe tremors of the right limbs. A long trial-and-error period of medication and stimulation parameter adjustments

followed, leading to reasonable clinical improvement. A year after reoperation the patient had to be admitted to a psychiatric ward due to psychosis. When these psychiatric symptoms subsided the patient experienced such a heavy disease burden that he opted for euthanasia.

Patient 4: 56-year-old female diagnosed with PD since eight years, had been treated with levodopa since seven years. This patient presented with a history of stiffness and tremor in the extremities, predominantly on the right side, and ON-OFF fluctuations. She received bilateral GPi treatment. There was little response after surgery. Medication and stimulation settings alteration only resulted in temporary improvement. After a few months the patient complained of increasing bradykinesia, tremors and OFF-periods, and her mood deteriorated. There were also complaints of dyskinesias in the jaw and paresthesia in the left leg. Further medication and stimulation adjustments were tried to no avail. Fusion imaging showed the right electrode 1.5mm above target and 3mm lateral to target, and the left electrode 2mm above target. 12 months after bilateral GPi DBS implantation the patient was re-operated to bilateral STN. Off-medication motor symptoms were improved by 34% 24 months after the conversion to STN DBS. Dyskinesias disappeared almost completely. Two years after the reoperation there were few complaints of motor problems. Some gait and balance problems persisted.

Patient 5: 36-year-old male diagnosed with PD since seven years, had been treated with levodopa since four years. He presented with a history of unpredictable ON-OFF alterations. In OFF-phase he suffered from bradykinesia and gait problems. He received bilateral GPi treatment. After surgery, the symptoms on the right side of the body ameliorated, symptoms on the left persisted. Medication and stimulation parameters were adjusted with little clinical effect. After a few months there was an increase in stiffness of the legs, gait initiation failure and apathy. Fusion imaging showed the right electrode 2mm above target. A procedure for electrode reposition was planned, but the patient expressed a wish for reoperation to the other target. Fifteen months after bilateral GPi DBS implantation the patient was re-operated to bilateral STN DBS. OFF-medication motor symptoms were improved by 36% 21 months after the conversion to STN DBS. The patient was satisfied with the treatment. There were some complaints of stimulation-induced hypertonia on the left extremities.

Center B

Patient 6: 59-year old male diagnosed with PD since 15 years, had been treated with levodopa since 12 years at the time of referral for DBS. He presented with a history of motor response fluctuations, dyskinesias and long OFF periods He suffered from cramps in the right foot and tremors in the left arm. He received bilateral GPi treatment. After a period of a few months with stimulation and medication adjustments a relatively stable situation was achieved. Four and a half years after bilateral GPi implantation the parkinsonian symptoms progressively worsened and although the clinical condition was better than before DBS, the ON-OFF fluctuations led to

impaired functioning in daily life. Fusion imaging showed both electrodes were located on target. 67 months after bilateral GPi DBS implantation the patient was re-operated to bilateral STN. A few weeks after this procedure the patient developed bacterial meningitis with lead infection after which the entire DBS system was removed. There was no available data on UPDRS scores after the procedure. Due to an improved motor response to solely medication and a deteriorating mental status the decision was made not to reoperate the patient.

Patient 7: 56-year-old male diagnosed with PD since 10 years, had been treated with levodopa since nine years. He presented with a history of response fluctuations, dyskinesia, rigidity and balance issues. The patient received bilateral GPi treatment. After the operation there was a clear reduction of OFF periods and dyskinesias. After several months the incidence of OFF periods and dyskinesia increased. A year and a half after starting DBS treatment the patient had severe OFF phases and ON phases without dyskinesia were seldom. Fusion imaging showed both electrodes were located on target. 23 months after bilateral GPi DBS implantation the patient was re-operated to bilateral STN. An MRI of the brain was done upon removal of the GPi leads, which showed both leads had been located in the dorsal part of the globus pallidus. After the second surgery the patient reported a great improvement with fewer OFF periods and dyskinesia. However, OFF-medication motor symptoms were improved by only 2% 13 months after the conversion to STN DBS. He also reported a dysarthria and increasing forgetfulness.

Patient 8: 42-year-old female diagnosed with PD since three years, had been treated with levodopa since three years. She presented with a history of bradykinesia, rigidity in the left arm, tremor in the right leg, and long and frequent OFF phases. The patient received bilateral GPi treatment. After the operation there was a clear improvement of the parkinsonian symptoms. After a year the patient developed tremor of the right hand, dystonic cramps in the left arm and leg and dyskinesia in the trunk and legs. There was an increase of OFF/ON fluctuations, blurred vision and rigidity. Fusion imaging showed both electrodes were located on target. 38 months after bilateral GPi DBS implantation the patient was re-operated to bilateral STN. OFF-medication motor symptoms were worsened by 73% 16 months after the conversion to STN DBS. Due to lack of clinical improvement after the operation, complementary subcutaneous apomorphine treatment was started. Motor symptoms were reduced, but there were complaints of hypersexuality and occasional suicidal ideations and episodes of auto-mutilation.

8

The effect of active contact localization on motor symptoms in deep brain stimulation of the subthalamic nucleus for Parkinson's disease

Authors

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Submitted

INTRODUCTION

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a therapeutic option for patients with advanced Parkinson's disease (PD) and motor symptoms that do not respond satisfactorily to medication adjustments.[1, 2] The STN is a small nucleus that contains regulatory circuitry of motor function, as well as limbic and associative pathways.[3] The motor pathways are mostly located in the dorsolateral part of the STN, whereas associative and limbic pathways comprise the ventromedial part of the nucleus.[4] Neighboring pathways include the internal capsule (mostly ventrolaterally), sensory pathways (dorsomedially), and cerebellar and oculomotor pathways (ventromedially).[5] The precise location of stimulation within the STN can affect the improvement of motor symptoms and induction of side-effects.[6] There is ample evidence that STN DBS vastly improves motor symptoms such as bradykinesia, tremor and rigidity, especially in the off-drug phase.[1, 2, 7-9] However, several adverse effects have been reported, such as impaired cognition, mood and behavioral changes.[10-15] A favorable outcome after DBS requires good patient selection, accurate implantation of the DBS electrodes and post-operative follow-up by an experienced DBS team.[16] A variety of DBS electrode locations in and in the near vicinity of the STN can lead to clinical improvement.[17]

Fusing of pre- and post-operative images is a commonly used technique to determine the actual lead location.[17-19] Contact coordinates are often defined as X, Y, and Z Cartesian coordinates relative to the midpoint between the anterior and posterior commissure (midcommissural point, MCP). Deviations from the pre-operatively planned target can be divided into systematic deviations and random deviations. Systematic errors lead to a constant deviation from the intended target in a certain direction, for example, a mean deviation of 1 mm anterior of the intended target of a large group of DBS leads. Random errors are deviations from the intended target in random directions and thus the mean coordinates of a large group of implanted leads may be the same as the mean coordinates of the intended targets. A smaller random error leads to a higher accuracy of implantation. Several studies found no difference in mean coordinates between patients that do or do not improve well after DBS.[17, 19, 20] This approach rules out a systematic error. To investigate a random error (i.e., accuracy), one must additionally analyze the euclidean distances from individual placed electrodes to the intended target.
When evaluating clinical response to stimulation, the same approach can be used for the distance between the individual active contact coordinates to the group mean of active contacts coordinates. If less accuracy implies less clinical improvement, the euclidean distance will be larger in patients that have less clinical response, that is, the deviation from the mean is larger in non-responders, but group average coordinates may be the same for responder and non-responders (figure 1). In this article we aim to explore this hypothesis in the patients that underwent STN DBS in the Netherlands SubThalamic and Pallidal Stimulation (NSTAPS) trial, which compared STN DBS and GPi DBS in advanced PD.[8]

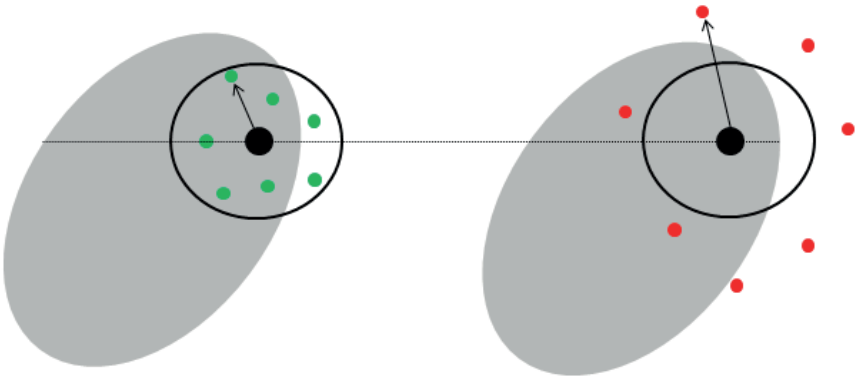

Figure 1. *The two grey ovals represent the subthalamic nucleus (STN). The black dots represent the mean coordinates of all active contacts in a study population. Hypothetically, these mean coordinates are the same for the patients that showed a good improvement after DBS (green dots) as for the patients that did not show a good improvement (red dots) after DBS. The euclidean distance of each individual active contact (arrow) from the mean coordinates is smaller in the group that responded well. The black circle represents an euclidean distance of 2mm from the mean of all active contacts. This is a two-dimensional representation of the three-dimensional actual situation.*

METHODS

Patients

Data of NSTAPS participants analyzed.[8] Additional selection criteria for this post-hoc analysis were: (1) randomization to STN DBS, (2) available post-operative imaging, and (3) available data on motor improvement 12 months after surgery.

Procedures

Patients were operated according to the local protocol of centers. The mid of the dorsolateral part of the subthalamic nucleus was targeted in all patients based on pre-operative MRI. Final electrode position was determined based on peri-operative (semi-) microelectrode recordings and macro-electrode stimulation. Post-operative stimulation settings were determined after screening of all contact points. Adjustment of stimulation and medication was performed at various points in time by a neurologist that was not blinded to treatment allocation. One year after surgery, a CT scan was repeated and fused with the pre-operative MRI to determine the coordinates of the individual contact for the purpose of this study. The coordinates of the active contact at 12 months post-operatively was calculated using SureTune™ (Medtronic Eindhoven Design Center, The Netherlands), a platform to visualize all patient specific pre-, intra- and post-op information into one common 3D space with AC-PC as common coordinate system.

Outcome measures

To test the hypothesis that the average euclidean distance from individual active contact to mean of all active contact points is larger in the non-responder group, we divided the electrodes based on the following two properties: (1) clinical responder vs non- responder and (2) short vector from active contact coordinates to the group mean coordinates (≤2mm) vs long vector (>2mm). This creates four groups: (1) responders and short vector, (2) responders and long vector, (3) non-responders and short vector, and (4) non-responder and long vector.

Definition of clinical response: The Unified Parkinson Disease Rating Scale part III in off-drug and on-drug phases was used to assess motor symptoms at baseline and 12 months.[21] The UPDRS-III was recalculated to left and right hemibody scores, using only the items that apply to one side of the body (UPDRS-III items 20-26, score range 0-36).[22] Hemibodies were divided into two groups, responders and non-responders, based on the improvement hemibody scores of motor symptoms after DBS. Responders were defined as an off-drug UPDRS-III score improvement after DBS of >30% of the baseline drug response:

$$\left(\left(\mathrm{UPDRS}_{\mathrm{hemi}_{\mathrm{base}_{\mathrm{off}}}} - \mathrm{UPDRS}_{\mathrm{hemi}_{12\mathrm{mo}_{\mathrm{off}}}}\right) \div \left(\mathrm{UPDRS}_{\mathrm{hemi}_{\mathrm{base}_{\mathrm{off}}}} - \mathrm{UPDRS}_{\mathrm{hemi}_{\mathrm{base}_{\mathrm{on}}}}\right)\right)$$

Calculation of vector: The means of all the coordinates were calculated per axis (X for laterality, Y for anteroposterior position, and Z for dorsoventral position) relative to the mid-commissural point. The distance from each active contact to the mean coordinate of the group (Δx,$\Delta y, \Delta z$) was calculated and transformed into an euclidean vector from this mean using the following formula: $euclidean\ vector = \sqrt{\Delta x^2 + \Delta y^2 + \Delta z^2}$. Active contact points at 12 months were retrieved from the database. In case of bipolair stimulation, the negative contact was used as active contact. No double monopolar settings were encountered.

Statistical analysis

First, total UPDRS-III scores, UPDRS-III hemibody scores, coordinates and euclidean vectors from the mean coordinates were compared between non-responders and responders. Independent sample t-tests or Mann-Whitney U-tests were used where appropriate. The difference in mean vector in the responder and non-responder group was analyzed using a Mann-Whitney U-test. Second, The vector from active contact to the group mean was dichotomized as follows: short vector (≤2mm) vs long vector (>2mm), effectively creating four groups based on short/long vector and responder/non-responders. Between-group differences were analyzed using a Chi-square test.

Active contact points, mean voltage, mean pulse width and frequency are reported descriptively for responders and non-responders.

Results

Of all 63 patients randomized to STN DBS, complete data on clinical improvement and stimulation settings were available. Post-operative imaging that was suitable to determine the contact coordinates was available for 83 electrodes. Patient characteristics of the patients on which suitable imaging was available are summarized in table 1.

Table 1. *Baseline characteristics (45 patients, 83 electrodes)*

Age (mean±SD) – yr	61.6±7.3
Disease duration (mean±SD) – yr	12.4±5.8
Male sex – no. (%)	62 (75%)
Duration of PD (mean±SD) – yr	12.4±5.8
Baseline UPDRS-III total off-drug score	42.8±15.0
Baseline UPDRS-III total on-drug score	16.3±8.3
Mattis Dementia Rating Scale (mean±SD, range, 0-144)	137.7±5†

**Unified Parkinson's Disease Rating Scale, motor examination*

† Spread of score between 125-144.

At baseline, the mean (±SD) UPDRS-III hemibody scores were 13.6±5.8 in off-drug phase and 4.7±3.3 in on-drug phase. 51 of the electrodes provided >30% clinical improvement, and 32 did not. Twelve months after surgery, the off-drug UPDRS-III hemibody scores were mean 6.3±4.3 and the on-drug scores were 3.4±2.9 (Table 2). The mean coordinates of the active contact points at 12 months relative to MCP did not differ between non-responders and responders (Table 3). The mean distance from the active contact to the mean of all active contacts was 2.2±1.1 mm in the responder group and 3.2±1.4 mm in the non-responder group (p=0.001, Figure 2a). The two-dimensional localization of the active contact compared to the mean is shown in Figure 2b and 2c. Of the active contact points, the location of 36 were within 2 mm of the mean coordinates of all contact points, and 47 were further away than 2 mm. Dichotomously assessed clinical improvement was significantly correlated with active contacts being within 2 mm (p=0.007, Table 4). Active contacts in the responder and non-responder group are listed in figure 3. Mean (±SD) settings in the responder group were: 2.6±0.5 V, 128±21 Hz, 64±9.3 μs, in the non-responder group: 2.5±0.5 V, 132±4.1 Hz, 62±6.6 microseconds.

Table 2. *UPDRS-III* hemibody scores (n=83)*

	Minimum	Maximum	Mean	SD
Baseline off-drug	3	27	13.6	5.8
Baseline on-drug	0	16	4.7	3.3
12-Months off-drug (on-stim)	0	21	6.2	4.3
12-Months on-drug (on-stim)	0	11	3.4	2.9

** Unified Parkinson's Disease Rating Scale motor examination*

Table 3. *Summary of Active Contact Data* (n=83)*

Mean	Non-responders (n=32)	Responders (n=51)	p
X-coordinate	11.9±1.4	12.1±1.3	0.47
Y-coordinate	2.0±2.3	1.7±1.5	0.53
Z-coordinate	-2.9±2.2	-3.0±1.5	0.80

**Coordinates are relative to the mid-commissural point. Laterality is always a positive number. Positive numbers are dorsal in the Y plane and posterior in the Z plain. An independent-sample t-test was used.*

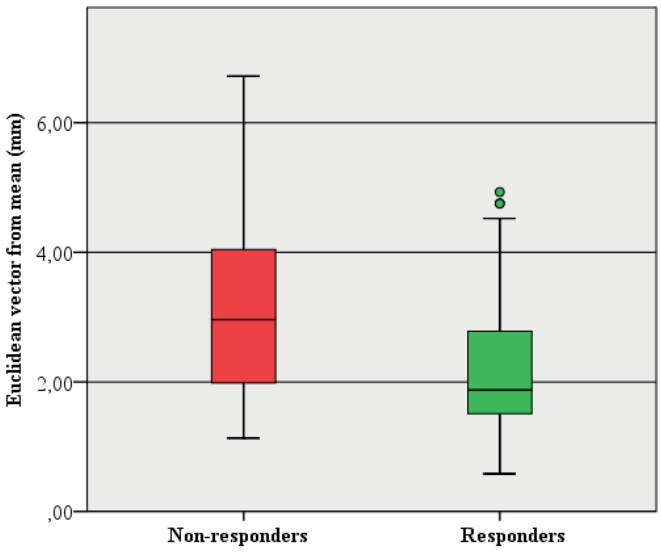

Figure 2a. *Euclidean vector from mean of active contacts of all patients*

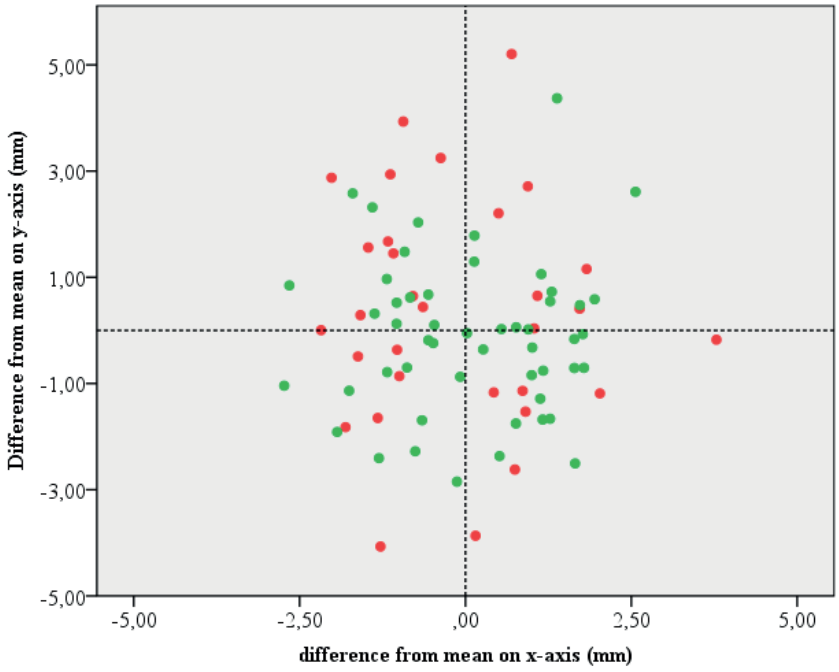

Figure 2b. *Position of active contact points compared to the mean of all patients (X-Y)*

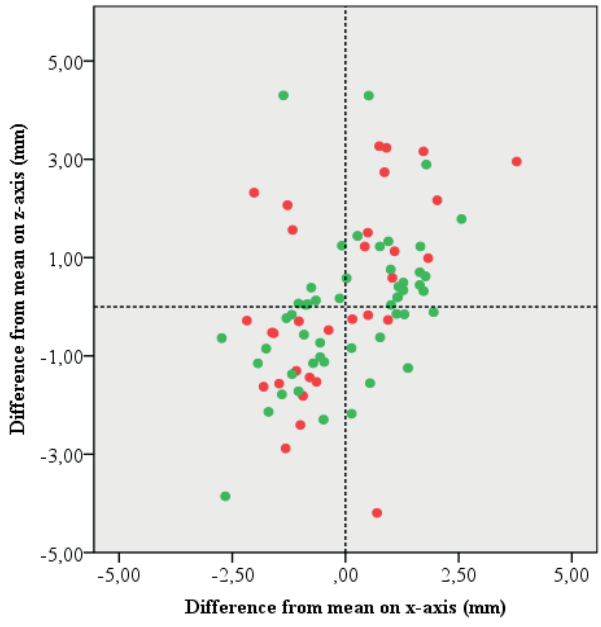

Figure 2c. *Position of active contact points compared to the mean of all patients (X-Z)*

Table 4. *Correlation between clinical improvement and euclidean distance from mean of all targets.*

Dichotomous improvement*	**<= 2mm**	**> 2mm**	**Total**
Non-responders	8	24	32
Responders	28	23	51
Total	36	47	83
Chi square test			p = 0.007

** Responders were defined as an off-drug UPDRS-III score improvement after DBS of >30% of the baseline drug response. UPDRS-III: Unified Parkinson Disease Rating Scale, motor examination.*

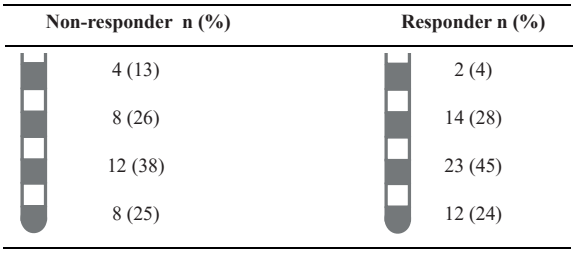

Figure 3. *Active contacts at 12 months after surgery.* Contacts are listed from most dorsal contact (top row) to most ventral contact (bottom row).

DISCUSSION

In our study, mean mid-commissural point based coordinates themselves are not correlated with clinical outcome. Hence, no structural targeting error was found that resulted in less clinical benefit. However, the length of the euclidean vector from the mean of all active contacts to the individual active contact is smaller in the responder group; that is, targeting accuracy was greater in patients with better clinical response, even though the difference was only 1 mm.

The most ventral and second-most ventral contact were the most frequently used contacts and closest to the initial pre-operative target. Thus, the clinically most beneficial site of stimulation one year after surgery is the near the peri-operatively determined final target of implantation. The more dorsal contacts were used in a minority of the cases (39% in the non-responder group and 32% in the responder group).

This study has several limitations. It is a post-hoc analysis and imaging 12-month post-operatively was not available in all patients for logistic reasons, which led to a reduction of the sample size. The baseline characteristics of this sample do not differ from rest of the NSTAPS cohort.[8] An additional limitation is het fact that the optimal site of stimulation was defined as the contact

that was active one year after surgery. Since the stimulation site can only be changed along the axis of the electrode, the true optimal site of stimulation in three-dimensional space may not be available for stimulation. This, however, is a limitation intrinsic to DBS.

CONCLUSION

No structural targeting error was found to be related to clinical response after DBS: the mean coordinates did not differ between responders and non-responders. However, an increased random error (less accuracy) was associated with less clinical response: the euclidean distance from individual active contacts to the mean of all active contacts was significantly larger in non-responders. Improving imaging, targeting and surgical techniques are very important factors in maximizing DBS efficacy in the future.

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9 |

General discussion

INTRODUCTION

Deep brain stimulation (DBS) is a well-established treatment option for medication induced motor response fluctuations (henceforth referred to as response fluctuations) in advanced Parkinson's disease (PD).[1-7] Stereotactic surgery has been increasingly used in the treatment of PD over the past four decades. In the 1970s stereotactic thalamotomy was established as a treatment for tremor and dyskinesias.[8,9] In the 1980 and 1990s, unilateral pallidotomy was applied in patients that were not considered good candidates for thalamotomy , and resulted in a great improvement of contralateral tremor, rigidity, bradykinesia, and dyskinesias.[10,11]

In the 1990s and early 2000s, lesioning had been largely replaced by deep brain stimulation, a technique that required bilateral implantation of electrodes into the basal ganglia that led to a vast reduction of motor symptoms and dyskinesias.[3-5,12-17] These DBS studies in this era investigated stimulation of the thalamus, globus pallidus parts interna (GPi), and subthalamic nucleus (STN). Whereas thalamic DBS resulted mainly in tremor reduction, GPi and STN DBS improved all motor symptoms.[3-5,12-17] In this era STN DBS was used more often than GPi DBS, due to knowledge on the role of the STN in the basal ganglia connectivity and expert opinions.[18] Over time, GPi DBS became more popular because STN DBS case reports and series showed post-operative impaired cognition, acute mood effects, psychosis, and even suicide.[5,6,19-22] Based on the anatomy of the much larger nucleus, it was assumed that these side effects would be less common in GPi DBS, but head-to-head comparisons were scarce.[5]

At this time, around 2006, two large trials were initiated to settle the debate over superiority of GPi DBS or STN DBS in a randomized controlled design: the Netherlands SubThalamic And Pallidal Study (NSTAPS; this thesis) and the American Veterans Affairs study.[23,24]

NSTAPS TRIAL DESIGN AND CHOICE OF OUTCOME MEASURES

At the time of the start of the trial, the two main clinical burning questions in the GPi vs STN debate were: (1) which nucleus provides more motor and functional improvement and (2) does STN DBS really lead to more side effects on cognition, mood, and, behavior?

Based on the available evidence in 2006, our hypothesis was that GPi DBS and STN DBS would result in similar motor improvement, but that GPi DBS would lead to more improvement of functioning due to less negative effects on cognition, mood and behavior.

To assess this, two primary outcomes were chosen for the NSTAPS trial: (1) one time-weighted score for functioning (health-related functioning) in both off-drug and on-drug phases and (2) a composite score for effects on cognition, mood, and behavior, albeit that outcome (1) was used for power calculations.

Choosing a primary outcome measure to capture all the effects of DBS in such a multi-faceted disease is challenging. GPi DBS and STN DBS also have different mechanisms of action,[25] and

thus can have different therapeutic effects and different side effects. Moreover, (side-)effects of interventions may vary during the course of a day which is an intrinsic characteristic of the disease. We chose a health-related functioning measure (i.e. disability measure) as one primary outcome for the NSTAPS trial. PD and its treatment may affect cognition, mood, and behavior.[16] These factors may influence the reliability of self-reported outcome measures when assessing an intervention that mainly improves motor features of the disease. Both cognitive impairment and mood have a major impact on quality of life scales,[26,27] which could cloud the effect of an intervention on symptoms and health-related functioning. Of course, possible effects on cognition and mood are relevant and may be evaluated through secondary outcome measures. Many scales for measuring handicap and quality of life are available, of which the PDQ-39 and the Parkinson's Disease Quality of Life questionnaire (PDQL) are the most extensively used studies scales in PD.[28-30] Although handicap and health-related quality of life represent important measures from a patient's point of view, they have serious disadvantages in clinical trials. The extent to which patients fulfil social roles and participate in their environment cannot be observed directly and depends not only on their functional ability but also on personal traits, social circumstances, living arrangements, and societal barriers (*e.g.*, accessibility of buildings). Similarly, health-related quality of life reflects the patient's perception of the consequences of disease, but depends on many additional factors, mostly psychosocial, other than the disease itself. Because impairments impact disability more than health-related quality of life (*i.e.*, disability measures are more responsive),[30] larger studies are needed when choosing health-related quality of life as primary outcome. In the primary assessment of treatment outcomes, the clinical scientist should therefore not focus on handicap and health-related quality of life, but rather on more direct and tangible manifestations of disease.

The disability domain (ADL, self-care, independence in general) is an appropriate primary endpoint for assessing health-related functioning for phase 3 clinical trials for several reasons. The ability to perform basic and complex activities of daily life is not only closely related to the disease process itself, it is observable, and also forms an essential component of a patient's quality of life.[31,32]

THE NSTAPS TRIAL FINDINGS

In contrast to our hypothesis we found no difference in effect on functioning on a time-weighted scale for off-drug and on-drug phase *(chapters 2 and 5),* one and three years after surgery. The improvement in the STN group was larger than in the GPI group, but not statistically significant. The incompletely filled-in diaries and the large contribution of the on-drug phase to the weighted score, have most likely contributed to this lack of difference.

However, at both one year and three years after DBS, the STN group showed significantly more

improvement of off-drug phase motor symptoms and functioning (*chapters 2 and 5*). Figure 1 is a graphical representation of the vast difference in improvement between the two groups. These results show that STN DBS is superior in reducing off-drug phase motor symptoms leading to improved functioning.

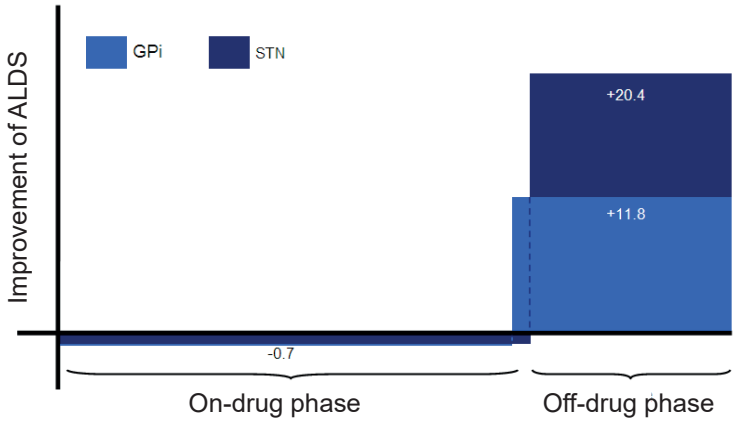

Figure 1. *Improvement of functioning on the AMC Linear Disability Scale (ALDS) is represented on the Y-axis.* The X-axis is a representation of the distribution of time during a day that patients spend in off-drug and on-drug phase. There is no differerence in functional improvement in the 2/3rd of the day that patients are in on-drug phase. However, the 1/3rd of the day that patients are "off", the improvement is twice as large in the STN group.

To understand the impact of these changes, the following examples may be useful: an average NSTAPS patient would just be able to independently have a shower pre-operatively. With an improvement of about 12 points (GPi group) the patient would be able to walk down a flight of stairs. However, with an improvement of 20 points (STN group), the patient would be able to independently visit a restaurant.

Our second important finding is that no differences were found regarding cognition, mood, and behavior between GPi DBS and STN DBS on a composite score. This contrasted with our initial hypothesis. Therefore, fear of complications in these domains is not a valid reason to opt for GPi DBS over STN DBS, which was common practice before the results of the NSTAPS study came available.[2,5,19,20,33-35] Apart from the composite score, individual neuropsychological tests were evaluated (*chapter 3 and 6*). These tests did not detect relevant differences between GPi DBS and STN DBS, but decline of cognitive function was seen equally in both groups. This decline can be attributed to disease progression, to the surgery itself, or to the stimulation. It is difficult to differentiate between these factors, since we did not include a control group that did not undergo surgery.

The secondary outcome measures also showed less use of medication and a lower battery use after STN DBS. These findings are in line with other publications.[1,4,5,13,36,37] A post-hoc analysis also showed greater improvement of balance items in the Unified Parkinson's disease rating scale. This finding needs to be confirmed in other studies.
A remarkable finding was the larger number of re-operated patients after GPi DBS. *Chapter 7* is dedicated to the description of these 14 patients including a systematic review on re-operated patients. About half of the patients converted to STN DBS can be considered a success. Publication bias might have led to an overestimation of the success rate, since six out of these eight success cases were from the systematic review. The number of patients that require conversion to STN DBS can be seen as an additional reason to initially prefer STN DBS over GPi DBS.
Finally, chapter 8 discusses the therapeutic effect in relation to the actual site of stimulation. The mean coordinates did not differ between the responder and non-responder groups after STN DBS, but the mean euclidean distance from individual active contacts to the mean of all active contacts was significantly larger for the non-responder group. Thus, in our study random deviations (less accuracy) from the ideal target appear to be a more likely cause of a suboptimal effect than structural targeting errors.

Summarizing, both GPi DBS and STN DBS have previously been proven to be effective treatment options for advanced PD. In contrast with our initial hypothesis, off-/on-drug time weighted functioning is not different for GPi DBS or STN DBS and STN DBS does not have more adverse effects on cognition, mood and behavior. Furthermore, this thesis shows that STN DBS gives more improvement of off-drug phase functioning and off-drug phase motor symptoms than GPi DBS. Also medication is reduced more after STN DBS and less battery power is needed. Although GPi DBS and STN DBS perform very similarly in many domains, the large difference in off-drug phase functioning leads to STN DBS being the preferred target in advanced PD. Table 1 shows an overview of the results of the NSTAPS trial.

Table 1. *Effects of deep brain stimulation of the globus pallidus pars internus and subthalamic nucleus based on results of the NSTAPS trial.*

	GPi DBS	tie	STN DBS
Overall health-related functioning		●	
Off-drug health-related functioning			●
Off-drug phase motor symptoms			●
Quality of life		●	
Dyskinesias		●	
Medication reduction			●
Cognition		●	
Mood and behavior		●	
Battery longevity			●*
Balance			?**

● = favors this treatment arm, with a tie meaning that no differences have been detected between the two group. Abbreviations: GPi DBS = deep brain stimulation of the globus pallidus pars internus, STN DBS = deep brain stimulation of the subthalamic nucleus. *Based on battery voltage, frequency and pulse width leading to a higher total electrical energy delivered after GPi DBS. **Post-hoc analyses of the one-year results of the NSTAPS trial show a greater improvement of axial symptoms after STN DBS, as discussed in chapter 2.

STRENGTHS AND WEAKNESSES OF THE NSTAPS TRIAL

The NSTAPS trial has several features, which make the trial unique. The NSTAPS trial is the world second-largest trial comparing GPi and STN DBS.[23,24]

As stated in *chapter 2,* the AMC Linear Disability scale was weighted for daily time spent in off- and on-drug phases to capture the fluctuating daily functioning of a patient with advanced PD in one score.[38] Although this was a very comprehensive and valid outcome measure from a clinimetric point of view, several issues arose that may have clouded the outcome on this scale. First, the three-day diaries that were needed for the time weighting were not always fully completed by patients at baseline and after a year. This led to a reduction of the sample available for analysis of this primary outcome. Second, DBS is known to improve mainly off-drug phase symptoms and functioning.[1,7] The weighted ALDS scores were determined by on-drug phase for about 2/3rd of the entire score. This diluted the large difference in functioning in off-phase between the GPi and STN group. In retrospect, using the *off-phase* improvement would have been a better option to detect a relevant difference between GPi DBS and STN DBS. Third, even though the ALDS is a valid, reliable and responsive scale, the UDPRS is a better-known scale in the movement disorders community and its clinimetric properties have also been extensively studied.[39,40] Many large RCTs investigating DBS use the off-drug phase Unified Parkinson Disease Rating Scale (UPDRS) motor score improvement as the primary outcome.[1,5,24,41,42] The one-year NSTAPS results (chapter 2) showed a very similar improvement in motor symptoms on the UPDRS and functioning on the ALDS. All these factors led us to using off-phase motor symptoms as a primary outcome in the study design for the three-year follow-up.

The second primary outcome was a composite score for cognition, mood, and behavior. All previous large randomized trials evaluated these domains only as a secondary outcome, if at all.[1,5,7,24,43]

One could argue that our dichotomous outcome was too crude of an endpoint to detect a difference between GPi DBS and STN DBS. However, participants only had to fail on one of the dichotomous questions in these domains, creating a high enough number of patients with a negative composite score to avoid a bottom-effect. For this reason the absolute number of patients with a negative composite score was high in both groups, but this was to be expected based on the choice of outcome measure. This does not necessarily mean that many patients experience a negative outcome in these domains, merely that the composite score is sensitive to change. This is reflected in the fact that functional status and quality of life improves, both in patients with positive and negative composite scores.

Many secondary endpoints were more elaborate neuropsychological, psychiatric, and socials scales that assessed the domains of our composite score in more detail. These analyses also showed no large between-group differences.

Even though a loss of power may have clouded the interpretation of the primary functional health outcome , the separate mean ALDS scores in on-drug and off-drug phase still portrayed the post-operative improvement very well.

An important factor for clinical relevance of our results is the external validity. The inclusion criteria of the NSTAPS study were similar to the criteria that we use in daily practice. All patients eligible for DBS were asked to participate in the trial. Exclusion based on baseline cognitive dysfunction was only done based on severely aberrant scores (Mattis Dementia Rating Scale score of 120 or less).[44] There was no age limit for inclusion. These criteria make the NSTAPS results very applicable to the growing number of older patients that are evaluated for DBS in daily practice. These criteria were stricter in most similar trials.[7,24,45]

NSTAPS TRIAL FINDING IN CONTEXT: WHERE DO WE STAND?

Two other randomized controlled trials (RCTs) have been performed that compare bilateral GPi and bilateral STN DBS. The first was published in 2005 and evaluated the effect on motor symptoms in off-phase.[5] Twenty patients (10 GPi, 10 STN) were followed during one year, after which the GPi group improved by 39% and the STN group by 48%. This difference was not statistically significant, possibly due to the small sample size.

The Veteran Affairs study that was initiated at approximately the same time as the NSTAPS trial, is a much larger (299 patients) US trial that showed an off-drug phase motor improvement of about 26% after 2 years in both the GPi and STN group.[24] The much lower effect on motor symptoms in comparison to previous studies is remarkable.[1,5,7] Since the motor improvement after STN DBS is nearly half of that in similar trials, one could question if something in the setup or execution

of this trial has led to an exceptionally low improvement after STN DBS. The only difference in baseline characteristics is the higher percentage of patients over the age of 70. However, one would expect that this would influence both surgical treatments equally. Since we do not have access to the individual patients data of this trial, we can only speculate on other explanations. A difference in surgical technique, targeting, or post-operative management of STN DBS could explain the relative lack of benefit in this trial.

Whereas the VA study did find an association between cognitive decline and diminished quality of life, we did not find such association (chapter 3).

Based on these three available randomized controlled trials several conclusions can be made. Improvement of motor symptoms is better after STN DBS (or similar if you take the Veteran Affairs Study) and this improvement persists up to at least three years after surgery. No large differences can be found in the domains of cognition, mood, and behavior up to three years after surgery. STN DBS requires a lower stimulation voltage and subsequent longer battery life. One could argue that the NSTAPS results show a larger improvement in the severity of dyskinesias after GPi DBS. However, this is an artifact of the study design. STN DBS reduces dyskinesias by tapering medication over time, while GPi DBS has a direct anti-dyskinetic effect.[46] NSTAPS protocol required patients to take their *baseline* levodopa equivalent dosages for the follow-up assessment, creating a skew comparison due to the different mechanism of action of GPi DBS and STN DBS on dyskinesia reduction. The reduction of time per day with bothersome dyskinesias did not differ between groups.

All findings that *do* differ between the two nuclei favor bilateral STN DBS. Thus, STN DBS is the preferred target for bilateral STN DBS.

RECOMMENDATIONS FOR FUTURE RESEARCH

Both GPi DBS and STN DBS have been extensively studied in the last decade. The VA trial and the NSTAPS trial provide insight into the symptomatic outcome, functioning, and quality of life and adverse effects. To our knowledge, no additional trials are currently being performed to compare the two targets. Ideally, an individual patient data meta-analysis of all randomized trials that involve GPi DBS and/or STN DBS should be performed to settle the differences found in motor improvement. Our group and others undertook such efforts, but these were unsuccessful. A selection of the DBS centers worldwide still use both GPi DBS and STN DBS for advanced PD. The method of patient selection for either one nucleus or the other is based on personal experience, since no prediction models can aid in this choice. In the Netherlands and many centers worldwide, STN DBS is now the target of choice for advanced PD based on the larger improvement of functioning and motor symptoms in the off-drug phase found in the NSTAPS trial.

Apart from DBS, continuous intrajenunal levodopa infusion and subcutaneous apomorphine

infusion are available for the treatment of response fluctuations.[47-49] Although trials have been performed that investigate the effectiveness of these treatments compared to oral medication, no studies have been published that compare these treatments head to head.[47-51] One randomized controlled trial comparing DBS and continuous intrajenunal levodopa infusion is currently including patients, while no such efforts are being undertaken for apomorphine versus another advanced therapy.[51]

As far as improving DBS treatment is concerned, future research goals will be to improve (1) current operation techniques and (2) improve DBS hardware and software.

An important new approach in DBS for PD is performing the entire surgery under generalized anesthesia, which seems to results in similar motor benefit in case series.[52-56] This technique depends on direct pre- and post-operative imaging to achieve accurate implantation, in some cases aided by micro-electrode recording. Intra-operative clinical assessment is not used, which presumably leads to less patient discomfort since generalized anesthesia can be applied. Future research needs to confirm the results in a larger and randomized controlled trial. Such efforts are currently being undertaken.

New DBS hardware is another area of continuous innovation. At the moment, the site and volume of stimulated brain tissue is determined by the current and selected active contact, which can only be changed along the dorsoventral axis of implantation. Since side-effects of DBS can be stimulation site dependent, steering the currency in a direction might lead to a better therapeutic window.[57] This has led to the development of a new electrode with 40 hexogonal contacts, which also allows steering of the current in the medial/lateral and anterior/posterior direction.[58] The additional clinical benefit of this new electrode has yet to be proven.

A third area of improvement in the future is so called 'closed-loop' stimulation. Currently, stimulation is applied to the target area at a set frequency, pulse width and voltage, irrespective of the local electric activity of the brain or clinical symptoms at that time. Ideally, stimulation would be tailored to the symptoms that a patient experiences at that moment in time. To achieve such adaptive stimulation two criteria have to be met: (1) correlation between local brain activity (*i.e.*, local field potentials) near the electrode and clinical symptoms, (2) and adaptability of stimulation to the local field potentials. Research projects on the feasibility and efficacy of such a technique are ongoing.[59,60]

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Summary

SUMMARY

This thesis concerns the comparison of bilateral deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) and nucleus subthalamicus (STN) in advanced Parkinson's disease (PD). The hypothesis of the study was that GPi DBS and STN DBS give a similar improvement in motor symptoms, but that GPi DBS would result in a better daily functioning due to fewer adverse effects on cognition, mood, and behavior.

Chapter 1 provides an introduction into symptoms and treatment of advanced PD. We discuss the technique and indication for DBS in PD. DBS is shown to improve motor symptoms (such as tremor, bradykinesia and rigidity) that initially responded well to dopaminergic treatment. DBS also reduces the time spent in off-phase, diminishes dyskinesias, and lowers medication use. In surgery there is a small chance of serious complications, such as infection, intracranial hemorrhage and hardware dysfunction.

Chapter 2 shows the one-year results of the NSTAPS (Netherlands Subthalamic And Pallidal Stimulation) trial. This randomized controlled trial investigated the outcome after GPi DBS and STN DBS in 128 patients with advanced PD. It showed that on a scale that represents functioning throughout the day, one year after surgery, no difference was found between GPi DBS and STN. No differences in the effects on cognition, mood, and behavior were found on a composite score. However, motor symptoms in off-phase and functioning in off-phase improved much more after STN DBS. Medication was reduced considerably more after STN DBS, and GPi DBS required stimulation at a higher voltage.

Chapter 3 shows the comparison of the one-year neuropsychological outcome after GPi DBS and STN DBS . Only small differences were found on the Stroop word reading and color naming, the Trail Making Test B, and on the WAIS similarities, with STN DBS showing greater negative change than GPi DBS. No clinically significant differences in neuropsychological outcome were detected between GPi DBS and STN DBS. A prediction model showed that older age and better semantic fluency at baseline predicted cognitive decline after DBS. The instability of currently available prediction models was discussed.

Chapter 4 presents the psychiatric and psychosocial outcome one year after GPi DBS and STN DBS. We found no clinically meaningful differences in: psychiatric diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders IV, depression scales, anxiety scales, mania scales, or personality inventories. Neither did we find any relevant within-group differences before and after surgery. Marital satisfaction remained stable after both types of surgery. We concluded that the decision for GPi DBS or STN DBS cannot be based on expected psychiatric or psychosocial effects.

Chapter 5 displays the three-year results of the NSTAPS trial. Of the initial 128 patients , 90 fully completed the three-year follow-up. We still found more improvement of motor symptoms after STN DBS . The composite score for cognition, mood, and behavior did not show between-group differences. The STN DBS group still showed a larger improvement in off-phase functioning. Medication and stimulation results were in line with the one-year results. We concluded that STN DBS still provided more off-phase improvement than GPi DBS. The risk for cognitive, mood, and behavioral complications is similar in both groups.

Chapter 6 summarizes the neuropsychological and psychiatric outcome three years after DBS. The number of applied tests was reduced to minimize patient burden of the investigations. No between-group difference was found on the following administered tests: Mattis Dementia Rating Scale, the Stroop color-word test, the Trail Making Test parts A and B, the Controlled Oral Word Association Test, category fluency, and the Dutch version of Rey's Auditory Verbal Learning Test. A small within-group deterioration was seen compared to the one-year results, which is probably the result of disease progression.
Psychiatric and psycho-social evaluation after three years showed few new psychiatric diagnoses and no differences on the previously mentioned scales for mood and behavior.

Chapter 7 describes the eight patients of the NSTAPS trial that were re-operated to STN DBS due to insufficient effect of the initial GPi DBS. We also reviewed the available cases in literature. A total (NSTAPS and case reviews) of 11 patients were re-operated to bilateral STN DBS and three patients to bilateral GPi DBS. Five out of 11 patients re-operated to STN DBS showed a large improvement of motor symptoms. None of the three patients re-operated to GPi DBS showed a large motor symptoms improvement. We concluded that re-operation to the STN is an option when GPi DBS fails. We have insufficient data to comment on conversion to GPi DBS.

Chapter 8 presents data from the NSTAPS that underwent STN DBS and had post-operative imaging available suitable for fusion. We looked at the three-dimensional coordinates of the active contacts one year after surgery. We hypothesized that not the mean coordinates, but the length of the vector from the optimal stimulation site determines clinical improvement. The electrodes were divided into two groups based on the motor improvement one year after DBS: responders and non-responders. A euclidean vector from the individual active contact points to the mean of all active contacts points was calculated and compared between responders and non-responders linearly and dichotomized.
Mean coordinates did not differ between responders and non-responders after STN DBS, but the euclidean distance from individual active contacts to the mean of all active contacts was significantly larger in non-responders. This was in line with the hypothesis.

Chapter 9 is a discussion on current PD research and its challenges. The variety in symptoms and the rapid fluctuations in severity make measuring outcome in PD research a complex and challenging task. The NSTAPS trial shows that in many facets of the disease, GPi DBS and STN DBS lead to a similar improvement. However, STN DBS gives more improvement of off-phase motor symptoms and functioning. In contrast with our hypothesis, no differences in adverse effects on cognition, mood or behavior were found. These findings lead to STN being the preferred target in the treatment of advanced PD. Future DBS research will focus on improving both the surgical technique and the DBS hardware and software. Some of the most exciting research in the near future will investigate DBS under generalized anesthesia, new electrodes able to steer the direction of current, and 'closed-loop' stimulation.

Samenvatting

SAMENVATTING

In dit proefschrift worden bilaterale diepe hersenstimulatie (DBS) van de globus pallidus pars interna (GPi) en nucleus subthalamicus (STN) als behandelmethode van de gevorderde ziekte van Parkinson (ZvP) vergeleken. De hypothese was dat GPi DBS en STN DBS een even grote verbetering van de motorische symptomen zouden geven, maar dat GPi DBS zou leiden tot een grotere verbetering in functioneren door minder bijwerkingen op het gebied van cognitie, stemming en gedrag.

Hoofdstuk 1 geeft een overzicht van de symptomen en behandelingsmogelijkheden van de gevorderde ZvP. We bespreken de operatietechniek van DBS en de indicatiestelling voor DBS bij de ZvP. DBS verbetert motorische symptomen (zoals tremor, bradykinesie en rigiditeit) wanneer deze symptomen initieel goed reageerden op dopaminerge medicatie. DBS vermindert de tijd die patiënten per dag in off-fase doorbrengen, vermindert bovendien dyskinesieën en leidt tot een verlaging van de medicatie. De ingreep geeft echter een kleine kans op ernstige complicaties, zoals een infectie, een intracerebraal hematoom of hardware dysfunctie.

Hoofdstuk 2 toont de één-jaars resultaten van de NSTAPS (Netherlands Subthalamic And Pallidal Stimulation) studie. Deze gerandomiseerde gecontroleerde studie onderzocht het effect van GPi DBS en STN DBS in een groep van 128 patiënten met de gevorderde ZvP. Dit onderzoek liet een jaar na de operatie, op een schaal die dagelijks functioneren evalueerde, geen verschil zien tussen GPi DBS en STN DBS. Er werd ook geen verschil gevonden op een composietmaat die de bijwerkingen op gebied van stemming, cognitie en gedrag onderzocht. Echter, de symptomen en het functioneren in de off-fase verbeterden aanzienlijk meer na STN DBS dan na GPi DBS. Ook kon de medicatie meer gereduceerd worden na STN DBS en werden er gemiddeld minder hoge voltages ingesteld.

Hoofdstuk 3 beschrijft de vergelijking van neuropsychologische uitkomsten één jaar na GPi DBS en STN DBS. Er werden enkel kleine verschillen gevonden op de *Stroop word reading and color naming*, de *Trail Making Test B*, en de *WAIS similarities* waarbij STN DBS een grotere achteruitgang toonde dan GPi DBS. Er werden geen klinisch relevante verschillen gevonden. Een predictiemodel toonde leeftijd en een betere baseline semantische fluency als predictoren voor cognitieve achteruitgang na DBS. De instabiliteit van huidige beschikbare predictiemodellen werd besproken.

Hoofdstuk 4 is gewijd aan de psychiatrische en psychosociale uitkomsten één jaar na GPi DBS en STN DBS. Er werden geen klinisch relevante verschillen gevonden op de volgende uitkomstmaten: psychiatrische diagnoses op basis van de Diagnostic and Statistical Manual of Mental Disorders IV, depressie schaal, angst schaal, manie schaal en persoonlijkheidsinventarisatie. Ook werden er geen verschillen gevonden binnen de groepen vóór en na DBS. Tevredenheid van patiënt en partner over de huwelijksrelatie veranderde niet na DBS. De conclusie was dat de keuze voor GPi DBS of STN DBS niet kon worden gebaseerd op de psychiatrische en psychosociale uitkomsten.

Hoofstuk 5 laat de drie-jaars resultaten van de NSTAPS studie zien. Van de 128 initiële patiënten konden er 90 de volledige drie-jaars follow-up voltooien. Er werd nog steeds meer verbetering van motorische symptomen in off-fase gevonden na STN DBS. De composietscore voor cognitie, stemming en gedrag toonde geen verschillen tussen de twee groepen. Het functioneren in off-fase was beter na STN DBS. De resultaten wat betreft medicatie en stimulatie instellingen waren ook in lijn met de bevindingen na één jaar. De conclusie was dat er na drie jaar nog steeds meer verbetering waar te nemen was na STN DBS op basis van de off-fase symptomen en off-fase functioneren, zonder een toename van bijwerkingen op gebied van stemming, cognitie en gedrag.

Hoofdstuk 6 geeft een samenvatting van de neuropsychologische en psychiatrische uitkomsten na drie jaar. Het aantal testen na drie jaar is verminderd om de last voor patiënten te minimaliseren. Er werden geen verschillen tussen GPi DBS en STN DBS gevonden op de volgende testen: Mattis Dementia Rating Scale, the Stroop color-word test, the Trail Making Test parts A and B, the Controlled Oral Word Association Test, category fluency, and the Dutch version of Rey's Auditory Verbal Learning Test. Ten opzichte van de één-jaars resultaten werd er in beide groepen een geringe achteruitgang aangetoond, waarschijnlijk te wijten aan ziekteprogressie. Psychiatrische en psychosociale evaluatie na drie jaar liet weinig nieuwe psychiatrische diagnoses zien ten opzichte van baseline en één jaar. Ook op de schalen voor stemming en gedrag werden geen verschillen tussen de groepen aangetoond, noch achteruitgang ten opzichte van baseline.

Hoofdstuk 7 is een beschrijving van de acht patiënten in het NSTAPS onderzoek die een conversie hebben ondergaan naar STN DBS omdat initiële GPi DBS onvoldoende verbetering gaf. Ook wordt een literatuur case review van heroperaties naar een andere kern beschreven. In totaal (NSTAPS en case review) werden 11 patiënten geheropereerd naar bilaterale STN DBS en drie patiënten naar bilaterale GPi DBS. Vijf van de 11 heroperaties naar STN DBS lieten een grote verbetering van motorische symptomen zien. Geen van de heroperaties naar bilaterale GPi DBS gaf een grote motorische verbetering. We concludeerden dat heropereren naar bilaterale STN DBS een optie is als GPi DBS onvoldoende verbetering geeft. We beschikken over onvoldoende data om te oordelen over conversie naar GPi DBS.

Hoofstuk 8 toont de data van NSTAPS patiënten die STN DBS hebben ondergaan waarvan postoperatieve beelden beschikbaar waren die geschikt waren voor fusie. De driedimensionale coördinaten van het actieve contactpunt één jaar na de operatie werden berekend. De hypothese was dat niet zozeer de gemiddelde coördinaten van de groep, maar een korte afstand tussen het actieve contactpunt van een individu en het gemiddelde van de groep belangrijk is voor de klinische verbetering. De elektrodes werden in twee groepen verdeeld, gebaseerd op de motorische verbetering na één jaar: 'responders' en 'non-responders'. De euclideaanse vector tussen de coördinaten van de individuele actieve contactpunten en de gemiddelde coördinaten van de groep werd berekend en vergeleken tussen responders en non-responders. De gemiddelde coördinaten tussen de responder en non-responder groep gaven geen verschillen te zien, maar de euclideaanse afstand was significant groter in de non-responder groep.

Hoofstuk 9 bevat een discussie over de huidige stand van zaken in het onderzoek naar de behandeling van de ZvP en de problemen waar men mee geconfronteerd wordt bij het meten van uitkomst van interventies. De variëteit in symptomatologie en de snelle wisseling en ernst van symptomen maken het meten van de uitkomst in onderzoek naar de ZvP een uitdagende taak. Het NSTAPS onderzoek toont aan dat op veel facetten zowel GPi DBS als STN DBS een vergelijkbare verbetering geven. STN DBS geeft echter meer verbetering in de off-fase symptomen en het off-fase functioneren. In tegenstelling tot onze hypothese werden er geen verschillen tussen de twee behandelingen gevonden op het gebied van cognitie, stemming en gedrag. Deze bevindingen leiden ertoe dat bij behandeling van de gevorderde ZvP, de STN DBS de voorkeur heeft boven GPi DBS.
Toekomstig DBS onderzoek zal zich richten op verdere verbetering van de operatietechniek en het ontwikkelen van nieuwe DBS hardware en software. Interessante punten in de huidige ontwikkeling zijn DBS onder algehele anesthesie, nieuwe elektrodes met de mogelijkheid om de stroomrichting te sturen, en de toepassing van zogenaamde 'closed-loop' stimulatie.

Curriculum Vitae

Personal information

Name	Odekerken, Vincentius Jozef Johannes (Vincent)
Nationality	Dutch
Date of birth	15 July 1983
Mother tongue	Dutch
Foreign Languages	English (near-native), French (elementary), German (elementary)

Education and Training

1995-2001	Grammar School, Gemeentelijk Gymnasium Hilversum
2001-2008	Medical School, University of Amsterdam – Academic Medical Center, graduated cum laude
2005-February till June	Institute of Neurology, University College London. Research internship Parkinson's disease
2008-2014	Resident Neurology, University of Amsterdam – Academic Medical Center
2008-present	NSTAPS (Netherlands SubThalamic And Pallidal Stimulation study) trail investigator, University of Amsterdam – Academic Medical Center
2014 – present	Movement Disorder Fellow and attending Neurologist, University of Amsterdam – Academic Medical Center

Educational Skills

2011-present	Lecturer for Experimental Neurobiology Master, University of Amsterdam
2014-present	Resident education: Practical Neurology sessions, Neuro-Ophtalmology, Neuro-anatomy, Management of Parkinson's disease
2015-present	Lecturer for Medical School curriculum , University of Amsterdam, on following topics: Clinimetrics, Parkinson's disease, Transient Loss of Consciousness, patient case workshops.

Organisational Skills

2002-2004	Events Manager and Financial Controller Epsteinbar, Medical Faculty
2008-2014	Website and protocol manager for Department of Neurology
2010-present	Public relations board of the Dutch Society for Functional Neurosurgery in Movement Disorders
2012-present	European Continuing Medical Training (ECMT): Deep Brain Stimulation Faculty Member
2013-present	Neurology representative for EVA (electronic work environment for AMC/VUmc hospitals) implementation and certified EPIC physician builder

Technical Skills

MS Office, SPSS, Reference Manager, RefMan, Endnote, EPIC smart tool and physician builder software

Artistic and athletic skills

Music, English and Dutch literature, bootcamp, running, cinematography

Awards

2010	David Moffie Award for best clinical presentation - Second Prize. Amsterdamsche Neurologen Vereeniging
2013	Best Dutch Article in the field of movement disorders for "Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. Lancet Neurol. 2013 Jan;12(1):37-44." Werkgroep bewegingsstoornissen, Nederlandse Vereniging voor Neurologie

References

1	Dr. R.M. de Bie, Academic Medical Center
2	Prof. Dr. J. Stam, Academic Medical Center
3	Dr. P.D. Limousin, University College London

Scientific publications

1	Odekerken V.J., de Bie R.M. Early treatment of Parkinson's disease with levodopa. Ned Tijdschr Geneeskd.2009;153:A286. [Article in Dutch]
2	Odekerken V.J., van de Munckhof P., Schuurman P.R., de Bie R.M. Dubbelzijdige diepe hersenstimulatie bij de ziekte van Parkinson. Tijdschr Neurol Neurochir 2013;114:143-8 [Article in Dutch].
3	Odekerken V.J., van Laar T., Staal M.J. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. Lancet Neurol. 2013 Jan;12(1):37-44.
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6	Odekerken V.J., Boel J.A., Geurtsen G.J. et al. Neuropsychological outcome after deep brain stimulation for Parkinson's disease. Neurology. 2015 Mar 31;84(13):1355-61.
7.	Thalamic deep brain stimulation for orthostatic tremor: Clinical and neurophysiological correlates. Contarino MF, Bour LJ, Schuurman PR, Blok ER, Odekerken VJ, van den Munckhof P, de Bie RM, van Rootselaar AF. Parkinsonism Relat Disord. 2015 Aug;21(8):1005-7
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10.	How Many Patients would Benefit from Steering Technology for Deep Brain Stimulation? Contarino MF, Brinke TR, Mosch A, Lelieveld W, Postma M, Odekerken VJ, Steendam-Oldekamp TE, Van Laar T, Kuijf ML, Tjepkema-Cloostermans MC, Schuurman PR. Brain Stimul. 2015 Oct 20. pii: S1935-861X(15)01213-9

Book publications

1.	Author chapter "Neuro-ophtalmology and Neuro-otology" of study book "Neurologie" by Hijdra et al. ISBN10 9035238850 (Dutch) .
2.	Author "Supranuclear eye motility disorders" in online education platform "Nervus" (Dutch). http://www.nervus-online.nl/

Graduate School Portfolio

Personal information

Name	Odekerken, Vincentius Jozef Johannes (Vincent)
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Date of birth	15 July 1983
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Presentations and Posters ECTS

Clinical presentations AMC Neurology 2008-2014: 16 (4 hours per presentation)	2.25
Scientific presentation AMC Neurology 2008-2014: 4 (4 hours per presentation)	0.5
Presentations at Amsterdamsche Neurologen Vereeniging: 3 (8 hours per presentation)	0.75
Poster at MDS Congres 2012 Dublin: 1	0.5
AMC interdisciplinary seminar on movement 2012	0.5
Presentation at Scientific Meeting Nederlandse Vereniging voor Neurologie 2013	0.5
Poster at Scientific Meeting Nederlandse Vereniging voor Neurologie 2013	0.5
Presentation at EMCT course 2013	0.5
Poster at MDS Congres 2013 Sydney	0.5
Presentation at MDS Congres 2013 Sydney	0.5
Poster at MDS Congres 2014 Sydney (2)	1
Presentation at MDS Congres 2014 Sydney	0.5
Presentation at EMCT course 2014	0.5

Journal club	ECTS
Weekly Journal Club AMC Neurology (2008-2015, 40 per year)	10

Scientific Conference	ECTS
MDS Congress 2012 Dublin (5 days)	1.25
MDS Congress 2013 Sydney (5 days)	1.25
MDS Congress 2014 Stockholm (5 days)	1.25

Seminars and Lectures	ECTS
AMC interdisciplinary seminar on movement 2012	0.1
Clinical seminars Amsterdamsche Neurologen Vereeniging 2008-2015 (6 per year,)	3.6
Scientific seminars Amsterdamsche Neurologen Vereeniging 2008-2015 (6 per year)	3.6

Teaching	ECTS
Parkinson's Disease course for Master Psychobiology (UvA Science Park) 2012-2015	1
Author Neuro-ophtalmology and Neuro-otology chapter of medical study book "Neurologie" by Hijdra et al. Printed June 2015.	1
European Continuing Medical Training: Long-term Follow-up DBS Patients 2013	1
European Continuing Medical Training: Long-term Follow-up DBS Patients 2014	1
European Continuing Medical Training: Long-term Follow-up DBS Patients 2015	1

General course	ECTS
BROK course 2013	0.9

Student mentoring

	ECTS
Marcel van Ooijen 2012-2013: Dopamine-agonists and brain stimulation	2
Raquel Hulst 2012-2013: Suicide after deep brain stimulation in Parkinson's disease	2
Ilse Dekker 2013: Neuropsychological and psychiatric outcome after deep brain stimulation	3
Timo ten Brinke 2014: Changing deep brain stimulation target after therapy failure in advanced parkinson's disease: a retrospective case series of the NSTAPS trial patients	2

Total

	ECTS
	44.95

Awards

2010	David Moffie Award for best clinical presentation - Second Prize. Amsterdamsche Neurologen Vereeniging
2013	Best Dutch Article in the field of movement disorders for "Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. Lancet Neurol. 2013 Jan;12(1):37-44." Werkgroep bewegingsstoornissen, Nederlandse Vereniging voor Neurologie

Dankwoord

DANKWOORD

Ik wil alle deelnemers aan de NSTAPS studie bedanken voor de tijd en energie die jullie in het onderzoek hebben gestoken. Ik heb veel van jullie geleerd.
Rob, je bent de drijvende kracht achter het Parkinson onderzoek in het AMC. Sinds we elkaar voor het eerst ontmoetten in 2003 heb je mij altijd geïnspireerd en stond je voor me klaar. Dank voor je steun, je geduld, je accuratesse. Je heldere denken en kritische blik op onderzoek maakt je tot een voorbeeld voor jonge wetenschappers.
Beste Ivo, de laatste jaren heb je mijn promotietraject ondersteund door mee te denken over tijdslijnen, deadlines en praktische ondersteuning. Je ben concreet en to-the-point. Deze structurering heeft mij veel geholpen.
Beste Rick en Pepijn, dank jullie wel voor de prettige samenwerking: de DBS operaties zijn een mooi voorbeeld van de neurochirurgische-neurologische synergie. Ik heb veel geleerd tijdens de operaties en genoten van jullie hartelijke persoonlijkheden.
Alle leden van de promotiecommissie, het is een eer dat jullie deel hebben willen uitmaken van deze dag.
Alle leden van het DBS team. Ten eerste Gosia, Marije, Miranda: jullie zijn de spil van de DBS zorg in het AMC. Gosia, heel erg bedankt voor al je tijd, precisie en altijd vrolijke stemming. Zonder jou was de NSTAPS niet zo'n geslaagd onderzoek geweest. Marieke, dank voor alle uitgebreide neuropsychologische onderzoeken die je bij onze patiënten heb uitgevoerd. Ben en Gert, dank voor de fijne samenwerking en jullie benaderbaarheid. Martijn, we boffen enorm met zo'n betrokken psychiater bij de DBS zorg. Lo en José : dank voor alle lessen in de neurofysiologische aspecten van DBS, jullie hebben letterlijk (een beetje) een bèta-man van me gemaakt.
En niet te vergeten Judith: sinds je deel uitmaakt van het NSTAPS team is mijn productiviteit verdubbeld. Je statistische vaardigheden, je neuropsychologische kennis en je werkethos maken je de ideale promotie-buddy. En je bent ook gewoon een heel leuk mens om mee samen te mogen werken. We zijn echt een heel goed team.
Beste Teus, Michiel, Arne, Carel, Peter, Thies, Guus, Jeroen, Mathieu, Fiorella: hartelijk dank voor alle moeite en tijd die jullie hebben gestoken in het NSTAPS onderzoek.
Dear Marwan, Patricia, and Steve: my first experience with DBS and science was at Queens Square. Thank you for your enthusiasm and dedication. You were a truly inspiring team to work with.
De Parkinson-mannen: Daan, Connie, Sven en Daan. Ik heb geluk dat ik zo veel kan lachen met directe collega's als met jullie. Soms mis ik 'onze' kamer wel een beetje.
De Medico's: ik bof met een dergelijke hechte vriendengroep. Ook al is iedereen nu wat drukker en meer verspreid over de provincie: een dergelijke vriendschap verwatert niet.

Ik wil alle lieve familieleden bedanken die mij hebben gesteund en begrip voor mij hebben gehad. Friso, bedankt voor het ontwerpen van de cover. Je mag trots zijn op je creatieve talent en oog voor detail.

Mijn paranimf Joppe. We kennen elkaar nu al zo lang. Wie had ooit gedacht dat je eerder zou promoveren dan ik. Ik ben trots op hoe hard je daar aan hebt gewerkt en hoe je de wetenschap combineert met je vaderschap. Je bent een goede vriend en fijne collega: hopelijk blijf je ook in het AMC werken.

Mijn paranimf Jos. Lieve Jos, ik ben trots en vereerd dat je mijn paranimf wil zijn. Je hebt me enorm geholpen op meer manieren dan ik kan benoemen. Je hebt me de pracht van de Engelse taal en literatuur bijgebracht, deelt mijn liefde voor Shakespeare. Je controleert onvermoeibaar al mijn Engelse artikelen. Je bent een lieve vader en een goede vriend. We gaan snel weer een keer naar Stratford-upon-Avon.

Lieve Nienke, je bent net zo'n belangrijke steun voor me geweest als Jos. Naast kritische blik, je enorme kennis van Office, goede inzicht in het opmaken van documenten en het raffineren van presentaties ben je als moeder ook altijd een enorme steun geweest. Ik ben trots op hoe hard je werkt en wat je bereikt hebt binnen zo'n mannenwereld als het bedrijfsleven.

Lieve Elize. Wat een life events weten wij in een korte tijd mee te maken. In al die drukte geef jij mij de tijd en ruimte om in de weekenden, avonden en vakanties aan mijn proefschrift te werken. Je bent voor mij een bron van inspiratie door je warmte, rechtvaardigheidsgevoel en menselijkheid. Daarnaast ben je een fantastische moeder; je bent zo lief met Lauren. Ik bof dat je mijn levensmaatje bent.