



Contents lists available at ScienceDirect

# Parkinsonism and Related Disorders

journal homepage: [www.elsevier.com/locate/parkreldis](http://www.elsevier.com/locate/parkreldis)

**Editor's Comment:** In an important contribution to a critical area in the management of PD, that of selecting the best target site for DBS, Boel et al. found that cognitive and psychiatric outcomes are no different for the STN and GPi targets at three years following surgery. This finding complements the same group's previous reports of outcomes at one year for this cohort, whose mean age at baseline was around 60, and had a duration of illness of around 10 years. Long term follow up of DBS outcomes is critical, and the findings of this study are very helpful for both physicians and patients. Apart from the established finding of a decline in verbal fluency, it is reassuring that there was no other striking category of neuropsychological deficit found.

**Jonathan Carr**, Associate Editor, University of Stellenbosch, Ward A-8-L, Tygerberg Hospital, Tygerberg, Western Cape, 7075, South Africa.

## Cognitive and psychiatric outcome 3 years after globus pallidus pars interna or subthalamic nucleus deep brain stimulation for Parkinson's disease



Judith A. Boel<sup>a, b, 1</sup>, Vincent J.J. Odekerken<sup>a, 1</sup>, Ben A. Schmand<sup>b, c</sup>, Gert J. Geurtsen<sup>c</sup>, Danielle C. Cath<sup>d, e</sup>, Martijn Figee<sup>f</sup>, Pepijn van den Munckhof<sup>g</sup>, Rob J. de Haan<sup>h</sup>, P. Richard Schuurman<sup>g</sup>, Rob M.A. de Bie<sup>a, \*</sup>, the NSTAPS study group

<sup>a</sup> Department of Neurology, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD, Amsterdam, The Netherlands

<sup>b</sup> Department of Psychology, University of Amsterdam, PO Box 19268, 1000 GG, Amsterdam, The Netherlands

<sup>c</sup> Department of Medical Psychology, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD, Amsterdam, The Netherlands

<sup>d</sup> Altrecht Academic Anxiety Center, Utrecht, The Netherlands

<sup>e</sup> Department of Clinical and Health Psychology, Utrecht University, PO Box 80125, 3508 TC, Utrecht, The Netherlands

<sup>f</sup> Department of Psychiatry, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD, Amsterdam, The Netherlands

<sup>g</sup> Department of Neurosurgery, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD, Amsterdam, The Netherlands

<sup>h</sup> Clinical Research Unit, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD, Amsterdam, The Netherlands

### ARTICLE INFO

#### Article history:

Received 31 May 2016

Received in revised form

12 September 2016

Accepted 18 September 2016

#### Keywords:

Parkinson's disease

Deep brain stimulation

Cognition

Psychiatry

Randomized controlled trial

### 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 Parkinson's disease (PD).

**Objective:** 1) To compare cognitive and psychiatric outcomes 3 years after GPi DBS versus STN DBS, and 2) to report on occurrence 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 assessments were 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:** Eighty-seven 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 0.17 and 0.87), and psychiatric questionnaires (p-values between 0.23 and 0.88) 3 years

**Abbreviations:** DBS, Deep brain stimulation; GPi, Globus pallidus pars interna; STN, Subthalamic nucleus; PD, Parkinson's disease; MDRS, Mattis Dementia Rating Scale.

\* Corresponding author.

**E-mail addresses:** [j.a.boel@amc.uva.nl](mailto:j.a.boel@amc.uva.nl) (J.A. Boel), [v.j.odekerken@amc.uva.nl](mailto:v.j.odekerken@amc.uva.nl) (V.J.J. Odekerken), [b.schmand@amc.uva.nl](mailto:b.schmand@amc.uva.nl) (B.A. Schmand), [g.j.geurtsen@amc.uva.nl](mailto:g.j.geurtsen@amc.uva.nl) (G.J. Geurtsen), [cath@xs4all.nl](mailto:cath@xs4all.nl) (D.C. Cath), [m.figee@amc.uva.nl](mailto:m.figee@amc.uva.nl) (M. Figee), [p.vandenmunckhof@amc.uva.nl](mailto:p.vandenmunckhof@amc.uva.nl) (P. van den Munckhof), [r.j.dehaan@amc.uva.nl](mailto:r.j.dehaan@amc.uva.nl) (R.J. de Haan), [p.r.schuurman@amc.uva.nl](mailto:p.r.schuurman@amc.uva.nl) (P.R. Schuurman), [r.m.debie@amc.uva.nl](mailto:r.m.debie@amc.uva.nl) (R.M.A. de Bie).

<sup>1</sup> These authors contributed equally to the manuscript.

<http://dx.doi.org/10.1016/j.parkreldis.2016.09.018>

1353-8020/© 2016 Elsevier Ltd. All rights reserved.

after DBS. The Mini International Neuropsychiatric Interview did not indicate a substantial number of psychiatric diagnoses after 3 years. Social functioning and marital satisfaction were comparable in both groups.

**Conclusions:** Three years after GPi DBS and STN DBS no pronounced between-group differences on measures of cognitive and psychiatric functioning could be demonstrated. Overall, cognitive and psychiatric outcome 3 years after DBS do not provide a clear direction for clinicians when considering which of these two surgical targets to choose.

© 2016 Elsevier Ltd. All rights reserved.

## 1. 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 there is no consensus 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 in motor improvement 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]. These contrasting results, direct the focus to the non-motor effects after GPi DBS and STN DBS.

Various degrees of cognitive decline and psychiatric side effects have been reported after DBS [5–9], but elaborate systematic long-term reports are limited. The Veterans Affairs (VA) study, a randomized controlled trial comparing GPi DBS and STN DBS, indicated superiority of GPi DBS on two cognitive measures 3 years after surgery [10]. Previously, we have reported that there were no clinically relevant between-group differences on neuropsychological, psychiatric, and social functioning 1 year after GPi DBS and STN DBS [11,12], and we anticipated that these previous findings would 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 and we descriptively report suicidal ideation, psychiatric diagnoses, social functioning, and marital satisfaction.

## 2. Materials and methods

The study design has been reported previously [13]. 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 [14], a Mattis dementia rating scale (MDRS) score of 120 or lower (out of 144) [15], 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 1:1 ratio, applying a minimization procedure according to drug use (levodopa equivalent dose <1000 mg vs  $\geq$  1000 mg) and treatment center. Patients as well as clinical,

neuropsychological, and psychiatric assessors were blinded for treatment allocation.

This multicenter trial was registered with [www.controlled-trials.com](http://www.controlled-trials.com), number ISRCTN85542074.

### 2.1. Neuropsychological tests and psychiatric questionnaires

Patients performed neuropsychological tests and psychiatric test assessments during the on-drug phase at baseline, 1 year, and 3 years, with the stimulators turned on at 1 year and 3 years.

The MDRS was included to assess global cognitive abilities [15]. Attention and working memory were assessed using the Stroop Color-Word test (Stroop word: reading black printed color words, Stroop color: naming ink colors, and Stroop interference: naming ink colors of incongruent color words) [16], the Trail-Making Test (TMT A: connecting numbers, TMT B: connecting numbers and letters while alternating) [17], and the subtest Letter-Number Sequencing of the Wechsler Adult Intelligence Scale III (WAIS-III LN: reordering a sequence of numbers and letters by naming the numbers in ascending order and the letters in alphabetical order) [18]. Executive functions were assessed using the Controlled Oral Word Association Test (COWAT, naming of words starting with a specific letter in 60 s, 3 trials) referred to as phonemic fluency [19], and category fluency (naming of words in a specific category in 60 s, 2 categories) referred to as semantic fluency [19]. The Dutch version of Rey's Auditory Verbal Learning Test was used to assess immediate and delayed memory. AVLT immediate recall: 15 unrelated nouns are read out loud and the patient is asked to recall as many words as possible; the sum of words recalled over 5 trials is referred to as AVLT total; the number of words recalled after 20 min is referred to as AVLT delayed recall [20]. Raw scores were normed appropriately by age, gender and/or education. Reported in this article are raw scores for the MDRS (max. score of 144), scaled scores for the WAIS-III LN subtest (mean of  $10 \pm 3$ ), and T-scores for all other neuropsychological tests (mean of  $50 \pm 10$ ). Higher scores represent better performance.

The Young Mania Rating Scale (YMRS) was used to assess the severity of manic symptoms; higher scores indicate more manic symptoms [21]. The Hospital Anxiety and Depression Scale (HADS) was used to assess anxious and depressive mood; higher scores indicate more distress [22]. 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) [23]. Psychiatric diagnoses were assessed according to the Mini-International Neuropsychiatric Interview (MINI) [24]. Social functioning was assessed using a network questionnaire in which membership of organizations was assessed (NESDA) [23]. Additionally, marital satisfaction was assessed by rating 9 relational aspects including, but not limited to motivation, personality, level of intimacy, and decision-making. These aspects were rated on a Likert scale from 1 (very dissatisfied) to 5 (very satisfied). Both patients and their

partners completed this questionnaire (see Appendix Table A.2 for the specific questions asked).

## 2.2. Statistical analyses

All analyses were based on the intention-to-treat principle. 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 use all 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 by comparing them to those who were still included using independent *t*-test or  $X^2$  test when appropriate. 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.

The significance level was set at 0.05 (two-sided test). We did not correct for multiple comparisons as we were interested in detecting adverse effects of the surgical interventions. 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) [25]. Statistical analyses were performed with IBM SPSS, version 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).

## 3. 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. 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 completed at least one but not all neuropsychological tests for the following reasons: fatigue (*n* = 1), time constraints (*n* = 4), or the inability of the patient to perform the test(s) (*n* = 4). Patients who were lost to follow-up at three years had shorter mean disease duration at baseline (lost to follow-up  $10.4 \pm 4.4$  years and not lost to follow-up  $12.3 \pm 5.0$  years,  $p = 0.04$ ), but were not different on the following baseline characteristics: surgical target (GPi DBS or STN DBS), MDRS score, HADS scores, YMRS score, age at disease onset, and the Unified Parkinson's Disease Rating Scale Motor Examination (UPDRS-ME) score in off-drug phase.

Nine patients were re-operated, 8 patients from bilateral GPi DBS to bilateral STN DBS and in one patient with bilateral STN DBS the right electrode was changed to GPi DBS.

### 3.1. 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, a cut-off often used for dementia. Three years after DBS there were no between-group differences on any of the neuropsychological tests ( $p$ -values range between 0.17 and 0.87). Fig. 1 visually presents the fitted mean normed values resulting from the linear mixed model analyses. Normed scores based on the original data are presented in Table 2.

### 3.2. Psychiatric outcome

Results indicated no between-group differences 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. Complete case analysis (excluding the incomplete cases) as well as linear mixed model analyses excluding patients who were re-operated to a different target resulted in similar outcomes for the above mentioned cognitive and psychiatric measures (data not shown).

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). Based on the MINI, one GPi DBS patient reported suicidal ideations between the 1-year and 3-year assessment (GPi *n* = 42, STN *n* = 45). None of the patients attempted suicide. None of the patients who died (*n* = 8) committed suicide, one of these patients asked for physician assisted death because of disability due to disease progression.

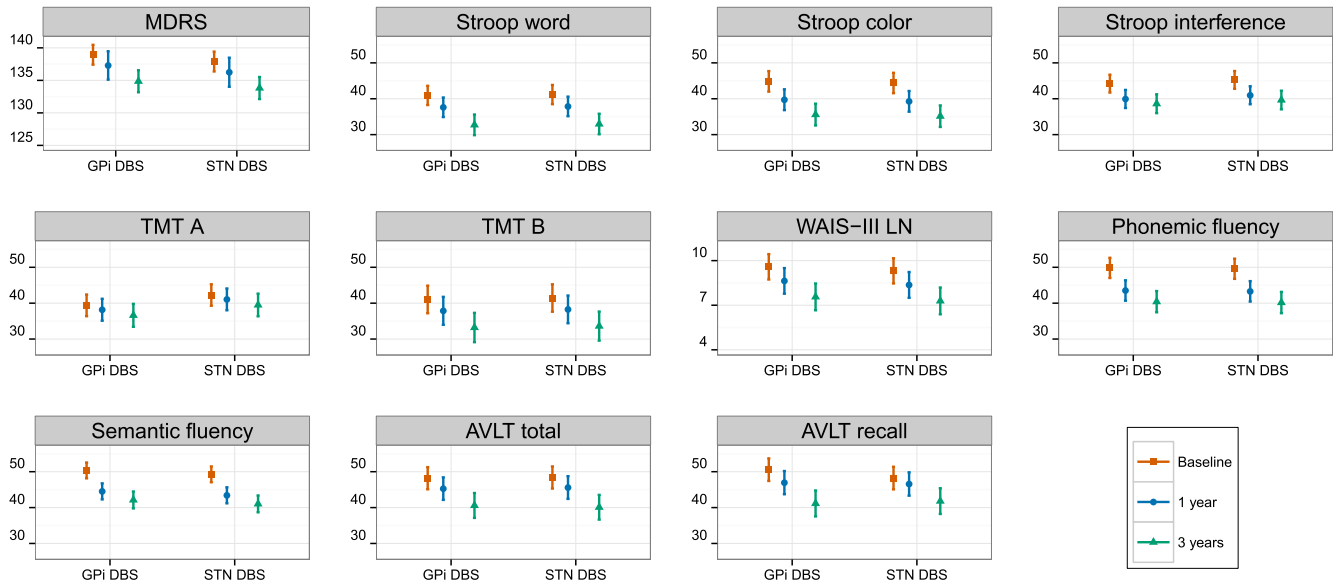
A total of 87 patients completed the MINI (GPi *n* = 42, STN *n* = 45) at the 3-year assessment. Regarding frequencies of diagnoses, two GPi DBS patients and four STN DBS patient experienced a depressive disorder between the 1-year and 3-year

**Table 1**  
Baseline demographic and clinical characteristics.

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

<sup>a</sup> Assessed by using a 3-day diary.

<sup>b</sup> Levodopa equivalent dose = regular levodopa dose  $\times$  1 + slow release levodopa  $\times$  0.75 + bromocriptine  $\times$  10 + apomorphine  $\times$  10 + ropinirole  $\times$  20 + pergolide  $\times$  100 + pramipexole  $\times$  100 + (regular levodopa dose + [slow release levodopa  $\times$  0.75])  $\times$  0.2 if taking entacapone.



**Fig. 1.** Fitted mean normed values resulting from the linear 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 <sup>a</sup>
	GPI DBS n = 62	STN DBS n = 62	GPI DBS n = 58	STN DBS n = 56	GPI DBS n = 39	STN DBS n = 39	
MDRS	138.7 (4.0)	138.1 (5.1)	137.3 (6.1) <sup>b</sup>	136.5 (7.4) <sup>b</sup>	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.

<sup>a</sup> 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.

<sup>b</sup> MDRS, GPI n = 21, STN n = 17. Change scores (baseline vs 3 years) can be found in appendix Table A.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.

assessment. Four GPI DBS patients experienced agoraphobia currently. Five GPI DBS patients and two STN DBS patients experienced substance induced psychotic disorders currently,

and one GPI DBS patient and two STN DBS patients experienced substance induced psychotic disorders between the 1-year and 3-year assessment. Complete frequencies of the MINI

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

	Baseline		1 year		3 year		P between-group GPI vs. STN
	GPI DBS	STN DBS	GPI DBS	STN DBS	GPI DBS	STN DBS	
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 at 3 years, using baseline as reference. YMRS scores were log 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.

can be found in [appendix Table A.1](#). Additionally, [Table A.2](#) displays the number of patients with a psychiatric disorder for the first time in life after surgery for the common psychiatric disorders.

### 3.3. Social functioning and marital satisfaction

In both DBS groups, the majority of patients were members of an organization 3 years after surgery (38 out of 42 GPi DBS patients and 40 out of 45 STN DBS patients). Most patients were members of a PD patient organization (GPi  $n = 31$ , STN  $n = 28$ ), and/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  $n = 28$ ).

Frequencies of patients and partners rating the various aspects of the marital satisfaction questionnaire as satisfied or very satisfied (the two highest ratings) were combined. On average 26 out of 32 (81%) GPi DBS patients 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 (very) satisfied. In the STN DBS group, 32 out of 37 patients (86%) rated the aspects as (very) satisfied, and 24 out of 31 partners did so (77%). Frequencies are displayed in [Appendix Table A.3](#). Additionally, a total of 15 patients experienced the loss of an important relationship in the year prior to the 3 years assessment (GPi  $n = 8$ , STN  $n = 7$ ).

## 4. Discussion

The current study indicates that 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 3 years after DBS [10]. 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” [9]. Our findings are therefore an important addition to the existing literature.

In our study, overall cognitive decline ranges between 0.3 and 1.0 SD 3 years after DBS compared to baseline (ranges of cognitive decline are not displayed specifically, but can be seen in [Table 2](#), subtracting 3 years scores from baseline scores). When visually inspecting [Fig. 1](#), there seems to be a steeper decline for both fluency tests in the first year after surgery (around 0.6 SD) compared to the decline between 1 year and 3 years (around 0.2 SD). Larger decline on fluency tests in comparison to other neuropsychological tests is a common finding reported after DBS [7,9]. A randomized controlled trial comparing unilateral GPi DBS and STN DBS showed persistence of impairment in verbal letter fluency also during off stimulation [26]. The authors suggested a specific surgical 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.

Aside from the three tests specifically mentioned above (phonemic fluency, semantic fluency, and the Stroop interference condition), the neuropsychological tests show an evenly distributed linear decline over time. Thereby indicating no specific operation effect for these tests, nor indicating a large change in the rate of cognitive decline between 1 and 3 years after DBS. This provides useful information for studies focusing on improving patient selection for DBS by predicting cognitive and/or psychiatric outcome

after DBS. Predictors for short-term outcome seem more relevant than those for long-term outcome.

Confirming our 1-year results [12], psychiatric outcome measures did not indicate a significant difference between GPi DBS and STN DBS 3 years after surgery. 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 [10].

Results on the MINI did not indicate a substantial number of psychiatric diagnoses after 3 years. Substance induced psychiatric disorders seem to occur more often after GPi DBS, which may be due to higher medication dosages compared to STN DBS. However, it is not possible to draw firm conclusions considering the small numbers (5 GPi DBS patients and 2 STN DBS patients). In the past experienced depressive disorders assessed at baseline (a depressive disorder experienced at any time prior to baseline assessment) are higher for the GPi DBS group. The influence of these past disorders is not clear, though it is reassuring that the DBS groups do not seem to differ on HADS scores at baseline as well as during the follow-up period. Additionally, it is noteworthy that more STN DBS patients experienced a depressive disorder for the first time between baseline and the 1-year assessment compared to GPi DBS patients. Three years after DBS, patients in both groups are active members of various organizations. Assessment of marital satisfaction does not indicate clear differences between GPi DBS and STN DBS 3 years after surgery. Nor does it indicate substantial discrepancies between the ratings of patients and their partners. However, more patients seem to be “very satisfied” in several domains compared to their partners. This seems to persist from baseline, as baseline frequencies display similar findings (published previously) [12]. At 3 years, based on the percentage of patients and partners in ratings ‘satisfied’ and ‘very satisfied’, it indicates the highest discrepancies for ‘support/encouragement’ and ‘considering wishes of partner’.

The dropout after 3 years was 32%, which can be of concern when interpreting results and one should apply caution here. However, a comparison between the patients still included after 3 years and those who dropped out did not reveal baseline differences on, for example, surgical target, MDRS score, and UPDRS-ME score in off drug phase. Descriptive reporting of psychiatric diagnoses, social functioning, and marital satisfaction may also limit interpretation. However, the findings do match our previous report [12] as well as our clinical experience and are reassuring findings contrasting the often in case studies reported negative psychiatric and social side effects after DBS.

Strengths of our study include the wide variety of outcome measures used, as well as the method of analyses including all available data (linear mixed model analyses). Finally, in chronic diseases long term follow-up is important, indicating the value of this study regarding neuropsychological and psychiatric outcomes up to 3 years after DBS. To our knowledge, this is only the second trial to compare neuropsychological and psychiatric outcome 3 years after GPi DBS and STN DBS [10].

## 5. Conclusion

Confirming the 1-year results from our trial, no pronounced differences on neuropsychological and psychiatric outcome were found three years after GPi DBS and STN DBS. A reassuringly low number of suicidal ideations and psychiatric diagnoses assessed by the MINI were reported. Social functioning and marital satisfaction are 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 they are considering which of these two surgical targets to choose.

## Study funding

The NSTAPS study group is supported by a grant from Stichting Parkinson Fonds (Hoofddorp, The Netherlands), Prinses Beatrix Fonds (The Hague, The Netherlands) (WAR05-0202), and Parkinson Vereniging (Bunnik, The Netherlands) (2013-R12). Funding sources had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.parkreldis.2016.09.018>.

## References

- [1] N.R. Williams, K.D. Foote, M.S. Okun, STN vs. GPi deep brain stimulation: translating the rematch into clinical practice, *Mov. Disord. Clin. Pract. Hob. I* (2014) 24–35.
- [2] V.C. Anderson, K.J. Burchiel, P. Hogarth, J. Favre, J.P. Hammerstad, Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease, *Arch. Neurol.* 62 (2005) 554–560.
- [3] K.A. Follett, F.M. Weaver, M. Stern, K. Hur, C.L. Harris, P. Luo, W.J. Marks Jr., J. Rothlind, O. Sagher, C. Moy, R. Pahwa, K. Burchiel, P. Hogarth, E.C. Lai, J.E. Duda, K. Holloway, A. Samii, S. Horn, J.M. Bronstein, G. Stoner, P.A. Starr, R. Simpson, G. Baltuch, A. De Salles, G.D. Huang, D.J. Reda, C.S.P.S. Group, Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease, *N. Engl. J. Med.* 362 (2010) 2077–2091.
- [4] V.J. Odekerken, J.A. Boel, B.A. Schmand, R.J. de Haan, M. Figeë, P. van den Munckhof, P.R. Schuurman, R.M. de Bie, N.s. group, GPi vs STN deep brain stimulation for Parkinson disease: three-year follow-up, *Neurology* 86 (2016) 755–761.
- [5] J.C. Rothlind, M.K. York, K. Carlson, P. Luo, W.J. Marks Jr., F.M. Weaver, M. Stern, K. Follett, D. Reda, C.S.P.S. Group, Neuropsychological changes following deep brain stimulation surgery for Parkinson's disease: comparisons of treatment at pallidal and subthalamic targets versus best medical therapy, *J. Neurol. Neurosurg. Psychiatry* 86 (2015) 622–629.
- [6] K. Witt, C. Daniels, J. Reiff, P. Krack, J. Volkmann, M.O. Pinsker, M. Krause, V. Tronnier, M. Kloss, A. Schnitzler, L. Wojtecki, K. Botzel, A. Danek, R. Hilker, V. Sturm, A. Kupsch, E. Karner, G. Deuschl, Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study, *Lancet Neurol.* 7 (2008) 605–614.
- [7] V. Voon, C. Kubu, P. Krack, J.L. Houeto, A.I. Troster, Deep brain stimulation: neuropsychological and neuropsychiatric issues, *Mov Disord* 21 (Suppl 14) (2006) S305–S327.
- [8] T.D. Parsons, S.A. Rogers, A.J. Braaten, S.P. Woods, A.I. Troster, Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis, *Lancet Neurol.* 5 (2006) 578–588.
- [9] H.L. Combs, B.S. Folley, D.T. Berry, S.C. Segerstrom, D.Y. Han, A.J. Anderson-Mooney, B.D. Walls, C. van Horne, Cognition, Depression Following Deep Brain Stimulation of the subthalamic nucleus and globus pallidus pars internus in Parkinson's disease: a meta-analysis, *Neuropsychol. Rev.* 25 (2015) 439–454.
- [10] F.M. Weaver, K.A. Follett, M. Stern, P. Luo, C.L. Harris, K. Hur, W.J. Marks Jr., J. Rothlind, O. Sagher, C. Moy, R. Pahwa, K. Burchiel, P. Hogarth, E.C. Lai, J.E. Duda, K. Holloway, A. Samii, S. Horn, J.M. Bronstein, G. Stoner, P.A. Starr, R. Simpson, G. Baltuch, A. De Salles, G.D. Huang, D.J. Reda, C.S.P.S. Group, Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes, *Neurology* 79 (2012) 55–65.
- [11] V.J. Odekerken, J.A. Boel, G.J. Geurtsen, B.A. Schmand, I.P. Dekker, R.J. de Haan, P.R. Schuurman, R.M. de Bie, N.s. Group, Neuropsychological outcome after deep brain stimulation for Parkinson disease, *Neurology* 84 (2015) 1355–1361.
- [12] J.A. Boel, V.J. Odekerken, G.J. Geurtsen, B.A. Schmand, D.C. Cath, M. Figeë, P. van den Munckhof, R.J. de Haan, P.R. Schuurman, R.M. de Bie, N.s. group, Psychiatric and social outcome after deep brain stimulation for advanced Parkinson's disease, *Mov. Disord.* 31 (2016) 409–413.
- [13] V.J. Odekerken, T. van Laar, M.J. Staal, A. Mosch, C.F. Hoffmann, P.C. Nijssen, G.N. Beute, J.P. van Vugt, M.W. Lenders, M.F. Contarino, M.S. Mink, L.J. Bour, P. van den Munckhof, B.A. Schmand, R.J. de Haan, P.R. Schuurman, R.M. de Bie, Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial, *Lancet Neurol.* 12 (2013) 37–44.
- [14] M.M. Hoehn, M.D. Yahr, Parkinsonism: onset, progression and mortality, *Neurology* 17 (1967) 427–442.
- [15] S. Mattis, Dementia Rating Scale Professional Manual, Psychological Assessment Resources, Inc, Odessa, Florida, USA, 1973.
- [16] J.R. Stroop, Studies of interference in serial verbal reactions, *J. Exp. Psychol.* 1935 (1935) 643–662.
- [17] R.M. Reitan, Trail Making Test Manual for Administration and Scoring, Reitan Neuropsychological Laboratory, Tucson, Arizona, USA, 1992.
- [18] D. Wechsler, WAIS-iii Administration and Scoring Manual, The Psychological Corporation, San Antonio, USA, 1997.
- [19] W.G. Rosen, Verbal fluency in aging and dementia, *J. Clin. Neuropsychology* 2 (1980) 135–146.
- [20] A. Rey, *L'examen clinique en psychologie*, Presses Universitaires de France, Paris, France, 1964.
- [21] R.C. Young, J.T. Biggs, V.E. Ziegler, D.A. Meyer, A rating scale for mania: reliability, validity and sensitivity, *Br. J. Psychiatry* 133 (1978) 429–435.
- [22] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, *Acta Psychiatr. Scand.* 67 (1983) 361–370.
- [23] B.W. Penninx, A.T. Beekman, J.H. Smit, F.G. Zitman, W.A. Nolen, P. Spinhoven, P. Cuijpers, P.J. De Jong, H.W. Van Marwijk, W.J. Assendelft, K. Van Der Meer, P. Verhaak, M. Wensing, R. De Graaf, W.J. Hoogendijk, J. Ormel, R. Van Dyck, N.R. Consortium, The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods, *Int. J. Methods Psychiatr. Res.* 17 (2008) 121–140.
- [24] D.V. Sheehan, Y. Lecrubier, K.H. Sheehan, P. Amorim, J. Janavs, E. Weiller, T. Hergueta, R. Baker, G.C. Dunbar, The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10, *J. Clin. Psychiatry* 59 (Suppl 20) (1998) 34–57, 22–33;quiz.
- [25] K.J. Rothman, No adjustments are needed for multiple comparisons, *Epidemiology* 1 (1990) 43–46.
- [26] M.S. Okun, H.H. Fernandez, S.S. Wu, L. Kirsch-Darrow, D. Bowers, F. Bova, M. Suelter, C.E.t. Jacobson, X. Wang, C.W. Gordon Jr., P. Zeilman, J. Romrell, P. Martin, H. Ward, R.L. Rodriguez, K.D. Foote, Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial, *Ann. Neurol.* 65 (2009) 586–595.