Brain Stimulation 13 (2020) 1697–1705

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Beneficial nonmotor effects of subthalamic and pallidal neurostimulation in Parkinson's disease☆

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ARTICLE INFO

Article history:
Received 7 November 2019
Received in revised form
7 August 2020
Accepted 25 September 2020
Available online 7 October 2020

Keywords:
Deep brain stimulation
Subthalamic nucleus
Globus Pallidus internus
Non-motor symptoms
Nonmotor symptoms
Quality of life

ABSTRACT

Background: Subthalamic (STN) and pallidal (GPi) deep brain stimulation (DBS) improve quality of life, motor, and nonmotor symptoms (NMS) in advanced Parkinson's disease (PD). However, few studies have compared their nonmotor effects.
Objective: To compare nonmotor effects of STN-DBS and GPi-DBS.
Methods: In this prospective, observational, multicenter study including 60 PD patients undergoing bilateral STN-DBS (n = 40) or GPi-DBS (n = 20), we examined PDQuestionnaire (PDQ), NMSScale (NMSS), Unified PD Rating Scale-activities of daily living, -motor impairment, -complications (UPDRS-II, –III, -IV), Hoehn&Yahr, Schwab&England Scale, and levodopa-equivalent daily dose (LEDD) preoperatively and at 6-month follow-up. Intra-group changes at follow-up were analyzed with Wilcoxon signed-rank or paired *t*-test, if parametric tests were applicable, and corrected for multiple comparisons. Inter-group differences were explored with Mann-Whitney-U/unpaired t-tests. Analyses were performed before and after propensity score matching which balanced out demographic and preoperative clinical characteristics. Strength of clinical changes was assessed with effect size.
Results: In both groups, PDQ, UPDRS-II, -IV, Schwab&England Scale, and NMSS improved significantly at follow-up. STN-DBS was significantly better for LEDD reduction, GPi-DBS for UPDRS-IV. While NMSS total score outcomes were similar, explorative NMSS domain analyses revealed distinct profiles: Both targets improved sleep/fatigue and mood/cognition, but only STN-DBS the miscellaneous (pain/olfaction) and attention/memory and only GPi-DBS cardiovascular and sexual function domains.

☆ Statistical analysis conducted by Dr. Haidar S. Dafsari, MD, University Hospital Cologne, Germany, and National Parkinson Foundation International Centre of Excellence, King's College Hospital, London, United Kingdom.

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https://doi.org/10.1016/j.brs.2020.09.019

Conclusions: To our knowledge, this is the first study to report distinct patterns of beneficial nonmotor effects of STN-DBS and GPi-DBS in PD. This study highlights the importance of NMS assessments to tailor DBS target choices to patients' individual motor and nonmotor profiles.

Introduction

In patients with Parkinson's disease (PD) an effective control of pharmaco-refractory tremor or motor complications in advanced disease stages may require a surgical therapy. Deep brain stimulation (DBS) provides a safe means of improving motor [1] and nonmotor symptoms (NMS) [2] as well as quality of life [3,4]. In principal, several DBS targets may be considered, each with their own advantages and disadvantages [5]. Subthalamic nucleus (STN) DBS enables a reduction of dopaminergic medication, whereas globus pallidus internus (GPi) DBS is more effective for the control of dyskinesia [3,6].

As reviewed by Kurtis et al. [7], studies using clinical scales or symptom-specific objective methods, show beneficial effects of STN-DBS on a wide range of NMS, such as sleep [8], urinary symptoms [9], gastrointestinal symptoms [10], olfaction [11], pain [12], and neuropsychiatric aspects [13,14], such as depression and anxiety. Ramirez-Zamora et al. [15] and Wang et al. [16] recently reviewed the current literature on target differences between STN and GPi DBS in PD on NMS such as cognition, mood and impulse control disorders. However, in contrast to the wealth of evidence available for nonmotor effects of STN-DBS, little is known about the effects of GPi-DBS on non-neuropsychiatric, non-neuropsychological NMS. Closely connected to this point, the differential effects of subthalamic and pallidal stimulation on a wide range of NMS have not been systematically investigated yet. Therefore, using comprehensive assessments with validated clinical scales, we explored NMS in STN-DBS and GPi-DBS. We hypothesized that, similar to STN-DBS, GPi-DBS has beneficial effects on the overall burden of NMS and that there are, however, differences regarding specific aspects of NMS for these two DBS targets.

Materials and methods

Design and ethical approval

This study was conducted as part of the DBS arm of the NILS study [17], a multicenter, observational, international study investigating NMS in patients with advanced PD in three DBS centers (ethical approval: Cologne master: 0012–145, German Clinical Trials Register number: 00006735; Sao Paulo: FMUSP–13716, 1.172.993; London: National Research Ethics Service SouthEast London REC3-10/H0808/141, 000010084). Results from the apomorphine, levodopa infusion therapy, and STN-DBS arms have previously been published [18,19]. All patients gave written consent prior to study procedures. The study was carried out in accordance with the Declaration of Helsinki.

Patients

PD diagnosis was based on the British Brain Bank criteria [20] and screening for DBS indication was carried out according to Movement Disorders Society guidelines [21]. As part of routine clinical assessments, levodopa challenge tests were considered satisfactory if >30% Unified PD Rating Scale (UPDRS)–III improvement was observed. Patients did not undergo DBS treatment if clinically relevant cognitive [60] and mood disorders were found in multi-disciplinary assessments by specialized neuropsychologists and neuropsychiatrists. To guarantee informed choice by patients, as per clinical routine, effect profiles of DBS targets were discussed with patients based on these assessments prior to surgery. Patients were informed about the possibilities of preferential outcomes of DBS targets based on previous studies and the experience of multi-disciplinary teams (e.g. STN-DBS for medication requirements and GPi-DBS for neurocognition and mood) [3].

Clinical assessment

Patients were assessed in the on-medication state (MedON) and in the medication and stimulation ON state (MedON/-StimON) at follow-up.

1) The Parkinson's Disease Questionnaire (PDQ), an instrument recommended by the Movement Disorders Society Scales Committee [22] for quality of life assessments in patients with PD, was collected. The 39-item PDQ and its abbreviated 8-item version [23,24] have been used in DBS studies before. The two versions consistently yield highly correlated results ($r = 0.96$) when converted to a Summary Index (PDQ-SI) [25]. We used this method, as only the abbreviated PDQ was available for a subset of patients (31/60). In all patients, the same PDQ version was used in pre- and postoperative assessments. The PDQ SI ranges from 0 (no impairment) to 100 (maximum impairment).
2) The UPDRS-I, –II, –III, -IV, Hoehn and Yahr, and Schwab and England scale were assessed for Mentation (range: 0–16), Activities of daily living (ranging from 0 to 48), Motor impairment (range: 0–108), Complications (range: 0–23), generalized motor dysfunction (range: 0–5), and ability to function in daily living (range: 0–100%). Higher scores indicate higher impairment in all scales, except for the Schwab and England Scale.
3) The NMS Scale (NMSS), a validated, well-established instrument, was used to survey nine domains of NMS (cardiovascular, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function, and miscellaneous consisting of items for pain, olfaction, weight gain, and excessive sweating) [26]. The NMSS ranges from 0 to 360 points and higher scores indicate higher NMS impairment.
4) The levodopa equivalent daily dose (LEDD) was used to assess medication requirements [27].

Statistical analysis

The assumption of normality was tested with the Shapiro-Wilk method. Inter-group differences of baseline parameters between the STN and GPi groups were analyzed with Mann-Whitney U-tests or unpaired t-tests, if parametric tests were applicable. Intra-group changes of outcome parameters from baseline to follow-up were tested with Wilcoxon signed-rank or paired t-tests. Multiple

comparisons, resulting from two DBS targets and the use of multiple tests, were corrected with Benjamini-Hochberg's method to balance out type I and type II errors [28]. Corrected p-values adjusted to the significance threshold $p < 0.05$ are presented unless stated otherwise. The magnitude of clinical responses were evaluated with relative changes ([mean $Test_{follow-up}$ − mean $Test_{baseline}$]/mean $Test_{baseline}$) and Cohen's effect size ([mean $Test_{baseline}$ − mean $Test_{follow-up}$]/SD $Test_{change\ scores}$) [29]. Confidence intervals were calculated for effect sizes based on noncentral t distribution [30]. Additionally, number needed to treat (NNT) were calculated ([1/percentage of patients improving >½ SD $Test_{baseline}$). Explorative Spearman correlations were calculated between change scores from baseline to follow-up for PDQ-8 SI and all other outcome parameters. Additionally, we explored correlations between changes of LEDD (L-dopa and dopamine agonists) and all other outcome parameters.

Furthermore, as our study included data from a real-life observational study of NMS, we used propensity score matching as a means to increase causal inference and minimize selection bias. The aim here was to find subcohorts of patients undergoing STN-DBS and GPi-DBS with accurately balanced preoperative demographic and clinical characteristics. All analyses were conducted with SPSS 24.0.0.0 (IBM Corp.) and Propensity Score Matching for SPSS (version 3.04) by Thoemmes et al. [31]. Variables included for propensity score matching were baseline PDQ SI, and NMSS total score, UPDRS-III MedON, and LEDD, and balance of covariates was tested for age at intervention, sex, UPDRS-I, −II, −III MedOFF, and -IV, and NMSS domains. Nearest-neighbor matching with a 0.25 caliper [32] without replacement was conducted employing a 1:2 ratio (GPi:STN). Balance diagnostics were conducted based on Cohen's effect size $|d|<0.25$ [32]. Subsequently, all analyses of clinical changes from baseline to follow-up were also carried out for the thus identified matched cohort. Even though the propensity score method was used to construct an accurately matching cohort, acknowledging the possibility of unknown confounders, we used independent samples tests for all further statistical tests for comparisons between the STN-DBS and GPi-DBS groups [33].

Results

Of the 75 consecutive patients with PD screened in our inpatient departments between August 2013 and December 2014, 60 patients underwent STN-DBS or GPi-DBS and were included in the final analysis (Fig. 1). In the STN-DBS group 40 patients (12 female) were aged 57.7 years ± 10.8 with 11.3 years ± 5.0 disease duration. In the GPi-DBS group 20 patients (9 females) were aged 56.6 years ± 9.8 with 11.4 years ± 3.9 disease duration. The median Hoehn and Yahr was 2.0 (interquartile range: 2.0–2.5) in the STN-DBS group and 2.5 (interquartile range: 2.0–3.0) in the GPi-DBS group.

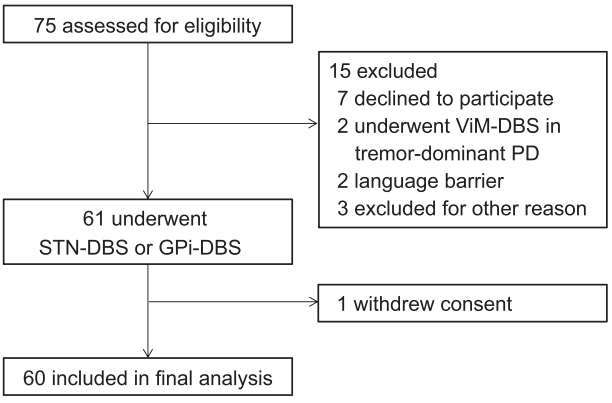

Fig. 1. Enrollment.

Propensity score matching resulted in a matched study cohort of 48 patients including 30 patients undergoing STN-DBS and 18 patients undergoing GPI-DBS (Table 1).

The results reported in this manuscript relate to the matched cohort. In addition, outcome changes in the original cohort are reported in the online supplementary tables e–1, e–2, e–3, and e–4.

Baseline characteristics in the matched cohort

Diagnostic statistics indicated a good balance of demographic and all main outcome parameters between the STN-DBS and GPi-DBS groups of the matched cohort. Accordingly, no significant differences were found for these parameters between the two groups. Additionally, as we explored NMSS domains, post-hoc balance diagnostic tests were also performed for these covariates and revealed a good balance for all domains except for cardiovascular symptoms and sexual function. As the NMSS domains were only used for exploratory analyses and the NMSS total score, in which the domains are summarized, was well balanced, this solution seemed acceptable.

Changes of outcomes at follow-up in the matched cohort

In both groups, PDQ SI, UPDRS-II, UPDRS-IV, Schwab and England Scale, and NMSS improved significantly from baseline to follow-up (all $p < 0.02$) (Table 2). As expected, LEDD reduction was significant for STN-DBS ($p < 0.001$) and not significant for the GPi-DBS group ($p = 0.325$). Post-hoc analyses of NMSS domains (Fig. 2) in the STN-DBS group resulted in significant improvements of sleep/fatigue ($p = 0.017$), mood/cognition ($p = 0.031$), attention/memory ($p = 0.035$), and the miscellaneous domain ($p = 0.008$) driven by olfaction (baseline: 2.6 ± 3.6; follow-up 1.3 ± 3.4; $p = 0.027$). In the GPi-DBS group, cardiovascular ($p = 0.020$), sleep/fatigue ($p = 0.010$), mood/cognition ($p = 0.001$), and sexual function ($p = 0.042$) improved at follow-up.

In the STN-DBS group, effect sizes were 'large' for LEDD and 'moderate' for UPDRS-II, -IV, and NMSS (Table 3). UPDRS-I and −III effect sizes were negligible and PDQ SI and Schwab and England scale were 'moderate'. In the GPi-DBS group, effect sizes were 'small' for UPDRS-I, Hoehn and Yahr scale, and LEDD reduction, 'moderate' for Schwab and England Scale and UPDRS-II, and 'large' for PDQ SI, UPDRS-IV, and NMSS. NNT results were favorable for STN-DBS regarding LEDD reduction, UPDRS-I, and −III (Table 4). Conversely, they were better for GPi-DBS regarding UPDRS-II, -IV, Hoehn and Yahr Scale, PDQ SI, and NMSS. NNT of Schwab and England Scale was balanced between both DBS targets.

A reduction of levodopa and of dopamine agonists was not correlated to changes of outcome parameters in STN- and GPi DBS (all $p > 0.05$).

Discussion

In this prospective, observational, international, multicenter study, we observed significant beneficial effects of STN-DBS and GPi-DBS on global NMS burden and specific aspects of NMS.

Motor disorder

In line with previous studies, motor outcomes, such as UPDRS-II, -IV, and Schwab and England Scale improved significantly for both

Table 1
Demographic characteristics and outcome parameters at baseline in unmatched and matched cohorts.

	Unmatched cohort						p	Matched cohort						p
	STN-DBS			GPi-DBS				STN-DBS			GPi-DBS			
	n	mean	SD	n	mean	SD		n	mean	SD	n	mean	SD	
Age	40	57.7	10.8	20	56.6	9.8	0.709	30	58.5	12.4	18	58.1	9.1	0.896
Disease duration	40	11.3	5.0	20	11.4	3.9	0.938	30	10.4	5.6	18	11.0	4.0	0.708
Sex (female/male) [%]	40	(12/28)	[30/70%]	20	(9/11)	[45/55%]	0.251	30	(11/19)	[36/63%]	18	(7/11)	[39/61%]	0.878
PDQ SI	40	33.6	13.5	20	29.3	12.1	0.572	30	27.8	11.5	18	28.2	12.2	0.831
UPDRS-I	40	2.4	1.8	20	2.9	2.3	0.497	30	1.9	1.6	18	2.7	2.2	0.278
UPDRS-II	40	11.5	6.2	20	9.6	5.3	0.242	30	11.2	5.1	18	10.2	5.2	0.518
UPDR-III MedOFF	40	42.2	9.6	20	41.4	8.1	0.735	30	42.2	12.6	18	42.1	8.2	0.962
UPDRS-III MedON	40	19.5	8.6	20	14.2	7.7	**0.023**	30	16.0	7.0	18	15.2	7.4	0.728
UPDRS-IV	40	5.4	3.8	20	4.6	3.0	0.414	30	5.6	3.4	18	4.6	3.1	0.306
H&Y (median) [interquartile range]	40	(2.0)	[2.0–2.5]	19	(2.5)	[2.0–3.0]	0.186	30	(2.0)	[2.0–2.5]	18	(2.0)	[2.0–2.5]	0.551
S&E	40	83.8	8.1	20	83.0	9.2	0.760	30	84.7	6.8	18	82.2	9.4	0.285
LEDD	40	1195.6	459.4	20	1161.0	533.2	0.795	30	1164.1	449.2	18	1166.2	563.2	0.988
NMSS	40	61.4	36.5	20	61.5	25.8	0.535	30	49.8	30.3	18	58.8	24.2	0.144
Cardiovascular	40	1.2	1.8	20	2.0	2.9	0.478	30	1.2	2.1	18	2.1	3.0	0.317
Sleep/fatigue	40	13.7	8.9	20	14.5	7.4	0.520	30	13.1	10.1	18	13.3	6.8	0.536
Mood/cognition	40	9.6	12.6	20	12.5	13.8	0.347	30	7.8	10.0	18	11.7	14.3	0.421
Perceptual problems/hallucinations	40	1.2	3.4	20	1.0	2.8	0.870	30	0.5	2.2	18	0.9	2.9	0.703
Attention/Memory	40	4.1	5.7	20	4.5	4.0	0.178	30	3.1	4.1	18	4.1	3.1	0.099
Gastrointestinal	40	5.6	5.7	20	4.6	5.2	0.507	30	4.9	5.9	18	4.6	5.4	0.931
Urinary	40	9.4	9.3	20	6.0	5.3	0.225	30	7.6	7.9	18	6.4	5.3	0.966
Sexual function	40	5.1	8.3	20	6.3	5.0	0.051	30	3.0	5.6	18	5.6	4.8	**0.010**
Miscellaneous	40	11.6	7.5	20	10.4	8.4	0.418	30	8.7	6.3	18	10.1	7.9	0.669

Abbreviations: GPi-DBS = Pallidal stimulation; **H&Y** = Hoehn and Yahr Scale, **LEDD** = levodopa equivalent daily dose; **NMSS** = Non-motor Symptom Scale; **PDQ SI** = Parkinson's Disease Questionnaire Summary Index; **S&E** = Schwab and England Scale; **STN-DBS** = Subthalamic stimulation; **UPDRS-I, -II, -III, and -IV** = Unified Parkinson's Disease Rating Scale-cognition, -activities of daily living, -motor impairment, and -motor complications.
Balance of covariates was assessed with Cohen's d = (mean STN - mean GPi)/SD GPi. A good balance of covariates (Cohen's d < 0.25) was found for all demographic parameters and main outcomes. Post-hoc, balance diagnostics were additionally conducted for NMSS domains with good performance in all domains except for 'Cardiovascular' and 'Sexual functions'. Uncorrected p values are presented for all comparisons of subthalamic and pallidal stimulation regarding demographic and clinical outcome parameters.

Table 2
Outcomes at baseline and follow-up in subthalamic and pallidal stimulation for the matched cohort.

		STN-DBS						GPi-DBS				STN- vs.GPi-DBS	
		Baseline		Follow-up				Baseline		Follow-up			
	n	mean	SD	mean	SD	**p**[a]	**n**	mean	SD	mean	SD	**p**[a]	**p**[b]
PDQ SI	28	28.8	10.8	20.9	12.6			28.2	12.2	16.7	8.9		
UPDRS-I	28	2.0	1.7	1.7	1.3	0.401	17	2.7	2.2	1.9	1.5	0.188	0.643
UPDRS-II	28	11.3	5.3	9.4	5.9	**0.014**	17	10.4	5.2	5.9	4.9	**0.014**	0.071
UPDRS-III	25	15.9	7.2	14.2	7.8	0.325	17	15.3	7.6	16.4	9.9	0.681	0.329
UPDRS-IV	28	5.4	3.3	3.4	3.0	**0.014**	17	4.5	3.1	1.4	1.6	**<0.001**	0.259
H&Y	28	2.3	0.4	2.2	0.6	0.551	18	2.4	0.5	2.3	0.4	0.325	0.520
S&E	28	84.3	6.9	89.3	8.1	**0.011**	17	82.4	9.7	89.4	7.5	**0.014**	0.798
LEDD	26	1214.8	435.4	676.8	390.1	**<0.001**	18	1166.2	563.2	1029.5	526.4	0.325	**0.008**
NMSS	28	51.6	30.5	34.9	22.3	**0.009**	18	58.8	24.2	37.2	14.3	**0.009**	0.511
Cardiovascular	28	1.0	2.0	1.0	2.6	0.749	18	2.1	3.0	0.5	1.1	**0.020**	0.146
Sleep/fatigue	28	13.5	10.3	8.2	7.0	**0.017**	18	13.3	6.8	8.5	6.4	**0.010**	0.066
Mood/cognition	28	8.3	10.2	4.6	6.5	**0.031**	18	11.7	14.3	2.2	3.4	**0.001**	0.664
Perceptualproblems/hallucinations	28	0.5	2.3	0.3	0.9	0.336	18	0.9	2.9	0.3	0.7	0.461	0.509
Attention/memory	28	3.3	4.2	2.1	2.4	**0.035**	18	4.1	3.1	3.1	2.6	0.199	0.229
Gastrointestinal	28	5.1	6.1	4.4	6.6	0.146	18	4.6	5.4	4.5	5.9	0.925	0.451
Urinary	28	7.9	8.0	6.7	7.6	0.183	18	6.4	5.3	6.4	6.3	0.925	0.389
Sexual function	28	3.3	5.8	2.3	5.0	0.096	18	5.6	4.8	3.2	4.6	**0.042**	0.373
Miscellaneous	28	8.8	6.4	5.3	6.3	**0.008**	18	10.1	7.9	8.4	7.5	0.537	0.829

Abbreviations: GPi-DBS = Pallidal stimulation; **H&Y** = Hoehn and Yahr Scale, **LEDD** = levodopa equivalent daily dose; **NMSS** = Non-motor Symptom Scale; **PDQ SI** = Parkinson's Disease Questionnaire Summary Index; **S&E** = Schwab and England Scale; **STN-DBS** = Subthalamic stimulation; **UPDRS-I, -II, -III, and -IV** = Unified Parkinson's Disease Rating Scale-cognition, -activities of daily living, -motor impairment, and -motor complications.
[a] Wilcoxon signed-rank test, respectively paired *t*-test, when parametric tests were applicable, with Benjamini-Hochberg correction for multiple comparisons due to multiple outcome parameters and two DBS targets.
[b] Mann-Whitney *U* test, respectively unpaired *t*-test, when parametric tests were applicable, with raw p-values. After Benjamini-Hochberg correction only LEDD in the unmatched cohort remained significant (p < 0.001).

DBS targets [3,6,34]. As expected, LEDD reduction was greater in the STN-DBS group [3,35] and motor complications improved more in the GPi-DBS group [6]. These results were confirmed by effect size and NNT.

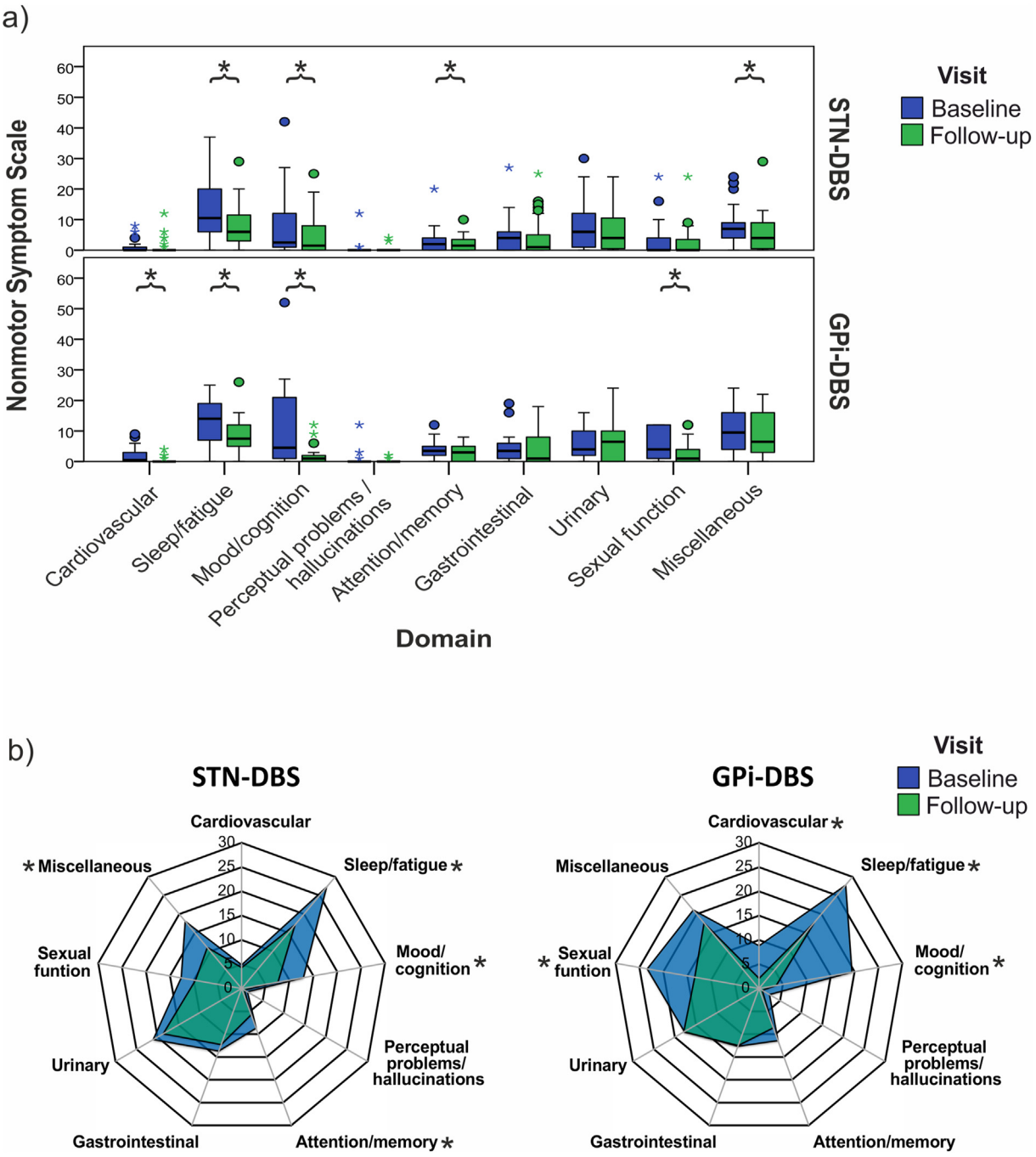

Fig. 2. Non-motor Symptom Scale at baseline and follow-up in the matched cohort for subthalamic and pallidal stimulation.
Abbreviations: GPi-DBS = Pallidal deep brain stimulation; STN-DBS = Subthalamic stimulation.
Fig. 2 illustrates Non-motor Symptom Scale (NMSS) domains at baseline (blue) and follow-up (green) for the STN-DBS and GPi-DBS groups in (a) clustered box-plots and (b) radar charts.
Significant intra-group improvements from baseline to follow are highlighted with black stars.
In Fig. 2a, outliers are represented by blue/green dots (2–3 SD), extreme outliers by small blue/green stars (>3 SD). In Fig. 2b, NMSS domain mean scores are presented as percentage of maximum domain scores. Bigger blue/green areas illustrate more severe NMS impairment.
In the STN-DBS group, beneficial effects were found for the NMSS domains sleep/fatigue, mood/cognition, attention/memory, and miscellaneous. In the GPi-DBS group, beneficial effects were observed for the NMSS domains cardiovascular, sleep/fatigue, mood/cognition, and sexual function.

Nonmotor symptoms

In accordance with previous studies, we observed an improvement of global NMS burden in patients undergoing STN-DBS [36]. To our knowledge, the present study is the first to report similar beneficial effects of GPi-DBS on global NMS. Additionally, as a novel observation, here we report beneficial effects of bilateral GPi-DBS on a range of specific NMS, such as cardiovascular and sexual function.

Few studies have compared NMS in STN-DBS and GPi-DBS [7]. Confirming results from previous studies, we observed an improvement of sleep/fatigue for both, STN-DBS and GPi-DBS [6].

Table 3
Relative changes and effect sizes for the matched cohort.

	Relative change		Effect size (CI)		Classification	
	STN-DBS	GPi-DBS	STN-DBS	GPi-DBS	STN-DBS	GPi-DBS
PDQ SI	−27.5	−40.9	0.53 (0.13–0.92)	0.86 (0.31–1.40)	moderate	large
UPDRS-I	−15.0	−28.3	0.19 (−0.19–0.56)	0.36 (−0.14–0.85)	–	small
UPDRS-II	−16.8	−42.9	0.55 (0.15–0.94)	0.76 (0.21–1.29)	moderate	moderate
UPDRS-III	−10.8	7.3	−0.01 (0.00–0.05)	0.17 (−0.41–0.73)	–	–
UPDRS-IV	−37.1	−70.1	0.56 (0.16–0.96)	1.09 (0.47–1.68)	moderate	large
H&Y	−3.9	−5.7	0.14 (−0.23–0.51)	0.27 (−0.20–0.74)	–	small
S&E	5.9	8.6	0.67 (0.25–1.08)	0.72 (0.17–1.24)	moderate	moderate
LEDD	−44.3	−11.7	1.19 (0.68–1.69)	0.27 (−0.20–0.74)	large	small
NMSS	−32.4	−36.8	0.65 (0.24–1.06)	0.96 (0.39–1.51)	moderate	large
Cardiovascular	0.0	−76.3	0.00 (0.00–0.00)	0.62 (0.11–1.12)	–	moderate
Sleep/fatigue	−39.2	−36.3	0.54 (0.14–0.94)	0.75 (0.22–1.27)	moderate	moderate
Mood/cognition	−44.6	−81.4	0.34 (−0.04–0.72)	0.74 (0.21–1.25)	small	moderate
Perceptual problems/hallucinations	−53.3	−68.8	0.17 (−0.20–0.54)	0.20 (−0.27–0.67)	–	small
Attention/memory	−37.0	−24.3	0.40 (0.01–0.78)	0.27 (−0.20–0.74)	small	small
Gastrointestinal	−12.7	−1.2	0.16 (−0.21–0.53)	0.01 (−0.45–0.47)	–	–
Urinary	−14.9	0.9	0.22 (−0.16–0.59)	0.01 (−0.36–0.36)	small	–
Sexual function	−28.6	−42.6	0.30 (−0.08–0.68)	0.52 (0.02–1.01)	small	moderate
Miscellaneous	−39.8	−16.5	0.55 (0.15–0.95)	0.20 (−0.27–0.67)	moderate	small

Abbreviations: CI = confidence interval; **ES** = effect size; **GPi-DBS** = Pallidal stimulation; **H&Y** = Hoehn and Yahr Scale, **LEDD** = levodopa equivalent daily dose; **NMSS** = Non-motor Symptom Scale; **PDQ SI** = Parkinson's Disease Questionnaire Summary Index; **RC** = relative change; **S&E** = Schwab and England Scale; **STN-DBS** = Subthalamic stimulation; **UPDRS-I, -II, -III, and -IV** = Unified Parkinson's Disease Rating Scale-cognition, -activities of daily living, -motor impairment, and -motor complications.
RC = (mean $Test_{follow\text{-}up}$ − mean $Test_{baseline}$)/$Test_{baseline}$.
ES = (mean $Test_{baseline}$ − mean $Test_{follow\text{-}up}$)/SD $Test_{change\ score}$.
ES: 'small' (0.20–0.49), 'moderate' (0.50–0.79), and 'large' (≥0.80).

Also in line with previous studies and guidelines on STN and GPi DBS, based on the greater relative change and effect size, we observed a better outcome of mood/cognition NMS in GPi-DBS [3,37]. The data from the original cohort confirms results from earlier studies on lower urinary tract symptoms in patients undergoing STN-DBS and GPi-DBS which reported beneficial effects only for STN-DBS [38,39], which in turn was also confirmed by other studies including urodynamic examinations [9]. As a beneficial effect of STN-DBS on urological symptoms was only observed in the original cohort before matching, larger randomized studies of urological outcomes are required to confirm these results. Similarly, for perceptual problems/hallucinations, as significant clinical improvements were observed before but not after matching and larger randomized trials are required. The fact that an improvement of perceptual problems/hallucinations was only observed in the STN-DBS group may be closely connected to the reduction of dopaminergic medication, which was approximately 50% in the STN-DBS group. This observation highlights, that mild to moderate MedON hallucinations may be considered as a nonmotor indication for STN-DBS rather than GPi-DBS as the LEDD reduction may be particularly beneficial. The present work also confirms previous studies which reported an improvement of pain [12] and olfaction [11] in patients undergoing STN-DBS. Lastly, comparing NMSS total scores, both DBS targets resulted in a significant improvement of global NMS burden and no significant difference was found between targets. However, the larger effect size and smaller NNT may be an indicator that GPi-DBS could result in a slightly advantageous global nonmotor outcome.

Table 4
Number needed to treat for the matched cohort.

	Number neededto treat	
	STN-DBS	GPi-DBS
PDQ SI	1.65	1.29
UPDRS-I	2.33	2.43
UPDRS-II	2.54	1.55
UPDRS-III	2.78	3.40
UPDRS-IV	2.54	1.55
H&Y	3.50	2.57
S&E	2.00	2.00
LEDD	1.30	3.00
NMSS	2.00	1.64
Cardiovascular	3.50	2.57
Sleep/fatigue	2.54	1.64
Mood/cognition	3.50	2.57
Perceptual problems/hallucinations	27.78	9.01
Attention/Memory	3.50	2.25
Gastrointestinal	4.00	5.99
Urinary	4.67	2.57
Sexual function	5.59	2.57
Miscellaneous	2.00	2.25

Abbreviations: GPi-DBS = Pallidal stimulation; **H&Y** = Hoehn and Yahr Scale, **LEDD** = levodopa equivalent daily dose; **NMSS** = Non-motor Symptom Scale; **PDQ SI** = Parkinson's Disease Questionnaire Summary Index; **S&E** = Schwab and England Scale; **STN-DBS** = Subthalamic stimulation; **UPDRS-I, -II, -III, and -IV** = Unified Parkinson's Disease Rating Scale-cognition, -activities of daily living, -motor impairment, and -motor complications.
NNT = (1/% of patients who improved > ½ $SD_{baseline}$) x 100.

One has to acknowledge that NMS are defined by exclusion and are the result of heterogeneous pathomechanisms [40,41]. Therefore, there is a strong case for assessing motor features as well as not only neuropsychological and neuropsychiatric NMS, but also a wider range of nonmotor aspects of PD. The aim of this assessment, e.g. with the validated, well-established NMSS used in this study, is to provide a well-informed choice of DBS target ('precision medicine') rather than the commonly used 'one-size-fits-all' approach [5,42]. The particular salience of this point is also based on observations from previous studies that NMS have a stronger relative importance for quality of life than motor examination as well as motor complications [43].

Quality of life

Based on a greater relative change, larger effect size, and smaller NNT in the matched GPi-DBS group, a slightly advantageous effect on quality of life was observed for this DBS target. This is also in accordance with a meta-analysis of previous comparative studies

[44] which showed a 40% quality of life improvement after GPi-DBS as observed in our study. The 25% quality of life improvement observed in our STN-DBS group strikingly resembles results of a randomized clinical trial by Deuschl et al. [4]. The underlying factors for a seemingly greater quality of life improvement in patients undergoing GPi-DBS are not well understood and seem to be not entirely explained by motor outcomes. Improvements of NMS and activities of daily living seem to be closely connected to QoL improvement. While the STN may still be the first choice as DBS target in many centers, mainly because LEDD and frequency of medication intake can be reduced to a greater extent, there is an ongoing debate about the optimal DBS target. Finding the most appropriate choice of DBS target based on individual profiles of motor and nonmotor aspects of PD, may contribute to achieving better quality of life outcomes.

Biological rationale

There are different mechanisms of action that may mediate the observed motor and nonmotor effects of DBS:

1) Direct effect: In line with the concept of a functional tripartition of the STN and the GPi [45], neurostimulation of specific subregions of these target nuclei elicits differential effect profiles. For example, studies have observed beneficial effects of neurostimulation of the nonmotor parts of the STN on mood and attention [41] or of the motor part of the GPi on motor impairment [46].
2) Network effects in basal ganglia-thalamo-cortical loops: As examples for network effects, STN-DBS induces blood flow changes in (1) cortex regions connected to the associative part of the STN correlating to cognitive functions [47,48] or (2) forebrain cortical centers involved in urinary bladder control correlating with voiding urge [9]. Furthermore, Cury et al. reported that STN-DBS modulates glucose metabolism in (3) the midbrain, cerebellum, and right frontal lobe correlating to beneficial effects on olfactory functions [49]. Middlebrooks et al. have reported beneficial effects of Globus pallidus externa stimulation on sleep and discussed that this effect may be mediated by pallido-thalamo-cortical loops crucial for the sleep and wake states, e.g. via projections to the reticular thalamic nucleus [50] which regulates local sleep [51]. However, the network effects of pallidal stimulation have been studied less, in particular for nonmotor outcomes [52].
3) Spread of current to regions in proximity of the target nuclei: Beneficial effects of STN-DBS on, e.g., sleep may be associated with a spread of current to neighbouring structures of the STN, such as the pedunculopontine nucleus [53], which is located approximately 5 mm ventral to the STN [54] and regulates the sleep-wake cycle [55].
4) LEDD reduction can result in less side-effects of dopaminergic medication, such as hallucinations, gastrointestinal symptoms and somnolence. However, we observed no linear relationship between LEDD total or LEDD of dopamine agonists in STN-DBS or GPi-DBS or pooled data. Nonetheless, in particular in the STN-DBS group, a postoperative reduction of LEDD below patient-specific side-effect thresholds may be an important contributing factor to the non-motor effects observed in this study. The present study can only report “net effects” of neurostimulation and reduction of dopaminergic medication and future studies including larger cohorts are needed to distinguish between these factors.

In summary, network modulation achieved by STN-DBS is currently being researched intensively [41,56,57]. However, little is known about non-motor outcomes following GPi-DBS. Future studies are needed to investigate a wide range of non-motor effects of pallidal stimulation.

Limitations

Propensity score matching indicated a good balance of demographic characteristics and clinical outcome parameters at baseline [59]. However, one has to acknowledge that while this method accounts for known outcome parameters/covariates of analyses, thus minimizing selection bias, an unbalance of unknown parameters cannot be ruled out. In our study, impulse control disorders were not systematically assessed and mood and cognition were only assessed with the corresponding sections of the UPDRS and NMSS. Further studies including detailed assessments of these specific factors are needed. While propensity score matching has advantages as a method providing a ‘pseudo-randomization’ in observational studies, it cannot replace a randomized clinical trial. However, in certain scenarios, such as in our database, the real-life use of treatment strategies may be of scientific interest and, here, propensity score matching provides an accurate approach to increase causal inference. An inclusion of a wide range of demographic and clinical parameters in the matching procedure and an implementation of strict comprehensive diagnostic statistics increase the validity of our results as well as the power of our statistical analyses. Although our cohort size was one of the biggest in studies on NMS, it may still be considered rather small (original cohort $n = 60$ and matched cohort $n = 48$). Even stricter matching configurations, such as the use of a 0.1 caliper, or Cohen’s d threshold $|d| < 0.1$, would have resulted in even smaller cohort sizes and were therefore not appropriate. As the present work analyzed data from an observational study, we did not conduct blinded assessments of clinical outcomes and the follow-up period of 6 months was short. Comparing long-term nonmotor outcomes for STN-DBS and GPi-DBS will provide a better understanding of preferential DBS targets and further studies in randomized controlled trials with longer follow-up periods are needed to confirm the findings presented here. To help the interpretation of our results, Cohen’s effect sizes were calculated to classify clinical responses into ‘small’, ‘moderate’, and ‘large’. Although confidence intervals of effect sizes were wide due to the relatively small cohort size, this approach was chosen because an alternative method, the minimal clinically important difference, to our knowledge, has not been reported for the NMSS and its domains yet [58].

Conclusion

This is the first study to systematically investigate a wide range of nonmotor aspects of PD in patients undergoing bilateral STN-DBS and GPi-DBS. We observed beneficial effects of subthalamic and pallidal DBS on global NMS burden and specific aspects of NMS. Sleep/fatigue and mood/cognition improved in both DBS targets, whereas distinct profiles were found for the attention/memory and miscellaneous domains, which improved in the STN-DBS group, and cardiovascular and sexual function domains, which improved in the GPi-DBS group. This study highlights the importance of comprehensive assessments of motor as well as nonmotor aspects of PD in the preoperative screening for DBS to enable better informed choices of DBS targets for individual patients. Implementing these assessments in clinical practice, could provide precisely personalized patient care. Further prospective, randomized, controlled trials reporting nonmotor outcomes for different DBS targets and other treatment strategies are required to compare their differential effects.

Author contributions

Haidar Salimi Dafsari – study concept and design, data acquisition, data analysis, drafting of the manuscript.

Maria Gabriela dos Santos Ghilardi – study concept and design, data acquisition, critical revision of the manuscript.

Alexandra Rizos – data acquisition, critical revision of the manuscript.

Veerle Visser-Vandewalle – surgical intervention, data acquisition, critical revision of the manuscript.

Keyoumars Ashkan – surgical intervention, data acquisition, critical revision of the manuscript.

Monty Silverdale – critical revision of the manuscript.

Julian Evans – critical revision of the manuscript.

Raquel C.R. Martinez – data acquisition, critical revision of the manuscript Rubens G. Cury – data acquisition, critical revision of the manuscript Stefanie T. Jost – critical revision of the manuscript Michael T. Barbe – critical revision of the manuscript Gereon R. Fink – critical revision of the manuscript.

Angelo Antonini – critical revision of the manuscript.

K. Ray Chaudhuri – data acquisition, critical revision of the manuscript.

Pablo Martinez-Martin – data analysis, critical revision of the manuscript.

Erich Talamoni Fonoff – study concept and design, surgical intervention, data acquisition, critical revision of the manuscript Lars Timmermann – study concept and design, data acquisition, critical revision of the manuscript **Co-investigators:** see separate file "Members of the Nonmotor Parkinson's Disease Study Group of the International Parkinson's and Movement Disorders Society"

Financial disclosures

Haidar S. Dafsari was funded by the Prof. Dr. Klaus Thiemann Foundation, the Koeln Fortune Program, and the Felgenhauer Foundation and has received honoraria by Boston Scientific and Medtronic which manufacture deep brain stimulation systems used in this study.

Maria Gabriela dos Santos Ghilardi reports no potential conflict of interest. Veerle Visser-Vandewalle is a member of the advisory boards and reports consultancies for Medtronic and Boston Scientific which manufacture deep brain stimulation systems used in this study.

Declaration of competing interest

Keyoumars Ashkan has received honoraria for educational meetings, travel and consultancy from Medtronic and Boston Scientific which manufacture deep brain stimulation systems used in this study.

Monty Silverdale reports no potential conflict of interest.

Julian Evans reports no potential conflict of interest.

Raquel C.R. Martinez reports no potential conflict of interest.

Rubens G. Cury reports no potential conflict of interest.

Stefanie T. Jost reports no potential conflict of interest.

Michael T. Barbe reports grants from Boston Scientific and Medtronic which manufacture deep brain stimulation systems used in this study.

Gereon R. Fink reports no potential conflict of interest.

Angelo Antonini reports personal consultancy fees from Medtronic and Boston Scientific which manufacture deep brain stimulation systems used in this study.

K. Ray Chaudhuri reports no potential conflict of interest.

Pablo Martinez-Martin reports no potential conflict of interest.

Erich Talamoni Fonoff is a consultant for Medtronic and Boston Scientific which manufacture deep brain stimulation systems used in this study.

Lars Timmermann reports grants, personal fees and nonfinancial support from Medtronic and Boston Scientific which manufacture deep brain stimulation systems used in this study.

This paper is independent research funded by the German Research Foundation (Grant KFO 219), the National Institute of Health Research (NIHR) Mental Health Biomedical Research Centre and Dementia Unit at South London and Maudsley NHS Foundation Trust and King's College London. Additionally, an unrestricted peer reviewed educational grant was provided to support coordination of the UK dataset from Medtronic.

Acknowledgements

The authors wish to thank patients for their consent to participate in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.09.019.

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Glossary

DBS: deep brain stimulation
LEDD: levodopa equivalent daily dose
NMS: non-motor symptoms
NMSS: Non-motor Symptom Scale
NNT: number needed to treat
PD: Parkinson's disease
PDQ-8 SI: 8-item PD Questionnaire Summary Index
QoL: quality of life
STN: subthalamic nucleus
UPDRS: Unified PD Rating Scale