RESEARCH ARTICLE

Nonmotor Symptoms Evolution During 24 Months of Bilateral Subthalamic Stimulation in Parkinson's Disease

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ABSTRACT: Background: The objective of this study was to investigate 24-month of effects of bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) on nonmotor symptoms in Parkinson's disease (PD).

Methods: In this prospective, observational, multicenter, international study including 67 PD patients undergoing bilateral STN-DBS, we examined the Non-motor Symptom Scale, Non-Motor Symptoms Questionnaire, Parkinson's Disease Questionnaire-8, Scales for Outcomes in Parkinson's Disease-motor examination, -activities of daily living, and -complications, and levodopa-equivalent daily dose preoperatively and at 5 and 24-month of follow-up. After checking distribution normality, longitudinal outcome changes were investigated with Friedman tests or repeated-measures analysis of variance and Bonferroni correction for multiple comparisons using multiple tests. Post hoc, Wilcoxon signed rank *t* tests were computed to compare visits. The strength of clinical responses was analyzed using effect size. Explorative Spearman correlations of change scores from baseline to 24-month follow-up were calculated for all outcomes.

Results: The Non-motor Symptom Scale and all other outcome parameters significantly improved from baseline to the 5-month follow-up. From 5 to 24-month, partial decrements in these gains were found. Nonetheless, comparing baseline with 24-month follow-up, significant improvements were observed for the Non-motor Symptom Scale (small effect), Scales for Outcomes in PD-motor examination showed a moderate effect, and Scales for Outcomes in Parkinson's Disease-complications and levodopa-equivalent daily dose showed large effects. Non-motor Symptom Scale change scores from baseline to 24-month follow-up correlated significantly with Parkinson's Disease Questionnaire-8, Scales for Outcomes in Parkinson's Disease-activities of daily living, and -motor complications change scores.

Conclusions: This study provides evidence of beneficial effects of bilateral STN-DBS on nonmotor symptoms at 24-month follow-up. The extent of nonmotor symptom improvement was directly proportionate to improvements in quality of life, activities of daily living, and motor complications. This study underlines the

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importance of nonmotor symptoms for holistic assessments of DBS outcomes. © 2018 International Parkinson and Movement Disorder Society

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In patients with advanced Parkinson's disease (PD), subthalamic nucleus (STN) deep brain stimulation (DBS) is a safe and effective treatment option improving quality of life (QoL) [1], motor[2], and nonmotor symptoms (NMS).[3]

The immediate and short-term beneficial effects of STN-DBS on NMS have been observed in a number of studies including patient-based questionnaires and clinician-based scales (e.g., for sleep,[4] pain,[5] depressive symptoms,[6,7] gastrointestinal symptoms, excessive sweating, and perceptual problems/hallucinations[3]. These observations are supported by a growing number of studies using laboratory-assisted objective measures for specific NMS (eg, polysomnography for sleep,[8] $^{13}CO_2$ excretion for gastric emptying,[9] urodynamic examination for urinary symptoms,[10] and sympathetic skin response for excessive sweating[11].[12] However, little is known about nonmotor effects beyond a 6-month short-term follow-up period. A pilot study using semistructured interviews in 17 PD patients reported beneficial effects of STN-DBS on autonomic, psychiatric, and sensory nonmotor fluctuations 2 years after surgery.[13] However, a nonvalidated assessment tool was used, the study cohort was small, and the study focused on NMS fluctuations, not on overall NMS burden and its relationship with QoL.

Here we report a wide range of NMS at 5- and 24-month follow-up in patients with PD undergoing STN-DBS. Based on our previous study, in which we observed improvement of sleep, perceptual problems/hallucinations, urinary symptoms, and miscellaneous symptoms, such as sweating and olfactory symptoms, at 6-month follow-up,[3] we hypothesized that beneficial effects on a wide range of NMS can also be observed at 24-month follow-up and that this translates to an improvement in QoL. We explored the differences between patient-based self-reported and clinician-rated assessments of nonmotor outcomes.

Materials and Methods

Design and Ethical Approval

In this ongoing, prospective, observational, multicenter, international study patients were consecutively enrolled in 3 DBS centers (Cologne, Germany, Manchester, UK, and London, UK) as part of the NILS study (German Clinical Trials Register: 6735).[3] The study was authorized by local ethics committees (Cologne 12-145; United Kingdom: NRES SouthEast London REC3, 10084, 10/H0808/141). All patients gave written consent prior to study procedures in accordance with the Declaration of Helsinki.

Participants

All patients had been diagnosed with PD based on British Brain Bank criteria.[14] Screening for DBS treatment was carried out according to Movement Disorders Society guidelines, and patients were considered eligible for DBS treatment if their levodopa test response was sufficient (>30% improvement, assessed by the Unified PD Rating Scale-III). Inclusion criteria for study participation were eligibility for DBS treatment based on these routine clinical assessments and the ability to consent. Exclusion criteria were: (1) clinically relevant hearing and vision impairment, (2) a language barrier interfering with patient assessments, and (3) clinically relevant neuropsychiatric or cognitive disturbances in assessments by a multidisciplinary team including specialized neuropsychiatrists and neuropsychologists.

Clinical Assessment

Patients were assessed at baseline (MedON) and at the 5- and 24-month follow-up visits after surgery (MedON/StimON) with the following scales.

Nonmotor Disturbances

1. The clinician-based Non-motor Symptom Scale (NMSS) was employed to investigate specific domains of NMS (cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal symptoms, urinary symptoms, sexual function, and miscellaneous symptoms).[15] The NMSS consists of 30 items for these aforementioned 9 NMS domains. In the miscellaneous domain, pain, sweating, weight changes, and olfaction are assessed; in the sleep/fatigue domain, falling asleep during daytime activities, fatigue, difficulties falling or staying asleep, and restlessness in legs are assessed. The NMSS surveyes symptoms over the previous 4 weeks and therefore reflects ON and OFF states. The NMSS ranges from 0 (no impairment) to 360 (maximum impairment), and its gradation and clinimetric properties are well suited to capture treatment effects.[3,16,17]

2. The self-reporting Non-Motor Symptoms Questionnaire (NMSQ) consists of 30 dichotomized questions that assess the occurrence of NMS over the previous 4 weeks.[18] The NMSQ ranges from 0 (no impairment) to 30 (maximum impairment). The rationale for assessing both NMS scales (despite thematic overlap) was that each scale captures a unique perspective on NMS: (a) clinician-rated and (b) patient-reported outcomes.

Quality of Life

The Parkinson's Disease Questionnaire-8 (PDQ-8) has previously been used in patients with PD and STN-DBS.[3,19,20] The PDQ is recommended for QoL assessments assessments by the Movement Disorders Society Scales Committee[21] and is commonly used for DBS studies in PD.[1,22,23] Results are reported as the PDQ-8 Summary Index (PDQ-8 SI) to help the interpretation of results and simplify comparisons with other studies. The PDQ-8 SI ranges from 0 (no impairment) to 100 (maximum impairment).

Motor Disturbances

The Scales for Outcomes in Parkinson's Disease (SCOPA)-A, -B, and -C were used to examine motor examination, activities of daily living, and motor complications, respectively. The SCOPA is an abbreviated version of the Unified Parkinson's Disease Rating Scale, from which it was derived,[24] and the two scales highly correlate.[2]. The SCOPA is a well-established, validated, reliable assessment tool with the advantage that its administration time is approximately four times shorter than the MDS-Unified Parkinson's Disease Rating Scale.[24-26] The SCOPA-A, -B, and -C range from 0 (no impairment) to 42, 21, and 12, respectively (maximum impairment).

The therapeutic medical regimen was recorded calculating the levodopa-equivalent daily dose (LEDD) according to the method of Tomlinson et al.[27]

Statistical Analysis

The Shapiro-Wilk test was used to evaluate the normality of distribution of clinical scores. Significant longitudinal outcome changes were analyzed with Friedman tests or repeated-measures analysis of variance, when parametric test criteria were fulfilled, and Bonferroni correction for multiple comparisons due to the use of multiple tests. To compare outcome changes between pairs of visits, post hoc Wilcoxon signed-rank and *t* tests, respectively, were employed. The strength of clinical responses was quantified with relative changes ([mean $test_{visit\ 2}$ - mean $test_{visit\ 1}$]/mean $test_{visit\ 2}$) and effect size ([mean $test_{visit\ 1}$ - mean $test_{visit\ 2}$]/SD $test_{visit\ 1}$).[28]

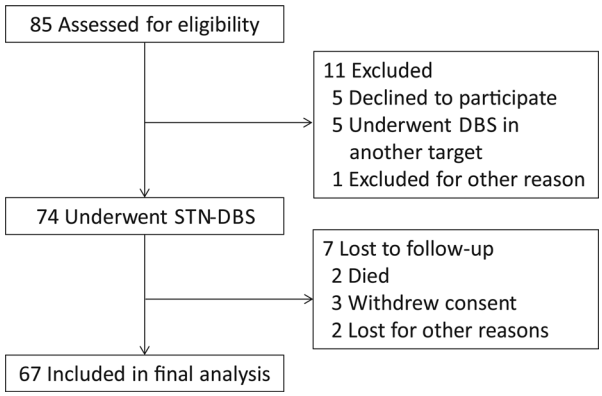

FIG. 1. Enrollement and Outcomes

To explore the relationship between changes in outcome parameters from baseline to 24-month follow-up, we calculated change scores ($test_{baseline}$ - $test_{24\text{-month follow-up}}$) and computed Spearman correlations of change scores for all outcome parameters. Furthermore, from the clinical point of view, we were also interested in nonmotor effects of STN-DBS in severely affected patients and therefore explored NMSS changes at the 24-month follow-up for the group of patients with the highest quartile of baseline NMSS.

Results

Of 85 consecutive patients with PD screened between 2013 and 2014 in our inpatients departments, 67 patients (50 men) underwent bilateral STN-DBS and were included in the final analysis (see Fig. 1). The mean age was 62.3 ± 7.8 years, and disease duration was 10.9 ± 4.8 years. The median Hoehn and Yahr score was 2.5 (interquartile range, 2.0-3.0).

Clinical Outcomes at Baseline and 5- and 24-Month Follow-up

NMSS total score, NMSQ, PDQ-8 SI, SCOPA-A, -B, and -C, and LEDD improved significantly in the longitudinal follow-up of the study (see Table 1). Post hoc tests revealed that NMSS total score and NMSQ improved from baseline to the 5-month follow-up (both $P < 0.001$). Subsequent decrements in gains from 5 to 24-month were significant for NMSQ ($P = 0.005$). Comparing baseline and the 24-month follow-up, no significant changes were found for the patient-based self-reported NMSQ, whereas the clinician-rated NMSS total score improved significantly ($P = 0.018$). All motor and QoL outcome parameters also improved at the 5-month follow-up (all $P < 0.001$). Decrements in gains from the 5- to 24-month follow-up were significant for PDQ-8 SI ($P = 0.001$) and SCOPA-B ($P = 0.006$). Comparing baseline and 24-month follow-up, we observed a

TABLE 1. Outcome parameters at baseline and 5- and 24-month follow-up

		Baseline		5-Month follow-up		24-Month follow-up			
	n	mean	SD	mean	SD	mean	SD	P^a	Post hoc tests[b]
NMSS total score[d]	67	63.2	34.3	44.7	24.4	50.4	31.3	**0.001**[d]	**a‡ b**
NMSS domains									
Cardiovascular[c]	67	1.9	3.4	1.3	2.3	2.4	±3.4	**0.018**	**c**
Sleep/fatigue[d]	67	16.1	9.5	9.6	8.9	10.2	8.5	**<0.001**	**a‡ b‡**
Mood/apathy	67	6.1	10.1	4.8	10.0	6.9	10.3	0.338	
Perceptual problems/hallucinations[c]	67	1.4	3.2	0.4	1.1	1.4	3.4	**0.008**	**a c**
Attention/memory	67	5.5	6.5	4.0	5.6	5.4	5.8	0.090	
Gastrointestinal[c]	67	6.1	7.2	5.6	6.4	7.0	5.9	**0.038**	
Urinary[c]	67	12.0	9.9	8.4	7.2	8.6	7.6	**0.038**	**a‡ b**
Sexual function	67	2.7	4.6	2.4	5.0	2.5	5.5	0.298	
Miscellaneous[d]	67	11.4	9.0	8.3	7.2	5.9	6.2	**<0.001**	**a b‡ c**
NMSQ[d]	61	10.9	4.6	8.5	4.0	10.3	4.5	**<0.001**	**a‡ c**
PDQ-8 SI[d]	65	33.3	17.4	23.3	14.4	30.6	18.5	**<0.001**	**a‡ c‡**
SCOPA-A[d]	61	12.8	6.0	8.7	4.9	8.9	5.0	**<0.001**	**a‡ b‡**
SCOPA-B[d]	67	7.4	3.4	5.4	2.8	6.7	3.7	**<0.001**	**a‡ c**
SCOPA-C[d]	67	5.0	3.0	2.4	2.4	2.7	2.4	**<0.001**	**a‡ b‡**
LEDD (mg)[d]	63	1121.6	515.2	632.6	358.4	684.5	438.8	**<0.001**	**a‡ b‡**

LEDD, levodopa-equivalent daily dose; NMSS, Non-Motor Symptom Scale; NMSQ, Non-Motor Symptoms Questionnaire; PDQ-8, 8-item Parkinson's Disease Questionnaire; SCOPA-A, -B, and -C, Scales for Outcomes in Parkinson's Disease-motor examination, -activities of daily living, and -motor complications, respectively..

[a]Friedman test or repeated-measures ANOVA when parametric test criteria were fulfilled.

[b]Wilcoxon signed rank or *t* test when parametric test criteria were fulfilled.

[c]Significant difference between visits ($P < 0.05$, Friedman test or repeated-measures ANOVA).

[d]Highly significant difference between visits ($P \leq 0.001$, Friedman test or repeated-measures ANOVA).

Post hoc comparisons (Wilcoxon signed rank or *t* test):

— Baseline vs 5 months of follow -up: **a**, significant ($P < 0.05$); **a‡**, highly significant ($P < 0.001$).

— Baseline vs 24 months of follow-up: **b**, significant ($P < 0.05$); **b‡**, highly significant ($P < 0.001$).

— 5 vs 24 months of follow-up: **c**, significant ($P < 0.05$); **c‡**, highly significant ($P < 0.001$)/

significant improvement in SCOPA-A ($P < 0.001$) and -C ($P < 0.001$) and LEDD ($P < 0.001$).

Comparing baseline with short-term follow-up at 5 months, effect sizes were moderate for NMSS total score, NMSQ, PDQ-8 SI, and SCOPA-A and -B, and large for SCOPA-C and LEDD. Effect sizes from baseline to the 24-month follow-up were small for NMSS total score and SCOPA-B, moderate for SCOPA-A and -C, and large for LEDD improvements.

Explorative Analyses of NMSS Domains and Items at Baseline and the 5- and 24-Month Follow-up

Explorative analyses of NMSS domain scores using Friedman tests resulted in significant longitudinal changes of the cardiovascular, sleep/fatigue, perceptual problems/hallucinations, gastrointestinal, urinary, and miscellaneous domains (see Table 1 and Fig. 2). In the miscellaneous domain, significant longitudinal changes were found for the items "inability to taste or smell" (baseline, 4.4 ± 4.5; 5-month follow-up, 2.9 ± 4.0; 24-month follow-up, 1.2 ± 2.6; $P < 0.001$) and "excessive sweating" (baseline, 3.0 ± 4.0; 5-month follow-up, 1.4 ± 2.9; 24-month follow-up, 1.8 ± 3.6; $P < 0.001$). In the sleep/fatigue domain, significant longitudinal changes were found for the items "falling asleep during daytime activities" (baseline, 3.0 ± 3.8; 5-month follow-up; 1.4 ± 2.9; 24-month follow-up, 1.3 ± 2.6; $P = 0.008$), "difficulties falling or staying asleep" (baseline, 5.6 ± 4.5; 5-month follow-up, 3.1 ± 4.1; 24-month follow-up, 3.4 ± 4.0; $P < 0.001$), and "restlessness in legs" (baseline, 3.3 ± 4.2; 5-month follow-up, 1.7 ± 3.1; 24-month follow-up, 2.4 ± 3.4; $P = 0.003$), whereas "fatigue" trended (baseline, 4.2 ± 4.2; 5-month follow-up, 3.1 ± 3.8; 24-month follow-up, 3.1 ± 3.5; $P = 0.070$).

Post hoc tests comparing baseline with the 24-month follow-up resulted in significant improvements for the sleep/fatigue ($P < 0.001$), urinary ($P = 0.022$), and miscellaneous ($P < 0.001$) domains. In the latter, items for "inability to taste or smell" ($P < 0.001$) and "sweating" ($P = 0.018$) significantly improved from baseline to the 24-month follow-up. In the sleep/fatigue domain, "falling asleep during daytime activities" ($P = 0.001$), "fatigue" ($P = 0.016$), and "difficulties falling or staying asleep" ($P < 0.001$) improved.

Comparing baseline with the 5-month follow-up, significant improvements were found for the sleep/fatigue, perceptual problems/hallucinations, urinary, and miscellaneous domains (all $P \leq 0.008$), again with improvements in "inability to taste or smell" ($P = 0.002$) and "excessive sweating" ($P = 0.001$). All

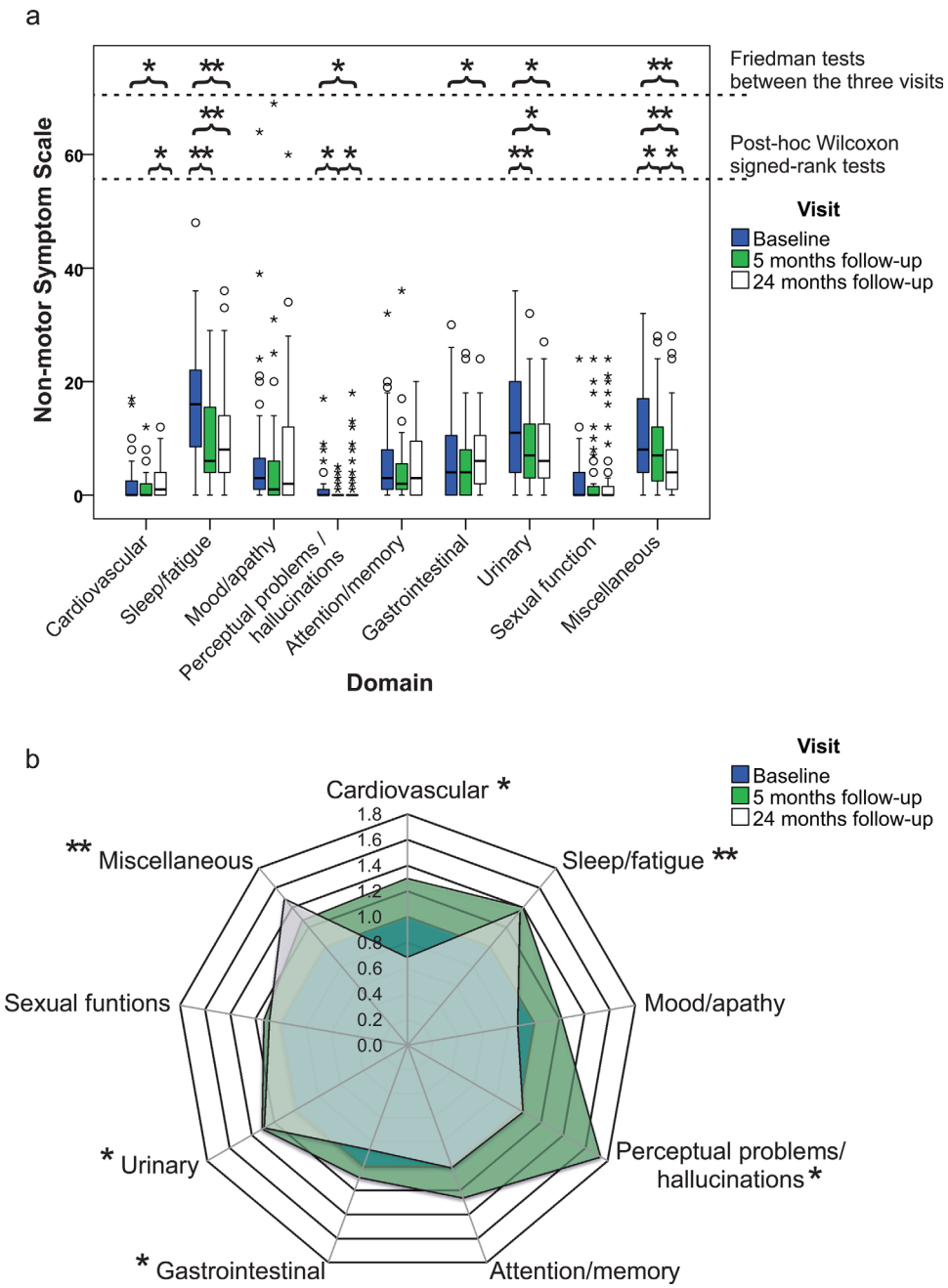

FIG. 2. illustrates Non-motor Symptom Scale domain scores at baseline (blue), 5 months follow-up (green), and 24 months follow-up (white) as clustered box plot (1a) and radar chart (1b). In the clustered box plot, small circles represent outliers (2-3 SD), small stars extreme outliers (>3 SD). Significant changes ($P < 0.05$) are highlighted with big stars, highly significant changes ($P \leq 0.001$) with two big stars. The upper row of big stars illustrates results from Friedman tests which compared all three visits. The lower rows of big stars represent post-hoc Wilcoxon signed-rank tests between pairs of visits. The domains 'Sleep/fatigue', 'Urinary', and 'Miscellaneous' significantly improved from baseline to 5 months follow-up and from baseline to 24 months follow-up, in case of the domain 'Miscellaneous' additionally with beneficial effects from 5 to 24 months follow-up. The domain 'Cardiovascular' did not improve from baseline to 5 months follow-up and significantly deteriorated from 5 to 24 months follow-up. The domain 'Perceptual problems/hallucinations' significantly improved from baseline to 5 months follow-up and significantly rebounded from 5 to 24 months follow-up just below baseline values. Patients' 'Gastrointestinal' domain scores significantly changed longitudinally and although post-hoc tests detected no significant changes between pairs of visits, most notably there was a 25% increase of mean values from 5 to 24 months follow-up (see Table 1 and Table 2). In the radar chart, the same results are presented as in the clustered box plot. However, all values are normalized to baseline values (computation: 2–follow-up/baseline). Therefore, baseline values for all NMSS domains are 1.0. Bigger green and white areas represent more improvement of specific NMS domains at 5 months and 24 months follow-up visits. Based on Friedman test results, NMSS domains are highlighted with one star for significant longitudinal changes ($P < 0.05$) and two stars for highly significant longitudinal changes ($P \leq 0.001$)

items in the sleep/fatigue domain improved significantly from baseline to the 5-month follow-up (fatigue, $P = 0.031$; all others, $P \leq 0.004$).

Effect sizes from baseline to the 24-month follow-up were small for the urinary and moderate for the sleep/fatigue and miscellaneous domains (see Table 2). In the

TABLE 2. Relative changes and effect sizes at 5- and 24-month follow-up

	Baseline to 5-month follow-up		Baseline to 24-month follow-up		5- to 24-month follow-up	
	RC (%)	ES[a]	RC (%)	ES[a]	RC (%)	ES[a]
NMSS total score[b]	-29.3	0.54	-20.3	0.34	12.8	0.23
NMSS domains						
Cardiovascular	-31.6	0.18	26.3	0.14	84.6	0.48
Sleep/fatigue[c]	-40.4	0.68	-36.6	0.62	6.3	0.07
Mood/apathy	-21.3	0.13	13.1	0.08	43.8	0.21
Perceptual problems/hallucinations	-71.4	0.31	0.0	0.00	250.0	0.91
Attention/memory	-27.3	0.23	-1.8	0.02	35.0	0.25
Gastrointestinal	-8.2	0.07	14.8	0.13	25.0	0.22
Urinary[b]	-30.0	0.36	-28.3	0.36	2.4	0.03
Sexual function	-11.1	0.07	-7.4	0.04	4.2	0.02
Miscellaneous[c]	-27.2	0.34	-48.2	0.61	-28.9	0.33
NMSQ	-22.0	0.52	-5.5	0.13	21.2	0.45
PDQ-8 Summary Index	-30.0	0.57	-8.1	0.16	31.3	0.51
SCOPA-A[c]	-32.0	0.68	-30.5	0.65	2.3	0.04
SCOPA-B[b]	-27.0	0.59	-9.5	0.21	24.1	0.46
SCOPA-C[c]	-52.0	0.87	-46.0	0.77	12.5	0.13
LEDD (mg)	-43.6	0.95	-39.0	0.85	8.2	0.14

ES, effect size; LEDD, levodopa-equivalent daily dose; NMSS, Non-Motor Symptom Scale; NMSQ, Non-Motor Symptoms Questionnaire; PDQ-8 SI, 8-item Parkinson's Disease Questionnaire Summary Index; RC, relative change; SCOPA-A, -B, and -C, Scales for Outcomes in Parkinson's Disease-motor examination, -activities of daily living, and -motor complications, respectively.
[a]Effect sizes: small, 0.20-0.49; moderate, 0.50-0.79; large, $\geq$ 0.80.
[b]Small effect size from baseline to 24-month follow-up.
[c]Moderate effect size from baseline to 24-month follow-up.

miscellaneous domain, the effect sizes were moderate for the "inability to taste or smell" (0.71) and negligible for other items. In the sleep/fatigue domain, the effect sizes were moderate for "falling asleep during daytime activities" and "difficulties falling or staying asleep" (0.45 and 0.49, respectively) and small for "restlessness in legs" and "fatigue" (0.21 and 0.26, respectively).

Explorative Correlation Analyses Between Outcome Parameters at 24-Month Follow-up

Table 3 illustrates Spearman correlations between all outcome parameters at the 24-month follow-up. NMSS total score improvement significantly correlated with improvements in NMSQ ($P = 0.004$), PDQ-8 SI

TABLE 3. Spearman correlations between change scores of all outcomes at 24-month follow-up

		NMSS total score	NMSQ	PDQ-8 SI	SCOPA-A	SCOPA-B	SCOPA-C
NMSQ	rho	0.363[b]					
	P	**0.004**					
	n	61					
PDQ-8 SI	rho	0.306[a]	0.183				
	P	**0.012**	0.157				
	N	67	61				
SCOPA-A	rho	0.149	0.006	0.285[a]			
	P	0.252	0.966	**0.026**			
	n	61	55	61			
SCOPA-B	rho	0.459[b]	0.244	0.361[b]	0.541[b]		
	P	**< 0.001**	0.058	**0.003**	**< 0.001**		
	N	67	61	67	61		
SCOPA-C	rho	0.299[a]	0.116	0.246[a]	-0.039	0.169	
	P	**0.014**	0.374	**0.045**	0.767	0.172	
	N	67	61	67	61	67	
LEDD	rho	-0.169	0.100	-0.068	-0.238	-0.249[a]	-0.177
	P	0.172	0.445	0.582	0.064	**0.042**	0.152
	n	67	61	67	61	67	67

LEDD, levodopa-equivalent daily dose; NMSS, Non-Motor Symptom Scale; NMSQ, Non-Motor Symptoms Questionnaire; PDQ-8 SI, 8-item Parkinson's Disease Questionnaire Summary Index; rho, Spearman's correlation coefficient; SCOPA-A, -B, and -C, Scales for Outcomes in Parkinson's Disease-motor examination, -activities of daily living, and -motor complications, respectively.
[a]Significant correlation at the 0.05 level (2-tailed).
[b]Significant correlation at the 0.01 level (2-tailed).

($P = 0.012$), SCOPA-B ($P < 0.001$), and SCOPA-C ($P = 0.014$), but not with SCOPA-A ($P = 0.252$) or LEDD ($P = 0.172$).

Explorative Analysis of 24-Month NMSS Outcome of Severely Affected Patients

In this group of 16 patients (11 men) aged 60.6 ± 8.5 years at intervention and with a disease duration of 12.8 ± 5.0 years, NMSS total score significantly improved longitudinally (baseline, 111.2 ± 31.7; 5-month follow-up, 51.3 ± 23.7; 24-month follow-up, 55.5 ± 40.7; $P < 0.001$). Post hoc tests showed significant improvement from baseline to the 5-month follow-up ($P < 0.001$) and from baseline to the 24-month follow-up ($P = 0.001$). Compared with the group of 17 patients (11 men) in the lowest NMSS quartile at baseline (age at intervention, 62.5 ± 8.3 years; disease duration, 12.1 ± 5.1 years; NMSS at baseline, 27.3 ± 9.8), the improvement in NMS was significantly greater in more severely affected patients ($NMSS_{change\ scores}$, 55.7 vs -10.7; $P < 0.001$).

Discussion

In this prospective, observational, international, multicenter study including a cohort of 67 patients with PD with a 24-month follow-up, we observed significant beneficial effects of bilateral STN-DBS on a range of NMS, such as sleep, daytime sleepiness, fatigue, urinary symptoms, olfaction, and sweating.

In line with previous studies, at the 5-month follow-up, bilateral STN-DBS improved QoL, nonmotor, and motor symptoms[1-3] with subsequent decrements in these gains at the 24-month follow-up. Comparing baseline with last assessment at 24-month, there was a significant improvement for the clinician-rated evaluation (NMSS total score), whereas on the self-reported NMSQ, the improvements were diminished by the significant "rebounding" effect from the 5- to 24-month follow-up.

Effects of STN-DBS on Specific Nonmotor Symptoms

The following specific nonmotor aspects of PD significantly changed in the longitudinal follow-up of the study:

- *Sleep*: In line with previous studies, we found a significant subjective improvement in sleep disturbance at the 24-month follow-up.[29,30] Previous studies using the Epsworth Sleepiness Scale found negative results for changes in daytime sleepiness at follow-ups from 3-6 to 24-month after STN-DBS.[29,31] To our knowledge, the present study is the first to report significant beneficial effects of STN-DBS on daytime sleepiness at the 24-month follow-up. Few studies have investigated fatigue in patients with PD treated with STN-DBS. Although short-term improvements in fatigue have been observed following STN-DBS, to our knowledge, the present study is also the first to report significant beneficial effects on fatigue at the 24-month follow-up.[32] In contrast, a study by Lilleng et al reported worsening of fatigue at follow-ups of 1-1.5 and 6-9 years after STN-DBS.[31] However, the cohort size of this study was relatively small (n = 16), and the results may have been influenced by the relatively high LEDD at both follow-up visits (approximately 810 and 910 mg). In this study the LEDD reductions was only 15% at follow-up of 1-1.5 years and 5 % at follow-ups of 6-9 years, whereas in our cohort we report a 39% LEDD reduction, from approximately 1120 to 685 mg, at the 24-month follow-up.
- *Urological symptoms*: To our knowledge, this is the first report of a 24-month improvement in urinary symptoms after STN-DBS. Previous studies including clinician-rated scales, urodynamic bladder examinations, and PET imaging have provided evidence for immediate and short-term effects of STN-DBS on bladder control mediated by a modulation of basal ganglia-thalamo-corticalloops and improved sensory gaiting.[3,33]
- *Olfaction*: A study by Guo et al provided evidence for improvement in odor identification at 6- and at 12-month follow-ups.[34] The authors discuss that this improvement may be mediated by modulation of the orbitofrontal and primary olfactory cortex, which may improve odor identification. Our study adds to the evidence for beneficial effects of STN-DBS on olfaction and extends the time frame to a 24-month follow-up after surgery.
- *Sweating*: A previous study using structured questionnaires on the presence or absence of excessive sweating reported significant improvement at 6- and 12-month follow-ups after STN-DBS.[35] Our study adds to this work by extending the time frame of beneficial effects to 24-month after STN-DBS and reporting subjective excessive sweating quantified as a nondichotomized outcome.
- *Further NMS*: In line with previous studies, we found improvement in perceptual problems/hallucinations at short-term follow-up after STN-DBS.[36] Also in line with previous studies, no improvement in cardiovascular symptoms was found on 5- and 24-month follow-ups after STN-DBS.[30,37] In contrast to previous studies,[5,13,38] we observed no improvement in pain in our cohort, possibly because pain was only assessed with one NMSS item and specific pain scales were not

employed in our study. A modulation of gastrointestinal symptoms by STN-DBS has previously been reported in a study by Arai et al, which reported improved $^{13}CO_2$ excretion at a 3-month follow-up.[9] In a study by Zibetti et al, information on the presence or absence of constipation indicated possible improvement at long-term follow-up.[30] However, the authors merely retrospectively extracted this dichotomized information from patient files and did not employ validated scales. Therefore, to our knowledge, the present study is the first to report significant modulation of gastrointestinal symptoms using clinician-rated validated scales in a prospective study with a 24-month follow-up. As post hoc test results were not significant, further studies including bigger cohorts are needed to investigate this issue.

Mechanisms of Nonmotor Effects of STN-DBS

NMS are a collection of different symptoms defined by exclusion and result from multineuropeptide dysfunction including central dopaminergic, cholinergic, noradrenergic, and serotonergic systems and also the peripheral nervous system.[39] As the pathomechanisms of NMS are not uniform, the following different mechanisms of action may mediate the observed beneficial nonmotor effects of STN-DBS resulting in different strength of clinical responses for specific NMS:

1. Direct modulation of the basal ganglia-thalamocortical loops may influence neural activity, for example, in the lateral frontal, anterior cingulate, and insular cortex and the thalamus, which in turn could, for example, improve NMS like bladder control and sweating.[10,11]
2. Closely connected to this point, via disinhibition of GPi-mediated thalamic excitability, STN-DBS may result in modulation of higher-order somatosensory association cortices, such as the orbitofrontal and primary olfactory cortices, which may impact, for example, the cognitive processing of olfactory information.[34]
3. Also connected to the first point, previous studies have provided evidence that sensory gaiting is a PD-related pathophysiological mechanism that is amenable to DBS but not necessarily to dopaminergic medication, for example, in bladder control[10] and pain.[40]
4. There is a spread of current to nuclei in proximity to the STN, such as the pedunculopontine nucleus, which is located within approximately 5 mm of the STN with even closer projections[41] and has previously been linked to improvement in sleep.[42] Conversely, nonmotor side effects, such as mood disorder, paresthesia, and vision impairment, may also result from a spread of current to brain regions in the proximity of the STN and be avoided by adjusting the current spread to another direction.[43]
5. Although no significant correlations between LEDD and NMSS total score or NMSQ were found, the reduction in dopaminergic medication requirements below patient-specific thresholds may at least in part influence nonmotor outcomes, such as gastrointestinal symptoms, daytime sleepiness, and perceptual problems/hallucinations, which are known to be affected by dopaminergic medication.[44] Further studies are needed to distinguish between stimulation and medication effects on these NMS.

As we were interested in the 24-month effects of STN-DBS relevant to the "real-life" experience of NMS and their impact on QoL, we did not test the immediate changes ON and OFF medication and stimulation, and the present analysis cannot distinguish between the effects of neurostimulation and medication. Therefore, here we merely present results of "net effects" on NMS in patients with PD undergoing STN-DBS. In this regard, a pilot study by Ortega-Cubero et al[13] provides information on the differential effects of medication and STN-DBS. The authors reported improvement in (1) severity of autonomic and sensory and (2) frequency of total nonmotor fluctuations by STN-DBS at the 24-month follow-up. However, the results of this study are difficult to interpret, as (1) this modulation was only observed for the MedON state, not for the MedOFF state, and (2) nonmotor fluctuations improved significantly from preoperative MedOFF to postoperative MedOFF/StimOFF at the 24-month follow-up. Further studies are needed to confirm these findings and explore how fluctuations of NMS per se translate into QoL improvement after STN-DBS.

The finding that NMSS total score improvement was significantly correlated with improvements in PDQ-8 SI, SCOPA-B, and SCOPA-C, but not with motor examination (SCOPA-A), is in line with our previous results at the 5-month follow-up[3] and is also in accordance with previous studies that reported that NMS may outweigh motor examination impairments as determinants of QoL.[45,46]

Limitations

As an observational, nonrandomized study, the present work has limitations. Although our cohort size (n = 67) is one of the largest in studies of its kind, it is still relatively small, and further prospective studies are required to confirm these findings. The multicenter design of our study is likely to reduce systematic bias caused by single-center studies. The clinical ratings were performed by unblinded raters, and because of the design of our database as a prospective,

observational study, only clinical ON states (MedON/StimON) were recorded. A systematic examination of nonmotor and motor symptoms with and without medication and DBS at follow-up could be informative to assess the immediate effects of STN-DBS and distinguish these from nondopaminergic nonmotor characteristics. As patients with clinically relevant neuropsychiatric or cognitive disturbances are excluded from DBS, findings for these NMS domains are prone to systematic bias. In this context our results may therefore not represent patients with a profile of very severe NMS burden because of neuropsychological impairments. The scales employed in our study assess NMS over the previous 4 weeks and therefore reflect a combination of ON and OFF states,[3] as we were interested in patients' "real-life" experience of NMS and their relationship with QoL outcomes. The NMSS and NMSQ are not feasible to examine nonmotor fluctuations that may also influence the overall NMS burden[35] and QoL outcomes in patients with PD undergoing STN-DBS. Further studies including, for example, patient diaries are required to investigate this issue. The observed difference between NMSS and NMSQ outcomes at the 24-month follow-up may result from (1) systematic bias because of interobserver variability (NMSS) and interpatient variability (NMSQ), (2) the clinimetric properties of the two scales (the NMSS has a favorable gradation ranging from 0 to 360 and is therefore particularly well suited to capturing treatment effects), or (3) the conceptual difference of these complementary scales (the NMSS captures the severity and frequency of NMS objectively rated by clinicians, whereas the NMSQ surveys dichotomized information on NMSs as self-perceived by the patient).

Conclusion

In patients with PD undergoing STN-DBS, we observed significant beneficial effects on several nonmotor features, such as sleep, daytime sleepiness, fatigue, urinary symptoms, olfaction, and sweating over a 24-month observation. These results were consistent with the significant 24-month improvement of the total burden of NMS, which was significantly correlated with QoL improvement. This study underlines the importance of NMS for holistic assessments of DBS outcomes.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's website.