Research Report

Bilateral Subthalamic Stimulation can Improve Sleep Quality in Parkinson's Disease

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Abstract.
Background: Sleep problems are among the most common non-motor symptoms of Parkinson's disease (PD). The PD Sleep
Scale 2nd version (PDSS-2) improved the original PDSS by adding more items on different aspects of sleep problems, making
it a more robust tool to evaluate the severity of sleep disturbances. However, previous studies on deep brain stimulation (DBS)
have not used the PDSS-2.
Objective: To determine if the PDSS-2 could detect improvement reliably in sleep problems after bilateral subthalamic nucleus
DBS for PD.
Methods: In this prospective study, 25 consecutive patients undergoing DBS implantation were enrolled. Patients were examined
twice: 1 week prior to the DBS implantation (baseline) and 12 months postoperatively. Severity of PD symptoms were assessed
by the Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS) and the Non-Motor Symptoms Scale (NMSS).
Presence and severity of sleep disturbances were specifically measured by PDSS-2.
Results: Total score of MDS-UPDRS improved from 81 (median, interquartile-range: 63–103) to 55 points (median, IQR:
46–75, $p < 0.001$). Health-related quality of life, measured by PDQ-39, also improved from 29 (IQR: 18–40) to 15 (IQR: 9–28)
points ($p = 0.002$). Most domains of NMSS also improved. At baseline 13 patients reported sleep problems, but 1 year after DBS
implantation only 3 did ($p = 0.012$). Although only 6 out of 15 items showed a significant decrease after DBS implantation, the
total score of PDSS-2 decreased from 24 (IQR: 17–32) to 10 (IQR: 7–18) points ($P < 0.001$).
Conclusions: Based on our results, PDSS-2 can detect improvements in sleep quality reliably after DBS implantation.

Keywords: Sleep, non-motor symptoms, subthalamic deep brain stimulation, restless legs syndrome

ABBREVIATIONS

ACE	Addenbrooke Cognitive Examination
BDI	Beck Depression Inventory
CGI-S	Clinical Global Impression–Severity
COMTI	Catechol-O-methyl transferase inhibitor
ESS	Epworth Sleepiness Scale
LED	levodopa-equivalent dosage
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	monoamine-oxidase inhibitor
MDS-UPDRS	The Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale
MOCA	Montreal Cognitive Assessment
NMS	Non-motor Symptoms

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NMSS   Non-motor Symptoms Scale
PDSS-2   Parkinson's Disease
            Sleep Scale 2nd version

INTRODUCTION

Recently the non-motor symptoms (NMS) of Parkinson's disease (PD) have been increasingly recognized as a major burden of quality of life [1, 2]. Among the NMS, sleep-related problems are the most important and troublesome. Although sleep problems can be present in up to 90% of PD patients, only a few study focused on the outcome of different therapeutic options to improve sleep quality.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established therapy for patients with PD having advanced motor complications. Previous electrophysiological and patient-reported outcome-based studies demonstrated the beneficial effect of STN DBS on sleep quality in PD [3–6].

Because sleep-related problems are certainly multicausal, instruments capable of measuring most domains of sleep-disturbances are needed in the clinical practice. Based on the systematic review and evaluation of sleep-related rating scales by the Movement Disorders Society Task Force [7], only a few scales were found to be appropriate for the PD population. The original Parkinson's Disease Sleep Scale (PDSS) [8] was published in 2002, and it had 15 visual analogue scale-based items. It was one of the first sleep scales designed specifically for PD. Higher values on PDSS indicate a better sleep quality. Although the application of PDSS was recommended by the MDS Task Force, they identified some weaknesses of the scale including the inability to specifically identify and measure the presence and severity of sleep apnea, rapid eye movements sleep behavioral sleep disorder (RBS) and restless legs syndrome RLS-related symptoms. To overcome these disadvantages, a new scale, the Parkinson's Disease Sleep Scale 2nd version (PDSS-2), was developed and published in 2011 [9]. The PDSS-2 scale is composed of 15 items evaluating three domains. Each item has a 5-point Likert-type scale ranging from 0: "Never" to 4: "Very often" (except for item 1 which is reversed). Each domain consists of clusters of five questions evaluating motor symptoms at night, PD symptoms at night and disturbed sleep [9]. The sum of the 15 responses gives the total score of PDSS-2 with the maximum value of 60 points and higher scores meaning more nocturnal disturbance. The reliability, precision and test-retest validity of PDSS-2 is good [9, 10], making it suitable for measuring changes over a longer period of time. PDSS-2 is thought to have better clinimetric properties and responsiveness to changes in sleep problems than the original PDSS [11].

Despite its advantages over PDSS, the assessment of sleep quality before and after bilateral STN DBS with the PDSS-2 has not been reported in the literature; thus, the responsiveness of the PDSS-2 to DBS treatment is unknown. The objective of the present study was to analyze how bilateral subthalamic deep brain stimulation therapy can change sleep disturbances as assessed by the newly developed PDSS-2 and the non-motor section of the Movement Disorders Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

MATERIALS AND METHODS

Patients

In this prospective study, 25 consecutive patients undergoing bilateral subthalamic deep brain stimulation at the University of Pécs were enrolled. All patients fulfilled the UK Brain Bank criteria for PD [12]. Each subject gave written informed consent in accordance with the ethical approval of the Regional Ethical Board (3617.316-24983/KK41/2009). Each patient was examined by a neurologist specialized in movement disorders.

Because the presence of minor or major neurocognitive disorder was a contraindication for DBS surgery, such patients were not included in this study [13]. Presence of dementia was defined as either achieving ≤125 points on the Hungarian validated version of the Mattis Dementia Rating Scale [14] and/or ≤22 points on the Montreal Cognitive Assessment [15] and/or fulfilling the criteria of dementia according to the DSM-IV-TR.

Patients were evaluated in ON state while receiving their usual antiparkinsonian and other medications. Subsequently, levodopa equivalent dosage calculations were performed [16].

Rating scales utilized in the study

Patients were examined twice: 1 week prior to the DBS implantation (baseline) and 12 months postoperatively. Severity of PD symptoms was globally assessed by the Hungarian validated version of the MDS-UPDRS [17]. The recently published MDS-UPDRS is a validated scale to assess non-motor aspects (Part 1) and motor aspects (Part 2) of experiences of daily

living, motor examination (Part 3) and motor complications (Part 4) [18]. Included in the non-motor part, MDS-UPDRS has two items evaluating the presence and severity of nighttime sleep problems (item 1.17) and daytime sleepiness (item 1.18). These two items serve as a screening tool for sleep disturbances and daytime sleepiness [19]. As a part of the MDS-UPDRS, the Hoehn-Yahr Scale was also taken to detect the overall severity of PD. Besides, we also applied the Clinical Global Impression – Severity scale (CGI-S) to evaluate the overall illness severity on a 7-item Likert-type scale: 1: normal, not at all ill; 2: borderline ill; 3: mildly ill; 4: moderately ill; 5: markedly ill; 6: severely ill; or 7: extremely ill.

To assess non-motor symptoms globally, the Non-Motor Symptoms Scale (NMSS) was also included. This scale is obtained by trained professionals and capable of simultaneously capturing the severity and frequency of nine non-motor domains typical for PD. Besides sleep, NMSS also evaluates cardiovascular, cognitive, mood, hallucinatory, gastrointestinal, urinary and sexual symptoms.

Presence and severity of sleep disturbances were specifically measured by PDSS-2. The threshold indicating sleep problems is 11 points for the Hungarian version of PDSS-2 [20]. Meantime, daytime sleepiness was assessed by the Epworth Sleepiness Scale [21] with the cutoff value of 8 points [20, 22].

As part of the neuropsychological domain, depression (Beck and Montgomery Depression Scales) and cognitive performance (Montreal Cognitive Assessment [15], Mattis Dementia Rating Scale [14] and Addenbrook Cognitive Examination [14]) were also examined. Health-related quality of life was measured by the Hungarian validated version of PDQ-39 [23].

Statistical analysis

All statistical analyses were carried out using the IBM SPSS software package (version 22.0.1, IBM Inc, Armonk, NY, USA). Because data from these scales were ordinal, non-parametric tests were applied. For description of the data, medians with interquartile range (IQR: 25th-75th percentile) were calculated. Wilcoxon signed rank test was applied for the comparison of baseline and follow-up values. To detect which item of PDSS-2 has changed significantly, we also used Bonferroni correction. For dichotomous variables (e.g., presence or absence of sleep-problems, usage of levodopa, etc.) McNemar test, and for categorical variables Chi-square tests were used. Statistical significance level was set at 5%.

RESULTS

Demographic and PD-related clinical data

The subject population consisted of 25 non-demented PD patients (18 males, age: 55.9 ± 8.7 years, disease duration: 11.0 ± 4.8 years). Nine patients had rigid-akinetic, 6 had tremor-dominant and 10 had mixed-type of PD. Hoehn-Yahr staging, medication usage and levodopa equivalent dosages are demonstrated in Table 1.

Severity of PD

While the antiparkinsonian medication was significantly reduced from 814 mg (median, IQR: 564–914 mg) to 420 mg (IQR: 250–594 mg, $p = 0.001$), the total score of MDS-UPDRS improved from 81 (median, IQR: 63–103 points) to 55 points (median, IQR: 46–75 points, $p < 0.001$). Besides, all domains of MDS-UPDRS also improved 12 months after DBS implantation (Table 1). Although the HY staging showed improvement, it did not reach the level of statistical significance ($p = 0.095$). However, significantly more patients (9/25) reported either no or borderline severity of PD after treatment compared to baseline based on the CGI-S scale (3/25, $p = 0.047$, Chi-square test).

Health-related quality of life also improved from 29 (IQR: 18–40) to 15 (IQR: 9–28) points ($p = 0.002$) measured by the PDQ-39 Summary Index.

Non-motor symptoms

With the exception of hallucinatory symptoms and sexual dysfunction, all domains of NMSS improved after DBS treatment. The total score of NMSS decreased from 68 (IQR: 46–85) to 40 points (IQR: 16–52, $p = 0.001$), whereas the Sleep domain of NMSS improved from 19 (IQR: 14–27) to 9 points (IQR: 6–16, $p = 0.002$, Table 1).

At baseline, 13 patients reported sleep problems (i.e., a total score of PDSS-2 ≥ 11 points), but 1 year after the DBS implantation only 3 did ($p = 0.012$, McNemar test). Simultaneously, the total score of PDSS-2 decreased from 24 (IQR: 17–32) to 10 (IQR: 7–18) points ($P < 0.001$). Although all domains of the PDSS-2 improved, only 6 items showed a significant decrease after DBS implantation. "Bed sleep quality", "Restlessness of legs and arms at night", "Urge to move legs and arms at night", "Uncomfortable and immobility at night", "Muscle cramps in arms and legs" and "Tremor

Table 1
Comparison of preoperative and postoperative medication, motor and non-motor symptoms of Parkinson's disease and the health-related quality of life

		Preoperative					Postoperative					Significance	test
		Mean or number of patients	Standard deviation	Median	Percentile 25	Percentile 75	Mean	Standard deviation	Median	Percentile 25	Percentile 75		
Medication	Levodopa dosage (in LED)	755.7	418.9	780	520	1000	282.9	316.4	250	0	455	0.000	W
	Dopamine-agonist doseage (in LED)	260.3	196.3	300	150	374	213.4	159.6	300	0	320	0.382	W
	Antiparkinson medication (in LED)	848.9	545.8	814	564	914	480.2	245.0	420	250	594	0.001	W
	Dopamine agonist usage	19 (76%)					18 (72%)					1.000	McN
	MAOI usage	2 (8%)					1 (4%)					0.125	McN
	Levodopa usage	25 (100%)					14 (56%)					0.001	McN
	COMTI usage	15 (60%)					6 (24%)					0.002	McN
MDS-UPDRS	Hoehn-Yahr Scale												
	(stages 1/2/3/4/5)	0/20/2/3/0					0/18/5/2/0					0.095	Chi
	CGI-S (1/2/3/4/5/6/7)	0/3/7/5/6/2/2					2/7/10/3/3/0/0					0.001	Chi
	MDS-UPDRS Part1	15.3	5.3	15	12	18	11.1	7.0	10	7	12	0.004	W
	Item 1.7 "Sleep problem"	2.4	1.3	3	2	3	1.3	1.5	1	0	3	0.003	W
	Item 1.8 "Daytime sleepiness"	1.8	0.8	2	2	2	1.2	1.1	1	0	2	0.063	W
	MDS-UPDRS Part2	19.8	9.0	22	12	27	12.4	5.9	12	9	16	0.000	W
	MDS-UPDRS Part3	41.3	17.3	39	29	53	31.8	11.2	29	24	40	0.012	W
	MDS-UPDRS Part4	6.7	3.6	6	5	9	3.5	2.9	3	2	5	0.000	W
	MDS-UPDRS Total	83.1	27.3	81	63	103	58.8	20.2	55	46	75	0.000	W
Non-motor symptoms	NMSS (Part 1, Cardiovascular problems)	4.3	4.1	4	0	6	2.5	3.1	1	0	4	0.049	W
	NMSS (Part 2, Sleep problems)	19.3	9.4	19	14	27	12.2	10.2	9	6	16	0.002	W
	NMSS (Part 3, Mood problems)	12.3	10.0	10	4	22	8.9	13.7	3	1	10	0.038	W
	NMSS (Part 4, Hallucinations)	0.3	1.2	0	0	0	0.4	1.6	0	0	0	1.000	W
	NMSS (Part 5, Memory problems)	6.3	6.3	6	1	8	3.4	4.1	2	0	6	0.004	W
	NMSS (Part 6, Gastrointestinal problems)	5.9	6.7	4	2	8	3.6	4.8	2	0	5	0.041	W
	NMSS (Part 7, Urinary problems)	9.8	9.6	6	3	14	5.4	5.5	4	1	8	0.042	W
	NMSS (Part 8, Sexual problems)	4.3	6.2	0	0	8	4.8	7.7	0	0	8	0.937	W
	NMSS (Part 9, Miscellaneous problems)	8.1	6.9	8	2	12	4.2	5.5	2	0	7	0.004	W
	NMSS Total score	70.7	32.3	68	46	85	45.6	38.8	40	16	52	0.001	W
	Presence of Sleep problems	12N/13Y					22N/3Y					0.012	McN
	PDSS-2 Total score	24.8	9.9	24	17	32	14.2	11.4	10	7	18	0.000	W
	Presence of daytime sleepiness	10N/15Y					16N/9Y					0.031	McN
	ESS Total score	9.3	5.2	9	6	13	7.1	5.2	5	4	11	0.003	W
	PDQ-39 Summary index	29.5	11.5	29	18	40	19.8	16.2	15	9	28	0.002	W
Neuropsychological	BDI Total score	12.2	5.9	11	7	16	9.5	8.1	7	5	11	0.039	W
	MADRS Total score	11.8	5.9	12	8	15	9.3	8.4	6	5	12	0.033	W
	MOCA	23.1	3.5	23	20	26	25.9	3.0	27	24	28	0.220	W
	Mattis	138.2	5.4	140	137	141	140.9	4.1	142	141	144	0.407	W
	ACE	86.4	7.1	87	81	91	86.8	6.5	89	86	90	0.423	W

Presence of sleep problems was defined as having ≥11 points on PDSS-2 and presence of daytime sleepiness was defined as having ≥8 points on ESS. Abbreviations: ACE = Addenbrooke Cognitive Examination; BDI = Beck Depression Inventory; CGI-S = Clinical Global Impression-Severity; COMTI = catechol-O-methyl transferase inhibitor; ESS = Epworth Sleepiness Scale; LED = levodopa-equivalent dosage; MADRS = Montgomery-Asberg Depression Rating Scale; MAOI = monoamine-oxidase inhibitor; MDS-UPDRS = The Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; MOCA = Montreal Cognitive Assessment; NMSS = Non-motor Symptoms Scale; PDSS-2 = Parkinson's Disease Sleep Scale 2nd version. Applied statistical tests: Chi = Chi-square; McN = McNemar test; W = Wilcoxon signed rank test.

Table 2
Postoperative changes in the PDSS-2 items and domains

Item	Name of item	Preop					Postop					Significance
		Mean	Standard deviation	Median	Percentile 25	Percentile 75	Mean	Standard deviation	Median	Percentile 25	Percentile 75	
1	Bed sleep quality	2.2	1.2	2	1	3	1.5	1.4	1	0	2	0.047
2	Difficulties falling asleep	1.7	1.3	2	1	3	1.0	1.3	0	0	2	0.280
3	Difficulties staying asleep	2.5	1.3	3	2	4	1.9	1.7	2	0	4	0.445
4	Restlessness of legs and arms at night	1.7	1.2	2	0	3	0.9	1.1	0	0	2	0.044
5	Urge to move legs and arms	1.6	1.4	2	0	3	0.7	1.1	0	0	1	0.043
6	Distressing dreams at night	0.8	0.9	1	0	2	0.5	1.1	0	0	0	1.000
7	Distressing hallucinations at night	0.2	0.5	0	0	0	0.1	0.4	0	0	0	1.000
8	Nocturia	2.7	1.1	3	2	4	1.8	1.5	1	1	3	0.137
9	Uncomfortable and immobility at night	2.1	1.4	2	1	3	0.8	1.1	0	0	1	0.008
10	Pain in arms and legs	1.6	1.5	1	0	3	0.9	1.1	0	0	2	0.597
11	Muscle cramps in arms and legs	1.6	1.3	1	1	2	0.8	1.2	0	0	2	0.042
12	Painful posturing in the morning	1.3	1.4	1	0	2	0.8	1.2	0	0	1	0.183
13	Tremor on waking	2.1	1.3	2	1	3	0.8	1.4	0	0	1	0.005
14	Tired and sleepy after waking in the morning	1.9	1.0	2	1	3	1.4	1.1	1	1	2	0.383
15	Snoring or difficulties in breathing	0.9	1.2	0	0	2	0.2	0.7	0	0	0	0.166
	Motor symptoms at night domain	7.5	4.1	7	5	10	3.6	4.0	3	0	5	0.001
	PD symptoms at night domain	6.3	3.6	6	4	9	3.0	3.7	2	0	4	0.002
	Disturbed sleep domain	11.0	4.5	11	8	14	7.6	5.3	7	3	12	0.001
	Total score of PDSS-2	24.8	9.9	24	17	32	14.2	11.4	10	7	18	0.000

Abbreviation: PDSS-2 = Parkinson's Disease Sleep Scale 2nd version; *p*-values are indicated after Bonferroni correction (based on Wilcoxon signed rank test).

on waking" items had significant improvement after Bonferroni correction (Table 2). This improvement in sleep quality was also captured by the MDS-UPDRS item 1.7 ("Sleep problems", Table 2).

Before DBS implantation, 15 patients reported daytime sleepiness (i.e., total score of ESS ≥ 8 points), which decreased to 9 patients 1 year after the operation ($p = 0.032$, McNemar test). Meanwhile, the total score of ESS improved from 9 (IQR: 6–13) to 5 (IQR: 4–11) points ($P = 0.003$, Table 1). However, we detected only a trend for improvement on item 1.8 ("Daytime sleepiness") of the MDS-UPDRS.

Both depression-measuring tools (BDI and MADRS) demonstrated a significant improvement in depressive symptoms; whereas, the neurocognitive performance on neuropsychological tests (MDRS, ACE and MOCA) did not change (Table 1).

DISCUSSION

The aim of the present study was to identify the beneficiary effects of bilateral subthalamic deep brain stimulation on sleep quality by the utilization of the recently developed PDSS-2. As far as the authors are aware, this is the first prospective study utilizing the PDSS-2 and MDS-UPDRS scales to assess the longitudinal changes in sleep disturbances. Since the PDSS-2 has distinctive items on different aspects of sleep disturbances specific for PD, we were able to analyze what components of sleep responded to DBS therapy.

Fulfilling our expectations, most non-motor symptoms (including mood, gastrointestinal, urinary, cardiovascular and sleep) improved by STN DBS according to the subscales of NMSS, MDS-UPDRS, BDI and MADRS scales. Not only the number of patients reporting clinically relevant sleep problems decreased, but also the general sleep quality measured by both Sleep section of the NMSS and the total score of PDSS-2 improved.

The analysis of individual components of PDSS-2 revealed that only a few distinctive components of sleep contributed to the observed improvement in sleep quality. According to our data, RLS-related problems (items 4 and 5: "Restlessness of legs and arms at night" and "Urge to move legs and arms"), some nocturnal OFF symptoms (items 9 and 11: "Uncomfortable and immobility at night" and "Muscle cramps in arms and legs"), tremor on waking (item 13) and general sleep quality (item 1) improved significantly after STN DBS therapy.

Previously, only a few studies utilized the MDS-UPDRS to reveal the changes associated with STN DBS. We identified a single study (Pubmed search, keywords: MDS-UPDRS and DBS, assessed on January 4, 2015) to determine if the MDS-UPDRS could detect improvement in both motor and non-motor symptoms after bilateral STN DBS for PD [24]. Although the authors concluded that all sections of MDS-UPDRS improved 6 months after DBS implantation, they did not find any improvement in item 1.7, "Sleep problems". Conversely, our study showed a significant improvement in "Sleep problems" and a trend for improvement in "Daytime Sleepiness" items of MDS-UPDRS after Bonferroni correction. These incongruent results might be due to methodological discrepancies (20 patients vs. 25 patients, 6-month vs. 12-month follow-up, parametric vs. non-parametric tests). Probably because of the longer follow-up time, we also experienced a more robust improvement in Part 1 (5 points –median vs. 3.1 points –mean) of the MDS-UPDRS.

To our knowledge, previous DBS studies have not used the MDS-UPDRS and PDSS-2 at baseline and post-DBS to track clinical symptoms. Although our sample size was small, the degree of improvement in motor symptoms, as a result of STN DBS in our study, was similar to the improvement reported in a large randomized trial of DBS that used the original UPDRS [25, 26]. Although the clinimetric properties of PDSS differ from those of PDSS-2 (15 visual analogue scales vs. 15 Likert-type scales grouping into 3 major domains, higher values on PDSS represent a better sleep quality vs. lower numbers mean a better sleep quality on PDSS-2), we can compare their responsiveness to STN DBS. Hjort et al. demonstrated a 31.9% improvement (from 79.8 to 105.3 points on PDSS) in 10 PD patients who underwent DBS implantation. Chahine et al. analyzed 17 patients (12 receiving unilateral and 5 bilateral DBS) 6 months after surgery and reported a 30.5% improvement (from 94.2 to 122.9 points on PDSS) [6]. On the contrary, one article (available only in Chinese) did not report any significant improvement on PDSS 1 year after the operation [27]. Despite the above mentioned discrepancies between the PDSS and PDSS-2, we measured a comparable improvement in sleep quality (58.3%, from 24 to 10 points, median values, $p < 0.001$).

CONCLUSIONS

Subthalamic deep brain stimulation not only can decrease the number of patients reporting clinically relevant sleep problems but also improve the general

sleep quality. This improvement can be consistently demonstrated by the PDSS-2, NMSS and the MDS-UPDRS. Besides sleep, most domains of non-motor symptoms and the health-related quality of life can be improved by DBS therapy.

The PDSS-2 has some advantages over the original PDSS in that it more comprehensively assesses the different aspects of sleep problems specific for PD. Because our results suggest that the PDSS-2 can reliably detect the sleep-related changes after DBS, we recommend that the PDSS-2 should be utilized in future DBS studies.

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GD 1, 2, 3
ZA 1B, 2C, 3B
PA 1B, 2C, 3B
EB. 1B, 2C, 3B
JJ 1A, 2C, 3B
BF 1C, 2C, 3B
AM 1C, 2C, 3B
MK 1C, 2C, 3B
SK 1B, 2C, 3B
IB. 1B, 2C, 3B
TD 1B, 2C, 3B
NK 1, 2, 3

FINANCIAL DISCLOSURES

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