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# The impact of subthalamic deep brain stimulation on sleep and other non-motor symptoms in Parkinson's disease

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ABSTRACT

*Introduction:* The non-motor symptoms have a major impact on quality of life in patients with Parkinson Disease (PD). We present results of the study on the impact of subthalamic deep brain stimulation (DBS-STN) on sleep and other non-motor symptoms in PD patients.

*Materials and methods:* Thirty-six patients with advanced PD were included into the study. Twenty four were evaluated with two-night polysomnography (PSG) before surgery and at 6 months after DBS programming. The whole group (n = 36) was assessed using motor, non-motor symptoms (sleep disturbances in particular) and quality of life measures (QoL), before surgery, 6 and 12 months after DBS programming.

*Results:* DBS-STN resulted in the significant deterioration of objective sleep parameters, as assessed by PSG, mostly in terms of total sleep time, sleep efficiency, duration of N1 and N2 sleep, wakefulness after sleep onset and sleep latency. At the same time, improvement in the subjective sleep measures, other non-motor symptoms (particularly fatigue, cardiovascular, gastrointestinal, and sexual symptoms) and QoL was identified. The subjective improvement of sleep, other non-motor symptoms and QoL was most prominent in the first 6 months after DBS-STN, diminished slightly (being still better than before surgery) after 12 months, in parallel to mood deterioration.

*Conclusion:* DBS-STN resulted in the subjective sleep quality improvement with worsening of objective (PSG) sleep parameters after 6 months. After 12 months all sleep clinical outcome measures were still better than before surgery, albeit worse when compared to the first follow-up visit. Subjective sleep quality correlated positively with mood.

## 1. Introduction

Parkinson's Disease (PD) is a progressive neurodegenerative disorder with a wide range of motor and non-motor symptoms. Deep brain stimulation (DBS) has a proven beneficial effect on motor symptoms, however, its impact on non-motor problems, and sleep particularly is not fully understood [1,2]. Polysomnography (PSG) remains the gold standard in the objective sleep assessments. Sleep and wakefulness disorders (SWD) in PD encompass a broad spectrum of symptoms including insomnia, disrupted sleep architecture and sleep fragmentation, rapid eye movement (REM) sleep behavior disorder (RBD), restless legs syndrome (RLS) and periodic limb movements of sleep (PLMS), vivid dreaming and hallucinations, sleep disordered breathing, excessive daytime sleepiness (EDS) and sleep attacks [3]. Previous sleep studies of PD patients pre- and post-DBS surgery had several limitations as short observation period and small number of participants [1–4].

In the previous studies, DBS-STN was demonstrated to improve subjective measures of sleep [1–8]. DBS-STN was shown to positively impact nocturnal sleep, especially sleep quality and patient-reported sleep problems. Daytime sleepiness was reduced only in a study by Dafsari et al. [8], whereas in other studies it remained unchanged [1,2,5–7]. Most authors speculated that the improvement of sleep could be related to enhanced nocturnal mobility and reduced fragmentation of sleep [1,2,4,7].

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To the best of our knowledge there have been only six studies published evaluating the impact of bilateral DBS-STN on sleep in PD patients with the use of polysomnography [1,2,9–14]. Most of the previous studies consisted of small groups (from 5 to 11 patients) [9–13] and only the most recent study by Baumann-Vogel et al. [14] included the group of 50 patients. Furthermore, these studies employed various designs and methods, patient selection criteria and outcome measures, which hinders direct comparisons of results. DBS-STN was found to increase duration of total sleep time and sleep efficiency in most studies and only in a study by Iranzo et al. [12] these parameters deteriorated slightly. Slow wave sleep, REM sleep latency and WASO were improved notably in most studies including the most recent study by Baumann-Vogel et al. Three studies showed increase in REM sleep [9,10,13], however, that was not confirmed in a study by Baumann-Vogel et al. In most studies, including a study by Baumann-Vogel et al., DBS did not affect RLS. PLMI index was doubled in a study by Baumann-Vogel et al., yet in other studies it remained unaffected. Only in one study, by Iranzo et al. [12], DBS-STN improved arousal index, in the remaining studies it remained stable or slightly increased [11,13,14]. Nishida et al. [13] found DBS-STN to alleviate RBD and to restore normal REM sleep with atonia, however, in other studies RBD was not influenced by DBS-STN [9–12,14]. Table 1 presents the most significant findings from the previous studies on bilateral DBS-STN effects on objective sleep parameters with comments on the study design.

The aim of our study was to evaluate subjective (sleep scales) and objective (PSG) sleep and other non-motor problems related to DBS STN.

## 2. Material and methods

Thirty-six consecutive patients with advanced PD, 21 males and 15 females, who fulfilled the Defer et al. CAPSIT [15] criteria to perform a routine DBS therapy, were enrolled into the study. The mean age was 59.2 ± 7.8 years (range 40–69) and the mean disease duration was 11.4 ± 4.3 years. The detailed demographic and clinical characteristics are presented in Table 2.

The initial evaluation included neurological and neuropsychological examinations. The former included levodopa challenge with the use of Unified Parkinson's Disease Rating Scale (UPDRS) part III performed at *on* and *off* stages. The latter was aimed at establishing the patient's cognitive status as normal, with mild cognitive impairment or demented according to Emre et al. level II criteria [16] and Litvan et al.'s level II criteria [17]. Cognitive screening was performed with Addenbrooke's Cognitive Examination-III (ACE-III) [18]. Mood was assessed with Beck Depression Inventory (BDI). Additionally, 1.5 T Magnetic Resonance Imaging (MRI) was performed.

All patients were evaluated with the Non-Motor Symptoms Scale (NMSS), Parkinson's Disease Sleep Scale (PDSS), Epworth Sleepiness Scale (ESS), Single-Question Screen for RBD (RBD1Q), Parkinson's Disease Quality of Life Questionnaire (PDQ-39), Schwab and England Activities of Daily Living Scale, Hoehn & Yahr, UPDRS parts II, III and IV. Patients who fulfilled criteria for the diagnosis of RLS were assessed with International RLS Study Group Rating Scale (IRLS).

Twenty-four patients agreed to participate in PSG examinations, however, in the course of the study one patient did not complete follow-up. Polysomnography evaluations were performed on two consecutive nights at a median of 1.5 weeks before surgery and again at a median of 6.5 months post DBS programming. The first nights were deemed the habituation nights and were not included in further analyses, except for 3 patients whose recordings from the second nights were unavailable due to technical difficulties.

The PSG examinations were performed in the sleep laboratory by a PSG technician and were scored by a physician certified in sleep medicine. The data from 2 electrooculography, 6 electroencephalography (F3-A2, F4-A1, C3A2, C4-A1, O1-A2, O2-A), 3 electromyography, 2 limb movement, 1 airflow, 1 electrocardiography and 1 oximetry

**Table 1**
The summary of the previous studies on bilateral DBS-STN effects on objective sleep parameters including statistically significant findings.

| Study | Number of patients | Mean age (years) | Increased parameters | Decreased parameters | Unchanged parameters | Comments |
|---|---|---|---|---|---|---|
| Monaca et al. [9] | 10 | 57.4 ± 5.2 | total sleep time, sleep efficiency, deep slow-wave sleep, paradoxical sleep | | number of awakenings during sleep | two all-night PSG recordings 1 month before surgery and three (control, stimulation "on", stimulation "off") all-night PSG recordings 3 months after surgery |
| Cicolin et al. [10] | 5 | 63.8 ± 3.3 | sleep efficiency, total sleep time, stage 3–4 NREM sleep, REM sleep, the longest period of uninterrupted sleep | WASO, REM latency | RBD, PLMS | two all-night PSG recordings 1 week before and 3 months after surgery |
| Arnulf et al. [11] | 10 | range of age: 40-60 | sleep efficiency, total sleep time, N2 sleep, | WASO, nocturnal motor symptoms | number of awakenings, PLMS, RLS, RBD | only patients with severe akinetic idiopathic PD and chronic insomnia, 3–6 months after DBS-STN, two PSG all-night recordings: one with and one without stimulation |
| Iranzo et al. [12] | 11 | 63.6 ± 7.8 | number of body position changes, the longest period of continuous sleep | arousal index | PLMS, RBD | two all-night PSG recordings 1 week before and 6 months after surgery |
| Nishida at al [13] | 10 | 57.5 ± 9.8 | improvement of general sleep architecture, deep slow-wave sleep, REM sleep, REM sleep with atonia | WASO, REM sleep without atonia | | one all-night PSG recordings during the week preceding surgery and the week after DBS programming |
| Baumann-Vogel et al. [14] | 50 | 61 ± 10 | total sleep time, sleep efficiency, N3 sleep; | WASO, REM sleep latency, PLMS | sleep latency, duration of N1, N2 and REM sleep, awakening index, body position changes, apnea–hypopnea index, RLS, REM sleep without atonia | one all-night PSG recordings 3.1 ± 3.6 months prior to surgery (baseline) and 7.7 ± 2.8 months after DBS surgery |

NREM - Non-rapid eye movement sleep, PLMS - Periodic limb movement disorder, PSG – Polysomnography, RBD - Rapid eye movement (REM) sleep behavior disorder, RLS - Restless Legs Syndrome, RWA – REM without atonia, WASO - wakefulness after sleep onset.

**Table 2**
Patient characteristics on the enrollment into the study.

| | |
|---|---|
| Number of patients | 36 |
| Sex, female/male | 15/21 |
| Age, mean (range) | 59.2 (40–69) |
| Age of first symptoms, mean (range) | 48.0 (30–61) |
| Disease duration, years, mean (range) | 11.4 (5–22) |
| Hoehn & Yahr state ON, stage 1/2/3 | 0/27/9 |
| Schwab and England Activities of Daily Living Scale, 90/80/70/60% | 1/3/20/12 |
| Side with dominant symptoms, left/right/symmetrical | 16/19/1 |

channels were recorded.

The patients underwent bilateral DBS-STN implantation and the initial programming of DBS was done at a median of 7.4 weeks after the surgical procedure.

The follow-up outpatient assessments included the same tests and were done at a median of 6.3 and 12.3 months after DBS programming, including 35 and 34 patients, respectively.

We collected the written informed consent from all patients and the study was approved by the Bioethics Committee at the local Medical University (NKBBN/54/2014).

### 2.1. Statistical analyses

We checked for the normal distribution of the data with the use of W Shapiro-Wilk test. The data were assessed by parametric (*t*-test) and non-parametric (Wilcoxon signed-rank, Mann–Whitney–Wilcoxon and Conover) tests appropriately. We sought for correlations with the use of Kendall and Spearman's rank correlation coefficient (Kendall's tau coefficient and Spearman's rho). The $\chi 2$ and the Fisher exact tests have been used to check the independence for categorical variables. Most of the variables that were found to be correlated with each other were further assessed with backward stepwise regression. The assumed significance level was $\alpha = 0.05$. The results have been generated using R statistics language [19].

## 3. Results

The detailed results of non-motor and motor scales comparing the baseline and 6 and 12 months follow-up visits, from the initial and follow-up polysomnographic recordings are displayed in Tables 3 and 4, respectively. The detailed results of correlations analysis are provided in Table 5.

The improvement of subjective measures of sleep was confirmed in PDSS throughout the study. However, it was most pronounced at 6-month follow-up and later slightly deteriorated (even though it was found to be statistically significant only when comparing preoperative and 12 months after DBS programming assessments). The daytime sleepiness (ESS) remained stable during the observation period. At preoperative evaluation 14 patients fulfilled criteria of International RLS Study Group for the diagnosis of RLS and this number was reduced to 10 patients at 6 months (1 new and 9 previously diagnosed) and at 12 months (2 new and 8 previously with symptoms). The severity of RLS (assessed by IRLS) decreased significantly both at 6 and 12 months follow-up visits compared to baseline. However, there was significant worsening of RLS between the 6 and 12 months. RBD symptoms were reported in questionnaires by 21, 13 (3 new and 10 previously recorded) and 15 (4 new and 11 previously recorded) patients, at baseline, at 6-month and at 12-month follow-up visits, respectively.

PSG examinations showed that DBS-STN significantly diminished total sleep time, sleep efficiency, duration of N2 sleep, and at the same time prolonged wakefulness after sleep onset (WASO), duration of N1 sleep and sleep latency. Moreover, DBS-STN decreased duration of N3 sleep and REM sleep, however these changes were not statistically significant. The arousal index remained stable at follow-up, however its subdivisions - respiratory event related (RER) and limbs movement-related (LMR) arousal indices significantly improved. The reduction of total limb movements index, periodic limb movements index (PLMI) and apnea–hypopnea was not statistically significant. REM sleep behavior disorder was not found in any patient on PSG examinations and REM atonia was preserved in all patients.

Regarding the NMSS score, improvement both at 6 and 12 months after DBS programming was observed. Furthermore, non-motor symptoms improved between these two follow-up visits. Among particular NMSS domains, fatigue, cardiovascular, gastrointestinal, sexual and other ("miscellaneous" domain no. 9) symptoms decreased after DBS.

The overall PDQ-39 score improved after DBS-STN, both at 6 and 12 months examinations. However, the deterioration of QoL between 6 and 12 months was observed. Among the PDQ-39 dimensions major improvement concerned mobility, activities of daily living (ADL), emotional well-being, stigma and bodily discomfort. Similarly to the total PDQ-39 score, these subdivisions deteriorated between the two follow-up visits. The improvement of PDQ-39 score was in concordance with better ADL measured by UPDRS part II score.

The severity of motor symptoms was reduced at 6 months after DBS programming, as assessed by UPDRS part III during the "on" state, with slight, but significantly increased median score after 12 months. UPDRS part IV, continued to improve between 6 and 12 months.

Mood, as assessed by BDI, significantly improved at 6 months after DBS-STN, however later we observed statistically relevant deterioration. There were no statistically significant changes on ACE-III in the whole group. Cognition, as assessed by a comprehensive neuropsychological examination, was mildly impaired (mild cognitive impairment, MCI) in 9 patients at baseline. After 6 months 9 patients presented MCI and 1 converted to dementia, while after 12 months dementia was diagnosed in 2 patients.

Correlations between severity of subjective sleep disturbances (PDSS) and non-motor symptoms (NMSS total score), quality of life (PDQ-39) and UPDRS part IV were noted at baseline and on both follow-up evaluations. The correlation between mood (BDI) scores and subjective sleep measures (PDSS) was statistically significant at all three assessments.

No relevant relationship between severity of motor symptoms (UPDRS part III) and subjective sleep measures (PDSS) or non-motor symptoms (NMSS total score) was identified. Patients with and without RLS differed in terms of the ADL impairment (UPDRS II), however, further statistical analysis did not detect any trends.

Significant relationships between motor (UPDRS III) and WASO, apnea-hypopnea index were identified at baseline, that were not observed on follow-up examinations. The relevant interrelation between severity of motor symptoms and REM sleep latency was observed only on follow-up PSG.

## 4. Discussion

Consistently with previous studies, we found improvement of subjective sleep quality after DBS-STN, whereas daytime sleepiness remained relatively stable. However, contrary to the previous studies, we generally observed deterioration of objective sleep quality after DBS-STN as was reflected by changes in most parameters at the follow-up PSG evaluation. We found reduction of total sleep time, sleep efficiency, the most restoring and recuperative stages of N3, REM and N2 sleep, on the other hand, the lightest sleep stage N1, WASO and latency of sleep were increased. Interestingly, and contrary to the most previous studies, we noted improvement in RER and LMR arousal indices, total limb movements, periodic limb movements and apnea–hypopnea indices. We also observed the remission of RLS symptoms in 43% of patients (6/14) and the new onset of RLS only in 2 patients after DBS-STN. We found improvement of RLS symptoms in patients who complained of them throughout the study, however, it was most prominent in the first 6 months and later slightly diminished. Even though, 21, 13 and 15

**Table 3**
The detailed results from non-motor and motor symptoms scales before the surgery, 6 and 12 months after DBS programming. Additionally data on medications doses are provided.

| Parameters | Preoperative evaluation median (range) (I) { mean[#]} | 6 months after DBS programming median (range) (II) { mean[#]} | 12 months after DBS programming median (range) (III) { mean[#]} | Statistics p value[a] | | |
|---|---|---|---|---|---|---|
| | | | | I vs. II | I vs. III | II vs. III |
| NMSS total score | 56 (15–112) | 36 (13–104) | 32 (15–104) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| Domain 1: Cardiovascular including falls | 0 (0–6) | 0 (0–4) | 0 (0–4) | ≤ **0.001** | ≤ **0.001** | ≥0.05 |
| Domain 2: Sleep/fatigue | 16 (1–42) | 6 (0–24) | 5 (1–24) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| Domain 3: Mood/cognition | 6 (0–21) | 2 (0–18) | 2 (0–18) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| Domain 4: Perceptual problems/ hallucinations | 0 (0–6) | 0 (0–9) | 0 (0–9) | ≥0.05 | ≥0.05 | ≥0.05 |
| Domain 5: Attention/memory | 4 (0–16) | 4 (0–18) | 6 (0–18) | ≤ **0.01** | ≤ **0.001** | ≤ **0.001** |
| Domain 6: Gastrointestinal tract | 2 (0–16) | 1 (0–14) | 2 (0–14) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| Domain 7: Urinary | 5 (0–29) | 3 (1–29) | 4 (0–29) | ≥0.05 | ≥0.05 | ≥0.05 |
| Domain 8: Sexual function | 2 (0–24) | 2 (0–24) | 2 (0–24) | ≤ **0.001** | ≤ **0.001** | ≥0.05 |
| Domain 9: Miscellaneous | 13 (0–33) | 9 (0–25) | 9 (0–25) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| PDSS | 80.6 (38–135.7) | 90.9 (57–142.7) | 87.9 (36.3–143.3) | ≥0.05 | ≤ **0.01** | ≥0.05 |
| ESS | 8 (0–23) | 7 (1–19) | 8 (1–18) | ≥0.05 | ≥0.05 | ≥0.05 |
| IRLS[@] | 23.5 (11–29) | 18.0 (9–26) | 19.5 (10–35) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| PDQ39 Total score | 59 (20–113) | 42 (4–87) | 48 (9–102) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| PDQ39 Mobility | 46.9 (5.0–95.0) | 30.2 (2.5–72.5) | 35.8 (2.5–90.0) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| PDQ39 Activities of daily living | 50.0 (8.3–95.8) | 20.8 (0.0–66.7) | 25.0 (0.0–75.0) | ≤ **0.001** | ≤ **0.001** | ≤ **0.01** |
| PDQ39 Emotional well-being | 29.2 (4.2–83.3) | 16.7 (0.0–66.7) | 25.0 (0.0–79.2) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| PDQ39 Stigma | 37.5 (0.0–87.5) | 18.8 (0.0–68.8) | 25.0 (0.0–87.5) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| PDQ39 Social support | 16.7 (0.0–75.0) | 16.7 (0.0–58.3) | 25.0 (0.0–66.7) | ≥0.05 | ≥0.05 | ≥0.05 |
| PDQ39 Cognitive impairment | 25.0 (0.0–75.0) | 25.0 (0.0–62.5) | 25.0 (0.0–68.75) | ≥0.05 | ≥0.05 | ≥0.05 |
| PDQ39 Communication | 25.0 (0.0–58.3) | 25.0 (0.0–58.3) | 33.3 (0.0–83.3) | ≥0.05 | ≥0.05 | ≥0.05 |
| PDQ39 Bodily discomfort | 50.0 (0.0–91.7) | 41.7 (0.0–66.7) | 41.7 (0.0–83.3) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| BDI | 10 (1–27) | 6 (0–35) | 7 (0–32) | ≤ **0.001** | ≥0.05 | ≤ **0.001** |
| ACE III | 91 (80–100) | 91 (70–99) | 92 (69–98) | ≥0.05 | ≥0.05 | ≥0.05 |
| UPDRS II | 17 (1–32) | 12 (0–27) | 13 (2–27) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| UPDRS III[&] | 15 (2–54) {17.97} | 14 (6–36) {16.06} | 17 (7–36) {17.52} | ≤ **0.001** | ≤ **0.05** | ≤ **0.001** |
| UPDRS IV | 9 (5–13) | 5 (2–12) | 5 (1–12) | ≤ **0.001** | ≤ **0.001** | ≤ **0.001** |
| H&Y | 2 (2–3) | 2 (2–3) | 2 (2–3) | ≤ **0.05** | ≥0.05 | ≤ **0.05** |
| S&E ADL | 80 (60–90) | 90 (60–100) | 90 (60–100) | ≤ **0.001** | ≤ **0.001** | ≥0.05 |
| LED (miligrams) | 1620 (670–3140) {1653.0} | 1060 (380–2750) {1132.4} | 1030 (380–2750) {1141.7} | ≤ **0.001** | ≤ **0.001** | ≥0.05 |
| LEV (miligrams) | 1250 (250–3150) | 600 (0–2650) | 700 (0–2650) | ≤ **0.001** | ≤ **0.001** | ≥0.05 |
| Amantadine (miligrams) | 300 (0–400) | 200 (0–400) | 200 (0–400) | ≥0.05 | ≥0.05 | ≥0.05 |

[a] Conover post-hoc test for unreplicated blocked data, [#]the mean is given in curly brackets for selected parameters that have normal distribution (as assessed by W Shapiro-Wilk test), [@]IRLS was done in patients who fulfilled criteria of International RLS Study Group for the diagnosis of RLS, [&]„on-state" scores, ACE III - Addenbrooke's Cognitive Examination III, BDI - Beck Depression Inventory, ESS -Epworth Sleepiness Scale, IRLSS - International RLS Study Group Rating Scale, LED - levodopa equivalent dose, LEV - total levodopa daily dose, LMR - Limbs movement-related, NMSS - Non-Motor Symptoms Scale, PDSS - Parkinson's Disease Sleep Scale, PDQ39 - Parkinson's Disease Quality of Life Questionnaire, RBD1Q - Single-Question Screen for RBD, UPDRS - Unified Parkinson's Disease Rating Scale.

patients reported RBD in questionnaires at baseline, at 6-month and at 12-month follow-up visits, respectively, we did not detect RBD nor the loss of REM atonia in any patient on PSG examinations.

Based on the previous studies several hypotheses were proposed to explain the impact of DBS-STN on sleep [1–4]. DBS-STN may improve sleep directly by affecting the sleep/wakefulness regulatory centers and/or indirectly by ameliorating nocturnal motor symptoms and decreasing the doses of dopaminergic medications. The discrepancies between our and previous results are challenging to explain. Duration of the disease and age at baseline were similar to other studies. However, the initial Hoehn & Yahr stage (H&Y) and UPDRS part III score were significantly lower in our patients (the number of patients at H&Y stage 1/2/3 were 0/27/9 respectively and UPDRS part III mean value of 17.97 points) as compared to the Baumann-Vogel et al. (the number of patients at H&Y stage 1/2/3 were 3/27/20 respectively and mean UPDRS part III was 25.1). Despite having less advanced PD, in our patients the objective sleep parameters on initial PSG evaluation (mean sleep efficiency, WASO, N1 and N2 sleep, of 67.2%, 141.1 min, 31.7 min and 213.6 min, respectively) were not significantly better, as could be expected, than that in Baumann-Vogel et al. study (67.5%, 99.9 min, 51.0 min and 140.7 min, respectively). Dopaminergic medications, particularly levodopa, amantadine and selegiline may exacerbate sleep fragmentation and lead to insomnia, nevertheless the information on medication regimens in the previous studies is limited. The most detailed report on medications was presented in the study by Baumann-Vogel et al. The mean levodopa equivalent dose (LED) in our study was 1653, 1132 and 1142 mg at baseline and the next 2 visits respectively, as compared to the mean of 1025 mg at baseline and 369 mg at 7.7 months after DBS implantation in a study by Baumann-Vogel et al.

Amantadine in particular, having been previously associated with decreased sleep efficiency [20], was used in a minority of patients

**Table 4**
The detailed results from the preoperative and follow-up polysomnographic recordings.

| Parameters | Preoperative evaluation median (range) { mean*} | Follow-up evaluation median (range) { mean*} | Statistics p value |
|---|---|---|---|
| Total sleep time (min) | 326 (244.5–440) {322.6} | 250.5 (107.5–402.5) {255.9} | ≤**0.01**[a] |
| Sleep efficiency (%) | 67.8 (50.6–91.7) {67.2} | 52.4 (22.4–83.9) {53.9} | ≤ **0.01**[a] |
| WASO (min) | 135.5 (29.5–217) {141.1} | 198.5 (75–329.5) {195.5} | ≤ **0.01**[a] |
| Sleep latency (min) | 10.5 (3.5–104.5) | 16.5 (0.5–66.5) | ≤ **0.05**[b] |
| REM sleep latency (min) | 126.5 (3.5–407) | 124 (0–426.5) | 0.703[a] |
| N1 sleep (min) | 33 (4–65.5) {31.7} | 63.5 (19–148) {69.4} | ≤ **0.001**[a] |
| N2 sleep (min) | 218.5 (93.5–275.5) {213.6} | 112.5 (29–207) {119.4} | ≤ **0.001**[a] |
| N3 sleep (min) | 29.5 (0–92) | 21.5 (0–84.5) | 0.076[b] |
| REM sleep (min) | 39 (4.5–126) | 28 (0–149) | 0.580[b] |
| Arousal index | 19 (1.7–47.6) | 20.6 (6–38.4) | 0.762[a] |
| Spontaneous arousal index | 16.7 (0–32.1) | 20.3 (5.1–37.6) | 0.386[a] |
| RER arousal index | 0.9 (0–28.6) | 0 (0–1.2) | ≤ **0.01**[b] |
| LMR arousal index | 0.9 (0–5.2) | 0.2 (0–2.9) | ≤ **0.01**[b] |
| Total limb movements index | 6.4 (0–110.9) | 3.7 (0–97.3) | 0.203[b] |
| PLMI | 2.7 (0–104.2) | 0.4 (0–88.5) | 0.319[b] |
| Apnea–hypopnea index | 1.1 (0–36.6) | 0 (0–12.4) | 0.089[b] |
| RBD | 0 | 0 | – |

LMR - Limbs movement related, PLMI - Periodic limb movements index, RBD - Rapid eye movement (REM) sleep behavior disorder, RER - Respiratory event related, UPDRS - Unified Parkinson's disease rating scale, WASO - Wakefulness after sleep onset.

* The mean is given in curly brackets for selected parameters that have normal distribution (as assessed by W Shapiro-Wilk test).

[a] Paired *t*-test.

[b] Wilcoxon-Pratt Signed-Rank Test.

(18%) at baseline and totally discontinued in Baumann-Vogel et al. study. However, the majority of our patients (66,1%) were on amantadine at baseline and last visit.

Selegiline was only marginally used in our group (6 at baseline and 3 at follow up) and its use was not reported by other authors.

The data on mood and cognition from previous studies are scarce. In a study by Iranzo et al. mood improved significantly at 6-month follow-up, however, Monaca et al. observed increase in depressive symptoms at 3-month follow-up. Cognition changes after DBS-STN were intensely studied in the past [21], however, there are no data on cognition from the abovementioned six studies.

In our study, mood improved significantly during the first 6 months after DBS-STN, however, later deteriorated. Although, after 12 months there was still some improvement compared to the baseline, it was no longer statistically significant. We did not observe any significant changes in cognition in our group, however 2/36 patients converted to dementia at 12 months follow up. The lack of information on cognition and mood from the previous six studies might influence the sleep outcome measures.

The placebo effect was demonstrated in PD patients and positively affected bradykinesia, rigidity, dyskinesia, however, its impact on non-motor symptoms (except for depression) was not thoroughly evaluated [22]. The cortically based anticipation of improvement and the resultant increase in dopamine release in basal ganglia are the main physiologic mechanisms [22]. The surgical interventions are associated with increased expectations compared to the oral medications, however, there is scarcity of data on that subject in PD patients treated with DBS [23]. Yeung Shi Chung et al. conducted a large meta-analysis and found the placebo effect on subjective sleep, however, no effect on objective sleep parameters in insomnia patients [24]. We speculate that in our patients the observed improvement of subjective sleep quality could be partly accounted for by the placebo effect of the surgery.

The discordance between subjective sleep perception and objective sleep measures was reported in many studies [25,26]. Patients with insomnia were found to underestimate sleep duration and overestimate WASO, whereas healthy controls had the opposite pattern [25]. The pre-sleep cognitive activity, effort put into sleeping and sleep fragmentation were found to be predictive of underestimation of total sleep time [27]. Positive mood when waking up was demonstrated to be predictive of overestimation of total sleep time, whereas, negative mood had the opposite effect [27,28]. Baillet et al. showed that the mood was not influenced by sleep quantity or sleep quality from the previous night [28]. The mechanisms underlying the mismatch between

**Table 5**
The detailed results of the correlations that were found to be significant.

| Variables | | Correlations | | | Backward stepwise regression |
|---|---|---|---|---|---|
| (S1 – before surgery, S2 - at 6-month follow-up, S3 – at 12-month follow-up) | | p value | Kendall's tau | Spearman's rho | p value |
| NMSS_S1 | DOD | ≤0.01 | 0.37 | 0.52 | ≤0.05 |
| PDSS_S1 | DOD | ≤0.05 | −0.27 | −0.34 | – |
| PDSS_S1 | NMSS_S1 | ≤0.001 | −0.53 | −0.72 | ≤0.01 |
| PDSS_S2 | NMSS_S2 | ≤0.001 | −0.41 | −0.59 | ≤0.01 |
| PDSS_S3 | NMSS_S3 | ≤0.001 | −0.43 | −0.63 | ≤0.01 |
| PDSS_S1 | PDQ39_S1 | ≤0.001 | −0.66 | −0.80 | ≤0.01 |
| PDSS_S2 | PDQ39_S2 | ≤0.001 | −0.50 | −0.68 | ≤0.01 |
| PDSS_S3 | PDQ39_S3 | ≤0.001 | −0.54 | −0.72 | ≤0.01 |
| PDSS_S1 | UPDRS part IV_S1 | ≤0.001 | −0.47 | −0.61 | ≤0.05 |
| PDSS_S2 | UPDRS part IV_S2 | ≤0.01 | −0.32 | −0.43 | ≤0.05 |
| PDSS_S3 | UPDRS part IV_S3 | ≤0.001 | −0.44 | −0.58 | ≤0.05 |
| PDSS_S1 | BDI_S1 | ≤0.01 | −0.39 | −0.52 | – |
| PDSS_S2 | BDI_S2 | ≤0.01 | −0.36 | −0.47 | – |
| PDSS_S3 | BDI_S3 | ≤0.05 | −0.25 | −0.38 | – |
| UPDRS part III_S1 | Apnea-hypopnea index (initial PSG) | ≤0.01 | 0.41 | 0.54 | ≤0.05 |
| UPDRS part III_S2 | REM sleep latency (follow-up PSG) | ≤0.05 | −0.39 | −0.54 | ≤0.05 |
| UPDRS part III_S3 | WASO (initial PSG) | ≤0.05 | 0.40 | 0.54 | ≤0.05 |

BDI - Beck Depression Inventory, DOD - Duration of Parkinson's disease, NMSS - Non-Motor Symptoms Scale, PDSS - Parkinson's Disease Sleep Scale, PDQ39 - Parkinson's Disease Quality of Life Questionnaire, REM sleep - Rapid eye movement sleep, UPDRS - Unified Parkinson's Disease Rating Scale, WASO - Wakefulness after Sleep onset.

subjective and objective sleep quality can be partially explained by disturbances of the fronto-parietal pathway related to executive control, as demonstrated in healthy controls by Hsiao et al. [26] To our knowledge there have not been studies investigating this phenomenon in PD. The discrepancies between subjective and objective sleep measures and their changes over time in our patients could be partly accounted for by the recognized improvement of mood. We hypothesize, that observed "rebound phenomenon", namely the rapid improvement in the first few months after DBS-STN and the following deterioration in ours and in the previous study by Dafsari et al. [8] was due to the mood changes. Therefore, the subjective ratings of PDSS and other sleep scales might be influenced by motor and mood improvement observed after DBS-STN.

Significant improvement of the most other non-motor symptoms (NMSS total score), with special emphasis on fatigue, gastrointestinal, bodily discomfort, activities of daily living, perceived social stigma and quality of life was similar to previous reports [7,8]. Interestingly enough, in contrast to previous studies we found significant improvement of perceived severity of cardiovascular and sexual symptoms. Likewise, in the study by Dafsari et al. we observed "rebound effect" in improvement of the above-mentioned symptoms.

Correlations between motor-, non-motor symptoms, subjective and objective sleep parameters were assessed only partially in previous studies. No associations between motor symptoms and total sleep time, sleep efficiency, slow wave sleep and subjective measures of sleep were found in a study by Monaca et al. [9]. Similar findings were presented by Nishida et al., who also did not observe any relevant interrelations between motor symptoms or reduction of dopaminergic medications and subjective measures of sleep. However, Baumann-Vogel et al. identified significant associations between improvement of sleep efficiency, WASO and UPDRS part III reduction, deep sleep and LED reduction.

In our study, we did not observe any relevant and consistent relationships between severity of motor symptoms and objective sleep parameters. Similarly to previous studies we did not identify associations between motor symptoms and subjective sleep measures or other non-motor symptoms. This may suggest another than simply dopaminergic origin of sleep problems, independent of motor scores. This finding is consistent with recent data emerging on the premotor and early stage PD, implicating nondopaminergic, in addition to dopaminergic, systems involvement in the SWD pathogenesis [29]. We found significant correlations between subjective sleep disturbances, non-motor symptoms, quality of life and complications of levodopa therapy (partially measured by UPDRS IV score). To our knowledge, the present study is the first one to report the relationship between mood and subjective sleep parameters.

The study has several limitations. First, the number of patients included in the study is relatively small (however bigger than the majority of the papers) and we cannot exclude sample selection bias. Second, due to the ethical issues (postponing DBS-STN surgery for more than a year in patients who are otherwise good candidates for the procedure), we did not have control group of PD patients, hence we cannot assess the impact of the progression of the disease itself on our results. However, the control group was not included in any of the previous studies.

On the other hand, the present study has several strengths. The follow-up is the longest to date and is the only one with two evaluations at 6 and 12 months after DBS-STN. In addition to PSG examinations, we conducted comprehensive evaluations of subjective sleep measures, other non-motor symptoms, neuropsychological state and medications intake.

In summary, we found that DBS-STN deteriorated objective sleep parameters, whereas, significantly improved perceived sleep disturbances, non-motor symptoms and quality of life. The observed subjective improvement was most prominent in the first few months after DBS-STN, later slightly diminished, which corresponded to changes in mood over time. We assume that the observed "rebound phenomenon" may be due to the concomitant mood changes.

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## Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## Declarations of interest

None.

## Author contributions

JD – clinical patient management, clinical data collection, compilation of study findings and writing of the manuscript.
MS - clinical patient management.
AK – neuropsychological evaluation.
EJS – manuscript writing.
KG – polysomnographic evaluation.
WL – neurosurgical management.
PW – statistical analysis.
JS - supervision of the study and writing of the manuscript.

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