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Modulation of specific components of sleep disturbances by simultaneous subthalamic and nigral stimulation in Parkinson's disease

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ABSTRACT

Objective: To compare the effect of simultaneous deep brain stimulation of the subthalamic nucleus and substantia nigra pars reticulata (STN + SNr-DBS) to conventional subthalamic stimulation (STN-DBS) on sleep quality in Parkinson's disease (PD) patients.

Methods: The study was a single-center, randomized, double-blind, cross-over clinical trial to compare the effect of STN-DBS vs. combined STN + SNr-DBS on subjective measures of sleep quality. Fifteen PD patients (2 female, age 62.5 ± 6.7 years) suffering from moderate idiopathic PD (disease duration: 12.0 ± 5.0 years, Hoehn & Yahr stage: 2.2 ± 0.4 in the MED-ON & STN-DBS-ON condition, Hoehn & Yahr stage: 2.6 ± 0.8 in the MED-OFF condition preoperatively) participated in the study. Sleep quality was evaluated in both stimulation conditions using the PDSS-2 score as a self-rating questionnaire covering several aspects of sleep disturbances.

Results: PD patients showed mild-moderate sleep disturbances (STN-DBS: PDSS-2 score 17.0 ± 11.0; STN + SNr-DBS: 14.7 ± 9.5) with slight but not significant differences between both stimulation conditions. Considering the different subitems of the PDSS-2, combined STN + SNr stimulation was superior to conventional STN stimulation in improving restless legs symptoms (RLS) at night (STN-DBS = 1.9 ± 2.7 STN + SNr-DBS = 1.0 ± 1.8; W = −2.06, p = 0.039) and immobility at night (STN-DBS = 1.5 ± 1.4 STN + SNr-DBS = 0.6 ± 0.8; W = −2.041, p = 0.041).

Conclusion: This study demonstrates the safety of STN + SNr-DBS compared to conventional STN-DBS on sleep in general with potential beneficial input on RLS symptoms and akinesia at night.

1. Introduction

Sleep disorders represent an integral part of the non-motor symptoms in Parkinson's disease (PD) [1] with considerable effect on quality of life [2] besides the meaning as a potential prodromal marker of PD [3]. Sleep-related disturbances correlate with clinical characteristics of PD patients such as longer disease duration, higher motor deficits and greater rates of depression.

Clinically, sleep disorders in PD comprise several different aspects such as insomnia per se, rapid eye movement sleep behavior disorder (RBD), excessive daytime sleepiness, restless legs syndrome (RLS), periodic limb movements in sleep, tremor or pain at night, nocturia, nightly hallucinations and sleep-related apnoe. These various features of sleep disturbances differ in etiology, pathophysiology and treatment [1]. Insomnia is one of the most common complaints in up to 80% of PD patients including impaired sleep onset, worsened sleep maintenance and early awakening due to multifactorial etiologies resulting in adjusted treatment options [4].

The therapeutic approach is challenging and needs to take into account the main etiological factors contributing to insomnia. Management of sleep disturbances include improvement of sleep hygiene habits, adjustment of dopaminergic medication in extended

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release formulations [5], usage of sedative antidepressants and antipsychotics, particularly in PD patients with vivid dreaming or hallucinations [4].

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a highly effective therapy with considerable impact on motor performance and quality of life [6,7]. STN-DBS has been demonstrated to improve non-motor symptoms [8] including subjective and objective measures of sleep [9,10]. There was evidence for stimulation induced increase of sleep efficiency and sleep time in some studies [9,11], whereas it was not in others [12,13]. Besides, there are conflicting results of STN-DBS on RLS as one sleep-disturbing component with some studies showing improvement [14,15] while others demonstrated deterioration [16,17] or no change of RLS [9] postoperatively. The effect of STN-DBS is assumed to modulate subcortico-cortical network activity. The basal ganglia output to the brainstem is of particular interest, since certain PD symptoms including sleep disturbances are predominantly attributed to pathology in brainstem circuits.

Recently, simultaneous stimulation of the subthalamic nucleus and substantia nigra (STN + SNr-DBS) has been introduced in PD patients with the primary goal to improve freezing of gait [18]. The nigral costimulation is of particular interest due to dense interconnections with the mesencephalic region, the pedunculopontine nucleus (PPN) [19,20] and consecutively the “downstream” locus coeruleus (LC). Both the PPN and LC represent important brainstem nuclei involved in the sleep-wake control [21,22]. In PD, it is assumed that PPN and brainstem excitability is reduced by increased inhibitory afferent basal ganglia input to brainstem nuclei, which might be relieved by STN-DBS. STN + SNr-DBS might be favorable to alleviate sleep disturbances in PD by intensified modulation of basal ganglia-brainstem projection through augmented release of inhibition of brainstem nuclei.

The aim of the current study was to test the hypothesis that co-stimulation of STN and SNr might be superior to STN-stimulation in sleep quality improvement and might have differential effects on sleep subcomponents.

2. Methods

2.1. Design

The study was a single-center, randomized, double-blind, cross-over clinical trial at the university clinic Hamburg (UKE) to compare the effect of STN stimulation vs. combined STN + SNr-DBS as described previously [23] (Fig. 1).

Prior to study inclusion, PD patients were in a stable treatment condition with no changes of medication or stimulation parameters within the last 4 weeks. At baseline visit, we did monopolar review of the most ventral contacts located in the SNr. The most common side effects were dysarthria, ataxia and dizziness in descending order. Side effect thresholds were 3.3 ± 0.9 mA (range 2.0–5.0 mA) in left SNr and 3.3 ± 1.1 mA (range 1.5–5.0 mA) in right SNr. Stimulation strength of at least 0.5 mA below the individual side effect threshold was chosen which was in the range described in literature [18]. The average stimulation parameters in SNr were 1.2 ± 0.5 mA (range 0.7 mA–2 mA) applied symmetrically on both sides. At baseline visit, PD patients were clinically characterized by MDS-UPDRS and then blinded and randomized to conventional STN stimulation or combined STN + SNr stimulation respectively (phase I). After three weeks, reprogramming was performed in a cross-over manner for the following three weeks (phase II). There was no washout period in between the two phases. All visits were performed after medication intake (MED-ON condition). Questionnaires (PDSS-2 scale, PDQ 39, BDI) were performed by blinded investigators at baseline and at the end of phase I and II. At the end, patients were unblinded and the preferred stimulation mode was programmed as permanent therapeutic stimulation. Medication and stimulation parameters were held constant during phase I and phase II of the study. Only in one case the stimulation amplitude in the SNr had to be reduced after two days due to dyskinesias. Four patients (3 males) withdrew from the study in the treatment arm STN + SNr-DBS.

2.2. Participants

Fifteen patients (2 female, age 62.5 ± 6.7 years) suffering from moderate idiopathic PD (disease duration: 12.0 ± 5.0 years, Hoehn & Yahr stage: 2.2 ± 0.4 in the MED-ON & STN-DBS-ON condition, Hoehn & Yahr stage: 2.6 ± 0.8 in the MED-OFF condition preoperatively) participated in the study (see Table 1). PD patients were studied if 1. bilateral electrode implantation in the STN for DBS was performed at least 5 months before 2. the deepest contacts of the implanted electrodes were positioned within the dorsal aspect of the SNr along image based electrode reconstruction (location of the electrode tip at least 4.5–6 mm inferior to AC-PC line) 3. dopaminergic medication was unchanged in the preceding 4 weeks. The position of the implanted electrodes (model 3389; Medtronic, Minneapolis, Minnesota, USA, in 10 cases, and 8-poled electrode model, Boston Scientific, Valencia, CA, USA, in 5 cases) was determined by coregistration of the preoperative T1-MRI-scans and post-operative CT-scans performed with Brainlab (iPlan software; Brainlab, Feldkirchen, Germany). Preoperatively, all PD patients were screened and selected for DBS surgery in accordance to common guidelines of DBS surgery (CAPSIT protocol [24]). Patients showed a significant improvement of the motor-subscore (III) of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) after intake of immediate-release soluble levodopa (MED-OFF 38.0 ± 17.7, MED-ON 12.0 ± 8.4, improvement of 67%). The daily levodopa-equivalent dose decreased from 990.3 ± 205.8 mg preoperatively to 654.7 ± 245.7 mg postoperatively. Sleep disturbances per se were not mandatory to participate in the study. Prior

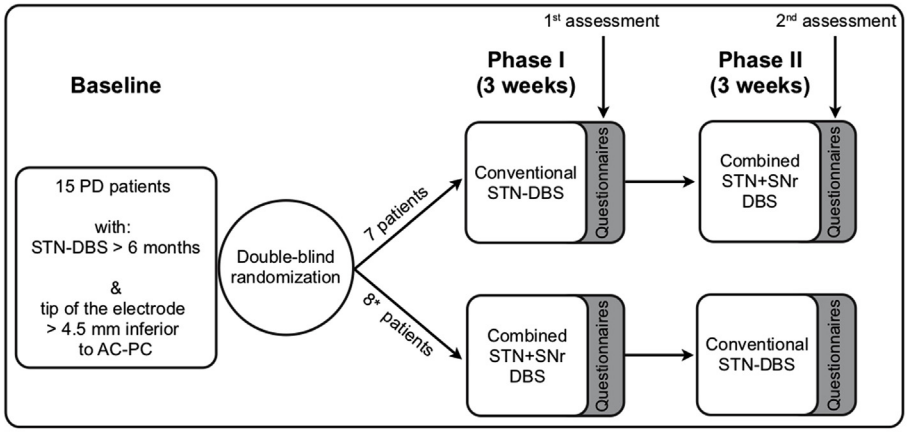

Fig. 1. Study design. The study was a single-center, randomized, double-blind, cross-over clinical trial to compare the effect of STN-DBS vs. combined STN + SNr-DBS on sleep quality in chronically implanted patients. After randomization, PD patients were programmed in the corresponding stimulation mode 1 (STN-DBS or STN + SNr-DBS). At the end of the first phase after 3 weeks, the 1st assessment was performed with subsequent reprogramming of the other stimulation mode 2 (STN + SNr-DBS or STN-DBS) for the second period lasting again for 3 weeks. After completion of the 2nd assessment, PD patients were unblinded and programmed into their preferred stimulation mode. *Note that 4 PD patients starting the phase I with a combined STN + SNr-DBS withdrew within the first week and terminated the study prematurely.

Table 1
Clinical and demographic characteristics of PD patients. "Disease duration [years]" is calculated from the date of the first diagnosis to the date of baseline measurement of the experiment. “DBS parameters” include: Active contacts, amplitude (volts or mA), pulse width (microseconds) and stimulation frequency (Hz), for the left and right electrode, respectively. Electrode coordinates are given in relation to the AC-PC line (mm) lateral to the midline (X), posterior to the mid-commissural point (Y) and inferior to the intercommissural plane (Z). Note that the deepest contacts were contact 0 and 8 (Medtronic) or contact 1 and 9 (Boston Scientific). Abbreviations: LEDD = levodopa equivalent daily dose, ME: Medtronic. BS: Boston Scientific, NA = not applicable.

Case Gender Age	Age at onset	Disease duration [years]	Time with DBS [months]	LEDD [mg]	DBS System	STN-DBS parameters	Combined STN + SNr-DBS parameters	X, Y, Z coordinates
						Left electrode Right electrode	Left electrode Right electrode	Left electrode Right electrode
1 M 61	38	23	54	1150	ME	1- 2- C+, 3.5V, 60 µs, 125 Hz 9- 10- C+, 2.7 V, 60 µs, 125 Hz	1- 2- C+, 3.5 V, 60 µs, 125 Hz; 0- C+, 2.0 V, 60 µs, 125 Hz 9- 10- C+, 2.7 V, 60 µs, 125 Hz; 8- C+, 2.0 V, 60 µs, 125 Hz	10.9, 2.2, 4.7 10.5, 3.8, 4.7
2 M 63	40	23	105	860	ME	1- C+, 1.9 V 60 µs, 125 Hz; 2- C+, 2.9 V, 60 µs, 125 Hz 9- C+, 1.9V, 60 µs, 125 Hz; 10- C+, 3.3 V, 60 µs, 125 Hz	2- C+, 2.9 V, 60 µs, 125 Hz; 1- 0- C+, 1.9 V (1.5 V), 60 µs, 125 Hz 10- C+, 3.3 V, 60 µs, 125 Hz; 8- 9- C+, 1.9 V (1.5 V) 60 µs, 125 Hz	11.2 1.9, 5.6 8.3, 5.5, 4
3 M 56	47	9	36	880	ME	1+ 2- C+ 2.2 V, 60 µs, 125 Hz 10- C+, 4.3 V, 60 µs, 125 Hz	2-C+, 2.2V, 60 µs, 125 Hz; 0- C+, 1.0 V, 60 µs, 125 Hz 10- C+, 4.3V, 60 µs, 125 Hz, 8- C+, 1.0 V, 60 µs, 125 Hz	9.5, 2.8, 6.4 11.2, 1.4, 7.2
4 M 67	51	16	60	600	ME	1- C+, 1.5 V, 60 µ, 125 Hz 9- 10- C+, 3.9 V, 60 µs, 125 Hz	1- C+, 1.5 V, 60 µ, 125 Hz; 0- C+, 2.0 V, 60 µs, 125 Hz 9-10- C+, 3.9 V, 60 µs, 125 Hz; 8- C+, 2.0 V, 60 µs, 125 Hz	9.6, 4.7, 6.6 11.7, 3.1, 3.2
5 M 65	56	9	9	300	ME	1- C+, 2.8 V, 60 µs, 125 Hz 9- C+, 3.0 V, 60 µs, 125 Hz	1-C+, 2.8 V, 60 µs, 125 Hz; 0- C+, 1.5 V, 60 µs, 125 Hz 9-C+, 3.0 V, 60 µs, 125 Hz; 8- C+, 1.5 V, 60 µs	10.9, 1.4, 7.7 11.1, 2.7, 6.7
6 M 74	65	9	9	360	ME	1- C+, 2.7 V, 130 Hz 9- C+, 2.6 V, 60 µs, 130 Hz	1- C+, 2.7 V, 60 µs, 125 Hz; 0- C+, 1.5 V, 60 µs, 125 Hz 9- C+, 2.9 V, 60 µs, 125 Hz; 8- C+, 1.5 V, 60 µs, 125 Hz	10.7, 2.6, 4.9 10.2, 2.5, 4.5
7 M 51	42	9	15	900	BS	2–30%, 3–70%, 3,4 mA, 60 µs, 125 Hz 10–20%, 11–80%, 4,0 mA, 60 µs, 125 Hz	1–23%, 2–23%, 3–54%, 4.4 mA, 60 µs, 125 Hz 9–20%, 10–16%, 11–64%, 5.0 mA, 60 µs, 125 Hz	8.8, 3.4, 7.4 7.1, 4.3, 6.4
8 M 57	57	7	18	580	BS	3–70%, 4–30%, 4.5 mA, 60 µs, 130 Hz 12–100%, 3.8 mA, 60 µs, 130 Hz	3–61%, 4–26%, 1–13%, 5.2 mA, 60 µs, 130 Hz 12–85%, 9–15%, 4.5 mA, 60 µs, 130 Hz	11.9, 3.4, 6.1 11.6, 2.7, 5.9
9 M 71	71	11	13	600	ME	1- C+, 3.5 V, 60 µs, 125 Hz 9- C+, 2.7 V, 60 µs, 125 Hz	1- C+, 3.5 V, 60 µs, 125 Hz; 0- C+, 1.0 V, 60 µs, 125 Hz 9- C+, 2.7 V, 60 µs, 125 Hz; 8- C+, 1.0 V, 60 µs, 125 Hz	1.3, 2.2, 6.2 12.2, 0.2, 5.2
10 M 66	54	13	6	300	ME	1- C+, 3.8 V, 60 µsec, 130 Hz 9- C+, 3.6 V, 60 µz 130 Hz	1–3.8 V 60 µsec 125 Hz 0–1.0 V 60 µsec, 125 Hz 9- C+ 3.6 V, 60 µsec, 125 Hz 8- C+ 1,0 V 60 µsec, 125 Hz	11.2, 6.5, 6.6 10.5, 4.2, 5.1
11 F 66	56	10	5	440	BE	5-6-7- (Ring) C+, 2.2 mA, 60 µsec, 130 Hz 13-14-15- (Ring) C+, 2.4 mA 60 µsec, 130 Hz	5- (23%) 6- (23%) 7- (23%) 1- (31%) C+, 2.9 mA, 60 µsec, 130 Hz 13-(24%) 14- (23%) 15-(23%) 9-(30%) C+, 3.1 mA 60 µsec, 130 Hz	10.9, 2.5, 5.7 10.4, 0.44, 5,2
12 F 66	57	9	5	700	ME	Withdrawal in phase I, experimental phase II not performed	2- C+, 2.4 V, 60 µs, 125 Hz; 0- C+, 0.7 V, 60 µs, 125 Hz 11- C+, 2.5 V, 60 µs, 125 Hz; 8- C+, 0.7 V, 60 µs, 125 Hz	10.2, 0.9, 5.2 9.0, 0.6, 7.8
13 M 55	42	13	23	700	ME	Withdrawal in phase I, experimental phase II not performed	3- C+, 2.9 V, 60 µs, 125 Hz; 0- C+, 0.7 V, 60 µs, 125 Hz 10- C+, 2.9 V, 60 µs, 125 Hz 8- C+, 0.7 V, 60 µs, 125 Hz	9.2, 2.8, 7.7 10.2, 2.4, 6
14 M 53	43	10	16	860	BS	Withdrawal in phase I, experimental phase II not performed	3-C+ 2,7 mA, 60 µs, 119 Hz; 1- C+, 0.7 mA, 60 µs, 119 Hz 12-/13- C+, 4,7 mA, 60 µs, 119 Hz; 9- C+, 0.7 mA, 60 µs, 119 Hz	10.73, 5.34, 6.87 7.72, 3.14, 6.82
15 M 66	57	9	5	590	BS	Withdrawal in phase I, experimental phase II not performed	13- (16%) 14- (45%) 15- (16%) 9- (23%) 4.5 mA, 60 µsec, 130 Hz 5- (29%) 6-(15%), 7- (29%), 1- (27%), 3.7 mA, 60 µsec, 130 Hz	11.64,4.03, 7.43 10.94, 2.17,6.17
						STN-DBS parameters	Combined STN + SNr-DBS parameters	X, Y, Z coordinates

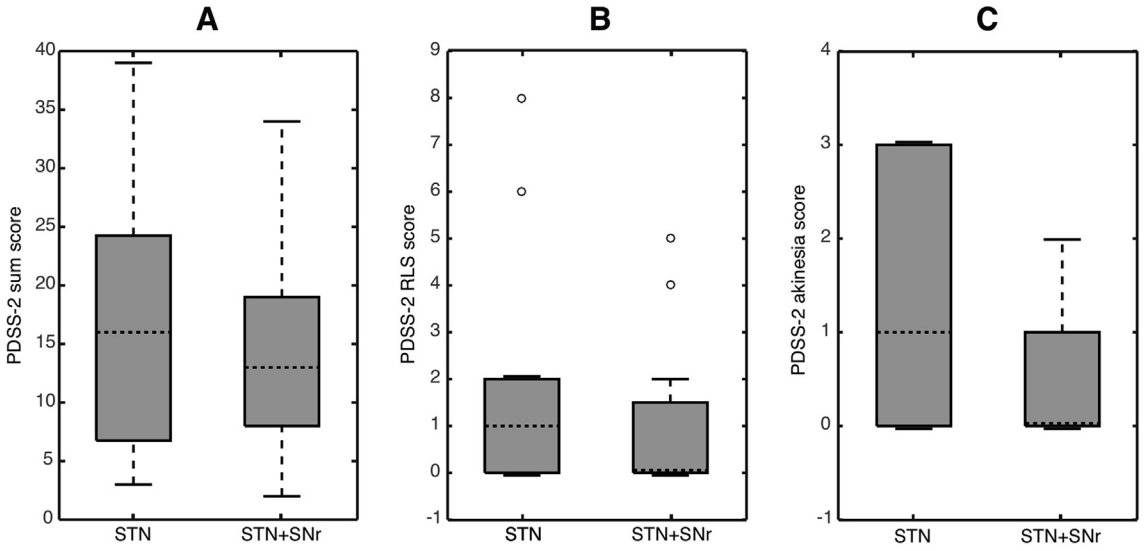

Fig. 2. Impact of STN-DBS and STN + SNr-DBS on PDSS-2 scores. The box plots represent the PDSS-2 values of 11 PD patients who completed the study (Conventional STN-DBS or combined STN + SNr-DBS). Values reported in the boxplots are median, interquartile range (IQR), whiskers (highest/lowest values of the data-set within 1.5 times of the IQR), and outliers (< 1st percentile and the > 99th percentile). Boxplots of the total PDSS-2 scores (a), PDSS-2 RLS subscore (sum of item 4 and 5) (b) and PDSS-2 akinesia scores (subitem 9) (c) are shown. STN + SNr is not superior to STN-DBS in improving the total PDSS-2, but in ameliorating specific subscores of the PDSS-2 such as RLS and akinesia at night.

to study enrolment, PD patients showed PDSS-2 score of 16.5 ± 11.04 (min 3 max 37) with 6 of 15 PD patients showing a PDSS-2 total score > 18 reflecting a sleep disorder severe enough to receive treatment or to be referred for further investigation in a center specializing in sleep disorders along the proposed cut off score in literature [25]. Three patients showed symptoms of RBD, four patients met the essential clinical criteria of RLS (NIH revision, 2003) and additional 2 PD patients had "RLS like symptoms" not fulfilling the complete essential criteria. Three of the patients took antidepressant drugs (Mirtazapin, Escitalopram) and two of the patients were treated with Clonazepam due to RBD. Medication remained unchanged during the trial. None of the study patients suffered from any other central neurological disorder beside PD, major medical or psychiatric disorder, stroke, seizure disorder, and history of psychotic disorders, dementia, or substance abuse. Further clinical details are summarized in Table 1. All participants had to read and sign informed consent. The study was approved by the local ethics committee (PV5281) and was conducted in agreement with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1967).

2.3. Questionnaires

To evaluate effects of STN-DBS or combined STN + SNr-DBS on certain aspects of sleep quality, the revised version of PDSS-2 (Parkinson's Disease Sleep Scale version 2) was used, which has been validated by a preceding multicenter study including validation of the different subitems [26]. The PDSS-2 is a questionnaire encompassing 15 questions, which are rated by the patients as a frequency measure within the last week (categories 0 = never; maximum 4 = very frequent, 6–7 nights in the last week). The questionnaire covers several aspects of sleep disturbances. Beside general sleep quality (item 1), it encompasses questions about difficulties falling (item 2) or staying asleep (item 3), nocturnal restless legs syndrome (item 4,5), vivid distressing dreaming (item 6), hallucinations (item 7), nocturnal urinary urge (item 8), immobility at night (item 9), pain (item 10), muscle cramps (item 11), painful posturing in the morning (item 12), tremor on waking (item 13), lack of repose from sleep (item 14) and sleep apnea (item 15). An overall sum score provides a general evaluation of sleep quality in PD patients. PDSS-2 ranges from 0 (no disturbance) - 60 (maximum nocturnal disturbance). Three domains were defined as proposed previously [26] with the domain "disturbed sleep" (item 1–3, 8, 14), "motor symptoms at night" (items 4–6, 12, 13) and "PD symptoms at night" (item 7, 9–11, 15). Besides, the Parkinson's Disease Questionnaire (PDQ 39) and BDI were assessed. Clinical assessments and questionnaires were performed by two neurologists with specialization in the field of movement disorders.

2.4. Statistics

Descriptive statistics in the main text include mean ± standard deviation (SD) of the mean, while in the boxplots median, interquartile range (IQR), whiskers (highest/lowest values of the data-set within 1.5 times of the IQR), and outliers (< 1st percentile and the > 99th percentile) are illustrated. Since four patients withdrew from the study due to intolerance of combined STN + SNr-DBS, analyses were performed in the remaining 11 patients completing the whole course of the study. Wilcoxon signed ranks test were performed to compare conventional effects of STN-DBS with combined STN + SNr-DBS (PASW Statistics for Mac, version 18.0, SPSS Inc., Chicago, IL, USA). Comparison between stimulation conditions was performed for the PDSS-2 total score, as well as assembled subitems such as general sleep quality and maintenance (items 1–3), RLS (item 4, 5), neuropsychiatric disturbance (item 6, 7), urinary incontinence (item 8), immobility at night (item 9), pain (item 10, 11), tremor (item 13) and sleep apnea (item 14, 15). In case of multiple significance tests, we present a note on the Bonferroni-corrected alpha level that should be accounted for. For comparisons of PDSS-2 items, the Bonferroni-corrected alpha level is $p \leq 0.003$, i.e., corrected for the 14 PDSS-2 subitem comparisons performed plus the PDSS-2 total score comparison. For the correlations, the Bonferroni-corrected alpha level is $p \leq 0.025$, i.e., corrected for the two correlations performed [27].

3. Results

PD patients showed mild-moderate sleep problems with a mean PDSS-2 score of 17.0 ± 11.0 with conventional STN-DBS and 14.7 ± 9.5 with application of combined STN + SNr-DBS. The severity of sleep problems was comparable to that described in the cohort of PD patients, in which the questionnaire has been tested and established [26]. Although the total PDSS-2 sum score tended to be slightly better

with combined STN + SNr-DBS, there was no significant difference between both stimulation conditions (W = −1.694, p = 0.09; Fig. 2a). Comparing stimulation effects in the three main domains comprising several subitems of the PDSS-2 "disturbed sleep", "motor symptoms at night" and "Parkinsonian symptoms at night" revealed no significant differences.

Considering the different subitems of the PDSS-2, there were no significant differences between stimulation conditions for sleep quality in general (STN-DBS = 4.5 ± 3.8, STN + SNr-DBS = 4.1 ± 3.8; W = −0.979, p = 0.327), neuropsychiatric components (STN-DBS = 0.8 ± 1.2, STN + SNr-DBS = 1.5 ± 2.2; W = −1.633, p = 0.102), pain (STN-DBS = 2.5 ± 2.2, STN + SNr-DBS = 2.0 ± 1.9; W = −0.94, p = 0.347), nocturnal urinary incontinence (STN-DBS = 2.82 ± 1.4, STN + SNr-DBS = 2.73 ± 1.1; W = −0.302, p = 0.763), tremor on waking (STN-DBS = 0.5 ± 0.9, STN + SNr-DBS = 0.2 ± 0.6; W = −1.732, p = 0.083) and sleep apnoe (STN-DBS = 1.5 ± 1.4, STN + SNr-DBS = 1.5 ± 1.4; W = −0.333, p = 0.739).

However, combined STN + SNr-DBS seemed to be superior to conventional STN-DBS in improving RLS symptoms at night (STN-DBS = 1.9 ± 2.7 STN + SNr-DBS = 1.0 ± 1.8; W = −2.06, p = 0.039; Fig. 2b) and immobility at night (STN-DBS = 1.5 ± 1.4 STN + SNr-DBS = 0.6 ± 0.8; W = −2.041, p = 0.041 Fig. 2c). Within the cohort of the 11 PD patients, who accomplished the study, 6 PD suffered from RLS symptoms according to PDSS-2 questionnaire. In that subgroup of 6 PD patients, in the condition with conventional STN-DBS, the RLS subscore of the PDSS-2 questionnaire was significantly higher (3.5 ± 2.8) compared to the STN + SNr-DBS condition (1.8 ± 2.2; W = −2.060, p = 0.039).

Spearman correlations were significant between the PDSS-2 sum score and the PDSI of PDQ 39 in the combined STN + SNr-DBS condition (r = 0.601; p = 0.05; Fig. 3a) and close to the alpha level in the STN stimulation condition (r = 0.582; p = 0.066; Fig. 3b), emphasizing the importance of sleep quality on general quality of life. There were no correlation of PDSS-2 sum score with UPDRS-III scores as an indirect measure of disease severity. PD patients were not depressed (BDI score STN DBS 6.5 ± 4.4; STN + SNr DBS 7.7 ± 6.4). Depression was not modulated by DBS mode (W = −1.015 p = 0.310), thus further correlation analyses did not seem reasonable in that cohort.

At the end, patients were unblinded and the preferred stimulation mode was programmed. 7 patients preferred the conventional STN-DBS, 4 patients STN + SNr-DBS. Only 1 PD patient with RBD terminated the study prematurely, all the other PD patients with characteristics of sleep disorders finished the study regularly.

4. Discussion

In this randomized, double-blind, cross-over study, the effect of combined STN + SNr-DBS compared to conventional STN-DBS on sleep quality was investigated by a self-rating questionnaire (PDSS-2). The effect of both stimulation modes was comparable in terms of the total PDSS-2 sum score comprising all different subcomponents of Parkinsonian sleep disturbance indicating stable outcome in terms of general sleep quality by STN + SNr-DBS. However, when assessing the single subitems of the PDSS-2, STN + SNr-DBS seemed superior to conventional STN-DBS in the improvement of the subitems RLS and immobility at night. This is the first report of safety in terms of general sleep during STN + SNr-DBS and potential additional benefit by STN + SNr-DBS compared to STN-DBS on RLS and akinesia at night in a small number of patients contributing to improved sleep quality. These findings need to be replicated in more specified prospective studies.

As reported earlier, four patients withdrew from the study ahead of time due to side effects in the combined STN + SNr stimulation regime [23]. Stimulation induced side effects were a general uncomfortable feeling, increased confusion and hallucinations, aggressiveness as well as a lack of beneficial effects of levodopa intake. The dropout of about

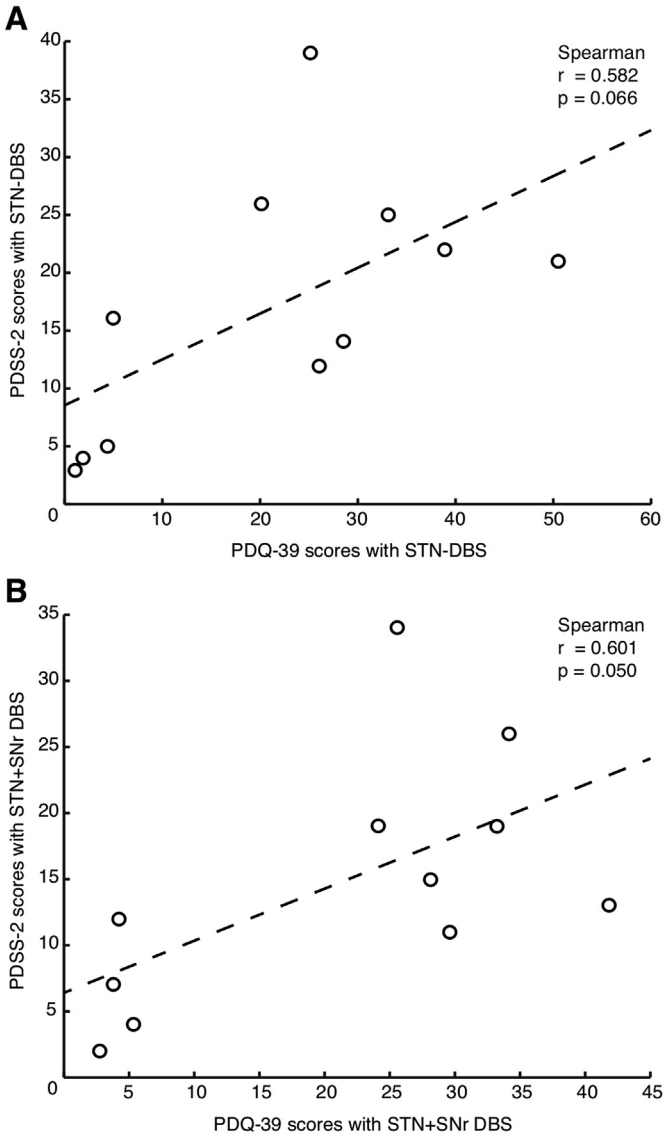

Fig. 3. Correlations of PDSS-2 and PDQ-39. Spearman correlations between PDSS-2 total scores vs. PDQ 39 while STN + SNr-DBS (a) and STN-DBS (b) are shown. The dotted line shows the best-fit linear relationship. Values inset give the statistics for the corresponding Spearman correlation. The PDSS-2 score correlate significantly with PDQ 39 while STN + SNr-DBS and approaches significance in STN-DBS condition emphazising the impact of sleep on quality of life.

one third of the investigated PD patients under combined STN + SNr-DBS needs to be emphasised, suggesting that for these patients this stimulation mode was not adequate or even disadvantageous. Previously, there were single reports of stimulation induced neuropsychiatric side effects of SNr stimulation [28], however STN + SNr-DBS with application of adjusted amplitudes was shown to be safe [18,23]. The stimulation associated side effects might be dependent on the preexisting medical and psychiatric condition, the exact electrode position within the nuclei and the voltage used for stimulation. All withdrawals were within the first week after change of stimulation parameters, we therefore propose to perform clinical follow-ups and assess STN + SNr-DBS carefully particularly in that time window to check for intolerance or side effects.

The rationale of potential beneficial effects of combined STN + SNr-DBS on sleep is the hypothesis of modified drive of basal ganglia-brainstem projections by the release of pathological inhibition of brainstem centers such as PPN and LC, which play a key role in a

complex landscape of neuronal systems including the basal forebrain, thalamus, hypothalamus in the regulation of sleep-wake cycles [21]. In PD patients, low-frequency PPN-DBS has been proven to ameliorate night-time sleep and daytime sleepiness and sleep architecture [22]. The intensified release of pathological PPN inhibition by combined STN + SNr stimulation could therefore also ameliorate sleep quality. However, we did not find an additional benefit of STN + SNr-DBS compared to conventional STN stimulation on the total PDSS-2 score or the PDSS-2 subitems falling or staying asleep.

We did find an additional benefit of STN + SNr-DBS on RLS symptoms in a small number of patients presenting with clinically relevant RLS, which is otherwise a common and highly relevant symptom in PD patients, impacting quality of life [29]. The effect of conventional STN-DBS on RLS is heterogeneous postoperatively [14–17]. Mechanisms underlying the beneficial effects of STN-DBS on RLS were proposed to be modulation of downstream diencephalo-spinal dopaminergic pathways [14], stimulation of inhibitory, postsynaptic D2/D3 receptors at the spinal cord [16] or modulation of basal ganglia projections to the pontine reticular formation [17,30].

Limitations of the study are the small sample size with an unbalanced proportion of males and females, the lack of preoperative sleep quality assessment, the heterogenous presentation of sleep and RLS symptoms, variations in disease duration and postoperative time. Besides, the study relies on subjective sleep data, on patient reported outcome assessed by the PDSS-2 scale. It would be helpful to support the findings by objective measures as polysomnographic data to underline the effect of STN + SNr on sleep quality.

The possible mechanism of action of STN + SNr-DBS on RLS is not clear and could be an enhanced modulation of subcortical routes as downstream dienzephalo-spinal, nigro-pontine pathways [17] or non-dopaminergic downstream pathways. Another option could be a reduction of the overnight OFF-time and therefore reduction of OFF-associated RLS, since improvement of overnight akinesia has been also observed in the PDSS-2 subitems in our study.

In summary, compared to conventional STN-DBS, combined STN + SNr-DBS had stable effects on general sleep quality, but was shown to have an additional beneficial impact on specific sleep-related components, particularly RLS symptoms and akinesia at night. These findings need to be replicated in larger, specifically designed trials with predominant RLS comorbidity.

Conflicts of interest

U. Hidding, A. Horn, L. Prilop, H. Braaß, O. Fründt, M. Westphal, A.K. Engel and J.A. Koeppen report no disclosures. A. Gulberti received travel reimbursements from Medtronic Inc. C. Pflug received honoraria as speaker and/or scientific advisory board member from Olympus. C. Choe received lecture fees from Pfizer. C. Buhmann served on the scientific advisory boards for Bial and Zambon and received honoraria for lectures from Abbvie, Bial, GE Healthcare, Grünenthal, TAD and UCB. D. Weiss reports grants and personal fees from Medtronic, Abott, Boston Scientific, during the conduct of the study. C. Gerloff reports personal fees and other from Bayer Healthcare and Boehringer Ingelheim, personal fees from Acticor Biotech, Sanofi Aventis Amgene, and Prediction Bioscience. C.K.E. Moll served as medico-scientific consultant to Abbott. W. Hamel received lecture fees and honoraria for serving on advisory boards and travel grants from Boston Scientific, Medtronic, and Abbott. M. Pötter-Nerger received lecture fees from Abbott and Licher, and served as consultant for Medtronic, Boston scientific and Abbvie.

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