The impact of subthalamic deep brain stimulation on sleep-wake behavior: A prospective electrophysiological study in 50 Parkinson patients

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Abstract: Study Objectives: This prospective observational study was designed to systematically examine the effect of subthalamic deep brain stimulation (DBS) on subjective and objective sleep–wake parameters in Parkinson patients. Methods: In 50 consecutive Parkinson patients undergoing subthalamic DBS, we assessed motor symptoms, medication, the position of DBS electrodes within the subthalamic nucleus (STN), subjective sleep–wake parameters, 2-week actigraphy, video-polysomnography studies, and sleep electroencepahalogram frequency and dynamics analyses before and 6 months after surgery. Results: Subthalamic DBS improved not only motor symptoms and reduced daily intake of dopaminergic agents but also enhanced subjective sleep quality and reduced sleepiness (Epworth Sleepiness Scale: -2.1 ± 3.8, $p < .001$). Actigraphy recordings revealed longer bedtimes ($+1{:}06 \pm 0{:}51$ hours, $p < .001$) without shifting of circadian timing. Upon polysomnography, we observed an increase in sleep efficiency ($+5.2 \pm 17.6\%$, $p = .005$) and deep sleep ($+11.2 \pm 32.2$ min, $p = .017$) and increased accumulation of slow-wave activity over the night ($+41.0 \pm 80.0\%$, $p = .005$). Rapid eye movement sleep features were refractory to subthalamic DBS, and the dynamics of sleep as assessed by state space analyses did not normalize. Increased sleep efficiency was associated with active electrode contact localization more distant from the ventral margin of the left subthalamic nucleus. Conclusion: Subthalamic DBS deepens and consolidates nocturnal sleep and improves daytime wakefulness in Parkinson patients, but several outcomes suggest that it does not normalize sleep. It remains elusive whether modulated activity in the STN directly contributes to changes in sleep–wake behavior, but dorsal positioning of electrodes within the STN is linked to improved sleep–wake outcomes.

DOI: https://doi.org/10.1093/sleep/zsx033

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Heide Baumann-Vogel, MD[1]; Lukas L. Imbach, MD[1]; Oguzkan Sürücü, MD[2]; Lennart Stieglitz, MD[2]; Daniel Waldvogel, MD[1]; Christian R. Baumann, MD[1]*; Esther Werth, PhD[1]*

*CRB and EW contributed equally to the study

[1]Departments of Neurology and [2]Neurosurgery, University Hospital Zurich, University of Zurich, 8091 Zürich, Switzerland

Disclosure of financial disclosures

HBV, LLI, OS, LS, DW report no financial disclosures; CRB received grants from Swiss National Science Foundation, HSM-2 Grant Canton of Zurich, UCB Pharma, AbbVie Pharma; EW received a grant from Swiss National Science Foundation

Disclosure of conflict of interests

HBV, LLI, OS, LS, DW, CRB, EW report no conflict of interests

Corresponding author:

Esther Werth, PhD; Dept. of Neurology; University Hospital Zurich; Frauenklinikstrasse 26; 8091 Zurich, Switzerland; Phone: +41-44-255-5535; Fax: +41-44-255-9201; esther.werth@usz.ch

Total number of figures: 3

Total number of tables: 4

Abstract

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Methods: In 50 consecutive Parkinson patients undergoing subthalamic DBS, we assessed motor symptoms, medication, the position of DBS electrodes within the subthalamic nucleus, subjective sleep-wake parameters, two-week actigraphy, video-polysomnography studies and sleep EEG frequency and dynamics analyses before and 6 months after surgery.

Results: Subthalamic DBS improved not only motor symptoms and reduced daily intake of dopaminergic agents, but also enhanced subjective sleep quality and reduced sleepiness (ESS: -2.1±3.8, P<0.001). Actigraphy recordings revealed longer bedtimes (+1:06±0:51 hours, P<0.001) without shifting of circadian timing. Upon polysomnography, we observed an increase of sleep efficiency (+5.2±17.6%, P=0.005) and deep sleep (+11.2±32.2 min, P=0.017), and increased accumulation of slow-wave activity over the night (+41.0±80.0%, P=0.005). REM sleep features were refractory to subthalamic DBS and the dynamics of sleep as assessed by state space analyses did not normalize. Increased sleep efficiency was associated with active electrode contact localization more distant from the ventral margin of the left subthalamic nucleus.

Conclusion: Subthalamic DBS deepens and consolidates nocturnal sleep and improves daytime wakefulness in Parkinson patients, but several outcomes suggest that it does not normalize sleep. It remains elusive whether modulated activity in the subthalamic nucleus directly contributes to changes in sleep-wake behavior, but dorsal positioning of electrodes within the subthalamic nucleus is linked to improved sleep-wake outcomes.

Key words: Parkinson's disease, deep brain stimulation, sleep, slow-wave activity, subthalamic nucleus

Statement of Significance

Sleep-wake disturbances are most frequent in Parkinson patients, but there is no larger systematic study to objectively examine the impact of subthalamic deep brain stimulation (DBS) on sleep in Parkinson patients. This study was designed to close this gap by prospectively applying electrophysiological examinations in 50 Parkinson patients. Subthalamic DBS improves sleep continuity, deepens sleep, increases accumulated slow-wave activity and improves excessive daytime sleepiness. However, the dynamics of sleep did not normalize. Dorsal placement of the active electrode increases the likelihood of a beneficial sleep effect. Whether this observation is due to a sleep-modulating effect of the subthalamic nucleus itself – a nucleus neighboring and connecting to multiple sleep-wake active neuronal areas – remains elusive, but this finding will guide future exploration.

Introduction

Sleep-wake disturbances affect up to 80-90% of patients with Parkinson's disease (PD), and often significantly impair quality of life.[1] Non-consolidated sleep with frequent awakenings, rapid eye movement (REM) sleep behavior disorder (RBD) with enactment of vivid dreams, and excessive daytime sleepiness are frequent complaints of PD patients. Polysomnography (PSG) findings in PD patients include decreased sleep efficiency, reduced total sleep time, impaired slow-wave activity, and rarefied REM sleep compared to healthy controls.[2]

Deep brain stimulation (DBS) in the subthalamic nucleus (STN) is a gold standard treatment for PD patients suffering from motor fluctuations or pharmacotherapy-refractory tremor. There is some evidence that STN stimulation may affect and even improve sleep-wake functions. In studies examining subjective sleep quality after subthalamic stimulation, overall sleep quality and total sleep time improved after STN-DBS.[3,4,5]

To date, most studies including objective polysomnographic measures have been small case series, with different patient populations, study protocols, various assessment time points, and electrode settings: Arnulf and colleagues evaluated 10 insomniac PD patients 3 to 6 months after STN-DBS, and found stimulation to increase total sleep time and sleep efficiency.[6] Similar findings have been made by Monaca et al. in 10 patients before STN-DBS and again after 3 months,[7] by Cicolin and colleagues in 5 patients before and 3 months after bilateral STN-DBS electrode implantation,[8] and by Merlino et al. in 15 patients one week before and after microsubthalamotomy.[9] On the other hand, Iranzo and colleagues evaluated 11 PD patients before and 6 months after bilateral STN-DBS implantation, but stimulation did not increase sleep efficiency.[10]

In all these studies, REM sleep and REM sleep-related motor outcomes seemed to be mostly unchanged by STN-DBS. However, Nishida and colleagues examined sleep in 10 PD patients one week before and one week after implantation of either unilateral or bilateral STN-DBS electrodes, and found increased REM sleep duration, and in one patient even resolution of

RBD.[11] There are also conflicting data on the effects of STN-DBS on RLS and periodic limbs movements, with some studies showing improvement[12,13] and others reporting deterioration of RLS on STN-DBS.[14,15]

Thus, given the fact that many confounding factors are likely to influence these results, such as age, dopaminergic medication, disease duration, the type of PD, motor outcome of DBS, and exact electrode placement, larger electrophysiological studies are needed to reliably analyze the impact of STN-DBS on sleep-wake regulation. Here, we studied sleep-wake behavior with subjective assessments, two-week actigraphy, and nocturnal PSG in 50 PD patients before and six months after subthalamic DBS.

Methods

This is an observational controlled trial to examine effects of STN-DBS on sleep-wake behavior in PD. The study protocol was approved by the local ethics committee (KEK Zurich) and written informed consent was given by participating patients.

Patients

We included 50 consecutive PD patients who were treated with bilateral STN-DBS. The first patient was recruited in January 2011 and the 50th patient was enrolled in October 2014. All diagnoses were made according to international standard criteria.[16] After inclusion we assigned two patient subgroups, akinetic-rigid (AR) and tremor-dominant (Tre) merged with mixed equivalent phenotype (Ae) (Tre+Ae) based on expert judgment.[17]

Quadripolar DBS leads (3389, Medtronic, Minneapolos, MN) were implanted in the STN in MR-based frame-guided awake surgeries supported by intraoperative microelectrode recording and standardized intraoperative test stimulation. The leads were connected to an

Activa® impulse generator (Medtronic). MR imaging, intraoperative recordings and test-stimulation were used for the determination of the margins of the STN and the related position of the active electrode contacts. Postoperatively, we adjusted DBS settings and medication according to the individual patients' needs over the first six postoperative months.

Clinical assessments

All evaluations were performed twice, within 3.1±3.6 months prior to surgery (baseline) and 7.7±2.8 months after implantation of DBS electrodes, i.e. on medication alone and on stimulation in combination with medication.

We examined motor outcomes with part III of the Unified Parkinson's Disease Rating Scale (UPDRS).[18] As this study was not designed to measure motor outcome after STN DBS, we did not ask patients to stop medication again for pure motor assessments. Therefore, all assessments with the UPDRS were performed in reasonably good ON conditions.

Furthermore, we calculated total L-dopa equivalent dose (LED) along previous recommendations.[19] In all patients, we registered the intake of benzodiazepines and z-drugs, antidepressants, neuroleptics, and amantadine. Antidepressants were grouped into compounds with sedative or activating properties, and mirtazapine with dosage-dependent effect.

All patients completed the Zurich sleep questionnaire. This questionnaire consists of items on sleep and sleep-wake disorders in general, sleep timing, questions on daytime complains, symptoms suggestive of sleep apnea, insomnia, parasomnia, narcolepsy features, restless legs syndrome and mood, usually by implementing a 5-point Lickert scale. Standardized self-rating questionnaires that have been validated in German, including the Epworth Sleepiness Scale (ESS) and the Fatigue Severity Scale (FSS) were also part of this questionnaire.[20,21] An ESS score >10 indicated subjective excessive daytime sleepiness, a FSS score >4 fatigue. In addition, all patients filled in a sleep log during actigraphy recordings which includes bed

time, getup time and notes about special events during the night and/or day. The presence of restless legs syndrome (RLS) was defined according to the International Restless Legs Syndrome Study Group (IRLSSG) criteria.[22] RLS diagnosis was made when all the four criteria were met.

Electrophysiological Assessments

All patients completed two-week rest-activity recordings at home and without scheduled restrictions to their sleep–wake behavior. To this end, we applied Actiwatch (Actiwatch AW2, Phillips-Respironics Oregon, USA), which was worn on the non-dominant arm, i.e. regardless of the side that was more affected by PD. We excluded days and nights with missing data and the first and the last day of the activity monitoring, as daytime rest-activity patterns were incomplete. Furthermore, we excluded the night spent in the sleep laboratory as bedtime and sleep duration were not freely chosen by the patient. On average, 13.5±2.1 days and 14.0±2.2 nights of actigraphic data per patient were analyzed.

Keeping in mind that PD patients can express marked movements during sleep (e.g. RBD), but on the other hand may appear resting during daytime hypokinesia, we chose a conservative approach when analyzing actigraphy data. We extracted the following measures for each subject using the standard software (Actiware version 6): Going-to-bed times and get-up times were identified automatically by the algorithm, then if needed manually adjusted by using information, first from markers when patients' pressing a button when going to bed and switching out the bed light and getting up in the morning, second from sleep logs, third from light data and forth from rest-activity pattern in hierarchical order. We calculated night rest duration, i.e. interval between going-to-bed and get-up time and 'midpoint rest time', also known as 'midsleep time' as an internal circadian time marker.[23] We calculated daytime activity, e.g. averaged activity counts from leaving the bed in the morning till going to bed at night, as a measure of general daily activity. Additionally, we calculated activity during the

rest episode at night, total moving time at night as scored mobile time during the rest episode, the movement bout-index, e.g. the number of continuous blocks with each epoch scored as mobile relative to the rest episode duration and the average duration of immobile bouts between movement bouts. During data acquisition medication was taken as needed but kept constant within each condition. The post-surgical rest-activity recording was performed under continuous 24 hours constant STN-DBS stimulation in combination with medication.

We performed PSG recordings with digital videography (Embla N7000, RemLogic v3.2) according to AASM standard criteria and as introduced before.[24,25] Two experienced sleep specialists (EW and HBV) scored and rescored all recordings.

Time in bed (TIB) of the two PSGs within the same subject was not identical. To avoid that sleep changes might only be due to differences in TIB, we adjusted TIB artificially for data analysis by matching the PSG length. Thus, the total time analyzed was identical for both conditions.

As sleep stage scoring can be difficult in Parkinson patients,[26] we made additional standardized considerations for assigning sleep stages in difficult cases. We compared presumed sleep patterns with patterns of definite wake periods. In the absence of EMG atonia, clear-cut rapid eye movement (REM)-like EEG/EOG pattern was sufficient to score an epoch as REM sleep when the epoch was close to clear detectable other stage R (stage of REM sleep) epochs and the epoch was neither Wake nor non-REM (NREM) sleep. We accepted poorly formed K complexes and sleep spindles to define NREM stage 2 sleep (N2) when the 30-s epoch was not fulfilling criteria for Wake (W), N1, N3 or stage R. Furthermore, we checked information from the synchronized audio-video recording to get behavioral pattern information (e.g., detection of typical dream enacting behavior). The stimulator was on during

the recording and patients took their medication as they needed. There was no visible stimulation artifact in our recordings.

We defined sleep period time as the time from sleep onset to "lights on". Sleep onset, sleep latency, sleep efficiency as the ratio of the total sleep time (TST) divided by sleep period time, REM sleep latency, wake time after sleep onset (WASO), periodic limb movements during sleep (PLMS), arousal index and respiratory events including the apnea-hypopnea index were also assessed.[24] To calculate a quantitative measure of sleep fragmentation, we assessed the number of awakenings per hour of sleep and the number of longer awakenings (>5 min, >15 min and >30 min).

RBD was evaluated by history-taking, by video-PSG information and by quantification of EMG activity during REM sleep. We applied the SINBAR EMG montage to detect REM sleep phasic and tonic EMG activity.[27] According to Frauscher and colleagues, a RWA index above 32 indicates the presence of REM sleep without atonia and therefore RBD.

Preprocessing of the EEG signal for further analysis included re-referencing the EEG to linked mastoid reference (for reducing electrocardiogram (ECG) and other artefacts), filtering (0.5 Hz high-pass, 40 Hz low-pass filter) and artefact identification on basis of a 5-s semi-automatically procedure based on power in the 0.75-4.5 Hz and 20-40 Hz bands and visual inspection.[28] Artefact-free 5-s EEG spectra were collapsed and matched with the corresponding sleep stage scores when at least 4 of 6 5-s epochs were artefact-free otherwise the whole 30-s epoch was rejected for further spectral analysis. Absolute-all-night power spectra were computed for NREM sleep (N1, N2, N3 for the two central derivations). The EEG power during NREM sleep from 0.5 to 4.5 Hz was defined as slow-wave activity (SWA). Furthermore, we assessed slow wave energy (SWE), a measure of dissipation of sleep pressure, as the cumulative sum of SWA during NREM sleep.[29] To show the progression of

mean SWE over time, total time analyzed of each single night was divided in 10 equal time bins and SWA was first averaged within each bin before accumulation over the whole night was calculated. Thus, we were able to visualize the time course of rising mean SWE from lights off till lights on despite the variability of total time analyzed of each patient.

Additionally, we performed state space modeling of spectral sleep EEG data as described before.[30] In short, we determined the frequency ratios of two selected frequency bands and we used the distribution of frequency ratios in a 2-dimensional space (specification and more detail see[30]). As a measure of dynamic properties of sleep, we calculated velocities in state space as the distance between two subsequent states divided by the time interval between these states.[30,31]

Statistics

We used means and within-patient difference means with standard deviation for descriptive comparative analysis of continuous data. Median and range was used for ordinal data. STN-DBS-induced changes in motor behavior and sleep and wake measures were tested for significance with paired t-tests or nonparametric testing when appropriate (McNemar, Wilcoxen Signed Rank Test). Bivariate correlation analysis was done by calculation correlation coefficient (Pearson or Spearman correlation, respectively) to reveal significant relations between clinical characteristics and sleep and wake outcome measures. We searched for predictors of sleep and wake outcomes by applying multiple linear regression analysis (forced entry method), with the selected sleep-wake outcome acting as the dependent variable, and demographic, clinical (motor and non-motor measure) and DBS stimulation measures as independent variables. Interaction effects were explored using the PROCESS Tool for SPSS.[32] For all analyses, p-values of 0.05 were considered to be significant, in case of multiple testing we multiplied the p-value by the number of comparisons and report this value

(Bonferroni method to correct type 1 errors for multiple comparisons). RemLogic software v3.2, SPSS version 22 and Matlab 2009/R2013b were used for data analysis.

Results

We studied 50 PD patients with a mean age of 61±10 years, mean disease duration of 12±5 years, mean pre-surgical on-medication Hoehn and Yahr stage of 2.3±0.6 (median: 2, min/max: 1/3), and mean pre-surgical on-medication UPDRS part III motor score of 25±10 (Tables 1). Before surgery, 54% reported sleep maintenance insomnia. Fatigue (FSS > 4) was present in 55% of patients, excessive daytime sleepiness (ESS > 10) in 44%. Ten out of 50 patients were on sedating medication. Five of 50 patients fulfilled the IRLSSG criteria of RLS.

STN-DBS effects on motor symptoms can be found in Table 2. On STN-DBS, motor symptoms on treatment were reduced by 35% (UPDRS part III), and total dopaminergic medication (LED total) by 61%. The use of antidepressant medication, either activating or sedating, neuroleptics, benzodiazepines, and z-drugs was similar before and on DBS (all McNemar tests $p>0.05$). Amantadine, on the other hand, was used by 18% of patients before, and by none after DBS operations (McNemar test $P=0.004$).

On DBS, patients indicated to sleep more (BL: 7:36±1:16 h, DBS: 8:17±0:53 h; Wilcoxon signed ranks test, $P<0.001$), but sleep maintenance insomnia was still present in 44 % of patients (BL: 54%; DBS: 44%; McNemar test, $P=0.405$). Less patients suffered from subjective excessive daytime sleepiness (BL: 44%; DBS 26%; McNemar test, $P=0.035$), but the prevalence of fatigue remained unchanged (BL: 55%, DBS: 48%; McNemar test, $P>0.664$. ESS decreased from 9.4±4.6 to 7.4±3.9 (paired t-test, $P<0.001$, within-patient difference -2.1±3.8, $P<0.001$), whereas FSS remained stable (BL: 4.2±1.4; DBS 4.1±1.6,

paired t-test, P=0.644; Figure 1A). On DBS, only one of the five patients with RLS still fulfilled the IRLSSG criteria of RLS.

Two weeks of rest-activity recordings with standard actigraphy confirmed longer bed times (Figure 1B): On DBS, patients went significantly earlier to bed and stayed longer in bed in the morning, resulting in a longer night time rest (BL: 7:02±1:06 h; on DBS: 8:08±0:43 h, paired t-test, P<0.001, within-patient difference +1:06±0:51 hours, P=0.005). 'Midpoint rest time' was similar, indicating stable circadian timing (BL: 03:00±00:49; DBS: 03:05±00:53 o'clock, paired t-test, P=0.326). Motor activity during the rest episode was similar pre- and on DBS in respect of activity (BL: 29±26; DBS: 27±19, Wilcoxon signed ranks test, P=0.781), total moving time (BL: 119±57 min; DBS: 120±52 min; Wilcoxon signed ranks test, P=0.546), movement bout-index (BL: 6.0±1.9 /h; DBS; 6.4±1.4 /h; paired t-test, P=0.099) and the average immobility duration between movement bouts (BL: 9.4±7.0 min, DBS: 7.8±2.7min, Wilcoxon signed ranks test, P=0.412). On the other hand, daytime activity was significantly lower on DBS (drop of -16± 34%, BL: 298±128; DBS: 223±84, paired t-test, P<0.001), however, the decrease of activity did not differ between motor PD subtypes.

PSG findings are given in Table 3 and Figure 1C-E. On DBS, we observed a significant within-patient difference increase in total sleep time (+21.2±74.9 min, P=0.016), sleep efficiency (+5.2±17.6%, P=0.005), and deep sleep (N3, +11.2±32.2 min, P=0.017), together with a reduction of WASO (-18.0±58.6 min, P=0.023) and shorter REM sleep latencies (-25.1±89.5 min, P=0.047). Sleep latency, the duration of N1, N2 and REM sleep were unchanged. Sleep fragmentation as assessed by awakening index and the number of longer awakenings was not altered on DBS (all Wilcoxon signed ranks test P>0.05). Also the number of body position changes during sleep was similar before and on DBS. Although deep sleep was increased, we could not identify a significant increase of SWA in our sample. However, accumulated SWA (=SWE) was significantly higher at the end of the DBS night (within-

patient difference +41.0±80.0%, P=0.005; Figure 1C). DBS had no impact on arousal index and AHI. On the other hand, PLMS indices almost doubled after surgery, but the prevalence of RLS remained unchanged (BL: 10%; DBS: 2%, McNemar test P=0.125). The increase in PLMS was associated with the reduction of dopamine agonists (Figure 1D).

STN-DBS had no impact on the RBD marker REM sleep without atonia (RWA) (Tab. 3). The occurrence of RWA above the SINBAR cut-off was similar before and after surgery (BL: 65.9%, DBS: 64.4%, McNemar test: P=1.000).

As a measure of dynamic properties of sleep, we calculated different parameters in state space. Both conditions showed well-defined clusters of sleep behavioral states (W, N2, N3, REM, Figure 2A, Figure 2B). Despite the improvement of sleep efficiency and deep sleep, DBS did not increase state space velocity but tended to further slow-down sleep-wake dynamics (Figure 2C). Distance between cluster centroids for each sleep stage were unaltered on DBS (all paired t-tests P>0.05).

Finally, we aimed at identifying predictors for a beneficial sleep-wake outcome (Table 4).

Increase in sleep efficiency was linked to higher UPDRS III reduction, i.e. more marked motor improvement on DBS, and a location of the active electrode pole more distant from the ventral margin of the STN. However, only the left stimulation electrode showed this specific effect (R=0.413, P=0.007; Figure 3). Same associations were found for total sleep time. There was no interaction effect of UPDRS III change and active electrode location for sleep efficiency and total sleep time (sleep efficiency: delta UPDRS III x left active electrode pole more distant from ventral margin of STN: b=0.61; upper and lower confidence interval -0.016 and 1.38; P=0.119; total sleep time similar result). This observation supports the notion that factors electrode location and motor improvement are independent. Absolute increase of deep sleep was only linked to higher reduction of LED. The model for SWE revealed two

significant predictors, a higher reduction in dopaminergic medication and AR versus Tre+Ae phenotypes: PD patients with predominant akinetic-rigid features gain more SWE on DBS compared to preoperative sleep than pooled tremor and equivalence phenotypes (Figure 1E). Otherwise, the two groups of PD phenotypes did not differ in terms of age, disease duration and Hoehn&Yahr stage, reduction of UPDRS III or total LED on STN-DBS. Finally, decreased WASO was linked to UPDRS III reduction and higher reduction of LED, and again active electrode pole location more distant from the ventral STN margin. No significant model could be fitted for the increased longer rest duration (actiwatch data) and for the improvement of subjective daytime sleepiness (ESS).

Discussion

This prospective study in 50 PD patients undergoing bilateral DBS in the STN revealed that stimulation - particularly in a dorsal position within the STN – ameliorated nocturnal sleep and daytime vigilance, without changing circadian rhythmicity. Subjective improvement of sleep-wake behavior was mirrored by longer bedtimes as shown by actigraphy recordings, and an increase of sleep efficiency, deep sleep and accumulated slow-wave activity upon PSG. The finding of subjective sleep improvement, increased sleep efficiency and enhanced deep sleep on STN-DBS is in agreement with most previous smaller studies.[6,10,8,11,33]

Do the observations of deeper and more consolidated sleep on STN-DBS indicate that stimulation normalizes sleep in PD patients? Although this study was not designed to find out whether DBS reinstates normal sleep – as we did not include a matched control group – some of its outcomes suggest that STN-DBS does *not* normalize sleep. First and foremost, we previously found decreased sleep-wake dynamics in PD patients compared to healthy controls as assessed by quantitative analysis of state space velocity.[31] State space velocity can be

interpreted as a measure for sleep state instability. On DBS, state space velocity became slower, thus did not normalize. Second, the occurrence of RBD was unchanged in regards to subjective complains, videographical assessments and amount of REM sleep without atonia. Third, PLMS became even more increased after DBS.

The finding of increased PLMS on DBS was linked to the reduction of dopamine agonists, however arousals from sleep did not increase, and therefore the clinical relevance seems questionable. In case of a history of RLS symptoms in a DBS-treated PD patient, however, treating physicians may want considering to continue treatment with dopamine agonists as their reduction may not only be associated with apathy, but also with enhanced periodic limb movements during sleep.[34] Current evidence on the impact of STN-DBS on comorbid RLS in Parkinson patients is conflicting[13,15], but in our study, the prevalence of RLS symptoms remained unchanged.

Another question is whether or not subthalamic stimulation directly impacts sleep-wake behavior, or whether improved sleep results from better nocturnal motor control. More consolidated sleep, i.e. higher sleep efficiency, decreased WASO and increased total sleep time during PSG, was associated with active left electrode contacts more distant from the ventral STN margins. On the contralateral side, similar findings were not found. Therefore and although asymmetric properties of non-motor medioventral segments of the STN have been proposed, the link between active electrode contacts and sleep consolidation must be discussed with utmost caution.[35] The hypothesis that maximized dorsolateral location of active electrode contacts – which is known to provide best motor effects – leads to improved sleep because of better nocturnal motor relief cannot be dismissed.[36] On the other hand, the number of body position changes during sleep was similar before and on DBS in the present study.

Still, the STN might play a role in sleep-wake regulation. Although this small nucleus is classically considered a relay of the indirect basal ganglia motor pathway, its connections exceed the motoric circuits.[37] The nucleus is located at the diencephalo-mesencephalic junction, posterolateral to the hypothalamus, and medial to the substantia nigra and red nucleus.[37] The STN is thus not far away from wake-promoting midbrain areas.[38,39] The nucleus has inhibitory connections to the anterior hypothalamus and the upper part of the mesencephalic reticular substance,[40] and glutamatergic innervations to the substantia nigra pars compacta which in turn innervate several brain areas involved in sleep regulation.[41] It has important reciprocal connections with the wake- and REM-modulating pedunculopontine tegmental nucleus (PPN).[42,43] The anterior STN projects to the baso-lateral amygdala and ventral-anterior thalamus[37] with the ventral and lateral thalamic relay nuclei possibly playing a role in producing wakefulness.[44]

This study has limitations. First, we cannot exclude that an order effect might contribute to the improvement of nocturnal sleep during PSG recording. Still, we found also a clear improvement in nightly rest duration in the two-week rest-activity data collection and a reduction of excessive daytime sleepiness.

Second, we did not withdraw antidepressants or benzodiazepines including z-drugs for sleep-wake studies. On the other hand, the frequency of the respective intakes did not differ between the two time-points. Third, electrode positioning within the STN must be regarded as an approximation. Neither MR imaging nor intraoperative testing for side effects routinely provide robust data. We consider, however, our microelectrode recordings which are taken along the posterodorsolateral towards anteroventromedial axis very reliable and used only those recordings with clear distinction between STN and other signals. Last not least, we did not implement classical PD sleep scales such as the Parkinson's Disease Sleep Scale (PDSS)

questionnaire which makes it difficult to compare some of our subjective results with other studies.

Acknowledgment

We thank Mechtild Uhl, Judith Meier and Janina Leemann for their help in patient care and data collection, and Dr. Ruth O'Gorman for the support writing the ethics.

Figure Legends

Fig. 1:

Subjective, actigraphically (Act) driven and polysomnographic (PSG) sleep-wake parameters before (baseline; BL, blue) and on deep brain stimulation (DBS, red) on medication and on stimulation in combination with medication, respectively. A: left: subjective daytime sleepiness (ESS, Epworth Sleepiness Score); right: subjective fatigue (FSS, Fatigue Severity Score). Statistics: ESS *P<0.001, n=50, FSS P=0.644, n=49; paired t-test. B: Averaged going-to-bed time, mid-rest time and get-up time during two-week actigraphy recording. Statistics: going-to-bed time *P=0.013; get-up time *P=0.001, 'midpoint rest time' P = 0.326, n=43, paired t-test. C: Main plot: Slow-wave energy (SWE) calculated by accumulation of slow-wave activity (SWA) over time. Left upper plot: All night deep sleep (N3); Right bottom plot: All night slow-wave activity (SWA). Statistics: paired t-test, n=50, N3 *P=0.017; SWE *P=0.034 (log transformed data); SWA P=0.107. D: Periodic limb movements during sleep (PLMS) index and arousal index at baseline (BL) and on subthalamic deep brain stimulation (DBS) in Parkinson patients with (DA+) and without (DA-) dopamine agonist treatment. Statistics: Mann-Whitney U test: *P<0.004, (Bonferroni corrected for multiple comparisons). BL DA+ n=34, BL DA- n=16, DBS DA+ n=22, DBS DA- n=28. E: Slow-wave energy (SWE) before and on subthalamic DBS in akinetic-rigid Parkinson patients (Type AR, n=27) and in tremor-dominant Parkinson patients (Type Tre+Ae, n=23). Statistics: Wilcoxon signed ranks test *P=0.02 (Bonferroni corrected for multiple comparisons).

Fig. 2:

A and B: Scatter plot of all behavioral states (W: wakefulness, N2: non-rapid eye movement/NREM sleep stage 2; N3: NREM sleep stage 3/deep sleep, R: REM sleep) in PD patients before (baseline; BL) and on bilateral deep brain stimulation (DBS) in the subthalamic nucleus mapped in a 2-dimensional state space. Each 5 s epoch is represented by

2 different EEG frequency ratios plotted on log/log axes. Color coding of the clusters is based on model-based sleep scoring for W, N2, N3, and R. Diamond symbols represent cluster centroids (average position of all states per sleep stage). All centroid positions remained stable. Statistics: all P>0.05. C: Average state space velocity before and on DBS for each behavioral state. Velocity was diminished in N2 (stage 2 sleep) and R (REM sleep), but not in wake or N3 (deep sleep). Statistics: N2 *P=0.010, paired t-test; R *P=0.002 Wilcoxon signed ranks test, n=50.

Fig. 3:

Association between the location of the lowest active electrode contacts in relation to the ventral margin of the left subthalamic nucleus (STN) and the change in sleep efficiency on deep brain stimulation (DBS). A: Schematic representation of the position of the quadripolar electrode in the STN. The borders of the STN have been assessed by MR imaging, microelectrode recordings, and intraoperative macrostimulation effects. The ventrodorsal extension has been assessed by microelectrode recordings along the electrode trajectory and represents the most reliable STN extension. Assumed functional STN parcellation and neighboring structures are indicated. In each patient, either monopolar (n=33; blue fields) or bipolar (n=17; red fields) stimulation of contacts has been applied, according to clinical stimulation effects. B: Position of the lowest active contact in relation to the ventral and the lateral STN margins. Monopolar stimulated contacts are indicated with blue diamonds, the lowest active contact in patient on bipolar stimulation with red diamonds. C: Relation between the dorsal distance of the lowest active electrode pole from the ventral STN margin and the change in sleep efficiency on DBS (R=0.413, P=0.007, n=39). Note: Figures B and C use the same scaling for ventrodorsal extensions, i.e. dots on the same horizontal line represent the same individual patients, as suggested by an exemplary horizontal light grey line.

Tables:

Table 1 - Patient characteristics before neurosurgical procedure.

Number of Parkinson patients	50
Sex (f / m)	18 / 32
Age (y)	61 (range 34 - 81)
Disease duration (y)	12 (range 3 - 22)
Hoehn & Yahr (preoperative, on-medication)	
St 1 / 2 / 3	3 / 27 / 20
UPDRS III (preoperative, on-medication)	25±10 (range 9-53)
Parkinson's disease type	
AR / Tre+Ae	27 / 23 (12+11)
Side with dominant symptoms (right/left)	31 / 19

UPDRS Unified Parkinson's Disease Rating Scale. Scores are on medication. Part III motor examination score. PD subtypes: AR: akinetic-rigid, Tre: tremor-dominant; Ae: mixed type.

Table 2 – Change in UPDRS scores and dopaminergic medication 6 month following STN-DBS.

N=50	BL	DBS	Change %	Statistics
UPDRS III	25.1 ± 9.7	15.6 ± 6.0	-34.9 ± 20.4	< 0.001
LED total (mg)	1025 ± 480	369 ± 376	-60.9 ± 37.2	< 0.001*
LED Lev (mg)	793 ± 450	309 ± 342	-50.8 ± 59.1	< 0.001*
LED DA (mg)	216 ± 210	55 ±103	-54.5 ± 109.2°	< 0.001*

*Results are mean ± SD, n=50. Change % within-patient difference means. UPDRS Unified Parkinson's Disease Rating Scale. UPDRS assessments are on medication (BL, baseline) and on stimulation in combination with medication (DBS), respectively. Part III motor examination part. Dopaminergic medication: LED levodopa equivalent dosage; Lev Levodopa; DA Dopamine agonist. °n=34 as only these patients had DA in BL. Statistics: paired t-test, *nonparametric Wilcoxon Signed Ranks Test.*

Table 3 - Polysomnographic findings before (BL) and after neurosurgical procedure (DBS).

	BL	DBS	Statistics
Total time analyzed (TTA, min)	410.4 ± 41.9	410.4 ± 41.9	n.s.
TST (min)	275.4 ± 68.1	296.6 ± 71.0	0.016*
Sleep latency (min to first N2)	34.9 ± 44.7	34.4 ± 35.0	n.s.*
Sleep efficiency (% of TTA)	67.5 ± 17.1	72.3 ± 16.1	0.016*
Sleep efficiency (% of SPT)	73.6 ± 16.0	78.9 ± 16.1	0.005*
REM sleep latency[a] (min, from sleep onset)	134.2 ± 73.9	109.1 ± 69.8	0.047*
WASO (min)	99.9 ± 58.9	80.3 ± 59.7	0.023
N1 (min)	51.0 ± 42.3	56.1 ± 30.0	n.s.
N2 (min)	140.7 ± 50.4	140.5 ± 46.5	n.s.
N3 (min)	42.6 ± 34.9	53.8 ± 43.3	0.017
REM sleep (min)	41.2 ± 27.4	46.2 ± 31.8	n.s.
RWA[a] (min)	24.6 ± 22.4	27.6 ± 27.0	n.s.*
RWA index[a] (%)	51.2 ± 31.8	48.8 ± 30.7	n.s.
RWA index[a] above SINBAR cutoff %	65.9 %	64.4 %	n.s.°
Arousal index (/h)	14.6 ± 10.7	16.6 ± 11.2	n.s.*
Awakening index (/h of TST)	5.9 ± 4.0	5.8 ± 5.6	n.s.*
Number of longer awakenings			
>5 min	3.7 ± 2.4	3.0 ± 2.4	n.s.*
>15 min	1.4 ± 1.2	1.1 ± 1.3	n.s.*
>30 min	0.6 ± 0.9	0.5 ± 0.6	n.s.*
AHI (/h)	6.2 ± 8.7	6.4 ± 9.3	n.s.*
AHI > 15 /h	12 %	14 %	n.s.°
PLMS index (/h)	12.3 ± 29.2	23.4 ± 33.6	0.023*
PLMS index > 15/h	16 %	40 %	0.002°
Urinary frequency	1.0 ± 0.9	1.0 ± 0.9	n.s.*
Number of position changes	10.7 ± 8.7	11.2 ± 10.9	n.s.*

Polysomnographic findings: results are mean ± SD, n=50. Values are on medication (BL, baseline) and on stimulation in combination with medication (DBS), respectively. TTA total

time analyzed; TST total sleep time; SPT sleep period time, time from sleep onset till final awakening. REM: rapid eye movement; WASO wakefulness after sleep onset; N1-3 non-REM sleep stage 1, 2 and 3. RWA REM sleep without atonia; SINBAR Sleep INsbruck BARcelona study group approach. [a] *n=40. AHI apnea-hypopnea index; PLMS periodic limb movement during sleep. Statistics: paired t-test, *nonparametric Wilcoxon signed ranks test, °McNemar test).*

Table 4 - Potential association between pre/post STN-DBS sleep parameter changes and PD type, STN-DBS motor outcome, STN-DBS dopaminergic medication change, and stimulation electrode localization (left electrode).

	ΔSleff	ΔWASO	ΔTST	ΔN3	ΔSWE
N	42	42	42	42	42
R2	0.389	0.407	0.347	0.361	0.372
ANOVA p-value	0.006	0.004	0.015	0.011	0.009
Parkinson type					
β-value	-0.243	0.238	-0.213	-0.217	-0.320
P-value	n.s.	n.s.	n.s.	n.s.	0.026
ΔUPDRS III					
β-value	-0.353	0.328	-0.344	-0.183	-0.119
P-value	0.014	0.020	0.020	n.s.	n.s.
ΔLED					
β-value	-0.266	0.312	-0.287	-0.514	-0.492
P-value	n.s.	0.027	n.s.	0.001	0.001
E-left-dorsal					
β-value	-0.020	0.003	-0.014	0.158	0.123
P-value	n.s.	n.s.	n.s.	n.s.	n.s.
E-left-ventral					
β-value	0.447	-0.448	0.397	-0.041	0.105
P-value	0.002	0.002	0.008	n.s.	n.s.
E-left-lateral					
β-value	0.032	-0.066	0.000	0.024	0.069
P-value	n.s.	n.s.	n.s.	n.s..	n.s.

Δ pre/post STN-DBS sleep parameter changes; Sleff sleep efficiency; WASO change of wakefulness; TST total sleep time; N3 deep sleep; SWE accumulated slow wave activity. N = number of subjects included in the linear regression analysis model. R2 square root of multiple correlation coefficients as a measure of variability in the outcome which is accounted for by the predictors. ANOVA p-value: result of testing the significance of the model. β-value standardized β coefficient showing the strength and direction the outcome will change; p-value showing the significance of the contribution to the predictor. n.s. not significant. PD subtypes entering the model: 0 = AR subtype, 1 = Tre+Ae subtype. E-left-dorsal / E-left-ventral / E-left-lateral left electrode localization from the STN border in

dorsal, ventral and lateral direction. Similar models including the right electrode instead of the left electrode: right electrode localizations were never significant predictors.

Supplemental Materials: non

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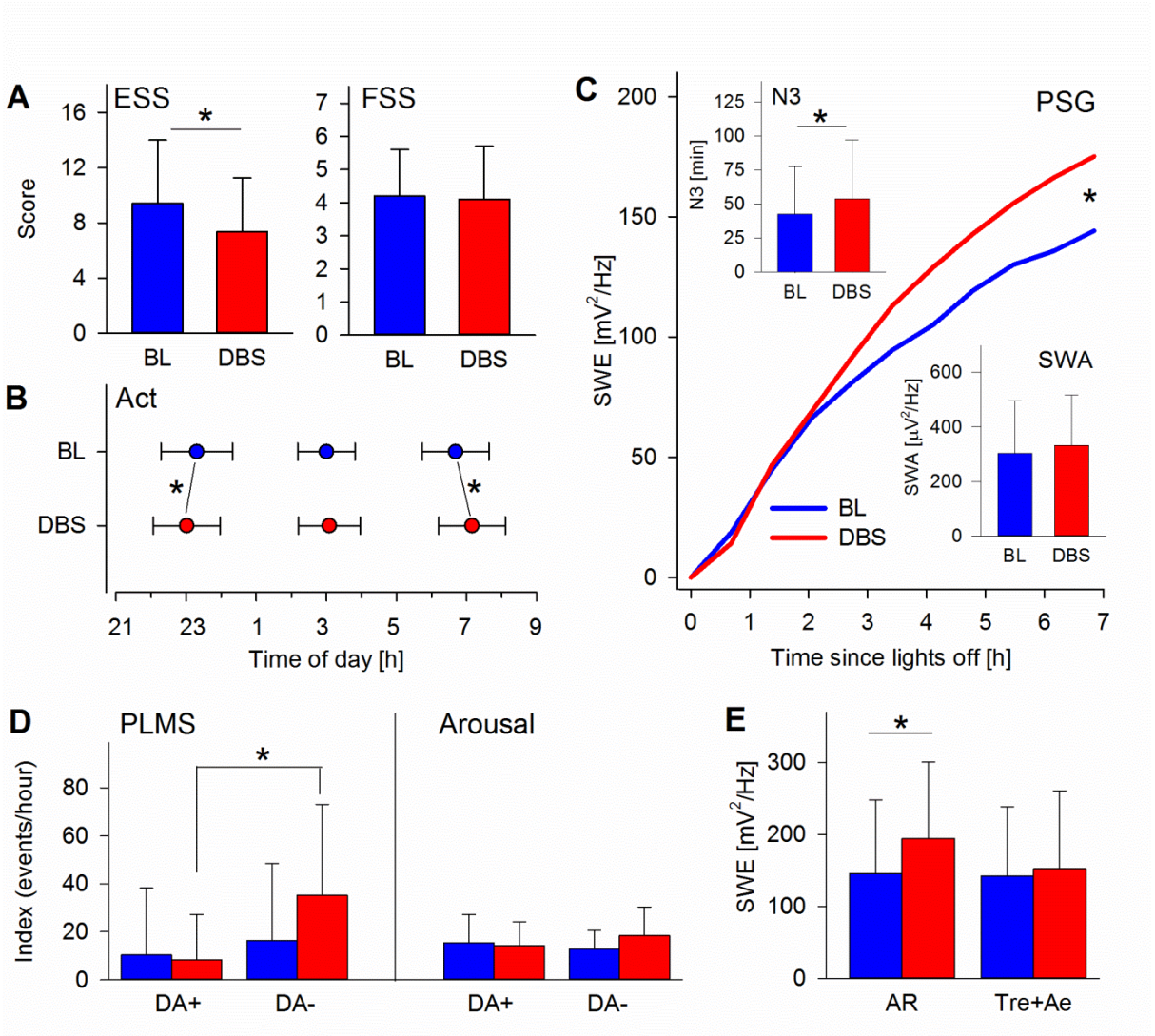
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Index (events/hour)
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E
SWE [mV²/Hz]
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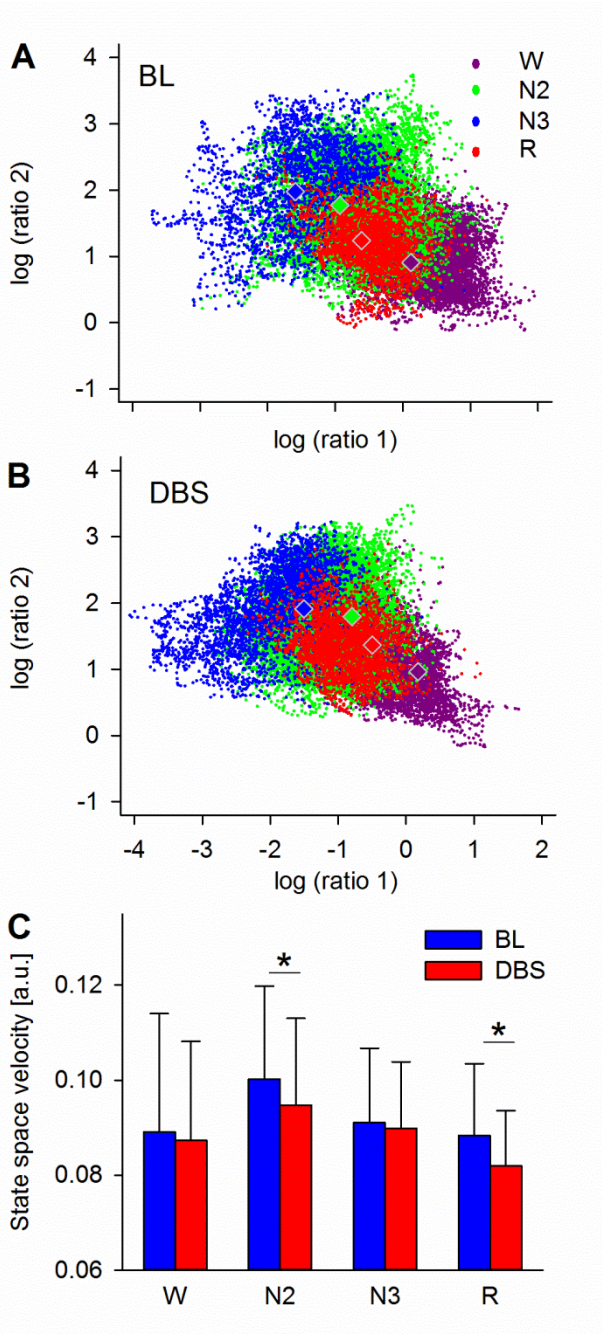
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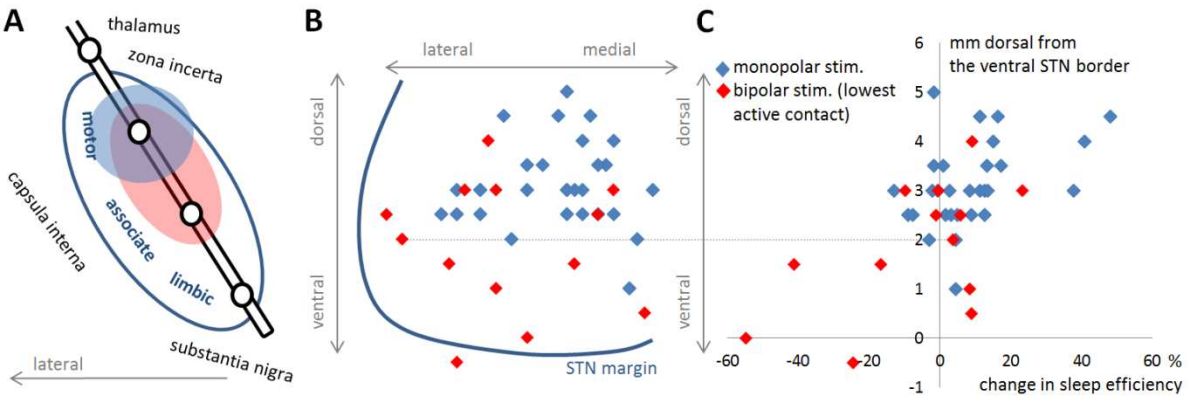
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