Slow-wave sleep and motor progression in Parkinson disease

Running head: Slow-wave sleep and Parkinson disease progression

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Abstract

Growing evidence from Alzheimer disease supports a potentially beneficial role of slow-wave sleep in neurodegeneration. However, the importance of slow-wave sleep in Parkinson disease is unknown. In 129 patients with Parkinson disease, we retrospectively tested whether sleep slow waves, objectively quantified with polysomnography, relate to longitudinal changes in Unified Parkinson's Disease Rating Scale motor scores. We found that higher accumulated power of sleep slow waves was associated with slower motor progression, particularly of axial motor symptoms, over a mean time of 4.6±2.3 years. This preliminary finding suggests that deeper sleep relates to slower motor progression in Parkinson disease.

Introduction

Parkinson disease (PD) is characterized by alpha-synuclein accumulation and progressive motor and non-motor symptoms, including sleep-wake disturbances.

Growing evidence suggests that sleep and particularly slow-wave sleep (SWS), i.e. deep non-REM (NREM) sleep, could play a role in neurodegeneration:[1] Sleep restriction accelerates and sleep enhancement decelerates beta-amyloid plaque formation in an Alzheimer disease mouse model.[2] In humans, cerebrospinal fluid beta-amyloid decreases during sleep and rises during wakefulness[2] - and specifically after SWS disruption.[3] Slow-wave sleep could counteract accumulation of beta-amyloid - and potentially alpha-synuclein - through glymphatic clearance[4] or reduced production.[5,6]

However, the importance of SWS in PD and its progression is unknown. We retrospectively analyzed whether SWS, objectively quantified with polysomnography, relates to motor progression in PD patients.

Methods

This study was conducted in accordance with the Declaration of Helsinki and after ethical approval (Kantonale Ethikkommission Zürich). We retrospectively included consecutive PD patients from our movement disorders outpatient clinic. Inclusion criteria were diagnosed PD,[7] overnight video-polysomnography in the in-house sleep laboratory - which is part of a routine diagnostic work-up in all patients with Parkinsonism - and longitudinal follow-up including standard clinical examinations every 3-6 months over at least 2 years. The earliest clinical visit close to polysomnography was selected as baseline, and the latest after polysomnography as end point. Clinical assessments included the Unified Parkinson's Disease Rating Scale motor part (UPDRS III), Hoehn and Yahr stage, motor phenotype[8], and daily levodopa equivalent dose (LED).[9] Exclusion criteria were other forms of Parkinsonism, or deep brain stimulation during the observation time.

Motor examinations were obtained on best medical treatment, which challenges a reliable estimation of motor progression. Thus, we focused on axial symptoms, which are less responsive to levodopa, and inevitably arise despite treatment, allowing a more accurate description of motor progression in PD patients on dopaminergic therapy.[10] We used an established axial UPDRS III sub-score, defined by several independent factor analyses of the UPDRS III, which consistently identified a dominant axial factor (arising from chair, posture, gait, postural stability, body bradykinesia) that clusters together with speech and facial expression.[11,12] We calculated annual changes of axial UPDRS III, total UPDRS III, and LED, using a previously implemented approach,[8] as follows: (follow-up measure - baseline measure)/observation time.

We performed quantitative sleep analysis as previously described by our group.[13] In brief, patients underwent a single-night polysomnography with digital videography (Embla N7000, RemLogic v3.2). Experienced sleep experts (E.W., R.P., H.B.V.) scored sleep stages according to the AASM manual.[14] EEG preprocessing included filtering (0.5 Hz high-pass and 40 Hz low-pass) and artifact removal, as previously described.[13] Readouts included total sleep time (TST), indices (events/hour) for apnea-hypopnea (AHI), arousal, and periodic limb movements during sleep (PLMS), percentages of wake after sleep onset (WASO), REM and NREM sleep stages 1-3 (N1, N2, N3), and REM sleep behavior disorder, diagnosed according to international criteria.[15] We computed slow-wave activity (SWA), i.e. EEG delta power (0.5-4.5 Hz), and slow-wave energy (SWE), i.e. accumulated power in the SWA band totaled over all epochs of N2+N3.[16]

We used SPSS (version 23.0, SPSS Inc., Chicago, IL, USA) and Matlab with statistical toolbox (MATLAB 2015b, Version 8.6; MathWorks Inc., Natick, MA, USA) for statistical analysis. Plotting and inspecting of residuals assured their normal distribution. We z-transformed all variables for statistical

analyses, yet tables and figures show raw data. First, we dichotomized the sample into patients with high and low SWE based on median sample level of SWE and compared motor progression between groups. Differences between groups were tested with the Wilcoxon rank-sum (continuous variables) or Chi^2 test (categorical variables), and differences between baseline and follow-up with the Wilcoxon signed-rank test. Annual changes of axial UPDRS III, total UPDRS III, or LED that significantly differed between groups were followed-up with repeated-measures ANOVA, to test whether progression over time differed between groups; baseline and follow-up measures were used as within-subject factor, and the dichotomized SWE as between-subject factor. Next, we related SWE as continuous independent variable to annual changes of the UPDRS III (dependent variable) within a linear regression model. Covariates were age, sex, motor phenotype, disease duration, symptom laterality, UPDRS III, LED (all at baseline), and sleep parameters selected based on group differences significant at $p<0.05$, to control for possible confounding (AHI, N1, N3, WASO; Sleep efficiency and TST differed between groups at $p<0.05$, but were not included to avoid collinearity). We chose two-sided tests and a conservative significance level of $p<0.01$. Standardized beta coefficients (*ß*), adjusted coefficient of determination (R^2), and 95% confidence intervals are reported.

Results

Table 1 summarizes patient characteristics, and Table 2 shows polysomnographic readouts. Median absolute time between baseline assessment and polysomnography was 9.6 months. In the entire sample, axial UPDRS III (z=9.16), total UPDRS III (z=4.4) and LED (z=8.26) significantly increased between baseline and follow-up (all $p<0.001$, Wilcoxon signed-rank test), indicating motor progression and increasing dopaminergic medication during the observation time of 4.6±2.3 years (mean±SD).

In patients with high SWE, axial UPDRS III progression was significantly slower, compared to patients with low SWE (Fig 1A). We corroborated this finding using SWE as a continuous variable in a linear

regression analysis across 127 patients (two out of 129 patients were excluded owing to missing data): Higher SWE was strongly associated with slower progression of axial UPDRS III (Fig 1B); all covariates were unrelated to the outcome. Similarly, SWE predicted progression of total UPDRS III (ß= -0.28 [-0.62, -0.19], p=0.008; adjusted R^2=0.28), but other covariates were also significant predictors: UPDRS III at baseline (ß= -0.44, p<0.001), and right-sided symptom laterality (ß=0.40, p=0.009), as previously reported.[8] Sleep-wake relevant medication did not differ between groups (Table 2). Dopamine agonists and related LED were unrelated to SWE and amount of N3.

Discussion

In this retrospective study, we tested whether SWS relates to motor progression in 129 patients with PD. We quantified sleep slow waves by means of SWE, i.e. accumulated SWA, from polysomnography. Motor progression was estimated based on longitudinal changes in UPDRS III. We found that higher SWE was associated with slower motor progression, particularly axial progression, over a mean observation time of almost 5 years.

This study was motivated by a lack of studies on the importance of SWS in PD, while growing evidence supports a role of sleep - particularly SWS - in Alzheimer disease.[1] Although purely associative, our finding implies that deeper SWS might relate to a more benign course of PD and underpins recently reported associations of sleep fragmentation with PD pathology[17] and worsening gait in PD.[18] In this line, our finding can be interpreted within the suggested framework of a bi-directional relationship between sleep and neurodegeneration.[1] As such, disrupted SWS could result from degeneration of sleep regulatory brain regions affected in PD. Vice versa, disrupted SWS could accelerate and consolidated SWS decelerate neurodegeneration and PD progression. These effects could be driven by SWS counteracting pathological protein accumulation through reduced production of alpha-synuclein owing to lower neurometabolic activity[5,6] or promotion of glymphatic clearance.[4] Although - in contrast to beta-amyloid -

alpha-synuclein primarily accumulates intracellularly, glymphatic clearance could theoretically slow its extracellular propagation[19], and novel evidence suggests that sleep-wake dynamics might regulate levels of alpha-synuclein in cerebrospinal fluid.[20]

However, we consider our finding as preliminary due to limitations. Owing to the retrospective study design, we observed data variability (e.g. 31 out of 129 patients were drug-naïve at baseline and none at follow-up). Moreover, lower SWE was associated with male sex, sleep-disordered breathing, and poor sleep quality, including more WASO and light NREM sleep at the expense of deep NREM sleep. However, these imbalances did not influence motor progression or its relationship with SWE, as we treated these variables as (non-significant) covariates. Despite the retrospective design, absolute time between baseline visit and polysomnography was rather short for many patients (median 9.6 months), allowing to conceptualize polysomnography as an approximate baseline measure.

Although objective sleep assessment in a relatively large sample is a strength of this study, SWE was quantified from one night without habituation polysomnography. Further limitations are lacking systematic data on non-motor decline, e.g. cognitive deterioration, and on several PD-related factors possibly affecting sleep, such as depression, nocturia, or nocturnal off-phenomena. Nevertheless, relevant bias towards patients with particularly disturbed sleep is unlikely, as we applied polysomnography for diagnostic purpose, irrespective of suspected sleep-wake disturbances.

Different physicians examined motor symptoms under dopaminergic treatment. Thus, inter-rater variability and dopaminergic treatment are potential confounders. However, all physicians were trained to the same standards. Further, by applying an established axial UPDRS III cluster[11,12] we focused on axial symptoms, which are less levodopa-responsive, capture key aspects of inevitable disease progression and, thus, support estimating motor progression in treated PD patients.[10]

In conclusion, we provide novel evidence suggesting that higher accumulated power of sleep slow waves is associated with slower motor progression in PD patients. Our data contributes to growing evidence for

an interplay between sleep and neurodegeneration,[1] extending the importance of SWS from a context of Alzheimer disease to PD. Further studies are warranted to confirm our preliminary finding and explore the role of SWS in neurodegeneration with special regard to its therapeutic potential.

Author contributions

SJS, LLI, PVO, DN and CHB contributed to the conception and design of the study; SJS, LLI, EW, RP, HBV, PVO, TM and CHB contributed to the acquisition and analysis of data; SJS and CHB contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

The authors have nothing to report.

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Figure legend

Figure 1: Higher slow-wave energy is associated with slower motor progression in Parkinson disease

A) In PD patients with high (n=65) and low SWE (n=64), axial UPDRS III values are shown at study baseline and follow-up, 4.6±2.3 (mean±SD) years later. While axial motor symptoms did not differ between groups at study baseline (p=0.87; Wilcoxon rank-sum test), patients with high SWE showed less axial motor impairment at study follow-up as compared to patients with low SWE (p<0.001; Wilcoxon rank-sum test; dashed lines). Time between baseline and follow-up visit did not differ between PD patients with high SWE (4.3±2.1 years) and low SWE (4.9±2.4 years; p=0.11; Wilcoxon rank-sum test). Progression of axial motor symptoms was slower in patients with high SWE compared to those with low SWE (SWE x time interaction: F (1, 128)=41.97; p<0.001; repeated-measures ANOVA, straight line). Whiskers indicate standard errors or mean. Asterisks (**) indicate significance at p<0.001.

B) Slow-wave energy is plotted against mean annual increase of the axial UPDRS III in 127 PD patients. Higher SWE predicted slower progression of axial motor symptoms (ß= -0.40, p<0.001; 95% confidence interval= -0.62 to -0.19, indicated by the red lines; adjusted R^2=0.19; from this linear regression analysis, two out of the total 129 were excluded owing to missing data); relevant covariates were controlled for.

Abbreviations: UPDRS III = part III of the Unified Parkinson's Disease Rating Scale; The axial UPDRS III comprises a cluster of axial motor symptoms from the UPDRS III (items 18, 19 and 27-31).[11,12] Higher numbers indicate greater motor symptoms; SWE = slow-wave energy (accumulated slow-wave activity during N2+N3);[16] patients were dichotomized based on median SWE into subgroups with high and low SWE.

Table 1: Demographical and clinical characteristics of all patients and subgroups with high and low slow-wave energy (SWE)

	All	High SWE	Low SWE	p
Sample size (n)	129	65	64	
Age at baseline (years)	62.7±10.7	61.4±10.1	63.9±11.2	0.08
Females (n)	46 (36 %)	29 (45 %)	17 (27 %)	**0.03**
Body Mass Index	25.2±4.31	24.91±4.31	25.54±4.33	0.39
Motor phenotype (MX / TD / AR)[A]	26 / 39 / 62	16 / 21 / 27	10 / 18 / 35	0.16
Dominant right side (n)	75 (58 %)	37 (57 %)	38 (60 %)	0.37
Drug-naïve at baseline (n)	31 (24 %)	15 (23 %)	16 (25 %)	0.80
Disease duration at baseline (years)	5.4±4.7	5.1±4.9	5.6±4.6	0.32
Hoehn and Yahr stage at baseline[B]	2.0±0.6; 2 (1-4)	2.0±0.5; 2 (1-4)	2.0±0.5; 2 (1-3)	0.21
Hoehn and Yahr stage at follow-up[B]	2.5±0.7; 2 (1-5)	2.3±0.6; 2 (1-5)	2.6±0.8; 2 (1-5)	**0.03**
Observation time (years)	4.6±2.2	4.3±2.2	4.9±2.4	0.11
Polysomnography-to-baseline (years; median)	1.8±2.3 (0.8)	1.8±2.3 (0.7)	1.9±2.2 (1.0)	0.61
Axial UPDRS III				
Baseline	5.8±3.3	6.0±3.6	5.7±3.0	0.87
Follow-up	9.8±4.5	8.3±4.0	11.3±4.6	**<0.001***
Annual change	0.9±0.9	0.6±0.6	1.3±0.9	**<0.001***
UPDRS III				
Baseline	20.5±8.9	18.8±8.8	22.1±8.7	**0.03**
Follow-up	25.3±12.3	22.0±11.5	28.6±12.3	**<0.001***
Annual change	0.8±3.3	0.4±3.2	1.3±3.3	0.18
LED (mg/d)				
Baseline	437.6±442.1	407.0±409.4	468.7±472.2	0.52
Follow-up	895.4±448.3	798.1±352.1	994.3±512.4	**0.04**
Annual change	114.0±132.4	107.4±132.3	120.7±133.2	0.47

Means±standard deviations are shown; bold letters indicate $p<0.05$, asterisk indicates $p<0.01$; Abbreviations: MX=mixed; TD=tremor-dominant; AR=akinetic-rigid; UPDRS III=part III of the Unified Parkinson's Disease Rating Scale; Axial UPDRS III comprises a cluster of axial motor symptoms from the UPDRS III;[11,12] LED = levodopa-equivalent dose; [A]Two undetermined, one in each group; [B]Three missing, one in patients with high SWE and two in patients with low SWE; Hoehn and Yahr stage is presented as mean±SD; median (range).

Table 2: Polysomnography characteristics and relevant medication of all patients and subgroups with high and low slow-wave energy (SWE)

	All	High SWE	Low SWE	p
Slow-wave energy (mV^2/Hz)	360.6±278.0	536.1±296.1	182.4±62.2	**<0.001***
Slow-wave activity (μV^2/Hz)	47.4±27.3	63.5±27.5	31.1±14.6	**<0.001***
Total sleep time (min)	314.5±69.9	328.8±64.4	300.0±72.7	**0.02**
Sleep efficiency (% of SPT)	73.8±15.5	77.1±14.9	70.5±15.5	**0.01**
Latency (min to first N2)	29.6±33.3	28.7±35.3	30.6±31.3	0.21
N1 (% of SPT)	13.8±8.2	11.0±5.4	16.6±9.6	**<0.001***
N2 (% of SPT)	38.5±12.1	39.5±11.4	37.4±12.7	0.33
N3 (% of SPT)	12.3±9.2	16.6±9.9	7.9±5.6	**<0.001***
REM (% of SPT)	11.8±6.6	12.5±6.9	11.2±6.2	0.37
WASO (% of SPT)	23.7±15.1	20.4±14.6	27.1±14.8	**0.01**
AHI (events/h)	10.3±16.5	8.7±15.2	12.0±17.7	**0.04**
AHI 5-14 (n)	26 (20%)	8 (12%)	18 (28%)	**0.03**
AHI 15-30 (n)	16 (12%)	8 (12%)	8 (12%)	0.97
AHI ≥30	12 (9 %)	5 (7.7 %)	7 (11.0 %)	0.40
Arousal index (events/h)	10.4±11.5	8.6±6.3	12.3±15.1	0.14
PLMS index (events/h)	10.3±16.5	9.9±21.3	10.8±25.4	0.39
REM sleep behavior disorder	79 (61 %)	37 (57 %)	42 (66%)	0.31
[1]Sedative antidepressants, during polysomnography	14 (10.9 %)	5 (7.7 %)	9 (14.1 %)	0.24
[1]Sedative antidepressants, ever prescribed	39 (30.2 %)	18 (27.7 %)	21 (32.8 %)	0.53
Clonazepam, ever (never during polysomnography)	37 (28.7 %)	22 (33.8 %)	15 (23.4 %)	0.19
Other benzodiazepines/z-drugs, during polysomnography	7 (5.4 %)	4 (6.2 %)	3 (4.7 %)	0.71
Other benzodiazepines/z-drugs, ever prescribed	22 (17.1 %)	8 (12.3 %)	14 (21.9 %)	0.15
Melatonin, ever (never during polysomnography)	9 (7.0 %)	5 (7.7 %)	4 (6.3 %)	0.75
[2]Antipsychotics, during polysomnography	6 (4.7 %)	4 (6.2 %)	2 (3.1 %)	0.41
[2]Antipsychotics, ever prescribed	11 (8.5 %)	6 (9.2 %)	5 (7.8 %)	0.77
Dopamine agonist during polysomnography (intake)	54 (42 %)	27 (42 %)	27 (42 %)	0.94

Dopamine agonist during polysomnography (LED mg/d)	123±181	111±171	146±191	0.66

Means±standard deviations are shown; bold letters indicate $p<0.05$, asterisk indicates $p<0.01$; Abbreviations: LED = levodopa-equivalent dose; SWE=slow-wave energy (accumulated slow-wave activity during N2+N3); REM=rapid eye movement; N1-3=Non-REM sleep stages 1-3; WASO=wake after sleep onset; AHI=apnea-hypopnea index; PLMS=periodic limb movements during sleep; SPT=sleep period time (sleep after first N2); [1]tricyclics, trazodone, mirtazapine; [2]clozapine, quetiapine.