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Impaired sleep microarchitecture is associated with locus coeruleus degeneration in Parkinson's disease

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ABSTRACT

Study objectives: Sleep disorders are common non-motor symptoms of Parkinson's disease (PD) that significantly impact patients' quality of life. Specifically, alterations in sleep microstructure – such as reduced slow-wave activity and sleep spindles - are prevalent in PD. The locus coeruleus (LC), the brain's primary source of noradrenaline, plays a pivotal role in regulating sleep and wakefulness and is highly vulnerable to neurodegeneration in PD. This study explores whether disruptions in sleep microarchitecture in PD are linked to LC degeneration.

Methods: We assessed polysomnography for sleep macroarchitecture, EEG spectral power, and spindle density in 32 PD patients and 24 age- and sex-matched controls. In a sample subset (n = 42), neuromelanin-sensitive MRI was performed, and LC neuromelanin contrast was correlated to sleep metrics.

Results: PD patients exhibited reduced slow-wave activity ($p < 0.01$), slow-to-fast frequency ratio ($p < 0.01$), and spindle density ($p < 0.05$) compared to HC subjects. LC neuromelanin contrast was diminished in PD patients ($p < 0.05$). Even though group differences were detected for slow-wave activity, a positive correlation between LC contrast and spindle density but not slow-wave activity was observed in the entire sample.

Conclusions: The findings indicate that spindle density, but not slow-wave activity, is associated with LC degeneration. Further research is needed to determine whether, besides this association, noradrenergic dysfunction is causal for impaired sleep microarchitecture and whether this connection also contributes to cognitive decline in PD and other neurodegenerative diseases, such as Alzheimer's disease.

1. Introduction

Sleep disorders are common non-motor symptoms of Parkinson's disease (PD) and have a substantial impact on patients' quality of life [1,2]. Surprisingly, the disparities in macroparameters of sleep between PD patients and healthy aged volunteers are subtle. A meta-analysis combining 63 polysomnographic studies revealed less than 3 % difference in REM (rapid eye movement) and NREM (non-REM) sleep stages [3]. However, studies have shown that sleep spindle density [4–8] and slow-wave activity are reduced in PD [9,10] and are associated with cognitive decline in PD [7,8,10,11]. Linking these changes in sleep microstructure to structural changes in associated brain regions could

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facilitate a more comprehensive understanding of the pathophysiology underlying disrupted sleep and cognitive impairment in PD [12–16].

There is mounting evidence of noradrenergic dysfunction in PD [17–20], which is assumed to contribute to cognitive decline in PD [17,21,22], a finding well-documented in the context of Alzheimer's disease. [23–28]. Neuropathological studies indicate that the locus coeruleus (LC), the brainstem structure that serves as the primary source of noradrenaline in the brain, is highly susceptible to PD pathology and is affected early in the disease course [17,18,29,30]. Furthermore, the LC has been identified as a key player in sleep regulation [31,32]. However, the LC's role in microsleep alterations in PD remains unclear. Given the impact of the LC on cognition and sleep physiology, noradrenergic dysfunction may be the underlying mechanism for the influence of non-REM sleep disruption on the progression of PD. Thus, our current study aimed to investigate whether changes in sleep spindle density and slow-wave activity were associated with LC degeneration.

2. Materials and methods

2.1. Participants

Seventy-one datasets from two case-control studies, which included deep phenotyping and polysomnography, were pooled for analysis [17,33,34]. To avoid potential confounds due to comorbidities, we excluded datasets from 6 healthy control (HC) subjects and 9 PD patients due to high apnea/hypopnea indices exceeding age-matched reference values (AHI, >20/hour) [35]. The final sample consisted of 24 HC subjects and 32 PD patients, all between 50 and 85 years old and non-demented (Montreal Cognitive Assessment score >22). PD diagnosis was established following the current consensus criteria [36]. Levodopa equivalent daily doses (LEDD) were calculated as previously proposed [37]. Disease severity was judged according to the Hoehn and Yahr stage [38], and motor symptoms were quantified using the MDS Unified Parkinson's disease Rating Scale part III (MDS-UPDRS III) after 12 h of medication withdrawal.

The local ethical committees approved the study, and all subjects provided informed written consent under the Declaration of Helsinki.

2.2. Polysomnographic data and analysis of sleep microarchitecture

Overnight video-polysomnography (PSG) was conducted using a mobile SOMNOscreen™ plus device, including 10 electrode recordings (according to the international 10/20 system: F3, F4, C3, C4, O1, O2, M1, M2, Fpz as grounding, and Cz as reference) as previously described [12,13]. Visual PSG scoring was performed on 30-s epochs according to the AASM Manual for the Scoring of Sleep and Associated Events, Version 3 [39]. We investigated sleep efficiency, sleep latency, absolute and relative time spent in each sleep stage, apnea-hypopnea indices, and periodic limb movement indices. Artifacts were marked manually.

2.3. Spectral power

Polysomnographic recordings were exported as EDF (European Data format) files and analyzed using custom-made Python scripts. First, EEG data was preprocessed by applying a 0.5 Hz high-pass and 40 Hz low-pass filter and resampled to 128 Hz (original sampling rate: 256 Hz). Visually scored artifacts and arousals were then removed from the analysis. We performed a Fast Fourier Transformation of 5 s segments to determine the spectral power of the delta (0.5 - 4 Hz), theta (4 – 8 Hz), alpha (8 - 12 Hz), sigma (12 – 15 Hz), and beta (15 - 32 Hz) frequency bands. Given that the objective of this analysis - based on our hypotheses and previous literature - was to examine slow-wave activity, further calculations were conducted using delta power exclusively. The extraction of delta power was performed using electrodes F3 and F4 (both referenced to the contralateral mastoid) during sleep stages N2 and N3 for spectral analyses, which is consistent with previous studies [9,40,41]. To avoid a potential bias due to interindividual differences in overall EEG amplitude, we normalized the spectral power of the respective frequency band to total spectral power (0.5 – 32 Hz). [42]. The power from the left and right hemispheres was averaged for further analysis. Additionally, slow-to-fast frequency ratios were calculated from absolute spectral power values ([delta]/[theta + alpha + beta + sigma]).

2.4. Spindle analysis

Spindle detection was carried out using a validated deep neural network (SUMO) [43]. To prepare the polysomnographic recordings for automated detection, we replicated the preprocessing used by SUMO [43]: raw signals were first resampled at 100 Hz and filtered with an 8th-order, phase-preserving Butterworth filter (0.3–30 Hz passband). Recordings were then normalized by z-transforming 115-s-long consecutive segments for each electrode to zero mean and unit variance. SUMO detected sleep spindles from electrodes C3 and C4 (referenced to the contralateral mastoid), and only those occurring during sleep stage N2 were analyzed (detections in other stages, arousals, or artifact regions were discarded). Spindles lasting less than 0.5 s were discarded, following the minimum duration criterium for spindles according to the AASM guidelines [39]. To estimate each spindle's mean amplitude and frequency, we followed a method from a prior study [44]. Spindle segments were bandpass filtered between 10 and 16 Hz using a zero-phase 4th-order Butterworth filter. The Hilbert transform was applied to compute instantaneous amplitudes, and the mean amplitude of a spindle was determined as the average of instantaneous amplitudes over the spindle duration. The frequency of a spindle was determined by identifying negative-to-positive zero-crossings of the filtered signal, calculating local frequencies as reciprocals of zero-crossing intervals, and averaging those local frequencies with associated instantaneous amplitudes above 3 μV (following Ref. [44]) to exclude likely non-spindle oscillations. Spindles without instantaneous amplitudes above 3 μV were discarded. For further analysis, parameters derived from electrodes C3 and C4 were averaged.

2.5. Neuromelanin-sensitive MRI

We acquired 2D axial turbo spin-echo (TSE) T1-weighted sequences in a subset of 29 Parkinson's disease patients and 13 HC subjects of our sample on a Siemens Trio 3T MR scanner using an 8-channel head coil with the following protocol: repetition time/echo time: 600 ms/9.2 ms, 26 averages, voxel size: 0.7 x 0.7 × 2 mm^3). Planes were acquired perpendicular to the dorsal brainstem. Four images (one HC subject and three PD patients) had to be discarded due to artifacts. This resulted in a final cohort of 26 PD patients and 12 healthy controls.

Neuromelanin MRI contrast of the LC was quantified using a voxel-wise analysis. TSE images were sinc-interpolated using PMOD 4.0 to achieve near-isotropic voxel dimensions of 0.5 × 0.7 × 0.7 mm^3. For coregistration to a study-specific template space, individual TSE images were padded by 50 voxels in all dimensions. A study-specific template was generated using the 'antsMultivariateTemplateConstruction2' function within Advanced Normalization Tools (ANTs v2.3.1) [45]. Three expert raters manually segmented the LC on the resulting template (CEJD, SR, MS), identifying hyperintense voxels bilaterally within the dorsal pons contiguous to the fourth ventricle using ITK-SNAP [46]. An LC mask was created based on all voxels for which at least two of the three raters could achieve a consensus in manual segmentation. Voxel intensities of individual TSE images were normalized to the pons background volume of interest (VOI). Group differences in LC neuromelanin contrast and the correlation between spindle density/slow-wave activity and LC neuromelanin contrast were computed voxelwise using nonparametric permutation inference with FSL's randomise, applying 5000 permutations after smoothing with a sigma of 2 mm [47]. Threshold-free cluster enhancement (TFCE)

statistics were used, and FDR correction was applied to account for multiple comparisons with a threshold of $p < 0.05$. In addition to the voxelwise analysis of the data, following previous studies [17,48], we also computed the mean of the 10 voxels with the highest intensity inside the LC mask for each subject.

2.6. Statistical analysis

We analyzed the data with RStudio 2024.12.0 + 467. Group data are presented as mean ± standard deviation unless otherwise stated. The normal distribution of the data was assessed using the Shapiro-Wilk test, Q-Q plots, and box plots. As appropriate, group comparisons were performed using *t*-tests, Mann-Whitney-U-tests, and Pearson's chi-squared tests. Significance was accepted at $p < 0.05$.

3. Results

3.1. Demographic and clinical data

PD patients had an average age of 67.2 ± 7.1 years, and 28 % of them were female. The average disease duration was 7.4 ± 5.6 years, and the Hoehn and Yahr stage was 2.4 ± 0.7. HC subjects did not differ significantly in age and sex (Table 1).

We did not observe statistically significant differences in sleep macroarchitecture parameters between HC subjects and PD patients, including sleep efficiency, sleep latency, sleep stages, AHI, and PLMI (Table 1).

3.2. Analysis of sleep microstructure

In PD patients, spindle density was significantly reduced (0.6 ± 0.5 versus 1.1 ± 1.1, $p = 0.021$, Table 2, Fig. 1C). The two groups had no differences in spindle configuration, including amplitude and duration.

PD patients exhibited reduced slow-wave activity during consolidated sleep compared to HC subjects (78.3 ± 6.4 versus 82.9 ± 5.2 %, $p = 0.004$, Table 2, Fig. 2B). Consequently, fractions of the remaining frequency bands, besides the alpha band, were increased (theta, $p < 0.01$; beta, $p < 0.001$), resulting in a lowered slow-to-fast ratio in PD patients (10.5 ± 5.9 versus 13.7 ± 5.1, $p = 0.008$). Comparable findings were obtained when analyzing sleep stages N2 and N3 separately (Supplementary Table 1).

3.3. Locus coeruleus neuromelanin contrast

According to both the voxelwise analysis (Fig. 3A) and the extraction of the 10 voxels with the highest intensities (Fig. 3B), PD patients exhibited a decrease in LC neuromelanin contrast compared to HC subjects.

Furthermore, a positive voxelwise correlation between spindle density and LC neuromelanin contrast was observed across all subjects in large parts of the right LC and middle and caudal portions of the left LC (Fig. 1A and B). However, we did not observe a correlation between LC neuromelanin contrast and slow-wave activity (Fig. 2A and C).

4. Discussion

Our findings revealed decreased slow-wave activity and spindle density in PD patients compared to HC subjects. In contrast, sleep macroparameters did not differ between the two groups. Additionally, we could link noradrenergic deterioration specifically with reduced spindle density. However, although slow-wave activity was reduced in PD patients, this parameter was not associated with LC neuromelanin contrast. This finding suggests that spindle density depends on locus coeruleus integrity.

Changes in sleep microstructure, specifically a decrease in slow-wave activity and spindle density, are part of physiological aging [49]. However, in neurodegenerative disorders such as PD, these changes are significantly amplified and associated not only with prevalent subjective sleep disturbances but also cognitive complaints [4–7,9,10,40]. The link between disrupted sleep and neurodegeneration is also considered bidirectional [50]. An association between disease progression and reduced slow-wave activity has been shown for PD. [51]. In animal studies, slow-wave activity correlated with glymphatic influx [52], suggesting a mechanism by which sleep disturbances through reduced clearance of toxic compounds, such as pathologic α-synuclein species in PD, might promote disease progression [53]. A recent study also showed an association between enlarged perivascular spaces, a potential correlate of glymphatic clearance, and slow-wave activity [41]. This data corroborate microsleep parameters as potential biomarkers for accelerated PD progression.

Table 1
Demographic and clinical characteristics and metrics of sleep macroarchitecture.

	HC (n = 24)	PD (n = 32)	p
Age [y]	66.8 ± 7.3	67.2 ± 7.1	0.837
Sex [f/m]	8/16	9/23	0.900[a]
BMI [kg/m^2]	25.4 ± 2.6	25.8 ± 4.5	0.888[b]
Clinical characteristics			
Time since diagnosis [y]		7.4 ± 5.6	
MDS-UPDRS III (ON)		29.6 ± 15.1	
MDS-UPDRS III (OFF)		40.7 ± 16.7	
Hoehn & Yahr stage		2.4 ± 0.7	
LEDD [mg]		641.0 ± 469.5	
MoCA	27.3 ± 1.6	26.7 ± 2.1	0.231[b]
Sleep macroarchitecture			
Sleep efficiency [%]	80.7 ± 12.8	79.4 ± 19.8	0.766[b]
Sleep latency [min]	14.4 ± 14.7	19.2 ± 50.4	0.180[b]
Wake [min]	90.6 ± 54.4	101.9 ± 81.5	0.941[b]
Wake [%]	19.5 ± 12.8	22.5 ± 18.0	0.889[b]
N1 [min]	75.4 ± 38.4	58.9 ± 25.3	0.090[b]
N1 [%]	15.4 ± 6.4	12.8 ± 5.2	0.103[b]
N2 [min]	181.5 ± 55.7	177.6 ± 68.6	0.812
N2 [%]	38.1 ± 10.4	38.7 ± 13.0	0.855
SWS [min]	69.6 ± 27.9	56.0 ± 33.0	0.107
SWS [%]	14.9 ± 6.0	12.2 ± 6.7	0.119
REM [min]	57.7 ± 24.0	63.6 ± 39.4	0.518
REM [%]	12.1 ± 5.0	13.9 ± 8.6	0.331
AHI [/h]	8.1 ± 6.8	6.7 ± 6.6	0.337[b]
PLMI	24.0 ± 36.0	36.4 ± 38.5	0.138[b]
RBD [y/n]	0/24	14/18	**<0.0001**[a]

Abbreviations: AHI = apnea-hypopnea index, BMI = body mass index, f = female, h = hour, HC = healthy controls, kg = kilogram, LEDD = levodopa equivalent dose, m = male or meter, MDS-UPDRS III = Movement Disorder Society Unified Parkinson's disease Rating Scale part III, mg = milligram, min = minutes, N = non-rapid eye movement sleep, PD = Parkinson's disease patients, PLMI = periodic limb movement index, RBD = REM sleep behavior disorder, REM = rapid eye movement sleep, s = second, SWS = slow wave sleep, y = years; [a]Pearson's chi-squared test, [b]Mann-Whitney-U-test.

Table 2
Metrics of sleep microarchitecture.

	HC (n = 24)	PD (n = 32)	p
Sleep microarchitecture			
Delta power [%]	82.9 ± 5.2	78.3 ± 6.4	**0.004**[a]
Theta power [%]	9.0 ± 2.3	11.4 ± 3.0	**0.005**
Alpha power [%]	4.2 ± 1.8	5.4 ± 3.3	0.173[a]
Beta power [%]	3.1 ± 1.2	4.9 ± 2.3	**<0.001**[a]
Slow-to-fast frequencies ratio	13.7 ± 5.1	10.5 ± 5.9	**0.008**[a]
Spindle analysis			
Density (spm)	1.1 ± 1.1	0.6 ± 0.5	**0.021**[a]
Mean amplitude (μV)	8.1 ± 1.7	9.0 ± 3.2	0.327[a]
Frequency (Hz)	13.1 ± 0.3	13.2 ± 0.3	0.271
Average duration (s)	0.8 ± 0.1	0.8 ± 0.1	0.712[a]

Abbreviations: HC = healthy controls, PD = Parkinson's disease patients, spm = spindles per minute, [a]Mann-Whitney-U-test; spindle amplitudes were derived from the Hilbert-transformed signal.

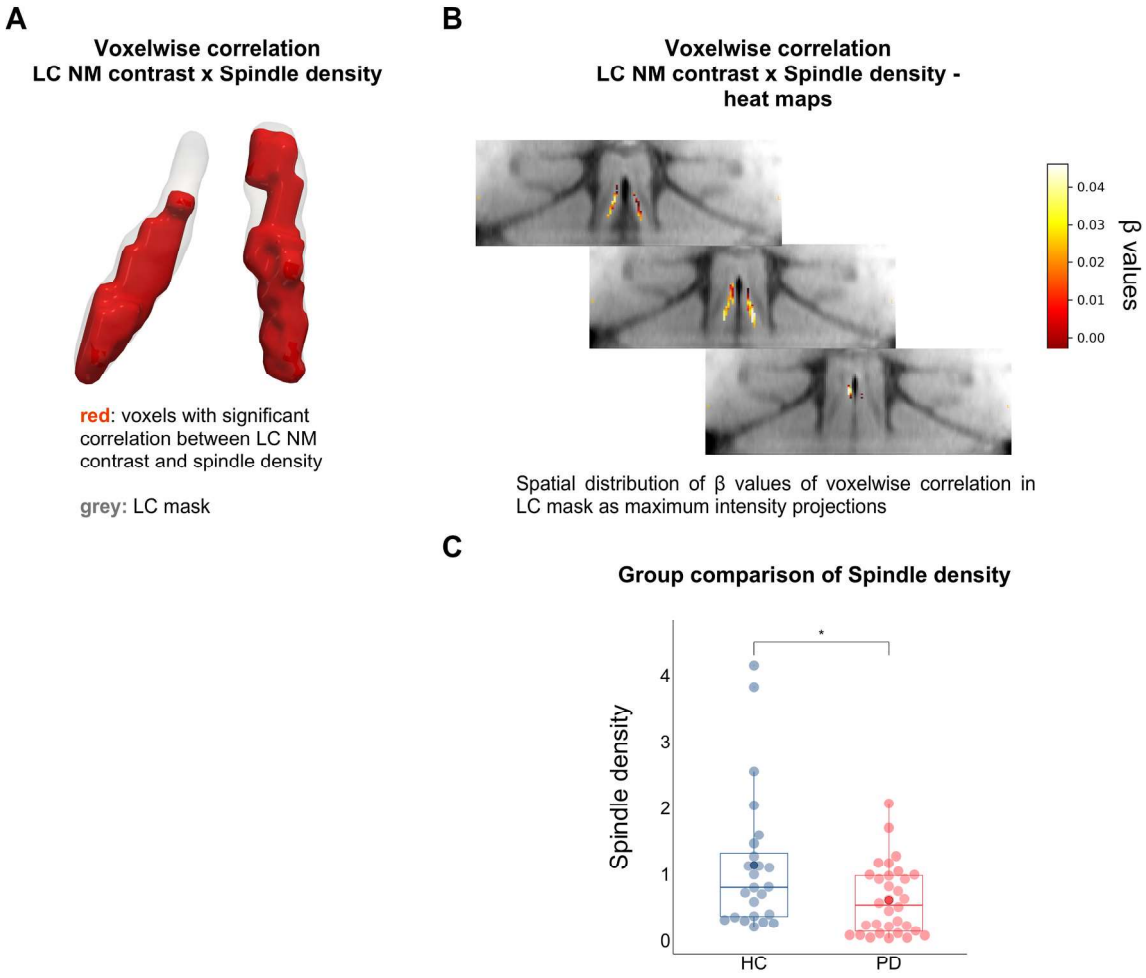

Fig. 1. Voxelwise correlations between spindle density and locus coeruleus (LC) neuromelanin (NM) contrast (A). Spatial distribution of β values for the correlation analysis as maximum intensity projections (B). Group differences between Parkinson's disease (PD) patients and healthy controls (HC) in spindle density (C). The LC mask is depicted in grey; significant voxels (according to threshold-free cluster enhancement (TFCE) statistics with 5000 permutations and after FDR correction) are shown in red (A). For illustrative purposes both statistical maps were resampled to a voxel size of 0.25 mm^3 isotropic and binarized. The left LC is shown on the left side of the image. Spindle density (derived from EEG electrodes C3/C4 during sleep stage N2) is reduced in PD patients (red dots) compared to HC (blue dots) (C). Mean values are depicted as singular dots with higher saturation (*$p < 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The noradrenergic system also plays a crucial role in regulating non-REM sleep [31,32] and glymphatic clearance [54]. During sleep, activation of the LC is significantly reduced [55–57] and mediates awakening upon sensory stimuli [58,59]. However, even during non-REM sleep, a tonic firing pattern of the LC persists [55]. Changes in LC activity are important for forming sleep spindles in rats [60]. Animal studies in mice showed that these changes are involved in infraslow oscillations, which alternate between periods of consolidated sleep (rich in sleep spindles) and vigilant sleep [31]. The integrity of the LC is a determining factor in sleep microarchitecture [61–63] and may, therefore, be considered the underlying pathomechanism for the observed reduction in spindle density in our sample. For cognition, the noradrenergic system is considered essential [21], and consequently, LC degeneration, impacting the primary source of noradrenaline in the brain, is associated with cognitive deficits in PD and Alzheimer's disease (AD) [24,26,64].

A recent study in AD reported a correlation between LC contrast and slow-wave activity [65], which contrasts with our findings in PD. This discrepancy may reflect the distinct pathophysiological trajectories of these two neurodegenerative disorders. In AD, degeneration of the LC has been shown to precede and predict cortical tau accumulation, even during presymptomatic stages [66,67]. The subsequent development of cortical tau pathology may directly disrupt cortical regions involved in slow-wave generation. In PD, by contrast, the LC is typically affected early by α-synuclein pathology, prior to the spread of pathology to cortical regions [68]. Consequently, the alterations in slow-wave activity observed in our sample may be caused by mechanisms that are, at least in part, independent of cortical neurodegeneration.

Additionally, sample-specific factors may have contributed to the observed discrepancy. In particular, a substantial proportion of participants with MCI or dementia due to AD were taking sleep medication and/or antidepressants, both of which may influence sleep architecture.

Another important consideration is the differential spatial pattern of LC degeneration in AD and PD. In AD, neuronal loss is most pronounced in the rostral part of the LC [25], whereas in PD, degeneration appears to primarily affect more caudal regions [48]. Given the functional heterogeneity of LC neuronal subpopulations and their distinct projection patterns, such region-specific vulnerability may differentially impact sleep microarchitecture.

In contrast, our findings in PD indicate that reductions in sleep spindle density may represent a more direct and specific correlate of noradrenergic dysfunction. Together, these results suggest that although the LC constitutes an early site of neurodegenerative change in both conditions, its functional consequences for sleep microarchitecture are likely to be disease-specific.

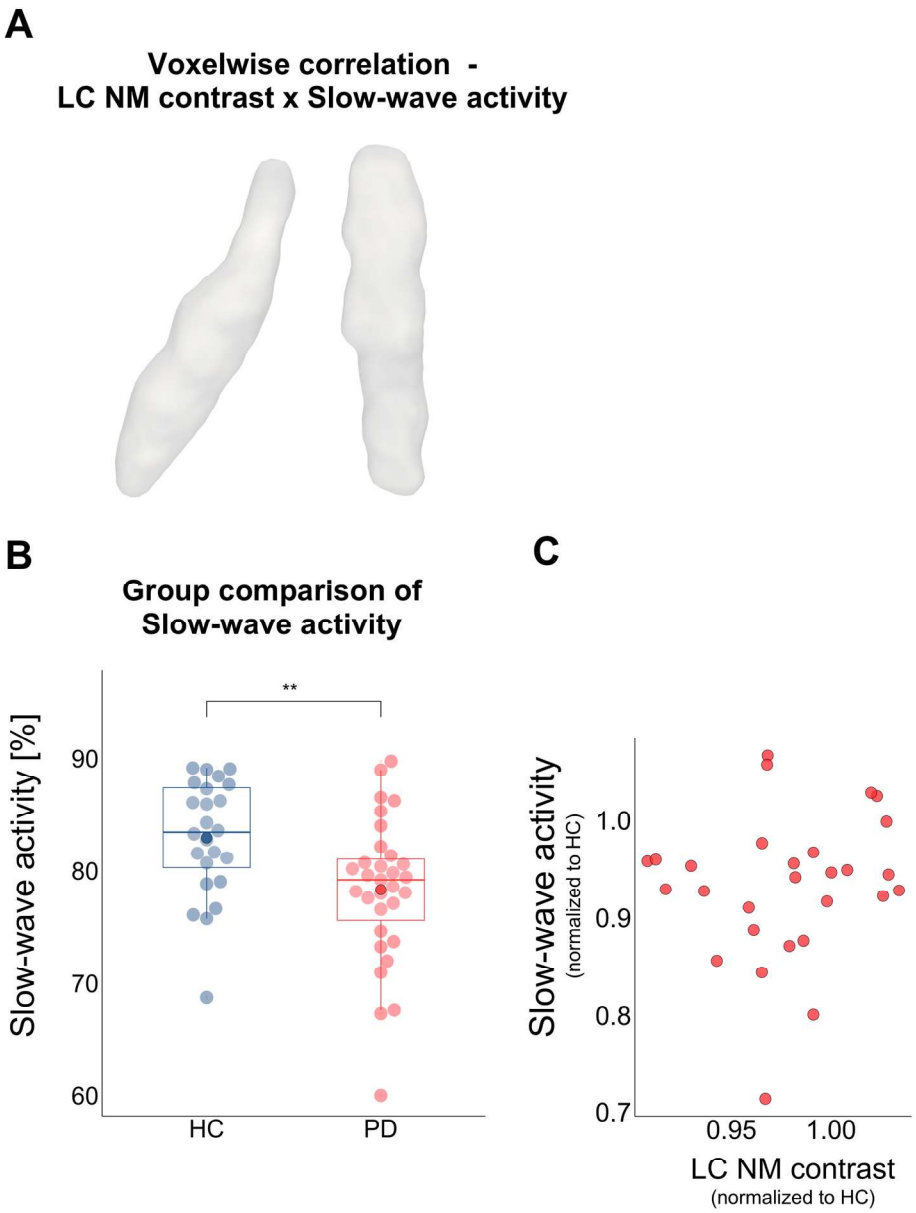

Fig. 2. Voxelwise correlations between slow-wave activity and locus coeruleus (LC) neuromelanin (NM) contrast (A). Group differences between Parkinson's disease (PD) patients and healthy controls (HC) in slow-wave activity (B). Scatterplot showing LC NM contrast and slow-wave activity of PD patients, normalized to the mean value of HC (C).
The LC mask is depicted in grey; significant voxels (according to threshold-free cluster enhancement (TFCE) statistics with 5000 permutations and after FDR correction) are shown in red (A). For illustrative purposes both statistical maps were resampled to a voxel size of 0.25 mm^3 isotropic and binarized. The left LC is shown on the left side of the image.
Slow-wave activity (derived from EEG electrodes F3/F4 and normalized to total spectral power, D) is reduced in PD patients (red dots) compared to HC (blue dots) (B). Mean values are depicted as singular dots with higher saturation (**$p < 0.01$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

While animal models involving ablation of the LC have demonstrated a subsequent reduction in slow-wave activity [69], our findings in PD patients did not show a direct correlation between LC neuromelanin contrast and slow-wave activity. This discrepancy may be explained by the underlying pathomechanisms. In contrast to the near-total loss of noradrenaline after LC ablation, PD involves a gradual, progressive degeneration of the LC. In this context, sleep spindles may be more susceptible to early-stage noradrenergic deterioration than the broader mechanisms generating slow-wave activity. Furthermore, the reduction in slow-wave activity observed in our PD cohort could be driven by multifaceted pathologies beyond the noradrenergic system, such as thalamocortical dysfunction, which may mask a specific LC-SWA correlation in this clinical population.

It is important to note that our study focused on sleep micro-architecture during unperturbed, overnight polysomnography. Previous research has shown that LC activation in mice can lead to a decline in slow-wave activity [59,60,70]. By measuring steady-state sleep parameters, we demonstrated that spindle density - but not slow-wave activity - is specifically associated with LC integrity in a standard sleep environment. However, future longitudinal studies are warranted to investigate whether the LC's role in slow-wave activity becomes more apparent when the system is under high homeostatic pressure, such as following prolonged wakefulness. Such research could clarify if PD patients exhibit an impaired rebound of slow-wave activity despite the lack

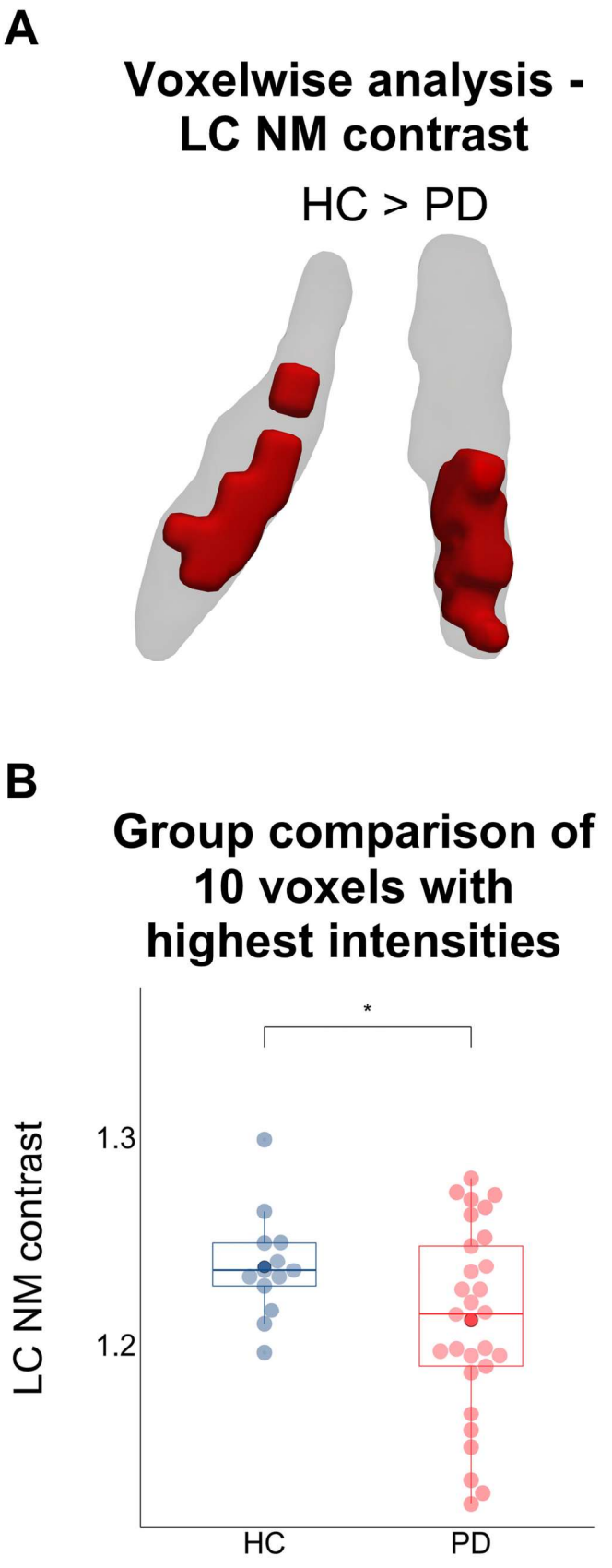

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Fig. 3. Group differences between Parkinson's disease (PD) patients and healthy controls (HC) in locus coeruleus (LC) neuromelanin (NM) contrast (as derived from voxelwise analysis (A) and extraction of the mean value of the 10 voxels with the highest intensities (B)). The LC mask is depicted in grey: significant voxels (according to threshold-free cluster enhancement (TFCE) statistics with 5000 permutations and after FDR correction) are shown in red (A). For illustrative purposes both statistical maps were resampled to a voxel size of 0.25 mm^3 isotropic and binarized. The left LC is shown on the left side of the image. Mean values are depicted as singular dots with higher saturation (B) (*$p < 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

of correlation in unperturbed sleep.

To our knowledge, we provide the first evidence of an association between LC degeneration and reduced sleep spindle density in humans. Taken together with the evidence on the link between noradrenergic dysfunction and cognitive deficits and data from animal studies [61], we hypothesize that the LC mediates between microsleep changes and cognition.

Our data's cross-sectional nature limits our study's conclusion. Longitudinal data on changes in microsleep parameters and in-depth neuropsychological testing during disease progression are warranted to provide further evidence for the association with noradrenergic dysfunction.

In spindle detection, manual scoring is considered the gold standard. However, this approach is highly time-consuming and only yields moderate inter-rater variability [71]. Automatic spindle scoring systems are available, but they mostly rely on detecting the specific physical features of spindles, such as amplitude and frequency [72]. In recent years, artificial intelligence techniques using neural networks have been shown to perform better than feature-based methods for event detection [73]. In this study, we used a recently proposed advanced spindle detection algorithm, SUMO (Slim U-Net trained on MODA), which is based on a deep neural network model [43]. SUMO outperformed available conventional algorithms and the majority of experts in the largest available manually scored dataset on spindles, MODA (Massive Online Data Annotation) [74]. Thus, our data suggest that automatic spindle detection based on deep learning is feasible even in PD patients and may be superior to conventional algorithms.

In conclusion, we observed an association between microsleep parameters and degeneration of the locus coeruleus in PD patients. Further studies are warranted to investigate if noradrenergic dysfunction is causal for impaired sleep microarchitecture and whether this association is related to cognitive decline in PD and other neurodegenerative diseases, such as Alzheimer's disease.

CRediT authorship contribution statement

Christopher E.J. Doppler: Writing – original draft, Visualization, Project administration, Investigation, Formal analysis, Data curation. **Nora Sembowski:** Investigation. **Dean Plottka:** Software, Formal analysis. **Maximilian Hommelsen:** Software, Formal analysis. **Sinah Röttgen:** Investigation. **Justus T.C. Schwabedal:** Software. **Simon J. Schreiner:** Writing – review & editing, Methodology. **Gereon R. Fink:** Writing – review & editing, Resources, Funding acquisition. **Per Borghammer:** Writing – review & editing, Resources. **Stephan Bialonski:** Writing – review & editing, Supervision, Software, Resources, Methodology, Formal analysis. **Michael Sommerauer:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Preprint respositories

A preprint version of this manuscript is available on medRxiv (https://doi.org/10.1101/2025.04.06.25325309).

Declaration of competing interest

The authors have no conflict of interest to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2026.108339.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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