MOVEMENT DISORDERS AND SLEEP – UNDERLYING MECHANISMS, CLINICAL ASPECTS AND TREATMENT

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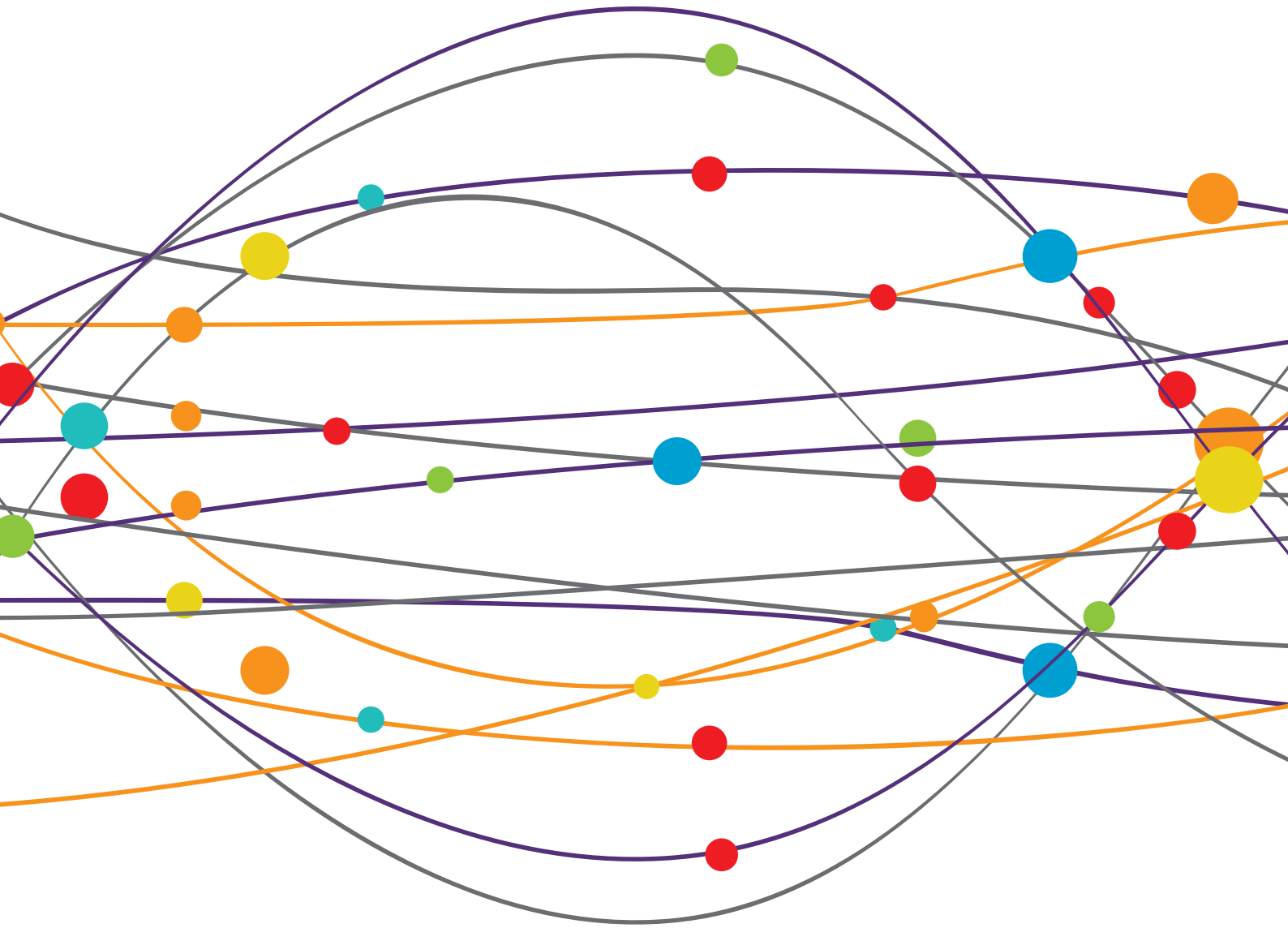

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MOVEMENT DISORDERS AND SLEEP – UNDERLYING MECHANISMS, CLINICAL ASPECTS AND TREATMENT

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EDITORIAL
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Editorial: Movement Disorders and Sleep – Underlying Mechanisms, Clinical Aspects and Treatment

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Editorial on the Research Topic

Movement Disorders and Sleep – Underlying Mechanisms, Clinical Aspects and Treatment

Nocturnal sleep dysfunction is a key problem in many movement disorders and one of the major non-motor symptoms in Parkinson's disease (PD) the world's fastest growing neurodegenerative disorder with consequences during waking hours at daytime as well as daily functioning (1). In PD for example, sleep dysfunction such as nocturnal waking and daytime somnolence was recognized by James Parkinson himself and continues to be a clinical challenge given the problems arise from the motor problems at night, neurotransmitter driven alterations in sleep architecture as well as drug related effects (2, 3). Non-motor endophenotypes of PD have been recognized and serotonergic dysfunction for instance in the raphe and limbic areas could drive aspects of sleep dysfunction in PD and some other related neurodegeneration (4).

In this special edition of the Frontiers in Neurology, sleep dysfunction in Movement Disorders is addressed focusing on possible pathophysiological mechanisms, clinical aspects of recognition, and awareness and treatment. Yousaf et al. provide a narrative review of the various types of molecular, structural, and functional neuroimaging techniques such as magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET) that have been explored to provide evidence base for assessing structural, functional and neurochemical correlates of sleep disturbances in PD and other movement disorders such as Huntington's disease and Multiple system atrophy. These data might eventually lead to new drug discovery or repurposing of existing molecules to treat aspects of sleep dysfunction, currently a key unmet need.

Excessive daytime sleepiness (EDS) can be a disabling problem in PD, particularly in the more advanced stages although EDS is also recognized as a prodromal feature of PD and present all through the various clinical stages of PD (5, 6). In some the problem may even result in a clinical syndrome resembling narcolepsy without cataplexy with functional consequences such as sudden onset sleep episodes during driving which can be precipitated by some dopaminergic drugs (7). Biomarkers to detect this variant within PD is therefore, important and Ashraf-Ganjouei et al. describe a Diffusion MRI connectometry study in PD patients with EDS vs. those without and report decreased MRI based connectivity in the left and right fornix, left and right inferior longitudinal fasciculus (ILF), left inferior and middle cerebellar peduncles. Sherbaf et al. describe another diffusion MRI connectometry study in RBD as well as depression, a prodromal NMS, in 93 treatment-naïve and non-demented early PD and report that these two non-motor symptoms may be associated with lower connectivity in several white matter tracts with involvement of short association fibers (U-fibers).

Prodromal and pre prodromal stages of PD are emerging as key areas where early treatment initiation may be a priority and REM sleep behavior disorder (RBD) is a clinical biomarker for the

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development of α-synucleinopathies as well as a predictor of early cognitive decline (8). Excessive daytime sleepiness (EDS) can also be a prodromal non-motor symptom of PD. Gjerstad et al. address these two key sleep related symptoms in PD and discuss the implications in early stages of PD as well as the regulators of gene expression and core clock genes such as CLOCK and ARNTL (BMAL1) and the potential association of dopaminergic therapies and circadian genetic markers in PD.

Clinical assessment of sleep dysfunction is crucial for assessing the problem, addressing efficacy of treatment as well as providing validated outcomes for value based healthcare and in several papers, Rodríguez-Blázquez et al., Kurtis et al., and Skorvanek et al. discuss the roles, clinimetrics as well as application potential of clinical scales used to assess sleep dysfunction in PD and other movement disorders. Bhidayasiri et al. report an international study between Thailand, Japan, and India where they report on the utility of a PD Home Safety Questionnaire and discuss implications for adaptations based on a novel concept of concept of Personal (P)-Environmental (E) fit. Restless Legs Syndrome (RLS) often complicate sleep in PD and a link between the two conditions remain viable yet controversial. This issue is discussed by Ferrini-Strambi et al. who argue the case for well-designed systematic and strongly controlled longitudinal studies to clarify the aforesaid relationship.

Wearable sensors and the use of digital technology has become a topic of major research and clinical interest in the field of movement disorders. Sleep has been an increasing focus of research in this field and Madrid-Navarro et al. provide an interesting cross-sectional study using a wrist-worn device combined with machine-learning so as to process and detect circadian rhythms of sleep, motor, and autonomic disruption in PD providing an index to multidimensional circadian monitoring.

Advanced therapies in PD have now been shown to have beneficial or occasionally disruptive effects on sleep in PD. Sharma et al. review the role of deep brain stimulation at different anatomical targets which may affect the sleep-wake cycle via multiple factors, including motor symptoms, medication adjustment, and direct modulation of sleep-wake centers in PD.

This edition of the special Research Topic addressing sleep dysfunction in movement disorders therefore, present a series of cutting edge papers with original research data including neuroimaging and other biomarkers as well as reviews spanning clinical aspects of sleep dysfunction in PD and other movement disorders including RLS. We hope that the frontiers in sleep research in movement disorders would be facilitated by work presented in this special edition.

AUTHOR CONTRIBUTIONS

KR drafted and revised the manuscript for intellectual content. CF-P and NT revised the manuscript for intellectual content.

REFERENCES

1. Ray Chaudhuri K, Titova N. Societal burden and persisting unmet needs of Parkinson's disease. *Eur Neurol Rev*. (2019) 14:3–9. doi: 10.17925/ENR.2019.14.1.28
2. Parkinson J. An Essay on the Shaking Palsy. 1817. *J Neuropsychiatry Clin Neurosci*. (2002) 14:223–36; discussion 222. doi: 10.1176/jnp.14.2.223
3. Falup-Pecurariu C, Diaconu Ş. Sleep dysfunction in Parkinson's disease. *Int Rev Neurobiol*. (2017) 133:719–42. doi: 10.1016/bs.irn.2017.05.033
4. Titova N, Padmakumar C, Lewis SJG, Chaudhuri KR. Parkinson's: a syndrome rather than a disease? *J Neural Transm*. (2017) 124:907–14. doi: 10.1007/s00702-016-1667-6
5. Chaudhuri, KR, Healy DG, Schapira AHV. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol*. (2006) 5:235–45. doi: 10.1016/S1474-4422(06)70373-8
6. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's Disease. *Mov Disord*. (2015) 30:1600–11. doi: 10.1002/mds.26431
7. Ylikoski A, Martikainen K, Sarkanen T, Partinen M. Parkinson's disease and narcolepsy-like symptoms. *Sleep Med*. (2015) 16:540–4. doi: 10.1016/j.sleep.2014.12.010
8. Siderowf A, Lang A. Premotor Parkinson's disease: concepts and definitions. *Mov Disord*. (2012) 27:608–16. doi: 10.1002/mds.24954

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ORIGINAL RESEARCH
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Multidimensional Circadian Monitoring by Wearable Biosensors in Parkinson's Disease

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Parkinson's disease (PD) is associated with several non-motor symptoms that may precede the diagnosis and constitute a major source of frailty in this population. The digital era in health care has open up new prospects to move forward from the qualitative and subjective scoring for PD with the use of new wearable biosensors that enable frequent quantitative, reliable, repeatable, and multidimensional measurements to be made with minimal discomfort and inconvenience for patients. A cross-sectional study was conducted to test a wrist-worn device combined with machine-learning processing to detect circadian rhythms of sleep, motor, and autonomic disruption, which can be suitable for the objective and non-invasive evaluation of PD patients. Wrist skin temperature, motor acceleration, time in movement, hand position, light exposure, and sleep rhythms were continuously measured in 12 PD patients and 12 age-matched healthy controls for seven consecutive days using an ambulatory circadian monitoring device (ACM). Our study demonstrates that a multichannel ACM device collects reliable and complementary information from motor (acceleration and time in movement) and common non-motor (sleep and skin temperature rhythms) features frequently disrupted in PD. Acceleration during the daytime (as indicative of motor impairment), time in movement during sleep (representative of fragmented sleep) and their ratio (A/T) are the best indexes to objectively characterize the most common symptoms of PD, allowing for a reliable and easy scoring method to evaluate patients. Chronodisruption score, measured by the integrative algorithm known as the circadian function index is directly linked to a low A/T score. Our work attempts to implement innovative technologies based on wearable, multisensor, objective, and easy-to-use devices, to quantify PD circadian rhythms in huge populations over extended periods of time, while controlling at the same time exposure to exogenous circadian synchronizers.

Keywords: Parkinson's disease, non-motor symptoms, sleep, wearable, circadian rhythms, wrist temperature, machine learning

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INTRODUCTION

Advances in sleep and circadian monitoring over the last 20 years have been limited in part by the lack of availability of objective tools capable of quantifying sleep and circadian function in a continuous, simple, and non-invasive manner. The development of wearable multisensor devices and mathematical procedures for big data processing to accurately quantify sleep and circadian disruption (CD) is taking on an important role in personalized medicine by detecting healthy living habits

and helping to diagnose and treat several pathologies, including Parkinson's disease (PD) (1).

Sleep–wake rhythm and circadian system status are currently analyzed by actimetry, combined with specific algorithms to determine the timing and intensity of movements, which are used to infer sleep parameters. This procedure can be useful to detect circadian sleep disorders, but cannot determine sleep and circadian disorders accurately due to the low specificity of actimetry to detect immobile wake states while laying in bed and the high influence of external conditions and volition itself (2). In addition to actimetry, newer techniques being developed include wrist temperature (WT) and light exposure sensors to measure daily fluctuations in sleep propensity, environmental synchronization and autonomic balance (3–5).

While the core body temperature falls before going to sleep and begins to rise in anticipation of waking up, skin temperature increases prior to bedtime and drops just after awakening, in close association with vasomotor skin tone under autonomic control (3–6). In fact, WT combined with actimetry have been validated in both healthy subjects and patients with sleep pathologies against sleep logs (3) and PSG (7), respectively, to determine sleep and CD under normal living conditions. Validation studies have also demonstrated a close association between evening WT increase and dim light melatonin onset (DLMO), suggesting that this rhythm can be a simpler way of measuring circadian phase than melatonin quantification (4). Furthermore, the WT rhythm has a high endogenous component and it is under genetic influence (8, 9), reflects sleep propensity (6, 10), and is also important for the dipping pattern of blood pressure (11).

Parkinson's disease is a common neurodegenerative disorder characterized by motor symptoms including tremors, rigidity, postural instability, and bradykinesia. However, it is accompanied or preceded by non-motor symptoms that can constitute a major source of frailty in this population (12). Sleep–wake disturbances in PD is one the most frequent and disabling non-motor symptoms (13) and can be secondary to several factors: reemerging motor symptoms during the night, mood disorders, medication, nocturia, parasomnias, and REM sleep behavior disorder (RBD); but it can also be due to direct circadian rhythm disruption caused by the neurodegeneration itself. The suprachiasmatic nucleus seems to be relatively intact in PD, but its neural pathways and the surrounding hypothalamus are more affected (14, 15). Furthermore, in early patients with PD, there is evidence for alterations in melatonin levels and in the expression of molecular clock genes (16). Other signs of circadian impairment in PD are a non-dipping pattern in arterial blood pressure and core body temperature rhythm impairment (17, 18).

This combination of motor and non-motor symptoms, the peculiarity of clinical manifestations for each PD patient, disease evolution and treatment effectiveness assessment make personalization a must, and multisensor devices based on ambulatory circadian monitoring techniques thus constitute a unique tool to bring e-health closer to this group.

Ambulatory circadian monitoring (ACM), a procedure proposed by Ortiz-Tudela et al. (3), is supported by wearable technology which combines four categories of variables useful for tracking complex neurological pathologies such as PD, since:

(1) wrist temperature rhythm is expected to be impaired in PD, as there is an abnormal thermoregulation in the distal skin, with an impaired vasoconstriction response to adrenergic stimulus (19, 20), as well as alterations in normal blood pressure pattern dipping (11).
(2) motor-related variables (integrated acceleration, time in movement and static hand position), indicate both wake states and cardinal motor symptoms of PD disease, and are more dependent on the subject's habits than they are on the circadian clock. They exhibit a lower genetic influence than the temperature rhythm (8).
(3) hand position variability. This indicates changes in body posture when the patient is lying in bed, which could become impaired along with the evolution of PD.
(4) exposure to light, the main circadian synchronizer (21), exposure can also counteract some circadian and motor symptoms in PD (22).

By combining these major and subrogate variables implemented in a ACM device, clinicians and researchers can have access to an immediate map of motor, autonomic and sleep circadian rhythms, which are useful for improving research, clinical diagnoses and treatment in patients with PD.

Considering how quality of life is affected in PD, there is an urgent need to develop and validate wearable technologies to make e-health available to this population of patients, and objectively track sleep, motor, autonomic disruption, and lifestyle habits. Thus, the aim of this work is to test a wrist-worn device for ACM, intended to personalize the evaluation of the multiple symptoms that manifest in neurodegenerative diseases, such as PD.

MATERIALS AND METHODS

Study Population

A cross-sectional study was undertaken with 24 adult volunteers: 12 patients with PD, who meet the diagnostic criteria according to the UK Brain Bank (PD group) and 12 healthy controls, who match the same demographic characteristics (control group). PD patients were selected by convenience sampling from among those who attended the Movement Disorders Unit of the Hospital Universitario Virgen de las Nieves, Granada (HUVN). Controls were recruited from among healthy non-complainers who were the relatives of students from the University of Murcia. Both groups were encouraged to maintain their normal life style during the week of study and were monitored under free-living conditions. All participants received appropriate information about the study and signed an informed consent form before their inclusion. The study was approved by the Ethics Committee of the University of Murcia and HUVN. All subjects gave written informed consent in accordance with the Declaration of Helsinki. One patient was longitudinally recorded three times, before, 1 week after, and 6 months after starting, using levodopa-carbidopa intestinal gel (LCIG) therapy, an effective treatment for advanced PD.

All patients were treated with L-dopa and/or dopaminergic agonists. Exclusion criteria were: diagnosis of dementia or severe psychiatric co-morbidity, fever, or infection in the previous 2 weeks, current smoking habit or alcohol abuse, diagnosis of diabetes mellitus for ≥10 years or undergoing insulin treatment for ≥5 years, clinical polyneuropathy, endocrinopathies (thyroidopathies or suprarenal gland diseases), arterial disease (Raynaud's, thoracic outlet syndrome), treatment with medications for excessive daytime sleepiness (i.e., modafinil), treatment with adrenergic agonist/blockers, or a connective tissue disease that could affect skin temperature. None of the patients were shift workers or engaged in transmeridian travel during the previous month. The same exclusion criteria were applied to the control group, in addition to meeting criteria for mood disorders, anything more than mild symptoms on any depression scale and psychopharmacological drugs use.

Trained interviewers assessed the severity of PD according to the Hoehn and Yahr stage. The patients' clinical disability was assessed according to the Unified Parkinson's Disease Rating Scale (UPDRS) and subscales. PD patients also completed non-motor and sleep assessments using the second version of the Parkinson's Disease Sleep Scale (PDSS-2), and the Parkinson's Disease Questionnaire. Subjects in both groups completed the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale. The Levodopa equivalent dose (LED) was determined in PD patients using standardized protocols.

Ambulatory Circadian Monitoring Device

A small, watch-like device for Ambulatory Circadian Monitoring, "Kronowise 3.0" (Kronohealth SL, Spain, **Figure 1**), was placed on the less affected hand in PD patients or the non-dominant hand in controls, in order to reduce possible masking by motor

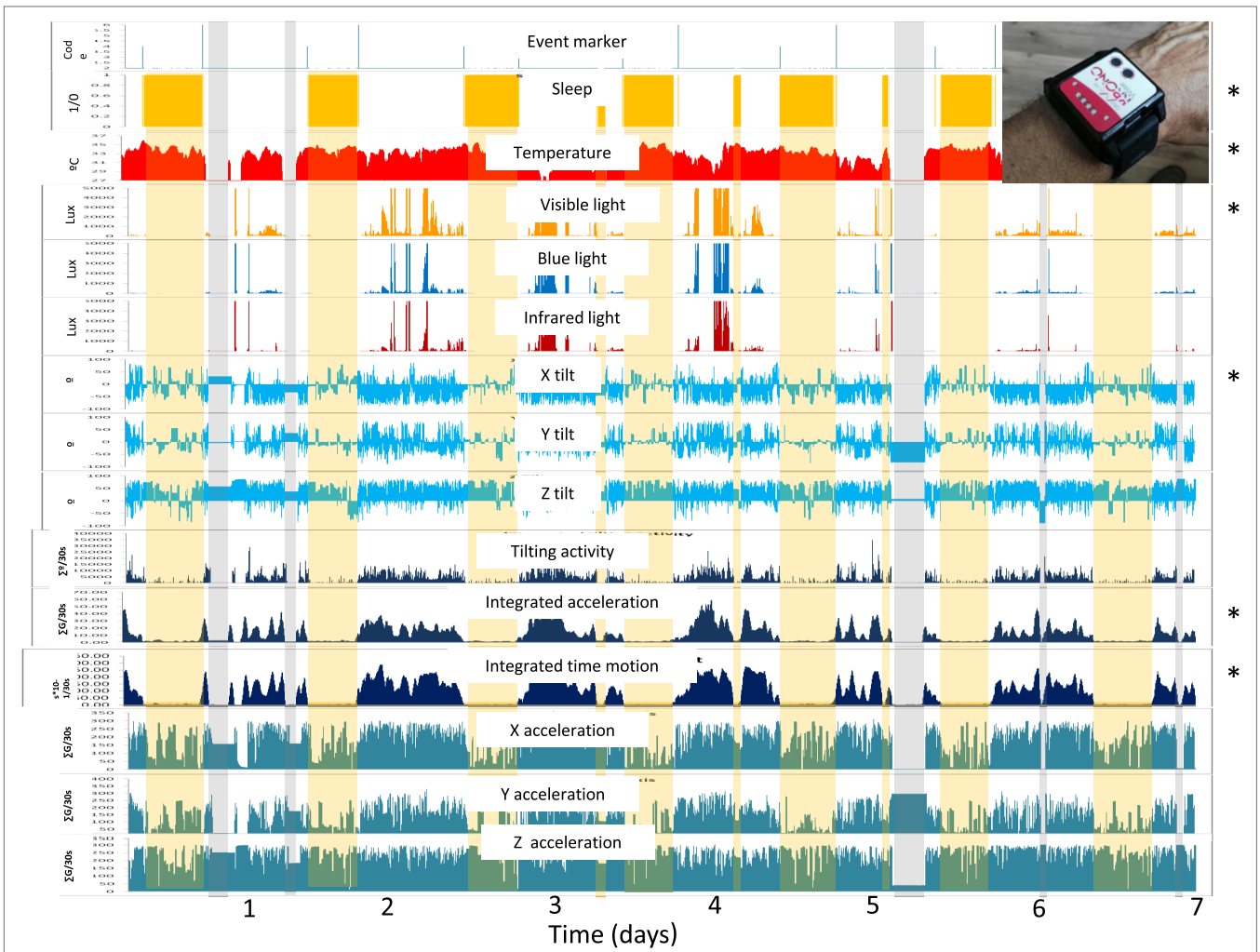

FIGURE 1 | Overview of the fifteen variables recorded during a full week by the ACM device on the wrist of a Parkinson's disease patient, as processed by Kronoware 10.0 software (Kronohealth SL). From top to bottom: events; sleep (orange bars); skin temperature (red) in °C; visible, blue, and infrared light (orange, blue and red) in luxes; three axis tilt (blue) °/epoch; integrated tilting changes, acceleration and time in movement (dark blue); and partial acceleration of each axis (green). Gray bars indicate "time off" from wearing the device while the yellow bar represents the inferred sleep periods. Asterisks indicate variables selected for the circadian and sleep characterization of Parkinson's disease patients.

activity on circadian variables. Wrist skin temperature, triaxial motor acceleration, wrist posture, light exposure in three spectral bands (visible, blue of 460–490 nm and infrared, >800 nm) and an electronic log (event marker) were continuously recorded at 10 (acceleration), 1 (skin temperature and light exposure), or 0.033 Hz (1 reading per epoch) for wrist position. The data were then processed and saved into 30 s epochs for 1 week. A total of 23,000,000 of raw data were internally recorded and processed, and 230,000 of them saved in a txt file for further analysis.

The Kronowise 3.0 device is provided with:

(1) a temperature sensor, with a precision of ± 0.1°C at 25°C and a resolution of 0.0635°C, housed in a separate chamber to avoid thermal interference from the battery and electronic components, with a metal plate in contact with the skin.
(2) A triaxial calibrated MEMS-accelerometer with a linear and equal sensitivity along the three axes, with a range of ± 2 g and a sensitivity of 0.001 g. The *y* axis of the device was aligned with the long axis of the radius; the *x*-axis corresponds to the radial–ulnar axis and the *z*-axis to the palmar–dorsal axis. The default sampling frequency was set at 10 Hz. From the accelerometer output, a total of five groups of motor-related variables were recorded: (a) tilt of the *x*, *y*, and *z*-axis, as the angle between each axis and the horizontal plane, expressed in °, which allows posture changes to be determined during conditions of immobility (i.e., sleep); (b) the sum of the degrees of change between the current and previous axis position; (c) the area under the curve, integrating the composite acceleration values per epoch; this variable indicates movement velocity and strength, but not the duration or frequency; (d) time in movement, as the cumulative time above a very low threshold (0.05 g) in periods of 0.1 s, in which a movement on any of three axis was detected; (e) the area under the curve for individual *x*, *y*, and *z* acceleration, in order to discriminate among types of motor activity (i.e., walking, running, typing, etc.).
(3) Three light sensors, on the front, determine visible, infrared, and blue light, with a range of between 0.01 and 43,000 lux, 16 bits of resolution, an internal auto-setting according to the luminance level, and suppression of flicker at 50/60 Hz. The infrared sensor was sensible to radiation from 800 to 1,070 nm, whereas the blue light detector was equipped with a Gaussian filter, which eliminates all visible radiation below 440 and over 500 nm. These wavelengths match the sensitivity of melanopsin retinal ganglion cells (460–480 nm). The infrared/visible light ratio makes it possible to determine the light source (i.e., natural, fluorescent, infrared, incandescent, or LED light).

Communication with the ACM device was established using Kronoware 10.0 software (Kronohealth SL, Spain) *via* a USB port. This software allows visual inspection before analysis to eliminate artifacts and the calculation of basic circadian and sleep parameters. Four calibrated Kronowise devices were used in this study, with minimal differences in recorded variables between them (coefficient of variation < 4%). Data were converted into a text file to be analyzed by the chronobiological software "Circadianware," implemented on the on-line Kronowizard platform (https://kronowizard.um.es/, University of Murcia).

From the data provided by the ACM device, we selected the following variables (**Figure 1**):

(a) wrist skin temperature (WT) (as a variable representative of autonomic balance at the skin vessel level).
(b) tilt of the *x*-axis, which oscillates between 0 for maximum horizontality, and 90 for maximum verticality.
(c) acceleration of movement.
(d) time in movement, calculated as the time, in periods of 0.1 s, in which a movement on any of three axes was detected. This information is particularly useful to discriminate between sleep and wake states.
(e) visible light exposure, to determine the intensity and timing of the main synchronizing input to the circadian system.

Data Analysis

To characterize the circadian pattern, a non-parametric analysis was performed as previously described (3, 6), including:

– interdaily stability (IS) over different days. This varies between 0 for Gaussian noise and 1 for perfect stability, where the rhythm repeats itself exactly, day after day.
– intradaily variability (IV), which indicates rhythm fragmentation; its values oscillate between 0 (when the variable is unfragmented) and 2 (Gaussian noise).
– the mean value and timing of the ten consecutive hours with the lowest values (L10V and L10T, respectively) of WT and sleep probability, and the mean value and timing of the 10 consecutive hours with the highest values (M10V and M10T, respectively) of acceleration, time in movement and light exposure. All these indexes score the extent of activation during the day.
– The mean value and timing of the five consecutive hours with the lowest values (L5V and L5T, respectively) of acceleration, time in movement and light exposure, and the mean value and timing of the five consecutive hours with the highest values (M5V and M5T, respectively) of WT and sleep probability. All these indexes score the restfulness of the sleep period.
– Relative amplitude (RA) refers to the difference between VM10 and VL5, divided by the difference between the two extreme percentiles, Pc95th M10V- Pc5th L5V for acceleration, time in movement and light exposure, with the percentiles extracted from a population of 90 healthy adults enrolled and using the KW3 device (https://kronowizard.um.es/, University of Murcia). The reference values for acceleration were: 40 and 1 for the 95th and 5th percentiles, respectively; 200 and 2 for time in movement; and 3 and 0 for light (log lux). Reference values were rounded to the upper and lower integer for the Pc95th and Pc5th, respectively. Since skin temperature and sleep probability exhibit an inverse pattern to that of motor activity and light exposure, their RA was referred to the difference between M5V and L10V, considering the 95th percentile for M5V and the 5th percentile for L10V (M5V-L10V)/(Pc95th M5V-Pc5th L10V). In this case, the reference values for skin temperature

were 35–30° C and 1 and 0 for sleep probability, at the 95th and 5th percentiles, respectively.
– The M10V acceleration/L5V time in movement (A/T) ratio.

Circadian Function Index (CFI)

Circadian function index was calculated to provide general information about the robustness of the circadian system status of an individual (3). It is computed as the average of IS, IV, and RA, but IV values are previously inverted and normalized between 0 and 1. Thus, a CFI close to 1 indicates a high amplitude, non-fragmented and stable rhythm.

Sleep Detection

To automatically detect sleep and wake periods, the TAP algorithm (3) was calculated using the Kronowizard website (https://kronowizard.um.es/, University of Murcia). As described by Ortiz-Tudela et al. (3), the TAP algorithm is based on the intra-subject normalization of three signals: wrist skin temperature, time of movement and variability of the *x*-axis tilt per epoch. Since the skin temperature rhythm is the inverse of that for motor activity and position variability, WT was reversed, and thus the maximum of the three daytime variables was considered. The arithmetic mean of the three normalized variables was then calculated in such a way that a 0 value indicated complete rest (sleep), while 1 corresponded to wakefulness and movement. An epoch was scored as sleep when TAP was under a default threshold, previously validated by PSG (7).

Weekly actograms were generated for all variables studied, as well as mean waveforms for every subject and group.

Statistical Analysis

Data were processed using Microsoft Office Excel 2007. Circadian parameters and PD rating and sleep scales were tested for normal distribution using the Shapiro–Wilk test. All circadian parameters were normally distributed except the ratio A/T. Statistical analyzes (repeated measures ANOVA followed by *post hoc* Bonferroni comparisons for paired samples and correlation analysis using the Pearson's correlation for normally distributed values and Spearman for not normally distributed values) were performed using SPSS v20.0 (SPSS, Inc. Chicago, IL, USA). Spearman correlations were applied for associations between A/T ratio and CFI score. Bonferroni adjustment was used to set alpha to 0.008 (0.05/6) for multiple comparison correction. Pearson correlations were used to evaluate the association between motor acceleration during daytime (M10V) and PD rating and sleep quality scales. Again, Bonferroni correction was used and alpha set to 0.008. To graphically describe data from PD and control subjects, the Box and Whisker plot method was employed, with the aid of Orange Canvas© software [University of Ljubljana, Slovenia; (23)]. All data were expressed as mean ± SEM.

Machine-Learning Analysis

All subjects included in our study were classified into PD or C classes using circadian and sleep parameters and by means of machine-learning analysis. This analysis was carried out using the Orange Canvas© software [University of Ljubljana, Slovenia; (23)].

Attribute selection was guided by the expert criterion of including indexes that provide complementary information to one another. Therefore, we aimed to select indexes representative of motor activity and sleep quality. This selection was performed according to the criterion of Information Gain (based on entropy reduction) statistics.

The discretization method used in our study was the Minimum Description Length (24). This is a top-down technique than recursively splits the attribute maximizing information gain, until the point where a new split would not add any new information to the predictions.

The model was evaluated through 10-fold cross-validation, calculating the sensitivity, specificity, accuracy, F1 score and ROC curve for PD discrimination.

RESULTS

The characteristics of the patients included in the PD group are detailed in **Table 1**, with ages ranging from 44 to 78 years, and no significant differences in age or gender as compared to the control group. The mean disease duration in the PD group was

TABLE 1 | Participant's characteristics.

Characteristics	Parkinson's disease (n = 12)	Controls (n = 12)
Age (years), mean ± SEM	65.83 ± 2.67	59.41 ± 1.9
Range	54–78	(p = 0.062) 53–72
Sex (F/M)	3/9	3/9
BMI, mean ± SEM	27.26 ± 0.57	25.9 ± 0.8
Range	24.7–30.8	(p = 0.31) 20–30.45
Disease duration (years), mean ± SEM	12 ± 1.8	
Range	3–20	
Levodopa equivalent dose (mg), mean ± SEM	1,152.5 ± 134.49	
Range	400–1,800	
Hoehn and Yahr (median) stage 2/2.5/3	3/3/6	
UPDRS total, mean ± SEM	43 ± 4.65	
Range	12–68	
UPDRS II, mean ± SEM	9.5 ± 1,41	
Range	3–17	
UPDRS III, mean ± SEM	25.75 ± 3.18	
Range	8–45	
UPDRS IV, man ± SEM	5.42 ± 1.28	
Range	1–13	
PDQ-39, mean ± SEM	48 ± 9.1	
Range	11–105	
PDSS-2, mean ± SEM	19.27 ± 3.28	
Range	3–39	
ESS, mean ± SEM	12.1 ± 1.37	7.17 ± 0.61
Range	4–17	(p < 0.001) 3–10
PSQI, mean ± SEM	7.6 ± 1.18	5.50 ± 0.54
Range	3–14	(p = 0.043) 3–8

F, female; M, male; BMI, body mass index; UPDRS, Unified Parkinson's Disease Rating Scale and subscales; PDQ-39, Parkinson's Disease Questionnaire; PDSS-2, Parkinson's Disease Sleep Scale 2; ESS, Epworth Sleepiness Scale; PSQI, Pitssburgh Sleep Quality Index.

12 ± 1.8 years (range of 3–20 years). None of the participants were previously diagnosed with restless legs syndrome or periodic limb movement disorder and only one patient suffered from mild obstructive sleep apnea.

The ambulatory circadian monitoring device allowed long-term non-invasive recording, with minimal discomfort for the subject. During the 168 days of recording there were no lost data attributable to the device or device removal due to discomfort. From the fifteen variables originally recorded by the device, we selected five, as already stated, for PD characterization, due to their complementarity: skin temperature, acceleration of movement, wrist position, and time in movement (motor symptoms) and exposure to visible light (environmental synchronization). The integration of the information from these five primary variables in the modular TAP algorithm allowed us to infer sleep–wake states (**Figure 2**).

As shown in **Figure 3**, the WT rhythm of healthy controls and PD patients shared common characteristics, which replicated the well-known daily rhythm already described in previous publications (3, 4, 6). In both groups, the WT increases just before bedtime, remains high and relatively stable during sleep and decreases upon awakening, with low and highly variable values during the active phase, and a secondary peak in the afternoon, associated with postprandial somnolence. On the contrary, exposure to light, acceleration and time in movement exhibits an inverse pattern, with lower values as sleep deepens.

However, PD patients show significant differences in all variables (**Table 2**). They exhibited flattened rhythms as a result of a significant reduction in nocturnal temperature (M5V, $p = 0.023$), sleep probability (M5V, $p < 0.001$) and diurnal acceleration (M10V, $p < 0.001$), together with an increase in nocturnal time in movement (L5V $p = 0.006$). Actual sleep time (not considering sleep latency and wake after sleep onset) was significantly reduced in PD (5:45 ± 0:48 h in PD vs. 6:43 ± 0:24 h in C, $p = 0.028$). In fact, sleep was particularly impaired in the second half of the night, accompanied by early light exposure in the morning and increased motor activity (**Figure 3**). None of the circadian phase markers differences, including the midpoint of sleep probability (M5T), sleep temperature (M5T), acceleration (L5T), time in movement (L5T), or light exposure (L5T), were statistically significant.

As a measure of chronodisruption, different parameters have been calculated, providing information about complementary aspects characterizing a robust circadian system (**Table 2**): regularity (IS), day–night contrast (relative amplitude), fragmentation (intradaily variability, IV), and the integrated score CFI. IS was lower in PD as compared to controls, both considering the mean of IS values for all variables ($p = 0.025$) and in particular, for sleep probability ($p < 0.001$). Similarly, day–night contrast was also lower in PD, as indicated by the overall RA mean ($p = 0.001$) as well as by RA for acceleration ($p < 0.001$), time in movement ($p = 0.007$) and sleep probability ($p = 0.000$). Fragmentation (IV) was higher and statistically significantly for acceleration ($p = 0.014$) and sleep ($p = 0.001$) in PD.

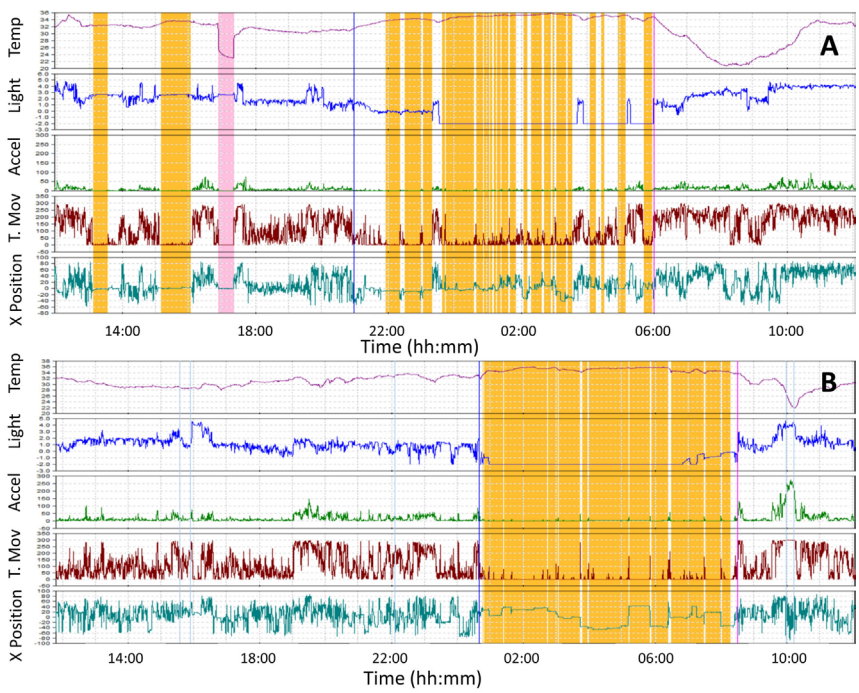

FIGURE 2 | Wrist temperature, light exposure, motor acceleration, time in movement, and 24 h sleep recordings representative for two subjects monitored in our study, one with Parkinson's disease (PD) **(A)** and a healthy control **(B)**. Note the high nocturnal sleep fragmentation, diurnal sleep, and low motor acceleration of PD. Skin temperature is shown as a red line, visible light in blue, acceleration in green, time in movement in dark red and wrist position (X tilt) in bluish green. Sleep is shown in orange bars. Sensor retrival is indicated by a pink bar.

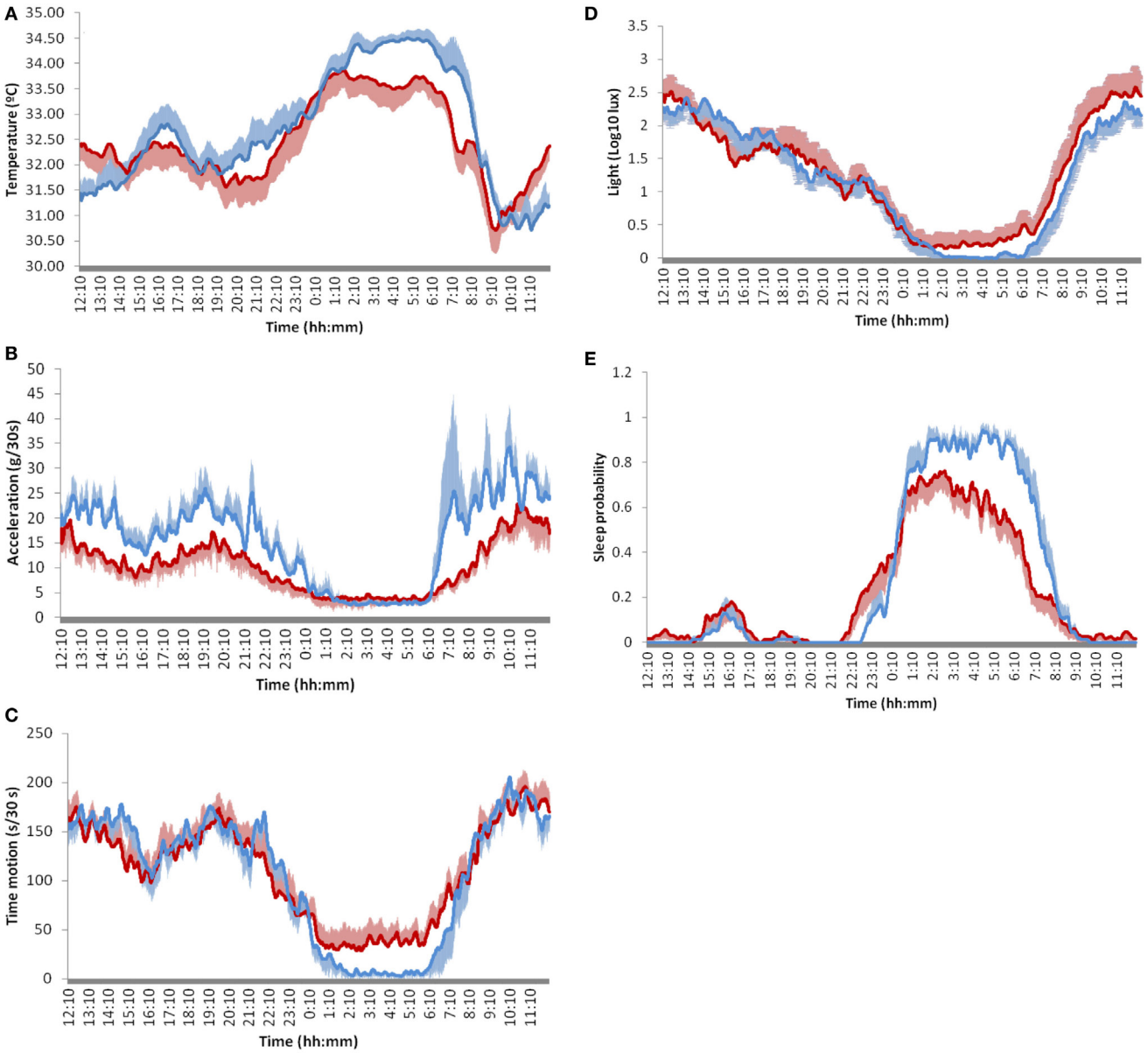

FIGURE 3 | Twenty-four-hour mean waveforms of selected circadian variables in Parkinson's disease patients (red line) and controls (blue line). **(A)** skin temperature, **(B)** acceleration, **(C)** movement duration, **(D)** light exposure, and **(E)** sleep probability. Values are represented as the mean ± SEM of 12 subjects for each condition recorded every 30 s during 7 days.

Consequently, as a result of the impairment observed in PD in most chronodisruption markers, the integrated CFI score was significantly lower, both overall ($p = 0.005$) and for each particular variable (acceleration $p = 0.002$, time in movement $p = 0.02$, and sleep $p = 0.001$), with the exception of light exposure and WT, as no statistically significant differences were detected in these cases.

Thus, ACM provides direct information, allowing discrimination between PD and healthy subjects. Using the Orange Canvas information gain algorithm, the parameters that allow for a better differentiation between PD and control subjects in each variable category were: (a) WT value during sleep (M5V), a reference to autonomic control of skin vasodilatation; (b) daytime acceleration (M10V), since it indicates motor impairment associated with bradykinesia; (c) time in movement during sleep (L5V), a marker of sleep quality and fragmentation; (d) nocturnal sleep (M5V), an index of restfulness; and (e) the M10V acceleration/L5V time in movement (A/T) ratio, which indicates day–night contrast in diurnal activity vs. quiet sleep (**Figure 4**).

However, and despite statistically significant differences in M5V for temperature between the PD and control subjects, great variability was observed among PD patients. While some of them exhibited low nocturnal temperatures, others still maintained WT

TABLE 2 | Circadian parameters representative of the diurnal and nocturnal phases and chronodisruption indexes of the variables selected.

	WT		Acceleration		Time in movement		Sleep		Light		Overall	
	Parkinson's disease (PD)	C	PD	C	PD	C	PD	C	PD	C	PD	C
Mean	32.4 ± 0.23	32.78 ± 0.14	9.39 ± 0.97**	14.58 ± 1.05	102.27 ± 7.61	102.45 ± 4.25	0.24 ± 0.02*	0.28 ± 0.01	1.29 ± 0.15	1.14 ± 0.06	–	–
M5V	33.79 ± 0.24*	34.45 ± 0.14	–	–	–	–	0.72 ± 0.04***	0.91 ± 0.01	–	–	–	–
M5T	3:10 ± 0:30	3:27 ± 0:38	–	–	–	–	3:32 ± 0:27	3:44 ± 0:17	–	–	–	–
L10V	31.68 ± 0.25	31.69 ± 0.24	–	–	–	–	0.03 ± 0.01	0.02 ± 0.01	–	–	–	–
L10T	14:28 ± 0:55	13:32 ± 0:29	–	–	–	–	14:14 ± 0:42	14:57 ± 0:45	–	–	–	–
M10V	–	–	13.55 ± 0.41***	22.59 ± 1.63	146.63 ± 8.67	158.13 ± 6.04	–	–	2:00 ± 0.16	1.98 ± 0.08	–	–
M10T	–	–	14:29 ± 0:25	14:28 ± 0:33	14:51 ± 0:34	14:28 ± 0:35	–	–	14:08 ± 0:19	13:52 ± 0:19	–	–
L5V	–	–	2.95 ± 0.61	2.52 ± 0.41	26.44 ± 7.4**	4.97 ± 0.57	–	–	0.00 ± 0.0	0.00 ± 0.00	–	–
L5T	–	–	4:03 ± 0:25	3:46 ± 0:16	4:02 ± 0:26	3:48 ± 0:16	–	–	3:43 ± 0:26	3:52 ± 0:16	–	–
IS	0.46 ± 0.05	0.55 ± 0.04	0.31 ± 0.03	0.35 ± 0.03	0.41 ± 0.04	0.48 ± 0.02	0.56 ± 0.05***	0.77 ± 0.02	0.57 ± 0.05	0.65 ± 0.03	0.46 ± 0.04*	0.56 ± 0.02
IV	0.003 ± 0.001	0.003 ± 0.001	0.38 ± 0.03*	0.28 ± 0.03	0.27 ± 0.02	0.24 ± 0.01	0.08 ± 0.02**	0.15 ± 0.01	0.08 ± 0.01	0.08 ± 0.01	0.16 ± 0.01	0.15 ± 0.01
RA	0.42 ± 0.04	0.55 ± 0.07	0.28 ± 0.03***	0.50 ± 0.04	0.60 ± 0.05**	0.77 ± 0.03	0.68 ± 0.05***	0.88 ± 0.01	0.60 ± 0.06	0.66 ± 003	0.54 ± 0.02**	0.67 ± 0.03
CFI	0.63 ± 0.03	0.70 ± 0.03	0.47 ± 0.02**	0.57 ± 0.02	0.62 ± 0.03*	0.71 ± 0.02	0.74 ± 0.03**	0.86 ± 0.01	0.71 ± 0.04	0.76 ± 0.02	0.65 ± 0.02**	0.72 ± 0.01
A/T	–	–	–	–	–	–	–	–	–	–	0.72 ± 0.11***	5.48 ± 1.03

*Values are the mean ± SEM. WT, wrist temperature; M5V and M5T, mean value and timing of five consecutive hours with the highest values; L10V and L10T, mean value and timing of 10 consecutive hours with the lowest values; M10V and M10T: mean value and timing of 10 consecutive hours with the highest values; L5V and L5T, mean value and timing of five consecutive hours with the lowest values; IS, interdaily stability; IV, intradaily variability; RA, relative amplitude; CFI, circadian function index; A/T, the M10V acceleration/L5V time in movement (A/T) ratio. Level of significance: *p < 0.05; **p < 0.01; ***p < 0.0.*

values similar to those of the healthy controls. Much less variability was observed in daytime acceleration or in time of movement during the night. In fact, the cutoff threshold of 15.8 G/30 s for the integrated acceleration and 0.021 s/epoch for time in movement makes it possible to discriminate most PD subjects from the control subjects (only 1 and 2 control subjects were misclassified as PD, using acceleration and time in movement, respectively) (**Figure 5**). Thus, the M10V acceleration/L5V time in movement (A/T) ratio was ultimately chosen as the best score to differentiate PD from controls and to characterize both motor impairment and sleep disturbance (two of the most common features in PD) based on movements during sleep.

The increase in A/T ratio was linked to a statistically significant higher CFI, a chronodisruption score (ranging between 0, highly chronodisrupted, to 1, a robust circadian system), which integrates in a single value the three main markers of a circadian healthy state, that it is, regularity, fragmentation and rhythm's amplitude (**Figure 6**). Thus, CFI of WT ($\rho = 0.532$, $p = 0.008$), acceleration ($\rho = 0.681$, $p < 0{,}001$), time in movement ($\rho = 0.621$, $p = 0.0012$), sleep ($\rho = 0.888$, $p < 0.001$) and overall CFI ($\rho = 0.792$, $p < 0.001$) increased as A/T did, while CFI for light exposure ($\rho = 0.363$, $p = 0.081$) was not statistically correlated with A/T ratio.

Although the A/T ratio was able to discriminate between subjects with Parkinson's and controls, and presented good associations with CD markers (CFI), no significant correlations were found between A/T and PD rating scales or subscales (UPDRS, $\rho = 0.157$, $p = 0.62$; UPDRS II. $\rho = -0.19$, $p = 0.55$; UPDRS III, $\rho = 0.41$, $p = 0.19$; UPDRS IV, $\rho = -0.34$, $p = 0.28$) and sleep quality scores (PDSS, $\rho = 0.12$, $p = 0.71$; PSQI, $\rho = -0.28$, $p = 0.37$). However, statistically significant negative relationships were found between acceleration during daytime (M10V) and sleep quality scales (PDSS-2, $\rho = -0.71$, $p = 0.008$; PSQI, $\rho = -0.74$, $p = 0.006$). After Bonferroni's correction for multiple comparisons, no other significant correlations between M10V and PD scales were observed (UPDRS, $\rho = -0.59$, $p = 0.046$; UPDRS II, $\rho = -0.623$, $p = 0.03$; UPDRS III, $\rho = -0.32$, $p = 0.24$; UPDRS IV, $\rho = -0.638$, $p = 0.025$).

In addition, we recorded the same patient three times throughout the course of the study (**Figure 7**). A 61-year-old woman with advanced PD was monitored before (**Figure 7A**), 1 week after (**Figure 7B**), and 6 months after starting intrajejunal infusion of LCIG (**Figure 7C**), an advanced therapy to ameliorate her motor symptoms.

The patient experienced an improvement in motor symptoms and in sleep quality. As it can be observed, LCIG therapy diminished the extreme chronodisruption (**Figure 7A**) characterized by low skin temperature and fragmented sleep and activity rhythms, restoring a more regular, contrasted, and synchronized circadian pattern in all recorded variables (**Figure 7B**). Once the sleep period was consolidated after the levodopa treatment, sleep time was characterized by an increase in WT, along with a sharp and pronounced decrease in light exposure, acceleration, time in motion and variability in X tilt (**Figure 7C**). In addition, the position according to the *x*-axis of the device provides relevant information regarding postural changes throughout the night. The A/T ratio increased from 0.15 to 0.75 and 1.99, 1 week and 6 months after the onset of treatment, respectively.

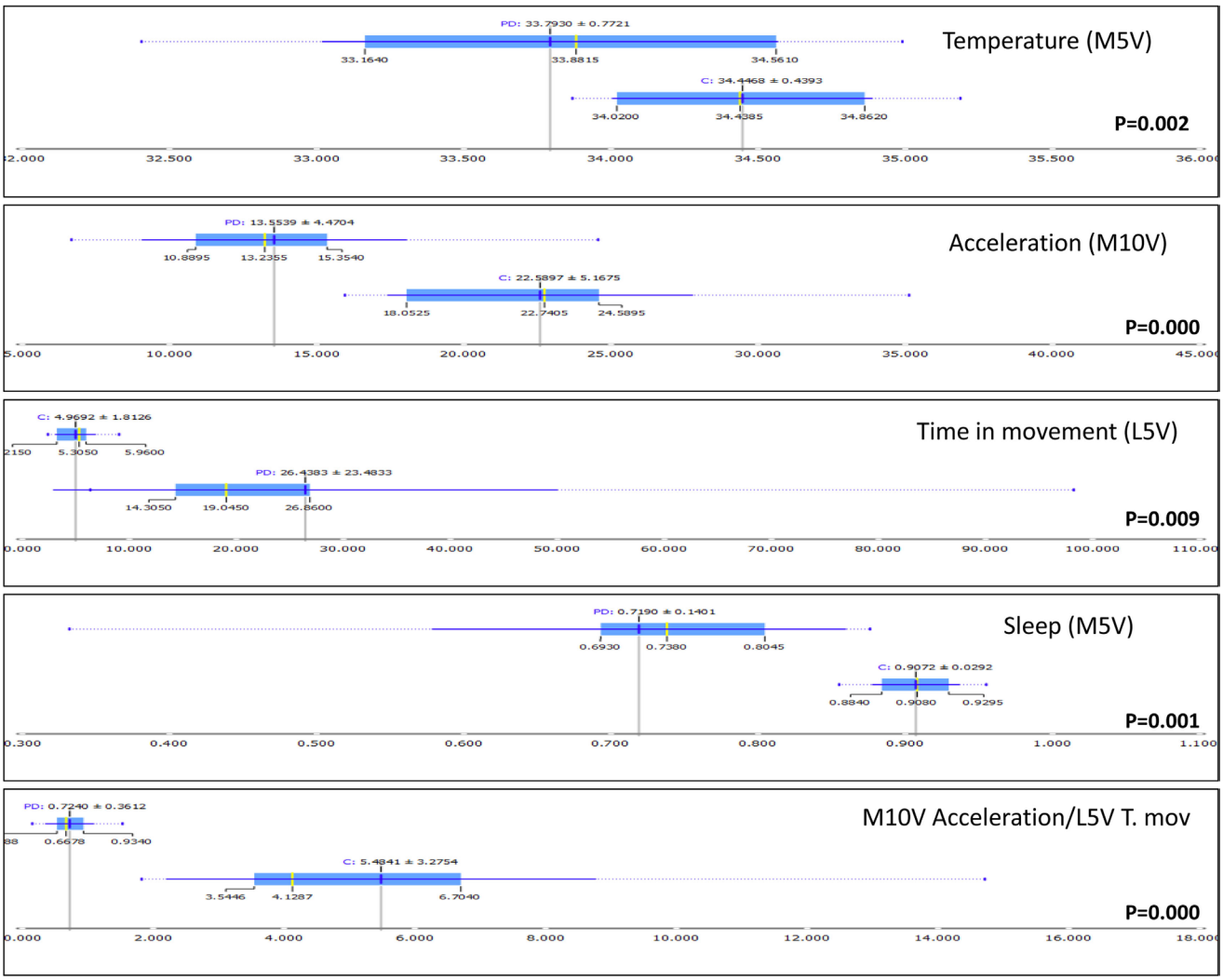

FIGURE 4 | Box plot representation of the distribution of most informative attributes selected according to the information gain procedure (Orange Canvas software) from complementary variables of Parkinson's disease (PD) and healthy controls (C). The mean values are illustrated by the dark blue vertical line. The blue highlighted area indicates the complete SD of the mean, while the median is represented by a gray vertical line. The thin blue line indicates the area between the first (25%) and the third (75%) quartile, while the thin dotted line represents the entire range of values (from the lowest to the highest value in the data set for the selected parameter).

DISCUSSION

The findings presented here demonstrate the ability of a multi-channel ACM device to monitor circadian rhythms and sleep, by collecting reliable and complementary information from motor (acceleration of movement and time in movement) and common non-motor rhythms (sleep and skin temperature) frequently disrupted in PD, with minimal discomfort for patients while they maintain their usual daily living activities. Acceleration during the daytime (indicative of motor impairment), time in movement during sleep (representative of sleep fragmentation) and their ratio (A/T) are the most frequent alterations we have found in PD. Chronodisruption measured by CFI [including IS, intradaily variability (IV) and day-night contrast], are directly linked to a low A/T score. The clinical scales used to evaluate sleep in Parkinson's patients are also negatively correlated with motor acceleration during the day.

The ACM device complies with all the requirements proposed by the SBSM Guide to Actigraphy Monitoring for actimeters (25), and even goes one step further, overlooking the actigraphic limitations by incorporating new sensors. Thus, ACM integrates new non-invasive measures, validated to predict circadian phase (4, 26), such as wrist skin temperature (WT), and blue, infrared, and full light spectrum. This, combined with the previously validated TAP algorithm, provides reliable information on sleep, circadian timing and chronodisruption.

In fact, WT shows a good correlation with the DLMO (4) and in combination with motor activity and body position, they have been validated by PSG to detect sleep–wake under normal living conditions (7) and in sleep pathologies, such as obstructive sleep

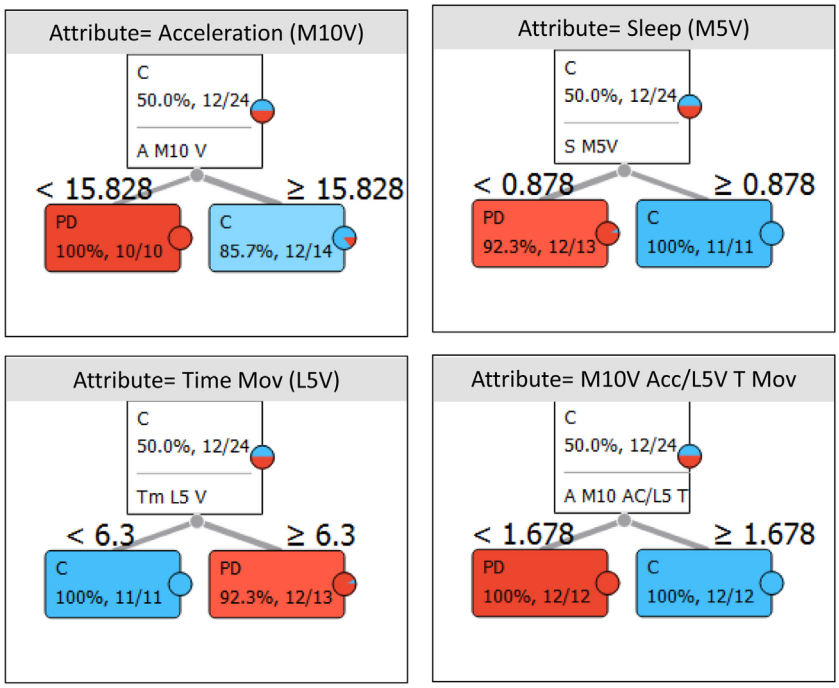

FIGURE 5 | Decision trees for Parkinson's disease (PD) and healthy controls (C) classification, using those attributes selected from the best discriminating variables and the categorical criteria used for its classification. The number of subjects correctly classified as PD (red box) or C (blue box) in showed inside each box, together with the cut-off point is the upper part of the box.

apnea (27). The ACM device permits up to fifteen variables to be recorded for 3 weeks in 30-s epochs. From these variables, we selected the five most representative, which have already been validated in healthy subjects: skin temperature, acceleration of movement, time in movement, light exposure, and variability of wrist position. From these variables, a sixth one, sleep probability, was inferred using a TAP algorithm, as previously described (3).

Our results show a flattened circadian pattern in PD patients as compared to the robust rhythmicity detected in healthy controls. This impairment was observed in most recorded variables and could promote a vicious cycle: a disrupted circadian system could contribute to the exacerbation of the clinical symptoms of PD patients and this, in turn, would induce greater chrono-disruption (13).

Skin temperature exhibits a well-known circadian pattern determined by an underlying circadian rhythm in thermal regulation and by homeostatic adjustments to environmental and body temperature changes. Since the sympathetic nervous system is the main system responsible for the skin vasomotor changes mediating skin temperature, the impairment of the sympathetic innervation of blood vessels reported in PD (28, 29) could be reflected in the skin temperature rhythm. In fact, our results show that WT decreased in PD during sleep, unlike in healthy subjects, whose temperature reaches maximum levels during the night. However, a great deal of variability was found, since some individuals show very low values in nocturnal and in 24-h mean temperature, while others are in the normal range (although in the lower part) that could reflect variability in sympathetic innervation impairment. Lower temperature during sleep seems to be associated with greater sleep fragmentation, low sleep efficiency, shallow sleep (7), and a non-dipping blood pressure pattern (11); these are also circadian impairments commonly observed in PD patients (30). Sleep disturbances are among the most frequent non-motor symptoms in PD, with an incidence as high as 90% (13). Non-motor symptoms can anticipate the diagnosis of PD by many years (12), thus constituting a possible predictive signal.

Besides changes in skin temperature, sleep timing is also associated in PD patients with elevated nocturnal motor activity time, as has been previously reported (31–33). L5V of time in movement, but not L5V for acceleration, is the most discriminant isolated parameter to differentiate PD patients from healthy subjects. Re-emergent motor symptoms during night, a higher incidence in restless legs syndrome, RBD and nocturia could be responsible for fragmented sleep and longer time in movement in our PD group (13).

By contrast, indexes of diurnal motor activity, such as acceleration integration (M10V), are especially lower in PD patients with respect to the controls. It has been published that diurnal motor activity is flattened overall in association with disease progression (34). These results may reflect the existence of a disrupted circadian rhythm in motor manifestations.

Considering that in our Parkinson's patients, acceleration, apart from indicating motor symptoms, is most greatly affected

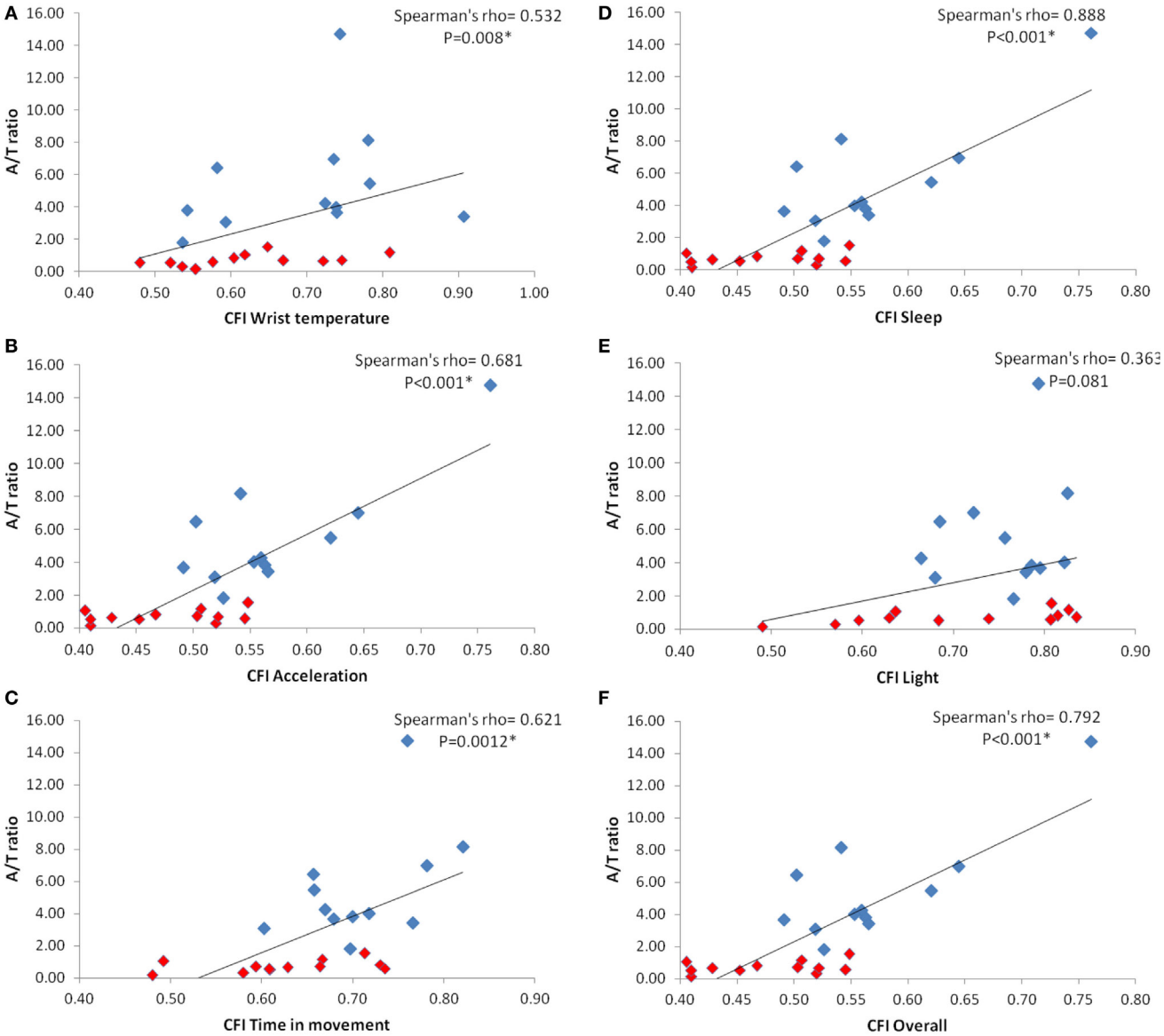

FIGURE 6 | Correlations between M10V Acceleration/L5V Time in movement (A/T ratio) and the circadian function index (CFI), a marker of chronodisruption, for every circadian variable: wrist skin temperature **(A)**; acceleration **(B)**; time in movement **(C)**; sleep **(D)**; light exposure **(E)**; and overall CFI **(F)**. Red squares correspond to Parkinson patients while blue squares indicate healthy controls. Spearman's correlation coefficient rho and its probability value is shown on the upper right of every panel. * indicates statistical significance after Bonferroni's correction.

during the daytime (with lower values), while time in movement (a marker of sleep quality) increases markedly during sleep time, the A/T ratio contributes to enhancing the differences and facilitates discrimination, constituting an objective score to differentiate PD patients from controls. In fact, reduced nocturnal–diurnal contrast in motor activity with disease severity has previously been reported (33), and a ratio of night-time to daytime motor activity (in acceleration units) has been already proposed to distinguish between controls and PD patients (35). However, the predictive accuracy of this ratio (91.7%) is lower than that of the A/T ratio proposed here (100%). The combination of two complementary methods of measuring motor activity during rest and active phases constitutes, to our knowledge, a significant improvement in scoring the evolution of PD, over a procedure based solely on acceleration. Moreover, the use of this score for a particular patient, before and after LCIG therapy, shows how the disease evolves, in close association with subjective and objective improvements in sleep.

Circadian disruption or significant impairment of the amplitude and synchronization between different rhythms and environmental

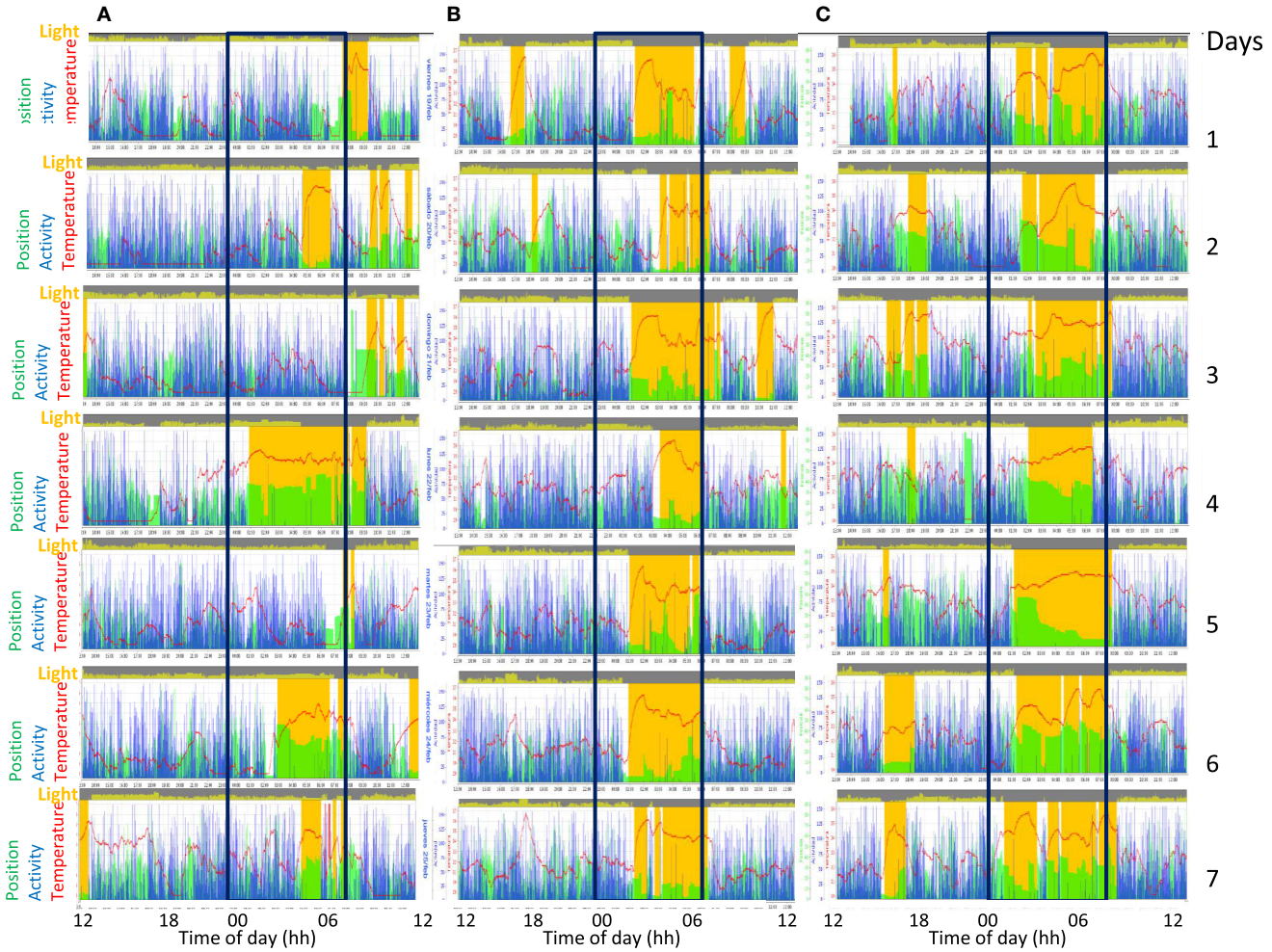

FIGURE 7 | Actograms from ACM recordings of the same patient with advanced Parkinson's disease, monitorized during 3 weeks: before **(A)**, 1 week **(B)**, and 6 months **(C)** after levodopa-carbidopa intestinal gel (LCIG), treatment. Each recorded day is represented sequentially in the same row. Sleep is shown in orange bars, motor activity in blue, wrist position (X tilt) in green, skin temperature as a red line, and visible light in yellow at the top of each day. Note the progressive improvement of circadian rhythmicity in response to LCIG treatment.

cues, has been related to a higher incidence and worsening of several pathologies, including metabolic syndrome, cognitive and affective disorders, cancer, accelerated aging, immunodepression, and cardiovascular disease, among others (36). Chronodisruption is common in many neurodegenerative diseases, such as Alzheimer disease and PD, and may contribute by itself to the biology of PD-associated neurodegeneration (17). Our results show that all CD indexes are severely affected in PD, including regularity, fragmentation, day and night contrast and overall circadian system scores, and in a way similar to that observed in the experimental model of Parkinsonism in rats (37).

Coinciding with previous results (17, 32), we confirm an increased intradaily variability in motor activity in PD that can be expanded to other variables, such as sleep, acceleration and time in movement, which presented lower regularity, high IV (an index of the rhythm's fragmentation, which is also impaired in Alzheimer disease and aging) (38), and amplitude reduction. Reduced amplitude can result from circadian system impairment on three levels: the circadian pacemaker itself, synchronization by input signals or output pathways. Since the suprachiasmatic nucleus appears to be relatively conserved in PD, attention should be paid to input and output pathways. Impairment of anatomical and functional characteristics of the retina have been documented in PD, including dopamine deficiency and impairment of visual acuity and sensitivity contrast (39). Circadian input could be also impaired by inappropriate light-dark exposure, the main circadian zeitgeber; however, we did not find any significant alteration in visible light exposure in PD with respect to healthy controls. In addition to exposure to a regular light–dark cycle, the robustness of the circadian system can be strengthened by consolidated and properly timed behavioral processes, such as physical activity and sleep through feedback mechanisms. In fact, the regularity of life habits facilitates synchronization of the circadian system and is, therefore, considered a protective factor against CD (40).

In addition, the fragmentation of sleep in PD patients could likely be responsible for a negative feedback on amplitude and synchronization of rhythms controlled by the central pacemaker and peripheral oscillators.

Output signals from the central pacemaker also appear to be affected in PD, as has been described for melatonin and cortisol secretion (16). Moreover, autonomic skin innervation (41) and distal skin temperature responses are also impaired in PD (20).

It is true that the reduced number of patients in this study makes it difficult to establish general conclusions about circadian rhythms in PD with non-motor symptoms, such as wrist skin temperature and the implication of autonomic vasomotor impairment. However, the main objective of our work was not the validation of a cutoff criteria to discriminate PD from healthy subjects, but to show the viability of a new technology that allows an objective and multidimensional approach to evaluating the symptoms of this disease, in addition to highlighting the heterogeneous character of the symptomatology of PD.

There are others limitations to our study. The patients with PD are very heterogenous with respect to their age and the severity of their illness, which may explain the high variability among patients for some circadian rhythms, such as WT. We did not take into account the differences in anti-Parkinsonism drug treatments or hypnotic medication, which could influence sleep quality in several ways (42, 43). Although only one of our participants was previously diagnosed of obstructive sleep apnea, and none of them presented restless legs syndrome or periodic limbs movement disorder, they were not systematically evaluated by PSG, thus we cannot exclude completely this possibility.

Our work demonstrates the viability of new experimental technologies based on wearable, multisensor and easy-to-use devices that allow a personalized, objective and multidimensional approach to evaluating both motor symptoms and circadian rhythm impairments in PD, which are also valid for other neurodegenerative disorders. Most importantly, these devices make it possible to quantify a large number of participants over extended periods of time, i.e., while treatment takes effect, thus evaluating its effectiveness. Still, large-scale experiments combined with sophisticated signal processing and machine-learning algorithms will be necessary to elucidate whether chronodisruption is a consequence of PD-specific neurodegeneration, or if it can promote the neurodegenerative process of PD.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of "Ethics Committee of the University of Murcia and HUVN" with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the "Ethics Committee of the University of Murcia and HUVN."

AUTHOR CONTRIBUTIONS

MR, JM, CM-N, AM-C, and FE-S designed the study and experiments and contributed to drafting the main body of the manuscript. FR-A and JM contributed to electronic design of ACM device. MC is responsible of data processing. CM-N, AM-C, and FE-S managed the subject recruitment and clinical evaluation.

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REFERENCES

1. Kubota KJ, Chen JA, Little MA. Machine learning for large-scale wearable sensor data in Parkinson's disease: concepts, promises, pitfalls, and futures. *Mov Disord* (2016) 31:1314–26. doi:10.1002/mds.26693
2. Sivertsen B, Omvik S, Havik OE, Pallesen S, Bjorvatn B, Nielsen GH, et al. A comparison of actigraphy and polysomnography in older adults treated for chronic primary insomnia. *Sleep* (2006) 29:1353–8. doi:10.1093/sleep/29.10.1353
3. Ortiz-Tudela E, Martinez-Nicolas A, Campos M, Rol MÁ, Madrid JA. A new integrated variable based on thermometry, actimetry and body position (TAP) to evaluate circadian system status in humans. *PLoS Comput Biol* (2010) 6:e1000996. doi:10.1371/journal.pcbi.1000996
4. Bonmati-Carrion MA, Middleton B, Revell V, Skene DJ, Rol MA, Madrid JA. Circadian phase assessment by ambulatory monitoring in humans: correlation with dim light melatonin onset. *Chronobiol Int* (2014) 31:37–51. doi:10.3109/07420528.2013.820740
5. Mullington JM, Abbott SM, Carroll JE, Davis CJ, Dijk D-J, Dinges DF, et al. Developing biomarker arrays predicting sleep and circadian-coupled risks to health. *Sleep* (2016) 39:727–36. doi:10.5665/sleep.5616
6. Sarabia JA, Rol MA, Mendiola P, Madrid JA. Circadian rhythm of wrist temperature in normal-living subjects. A candidate of new index of the circadian system. *Physiol Behav* (2008) 95:570–80. doi:10.1016/j.physbeh.2008.08.005
7. Ortiz-Tudela E, Martinez-Nicolas A, Albares J, Segarra F, Campos M, Estivill E, et al. Ambulatory circadian monitoring (ACM) based on thermometry, motor activity and body position (TAP): a comparison with polysomnography. *Physiol Behav* (2014) 126:30–8. doi:10.1016/j.physbeh.2013.12.009
8. Lopez-Minguez J, Ordoñana JR, Sánchez-Romera JF, Madrid JA, Garaulet M. Circadian system heritability as assessed by wrist temperature: a twin study. *Chronobiol Int* (2015) 32:71–80. doi:10.3109/07420528.2014.955186
9. Garaulet M, Madrid JA. Chronobiological aspects of nutrition, metabolic syndrome and obesity. *Adv Drug Deliv Rev* (2010) 62:967–78. doi:10.1016/j.addr.2010.05.005
10. Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. Functional link between distal vasodilation and sleep-onset latency? *Am J Physiol Regul Integr Comp Physiol* (2000) 278:R741–8. doi:10.1152/ajpregu.2000.278.3.R741
11. Blazquez A, Martinez-Nicolas A, Salazar FJ, Rol MA, Madrid JA. Wrist skin temperature, motor activity, and body position as determinants of the circadian pattern of blood pressure. *Chronobiol Int* (2012) 29:747–56. doi:10.3109/07420528.2012.679328
12. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* (2009) 8:464–74. doi:10.1016/S1474-4422(09)70068-7
13. Videnovic A, Lazar AS, Barker RA, Overeem S. "The clocks that time us"-circadian rhythms in neurodegenerative disorders. *Nat Rev Neurol* (2015) 10:683–93.

14. French IT, Muthusamy KA. A review of sleep and its disorders in patients with Parkinson's disease in relation to various brain structures. *Front Aging Neurosci* (2016) 8:114. doi:10.3389/fnagi.2016.00114
15. Breen DP, Nombela C, Vuono R, Jones PS, Fisher K, Burn DJ, et al. Hypothalamic volume loss is associated with reduced melatonin output in Parkinson's disease. *Mov Disord* (2016) 31:1062–6. doi:10.1002/mds.26592
16. Breen DP, Vuono R, Nawarathna U, Fisher K, Shneerson JM, Reddy AB, et al. Sleep and circadian rhythm regulation in early Parkinson disease. *JAMA Neurol* (2014) 71:589–95. doi:10.1001/jamaneurol.2014.65
17. Videnovic A, Willis GL. Circadian system – a novel diagnostic and therapeutic target in Parkinson's disease? *Mov Disord* (2016) 31:260–9. doi:10.1002/mds.26509
18. Zhong G, Bolitho S, Grunstein R, Naismith SL, Lewis SJG. The relationship between thermoregulation and REM sleep behaviour disorder in Parkinson's disease. *PLoS One* (2013) 8:e72661. doi:10.1371/journal.pone.0072661
19. Shindo K, Iida H, Watanabe H, Ohta E, Nagasaka T, Shiozawa Z. Sympathetic sudomotor and vasoconstrictive neural function in patients with Parkinson's disease. *Parkinsonism Relat Disord* (2008) 14:548–52. doi:10.1016/j.parkreldis.2007.12.004
20. Antonio-Rubio I, Madrid-Navarro CJ, Salazar-López E, Pérez-Navarro MJ, Sáez-Zea C, Gómez-Milán E, et al. Abnormal thermography in Parkinson's disease. *Parkinsonism Relat Disord* (2015) 21:852–7. doi:10.1016/j.parkreldis.2015.05.006
21. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science* (2002) 295:1070–3. doi:10.1126/science.1067262
22. Paus S, Schmitz-Hübsch T, Wüllner U, Vogel A, Klockgether T, Abele M. Bright light therapy in Parkinson's disease: a pilot study. *Mov Disord* (2007) 22:1495–8. doi:10.1002/mds.21542
23. Demšar J, Curk T, Erjavec A, Hočevar T, Milutinovič M, Možina M, et al. Orange: Data Mining Toolbox in Python. *J Mach Learn Res* (2013) 14:2349–53.
24. Fayyad UM, Irani KB. Multi-interval discretization of continuous-valued attributes for classification learning. *Artif Intell* (1993) 13:1022–7.
25. Ancoli-Israel S, Martin JL, Blackwell T, Buenaver L, Liu L, Meltzer LJ, et al. The SBSM guide to actigraphy monitoring: clinical and research applications. *Behav Sleep Med* (2015) 13(Suppl 1):S4–38. doi:10.1080/15402002.2015.1046356
26. Kolodyazhniy V, Späti J, Frey S, Götz T, Wirz-Justice A, Kräuchi K, et al. Estimation of human circadian phase via a multi-channel ambulatory monitoring system and a multiple regression model. *J Biol Rhythms* (2011) 26:55–67. doi:10.1177/0748730410391619
27. Martinez-Nicolas A, Guaita M, Santamaría J, Montserrat JM, Rol MÁ, Madrid JA. Circadian impairment of distal skin temperature rhythm in patients with sleep-disordered breathing: the effect of CPAP. *Sleep* (2017) 40:1–10. doi:10.1093/sleep/zsx067
28. Wang N, Gibbons CH, Lafo J, Freeman BSR. α-Synuclein in cutaneous autonomic nerves. *Neurology* (2013) 81:1604–10. doi:10.1212/WNL.0b013e3182a9f449
29. Zange L, Noack C, Hahn K, Stenzel W, Lipp A. Phosphorylated α-synuclein in skin nerve fibres differentiates Parkinson's disease from multiple system atrophy. *Brain* (2015) 138:2310–21. doi:10.1093/brain/awv138
30. Ejaz AA, Sekhon IS, Munjal S. Characteristic findings on 24-h ambulatory blood pressure monitoring in a series of patients with Parkinson's disease. *Eur J Intern Med* (2006) 17:417–20. doi:10.1016/j.ejim.2006.02.020
31. van Hilten B, Hoff JI, Middelkoop HA, van der Velde EA, Kerkhof GA, Wauquier A, et al. Sleep disruption in Parkinson's disease. Assessment by continuous activity monitoring. *Arch Neurol* (1994) 51:922–8. doi:10.1001/archneur.1994.00540210094018
32. Whitehead DL, Davies ADM, Playfer JR, Turnbull CJ. Circadian rest-activity rhythm is altered in Parkinson's disease patients with hallucinations. *Mov Disord* (2008) 23:1137–45. doi:10.1002/mds.22057
33. Niwa F, Kuriyama N, Nakagawa M, Imanishi J. Circadian rhythm of rest activity and autonomic nervous system activity at different stages in Parkinson's disease. *Auton Neurosci* (2011) 165:195–200. doi:10.1016/j.autneu.2011.07.010
34. van Hilten JJ, Hoogland G, van der Velde EA, Middelkoop HA, Kerkhof GA, Roos RA. Diurnal effects of motor activity and fatigue in Parkinson's disease. *J Neurol Neurosurg Psychiatry* (1993) 56:874–7. doi:10.1136/jnnp.56.8.874
35. Nass A, Nass RD. Actigraphic evidence for night-time hyperkinesia in Parkinson's disease. *Int J Neurosci* (2008) 118:291–310. doi:10.1080/00207450701591065
36. Madrid-Navarro C, Sánchez-Gálvez R, Martinez-Nicolas A, Ros M, García J, Madrid JA, et al. Disruption of circadian rhythms and delirium, sleep impairment and sepsis in critically ill patients. Potential therapeutic implications for increased light-dark contrast and melatonin therapy in an ICU environment. *Curr Pharm Des* (2015) 21:3453–68. doi:10.2174/1381612821666150706105602
37. Lax P, Esquiva G, Esteve-Rudd J, Otalora BB, Madrid JA, Cuenca N. Circadian dysfunction in a rotenone-induced parkinsonian rodent model. *Chronobiol Int* (2012) 29:147–56. doi:10.3109/07420528.2011.649870
38. Carvalho-Bos SS, Riemersma-van der Lek RF, Waterhouse J, Reilly T, Van Someren EJW. Strong association of the rest–activity rhythm with well-being in demented elderly women. *Am J Geriatr Psychiatry* (2007) 15:92–100. doi:10.1097/01.JGP.0000236584.03432.dc
39. Archibald NK, Clarke MP, Mosimann UP, Burn DJ. The retina in Parkinson's disease. *Brain* (2009) 132:1128–45. doi:10.1093/brain/awp068
40. Martinez-Nicolas A, Madrid JA, Rol MA. Day–night contrast as source of health for the human circadian system. *Chronobiol Int* (2014) 31:382–93. doi:10.3109/07420528.2013.861845
41. Nolano M, Provitera V, Manganelli F, Iodice R, Stancanelli A, Caporaso G, et al. Loss of cutaneous large and small fibers in naive and l-dopa–treated PD patients. *Neurology* (2017) 89:776–84. doi:10.1212/WNL.0000000000004274
42. Sixel-Döring F, Trautmann E, Mollenhauer B, Trenkwalder C. Age, drugs, or disease: what alters the macrostructure of sleep in Parkinson's disease? *Sleep Med* (2012) 13:1178–83. doi:10.1016/j.sleep.2012.06.009
43. Bolitho SJ, Naismith SL, Rajaratnam SMW, Grunstein RR, Hodges JR, Terpening Z, et al. Disturbances in melatonin secretion and circadian sleep-wake regulation in Parkinson disease. *Sleep Med* (2014) 15:342–7. doi:10.1016/j.sleep.2013.10.016

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Exploring Bedroom Usability and Accessibility in Parkinson's Disease (PD): The Utility of a PD Home Safety Questionnaire and Implications for Adaptations

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Background: Although bedrooms are identified as a major location for accidents among Parkinson's disease (PD) patients, there are no studies that specifically evaluate the bedroom environments of PD patients.

Objective: To examine the physical bedroom environment of patients with PD by generating a home safety questionnaire to rate bedroom accessibility and usability specifically for PD patients, and piloting it in a small set of PD patients, to identify environmental barriers and recommend adaptations to reduce accident risks.

Methods: Questionnaire development was based on the concept of Personal (P)-Environmental (E) fit. The P component covers five clinical domains that contribute to a patients' current state of health, including PD-related motor symptoms, PD-related non-motor symptoms, gait and balance impairments, comorbidities, and limitations on specific activities. The E component focuses on both indoor (bedroom, bathroom, living room, stairs, and kitchen), and outdoor (outdoor area and entrance) areas within a home where PD patients commonly get injured. Total score for the whole questionnaire is 171. A higher score indicates more P-E problems.

Results: Comprehension of questions was tested for content validity with an item-objective congruence index of above 0.6 for all items. High internal consistency (reliability) was confirmed by Cronbach's alpha coefficient of 0.828 (r). The pilot in five PD patients gave a mean total score of 48.2 ± 7.29 with a mean score on personal and environmental components of 16.8 ± 5.12 and 31.4 ± 4.51, respectively.

Conclusion: This PD home safety questionnaire is a valid and reliable instrument for examining P-E problems by a multidisciplinary team during their home visits. More studies, involving a large number of PD patients, are needed to establish its utility as a screening instrument in PD patients to assess for home adaptations.

Keywords: Parkinson's disease, nocturnal symptoms, bedroom adaptation, accessibility, usability

INTRODUCTION

Injuries are common among patients with Parkinson's disease (PD), frequently occurring at home and most likely in bedrooms (30%), but also in living areas (19%), kitchens (15%), and gardens (14%) (1). Most injuries at home occur as a result of falls in the morning when patients are likely to be in the "off" state, and lose their balance while attempting to get out of bed or during transfers from bed to chair, or get out of bed and trip while walking over a carpet or different surface to their bedroom toilet (2, 3). These two scenarios demonstrate well that imbalance in PD can be due to either motor fluctuation from the disease itself or physical barriers (uneven floor surface). It is not only intrinsic factors (e.g., PD itself, lower extremity weakness, and vision impairment) that contribute to falls in PD, but home hazards, particularly in the bedroom, which are contributing factors in home-associated injuries. As PD progresses, environmental limitations often exceed the functional capacity of the individual patient, resulting in a mismatch between the personal component (P), due to the disease itself, and environmental (E) barriers, mostly located in the patient's own home (4). P-E fit problems have been shown to contribute to falls in PD patients and are associated with negative health outcomes (5).

In a recent systematic review of home environmental adaptation (HEA) in PD, very few publications were dedicated to the study of this area, and were limited by small numbers of subjects, cross-sectional design without prospective cohorts, and a lack of specific instruments for evaluating P-E fit in PD patients (6). Despite the limited evidence, PD patients were found to have more P-E fit problems than controls, requiring significantly more adaptations in the area of personal care (including bedroom) than control subjects, becoming less independent with more functional limitations (4, 7). In the most recent study, balance problems and inappropriate use of walking devices were identified as major contributors to housing accessibility problems that seem to worsen as the disease advances (8).

While bedrooms were identified as a major location for accidents among PD patients, there are no studies that specifically evaluate bedroom environments in PD patients. As most PD patients spend approximately one-third of each day in their own bedrooms, it is surprising that intervention studies on bedroom adaptations, that could potentially lessen the risk of falling, are virtually non-existent. However, the benefits of bedroom adaptations, including installation of night lights and bed height adjustment, in addition to other home modifications and training, have been observed in frail older adults (not reported to have PD) with a 37% reduction in fall rate when compared to the period prior to the intervention (9). In reality, it seems that what happens in bedrooms is regarded as private and patients or families seem reticent to share the difficulties that patients experience in their bedroom during the night with their physicians (10). This assumption is supported by the fact that very few PD patients (9%) are referred to therapists who are qualified to perform home safety assessments and recommend modifications (11). The lack of referrals is despite patient's perception that nighttime motor disabilities are the most difficult symptom to improve with current medications; thus, reinforcing an urgent need for studies that reveal the challenges patients experience in their own bedrooms and possible interventions (12, 13). Therefore, the aim of our study is to examine the bedroom environment of patients with PD by generating a scored questionnaire to rate bedroom accessibility and usability specifically for PD patients, and piloting this scale in a small set of PD patients to identify environmental barriers and propose recommendations for adaptations. In this study, we focus our detailed analysis on the bedroom by providing a descriptive analysis of these locations for future adaptations.

METHODS

Concept and Development of the PD Home Safety Questionnaire

The PD home safety questionnaire was developed at the Chulalongkorn Centre of Excellence for Parkinson's Disease and Related Disorders (Chulapd, www.chulapd.org) to determine P-E fit among PD patients who may be at risk of injury in their own homes (Data Sheet S1 in Supplementary Material). The questionnaire items were generated by Chulapd multidisciplinary team (MDT) members, consisting of two movement disorder neurologists (Roongroj Bhidayasiri and Onanong Jitkritsadakul), two PD nurses (Nitinan Kantachadvanich and Kamolwan Boonpang), one physical therapist (Nicharee Aungkab), and two architects who specialize in geriatric housing (Thitiporn Jantanapornchai and Sarawan Pensook), to cover personal and environmental components related to PD. K. Ray Chaudhuri and Nobutaka Hattori independently reviewed questionnaire items and provided comments. All members are bilingual and all health-care professionals have extensive experience, of at least 5 years, in the care of PD patients. The development of a PD home safety questionnaire is based on the P-E fit concept originally proposed by the Housing Enabler (HE) investigators when examining the impact of personal limitations on the accessibility and usability of a patient's home environment (14). While accessibility is a relative concept, describing the encounter between the individual's functional capacity and environmental barriers, usability generally denotes the ability of a person to move around, be in, and use an environment on equal terms with other individuals (15). Therefore, the PD home safety questionnaire is constructed to have items representing both the personal component, related to PD, and the environmental component, incorporating the physical barriers in a patient's own home that may affect accessibility or usability. Prior to its development, a literature review was conducted to identify existing questionnaires that have been widely used in the field of HEA. Since all identified questionnaires were primarily developed for older people living in the community with chronic disorders, not specifically PD patients, we only selected questionnaires used as part of successful home safety programs with published results in peer-reviewed journals as models for our questionnaire namely the "HE," the "usability in my home questionnaire," and the "housing-related control belief questionnaire" (14, 16, 17).

The personal component of our PD home safety questionnaire covers five clinical domains that contribute to a patients' current state of health, including PD-related motor symptoms,

PD-related non-motor symptoms (NMS), gait and balance impairments, comorbidities, and limitations on specific activities (Data Sheet S1 in Supplementary Material). The items under each domain are derived from standardized questionnaires or rating scales. For PD-related motor and NMS domains, items were developed from, and rated in accordance with the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) (18), the non-motor scale (19), the mini-mental state examination (MMSE) (20), Hamilton's depression and anxiety rating scale (21), the Parkinson's Disease Sleep Scale-revised version (22), and the criteria for orthostatic hypotension as defined by the consensus statement of the American Autonomic Society and the American Academy of Neurology (23). For the gait and balance domain, items were selected from the activity of daily living section of the UPDRS, divided into gait and balance subdomains. Items on comorbidities were categorized into visual symptoms (V), hearing ability (E), joint problems for weight bearing (J), and weight change of either morbid obesity or significant weight loss. Specific activities were selected from the 16-item Activities-specific Balance Scale that has been identified to influence balance confidence in PD patients (3). All items are based on a "yes" or "no" response if patients had experience these symptoms within the past week. Each item was carefully reviewed by members of the MDT and all members had to agree to include each item. In the case of a discrepancy, all members assessed the evidence again and arrived at a consensus. A total of 36 items were included in a final version with each item generating one score. Since the severity of parkinsonian symptoms of each patient may be differentially affected in different parts of the body, the raters are requested to rank the top three most severe symptoms and multiply the score of these symptoms by two to ensure that the score summation reflects the total symptom burden of individual patient. Therefore, for the personal component, the maximal total score is 59 with a higher score indicating more severe symptoms.

For the environmental component, the MDT took into consideration which areas in the home were associated with the commonest occurrence of injury in PD patients, including both indoor (bedroom, bathroom, living room, stairs, and kitchen), and outdoor (outdoor area and entrance) areas (Data Sheet S1 in Supplementary Material). At each location, items were included if, by consensus of the MDT, they are common physical barriers experienced by PD patients. Similar to the personal component, patients are request to provide a "yes" or "no" response if they had encounter this problem within the previous week. Each item is also categorized by whether it is related to accessibility, usability, or if the patient had encountered an injury in this location within the previous week. In this environmental section, there are 8 items for the bedroom, 12 items for the bathroom, 7 items for living room, kitchen, and stairs each, 9 items for outdoor area, and 6 items for entrance, giving a total score of 112. A higher score indicates more physical barriers for the individual patient. Specifically, for the bedroom environment, two items (bed height and lighting) are related to accessibility while the other six items are considered as part of the usability evaluation (service area, handrails, environment for good sleep, path width, floor, and reliance on assisted device).

Content Validity

Comprehension of all items was tested for content validity by another expert panel (three movement disorder neurologists, two architects with expertise in geriatric housing, and one PD nurse) who were not involved with item generation. The index of item-objective congruence (IOC) was conducted on all questionnaire items, demonstrating a positive content validation with the IOC index of above 0.6 on all items. The questionnaire was then reviewed by another set of health-care practitioners (one general internist, one general neurologist, one nurse practitioner, one physical therapist, and one occupational therapist), who regularly see PD patients and are likely to implement this type of questionnaire, to ensure that they fully understand the instructions and contents. Only minor revisions to the wordings and grammatical corrections were allowed at this stage.

Reliability (Internal Consistency)

We performed the reliability test by determining Cronbach's alpha coefficient in five health-care professionals, consisting of one neurologist, one general internist, two nurse practitioners, and one occupational therapist in a single PD patient's home. Cronbach's alpha of this questionnaire was 0.828 (r), demonstrating high internal consistency.

IMPLEMENTATION OF THE PD HOME SAFETY QUESTIONNAIRE IN A PILOT TRIAL

As a pilot trial, the PD home safety questionnaire was employed by another MDT, who was not involved with the item generation and validation process, in five PD homes. Eligibility criteria were the homes of PD patients who had a diagnosis confirmed by a movement disorder neurologist using the standard diagnostic criteria and had been resident in this home for more than 10 years without prior adaptations. All patients must have carers who were their spouses and share the same bedroom environment. All patients were identified by the MDT to have both disabling symptoms from PD and housing problems, particularly in their bedrooms, requiring adaptations. Patients with significant comorbidities were excluded as it would be difficult to establish if environmental barriers occur as a result of PD or other disorders. Due to transport limitations, only those patients who resided in Bangkok were invited to participate. From the eight PD patients who were randomly selected and satisfied the above criteria, three declined the invitation to participate in this pilot trial (response rate = 62.5%). The main reason for refusal was being too embarrassed to show their houses to the MDT. The study was approved by the Ethics Committee of Chulalongkorn University and informed consent was obtained from all participants. Clinical demographics of all five patients were shown in **Table 1**. Other clinical descriptions and their housing conditions were described as follows (**Figures 1A–E**).

Patient 1

Patient 1, aged between 55 and 59 years old, has a 9-year history of PD (**Figure 1A**). Current problems are motor fluctuations with

TABLE 1 | Demographic data of five Parkinson's disease (PD) patients.

Items	Mean ± SD	Min–Max
Age (years)	66.2 ± 6.76	55–73
Disease duration (years)	8.6 ± 3.58	5–13
PD diagnosis	5 (100%)	
Male gender	4 (80%)	
History of falling in the past 1 month	4 (80%)	
Number of urination per night in the past 1 month	3.00 ± 1.73	0–4
Types of assisted device used		
• Cane	2 (20%)	
• Walker	1 (40%)	
• Wheelchair	1 (20%)	
• None	1 (20%)	
Number of falls during the past month	13.2 ± 26.20	0–60
Total LED	659.5 ± 462.76	50–1,235
MoCA	26.67 ± 3.51	23–30
MMSE	25.60 ± 4.28	19–30
HY score	3.2 ± 0.83	2–4
Total UPDRS	44.8 ± 16.62	23–69
UPDRS part 1	1.00 ± 1.00	0–2
UPDRS part 2	12.20 ± 6.06	5–19
UPDRS part 3	24.80 ± 7.76	12–33
UPDRS part 4	3.80 ± 1.79	2–6
PDSS-2 score	28.00 ± 9.27	16–40

LED, levodopa equivalent dose; UPDRS, the Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; MMSE, mini-mental state examination; HY, Hoehn and Yahr stage; PDSS-2, Parkinson's disease sleep scale-revised version.

both "on" and "off" period freezing of gait (FOG), particularly when walking through a narrow entrance and during turning. The patient falls once or twice a month, mostly after getting out of bed in the evening to go to the adjacent bathroom. In addition, the patient complains of increasing difficulty in walking upstairs due to leg weakness. The patient lives with a carer who in a two-story house with the bedroom and main bathroom on the second floor. The MMSE score was 27.

Patient 2

Patient 2, aged between 65 and 70 years old, had a 13-year history of PD (**Figure 1B**). Due to intractable motor fluctuations, the patient underwent bilateral globus pallidus interna deep brain stimulation 2 years ago with remarkable results in a reduction of dyskinesia and improved "on" periods. However, the balance remains troublesome, particularly during turning in a small bathroom with a tendency to fall backward. The patient falls in the bathroom on almost weekly basis while attempting to turn from the sink to go and sit on a toilet seat. Another common circumstance is when the patient turns in front of the wardrobe. Other complaints include drooling and mumbling speech. The patient lives with a carer in a downstairs bedroom with an adjacent bathroom. The patient was noted to have visual hallucinations in the evening. The MMSE score was 24.

Patient 3

Patient 3, aged between 55 and 59 years old, has a 5-year history of postural instability and gait dysfunction PD (**Figure 1C**). Despite levodopa benefits, FOGs remain intractable with numerous fall episodes, mostly in the bedroom while changing clothes in an upright position. The patient also falls frequently when walking from the bed to the adjacent bathroom as the route requires three turns leading to FOG. The left leg was broken last year as a consequence of one of these falling episodes. The patient lives in a one-story house with a carer. The MMSE score was 30.

Patient 4

Patient 4, aged between 55 and 59 years old, has a 11-year history of PD (**Figure 1D**). The patient lives in a four-story house with a bedroom and adjacent bathroom located on the second floor. The main problem is frequent "on" period FOG, leading to falls in the early morning when walking from the bed to the toilet. The patient also suffers from nocturnal hypokinesia and early morning off. The patient's partner who is a carer also has a walking difficulty due to a recent hip replacement. The MMSE score was 28.

Patient 5

Patient 5, aged between 70 and 75 years old, has a diagnosis of PD dementia for 4 years (**Figure 1E**). The MMSE score was 19. In addition to cognitive difficulties, the patient reports problems with vision, described as an inability to focus and a lack of depth perception. The carer believes that poor vision contributes to nighttime falls when the patient has 4–5 episodes of nocturia and attempts to get out of bed to go to the bathroom. The patient refuses to wear diapers during the night. The carer finds the situations at home increasingly difficult to cope with.

The administration of the PD home safety questionnaire follows two steps. Step 1: personal component: interview and observation of functional limitations and comorbidities on five domains as described above. All items are dichotomously assessed (yes = 1/no = 0). The interview of this section is led by the neurologist of the MDT with the whole process taking approximately 1 h. Step 2: environmental component, involves the assessment of seven locations of both outdoor and indoor, led by the physical therapist or occupational therapist of the MDT. This step does not involve the PD patient, taking approximately 2 h to complete the process. All statistical analysis was performed using SPSS version 22.0 software (Chicago, IL, USA). A significant level of $p < 0.05$ was set for all statistical tests. Descriptive statistics were performed for all demographic variables expressed as mean ± SD for continuous variables or frequency counts and percentage for categorical variables. Spearman correlation coefficient (r) was used to determine the strength of correlation as weak, moderate, or high.

RESULTS

The results of our pilot trial in five PD patients have demonstrated the utility of the PD home safety questionnaire in capturing functional limitations in both personal and environmental aspects of PD. The demographic data and clinical characteristics of PD patients are shown in **Table 1**. All five PD patients in this pilot trial experienced their main difficulties in gait and balance with mainly FOG with frequent falls, and mostly located in their bedroom and adjacent bathrooms. The mean total score of the PD home safety questionnaire was 48.2 ± 7.29 with a mean score on personal and environmental components of 16.8 ± 5.12 and

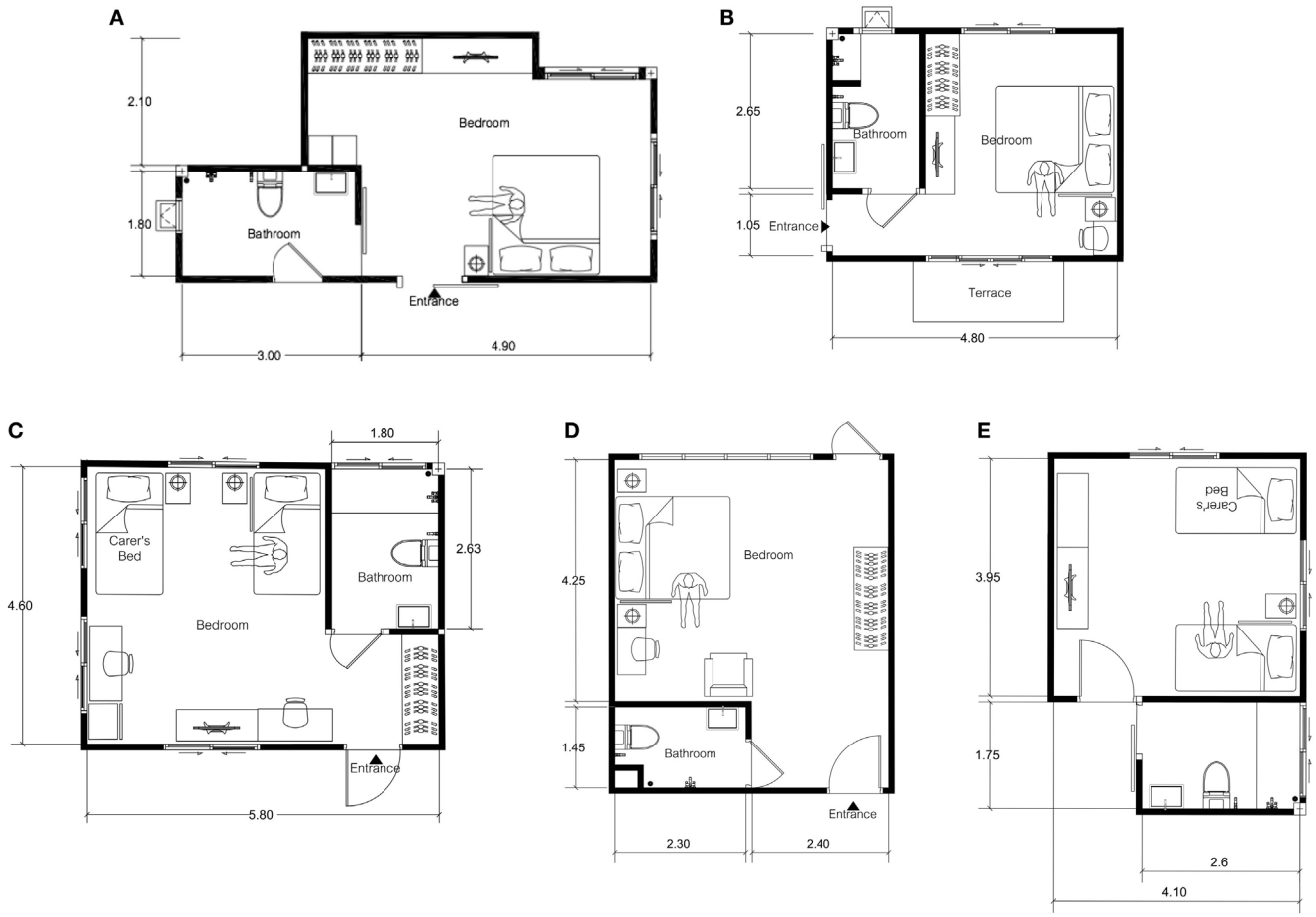

FIGURE 1 | Floor plan of Parkinson's disease patient's bedrooms and adjacent bathrooms, labeled as **(A–E)** for patients 1–5 consecutively.

31.4 ± 4.51, respectively (**Table 2**). With regards to the functional profile in personal component, limitations were demonstrated as a score in each domain of motor, NMS, gait and balance, and ability on specific activities. However, the gait and balance score was relatively high when compared to scores in other domains, consistent with the clinical history, demonstrating the validity of our questionnaire in differentiating the contribution of individual symptom to the whole functional limitations in an individual patient. For the environmental component, we observe a score in all domains, reflecting the presence of environmental barriers in all areas as a result of PD. In the bedroom environment, problems identified were mainly concerned with accessibility, with four out of five PD homes (80%) having bed height higher (55–60 cm) than recommended standard value (45–50 cm) and no supported bed rails available to assist patients when getting out of bed (**Table 3**). Moreover, two out of four patients (50%) reported minor injuries as a result of bed height problems. Inadequate lighting in the bedroom was also identified in two out of five PD homes (40%) with one patient claiming to have fallen as a consequence. In this pilot group of five PD homes, fewer problems were identified on usability items compared to accessibility items in the bedroom environment (**Table 3**). One out of the five homes was found to have furniture not secured in its place causing narrow walkways in the bedroom and a slippery floor was identified in another PD home during the MDT visit.

Correlation analysis between personal and environment components of the PD home safety questionnaire revealed a number of significant findings. High and significant correlations were observed between comorbidities and total scores of the questionnaire ($r = 0.889$, $p = 0.044$), and a similar observation was also demonstrated between limitation of specific activities and total score of the questionnaire ($r = 0.892$, $p = 0.042$) (Data Sheet S2 in Supplementary Material). Analysis within the personal component indicated high and significant correlations between motor symptoms as well as gait and balance impairments and total scores of the personal component (motor: $r = 0.894$, $p = 0.041$; gait: $r = 0.949$, $p = 0.014$). For the analysis of the environmental component, high and significant correlation was observed between indoor sum scores and total scores of the environmental component ($r = 0.975$, $p = 0.005$).

Descriptive Analysis of Bedrooms and Adjacent Bathrooms of Five PD Homes

The descriptive analysis of the bedrooms of the five PD patients was conducted by the MDT, led by the physical therapist and architect who specializes in geriatric housing (**Figures 1A–E**). In

TABLE 2 | Results of PD home safety questionnaire in five PD patients.

Scoring	Total score	Min–Max
Total PD home safety score (171 points)	48.20 ± 7.29	(38–54)
Personal component score (59 points)	16.80 ± 5.12	(9–23)
• Motor component (9 points)	3.00 ± 1.73	(0–4)
• NMS component (24 points)	4.60 ± 1.52	(2–6)
• Gait and balance score (12 points)	5.40 ± 2.51	(1–7)
• Comorbidities score (7 points)	0.80 ± 1.09	(0–2)
• Limitation of specific activities score (7 points)	3.00 ± 1.22	(2–5)

Scoring	Total score	Accessibility score	Usability score	Injury score
Environmental component score (112 points)	31.40 ± 4.51 (26–38)	7.80 ± 2.04 (6–11)	11.20 ± 2.77 (7–14)	9.80 ± 4.65 (4–17)
Outdoor				
• Outdoor area (18 points)	6.80 ± 1.92 (5–10)	2.40 ± 1.14 (1–4)	2.40 ± 0.55 (2–3)	2.00 ± 2.12 (0–5)
• Entrance (12 points)	4.20 ± 1.48 (2–6)	2.00 ± 0.71 (1–3)	1.80 ± 1.09 (0–3)	0.40 ± 0.54 (0–1)
Indoor				
• Stairs (14 points)	4.00 ± 0.70 (3–5)	0.40 ± 0.55 (0–1)	2.80 ± 0.84 (2–4)	0.60 ± 0.89 (0–2)
• Living room (14 points)	3.20 ± 1.92 (1–6)	NA	0.20 ± 0.45 (0–1)	2.20 ± 1.48 (0–4)
• Kitchen (14 points)	3.20 ± 1.92 (1–6)	0.60 ± 0.89 (0–2)	0.40 ± 0.54 (0–1)	0.80 ± 0.84 (0–2)
• Bathroom (24 points)	7.00 ± 1.22 (5–8)	1.20 ± 0.84 (0–2)	3.00 ± 1.22 (2–5)	2.60 ± 2.30 (0–6)
• Bedroom (16 points)	3.00 ± 1.41 (1–4)	1.20 ± 0.84 (0–2)	0.60 ± 0.54 (0–1)	1.20 ± 1.30 (0–3)

Values in parentheses were shown as min–max.
PD, Parkinson's disease; NMS, non-motor symptoms.
Total score of PD home safety questionnaire is 171 points. The total scores of personal and environmental components are 59 and 112 points, respectively. The total scores of individual domains in the personal component are as follows: PD-related motor symptoms 9 points, PD-related NMS 24 points, gait and balance impairment 12 points, co-morbidity 7 points, and limitation of specific activities 7 points. The total scores of individual domains in the environmental component are as follows: outdoor area 18 points, entrance 12 points, stairs 14 points, living room 14 points, kitchen 14 points, bathroom 24 points, and bedroom 16 points.

TABLE 3 | Summary score for bedroom assessment in five Parkinson's disease patients.

Bedroom	Problem with accessibility (yes = 1/no = 0)	Problem with usability (yes = 1/no = 0)	Injury as a result of the problem (yes = 1/no = 0)	Score summary	Remarks
Service area		1	0	1	– Pathway narrower than 90 cm – Furniture is not secured in its place
Handrails		0	0	0	– No handrails installed at necessary location in the room
Environment for good sleep		0	0	0	– Pollutants identified (noise and/or air)
Bed height	4		2	6	– Unsuitable height for bed (lower than 45 cm or higher than 50 cm) – No support bar to assist getting out of bed
Path width		0	0	0	– Less than 0.9 m
Floor		1	1	2	– Slippery floor
Lighting	2		1	3	– Scenario 1: sleep—more than 5 lx – Scenario 2: activity in bedroom—less than 100 lx
Reliance on assisted device		0	0	0	– Assisting person could be interpreted as an assisted device
Score summary	6	2	4	12	

The score represents the number of bedroom with problems in accessibility, usability, or reported injuries as a consequence.
Lux, a standardized unit of measurement of the light illuminance.

addition to a physical evaluation of bedroom environments, we also interviewed PD patients and their carers on challenges they encountered during the night based on their nighttime activities. As noted from **Table 1**, nocturia was common with an average of three episodes per night. Most patients experienced FOG on their nighttime trip to the bathroom with reports of inadequate lighting. Common findings are summarized below with proposed recommendations for adaptations.

(1) Beds of all five patients were located too far from the bathrooms for patients to get there and back quickly. Therefore, the beds should be relocated closer to the bathrooms.

(2) Most patients encountered obstacles resulting from the layout of their homes on their walk to the bathrooms. In one home, the patient had to walk through two doorways with three turns to reach his bathroom. Clean and uncluttered spaces make a space feel larger and are important for PD patients who need clear floor space to maneuver in and around the bedroom with a walker or wheelchair or to and from the bathroom at night.

(3) Inadequate lighting was observed in all five bedrooms as all patients used dim lights to promote their sleep. Our recommendation is to install adequate lighting or automatic night lights to help patients find their way during the night.

(4) In three out of five patients (60%), the bed height was found to be 55–60 cm as carers had installed bed risers to help patients get out of bed. If the bed is too high, patients may be at risk of significant injury from falling out of bed. This is a potential risk among PD patients, particularly the ones with parasomnias. Our recommendation is to adjust bed height to be between 45 and 50 cm, which is considered optimal for the elderly population. Bed rails should be installed to prevent patients from falling out of bed and to assist patients with getting out of bed.
(5) Bedroom carpets were found in four bedrooms (80%). They should be removed to prevent tips and falls at night.

DISCUSSION

This study describes the development of a PD home safety questionnaire, outlining the developmental process under an MDT specializing in PD. The results confirm the validity of the contents and reliability when implemented by an individual member of a multidisciplinary group. The questionnaire was piloted in five PD patients in their own homes, demonstrating its utility in capturing functional limitations as reflected in the personal component and environmental barriers as indicated by the environmental component of this questionnaire. The relatively high scores on gait and balance domain as well as bedroom and bathroom domains are consistent with the clinical histories of all five patients which are dominated by frequent FOG and falls within bedrooms and adjacent bathrooms. Though limited by a small number of subjects, correlation analysis also revealed significant contributions of comorbidities and limitation of specific activities on the total questionnaire score. Motor, gait, and balance symptoms were found to have a significant influence on the personal component score, providing another evidence to support the effect of gait and balance on disease burden (24). Importantly, the significant correlation between indoor scores and the total environmental component scores highlights the important contribution of indoor barriers on the environmental problems faced by PD patients, consistent with prior literature documenting frequent occurrence of indoor injuries among PD patients (1). While our results are exploratory, they provide preliminary, but objective, evidence on environmental barriers that may occur as a result of functional limitations in PD.

When reviewing a patient's symptom, physicians often focus on the clinical features of individual symptoms, and severity, but ignore on the circumstances or situations where these symptoms occur. A good example is the symptom of FOG where the episodes are often described in relation to a patient's "on" or "off" periods and whether the patient fall as a consequence, but on many occasions, environmental aspects of FOG episodes are not described. This incomplete information has led physicians focus their treatment of FOG on medications that improve "on" periods that are often found to be insufficient in ameliorating FOG episodes. Looking at environmental perspectives of FOG, there are clearly physical barriers, contributing to repeated occurrence of FOG, including narrow spaces, insufficient lighting, abundance and disorganization of furniture items, home uncleanliness, and clutter. While it seems clear from patient's descriptions that environment barriers are another important contributing factor to FOG, the therapeutic evidence on environmental adaptations is still lacking, rated as level D (expert opinion), in contrast to several pharmacologic agents receiving a stronger level of evidence (A or B) (25). We propose that each individual symptom of PD, whether it is motor or non-motor, should be reviewed from both personal and environmental perspective so we can ensure that P-E fit is maintained in an individual patient for as long as possible.

While physicians have instruments to evaluate physical symptoms of PD (for example, tremor, gait, or balance), specific instruments for determining environmental barriers among PD patients are still lacking (6). Fortunately, a number of instruments, although originally developed for the elderly in the community without specific disorders, have recently been employed with PD patients. The HE questionnaire, developed for assessment of housing accessibility, is a comprehensive scale based on the notion of P-E fit, taking into account that functional limitations constitute an important component of accessibility problems (26). The HE has recently been studied in over 250 PD patients across all Hoehn and Yahr stages, identifying the significant contribution of balance problems and dependence of walking devices in reducing home accessibility (8). Although the HE has been shown to be a valid and reliable instrument for assessment of housing accessibility, it is a comprehensive instrument requiring special training to administer, and even though it is comprehensive in terms of including all body parts that involve in mobility, the personal items of the HE is not specific for PD symptoms, lacking the contribution of NMS. Therefore, it is doubtful that the HE can be implemented during a PD home visits by an MDT as intended for the PD home safety questionnaire. As a result, we have adopted the concept of P-E fit as proposed by the HE developers, but incorporated specific items of PD symptoms, and simplified the contents so it can be used by a PD MDT during their regular home visits to identify potential areas for home adaptations. Although preliminary, our results acknowledge the significant contribution of balance impairment as one of the main functional limitations, consistent with what has recently been shown with the HE (8), and highlights the bedroom and adjacent bathroom areas of major environmental barriers, supporting previous reports that these areas are common locations for home injuries among PD patients (1).

In recent years, there has been an increasing interest in evaluating the symptoms of PD, treatment responses, and a patient's daily performance in their own homes, resulting in the development of different types of home battery tests, home monitoring, and remote assessment devices (27, 28). While most devices are developed for specific parkinsonian symptoms or activities (personal component), a specific location within the home has not been considered as a target for adaptations in most published studies. We would like to highlight the importance of the bedroom for wellbeing as we all, not just PD patients, spend approximately one-third of our daily life in this location. In PD patients, the situation is even worse as up to 97% of PD patients experience at least one PD-related nighttime symptoms and treatments for these symptoms are considered unsatisfactorily by most patients (12, 13, 29). The impact of nighttime symptoms on carers has

also been demonstrated in terms of increased total carer burden, stress, and poor sleep quality (30). On the environmental side, we are not aware of any published studies that evaluate the efficacy of bedroom and bathroom adaptations for the reduction of injuries (e.g., falls) or the improvement of sleep quality of either patients or their carers. General guidance for bedroom and bathroom modifications are usually provided by professional societies or organizations, but specific recommendations are generally unavailable (31, 32). The data from our pilot study provides a preliminary evidence that physical barriers in the bedrooms of PD patients significantly contribute to P-E fit problems, and should receive a high priority for interventional research.

Our study findings are limited to the validation of PD home safety questionnaire and a pilot trial in a small number of PD patients. Therefore, though it confirms the validity of this questionnaire among PD patients, more studies involving a large number of PD patients are needed to establish its utility as a screening instrument in PD patients who may be candidates for home adaptation. In addition, specific outcomes (e.g., falls at home) should be included in order to determine the sensitivity and specificity as well as a cutoff point for this questionnaire. The time required for full assessment of this questionnaire by a PD MDT is another limitation for implementing it in a routine clinical practice. While the PD home safety questionnaire is developed to enable a full assessment of home environment, the results of our first study focus on the issues of bedroom environment as previously identified as the most common location for PD-associated injuries. Further studies are being planned by our group to implement the PD home safety questionnaire in more subjects to identify specific barriers in other locations as well as the results of adaptations. The strength of our study is the involvement of a PD MDT in the generation and validation of this questionnaire, and that the evaluation was also conducted by a PD MDT in the patient's own homes. However, it is limited by the lack of control subjects, the small number of PD patients in the pilot trial, and that bedroom and bathroom-related injuries were not clearly defined, for example, the number of falls.

In conclusion, optimal evaluation of PD patients should not be limited to the physical symptoms of the actual patients, but environmental aspects should also be considered as important contributing factors to patient's safety, quality of life, and wellbeing. Based on the notion of P-E fit, environmental barriers are likely to emerge as the disease advances, necessitating the need for MDT assessment of both personal and environmental contributions to a patient's functional limitations. In this study, we provide a validated assessment of the PD home safety questionnaire for screening for potential P-E problems by an MDT during their PD home visits. As we all, including PD patients, spend almost one-third of our day in our bedrooms, we propose that the bedroom should receive a priority for HEA research as treatment of individual nighttime symptoms of PD patients, together with appropriate bedroom adaptations, is likely to result in better sleep quality and reduction in nighttime-related injuries for the patients, and decreased burden for their carers.

ETHICS STATEMENT

The protocol was approved by the ethics committee of Chulalongkorn University. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

Research project: conception (RB, OJ, and JS), organization (RB, NK, SPensook, and KB), and execution (RB, OJ, JS, NK, SPensook, KB, KC, TJ, NA, and NH). Statistical analysis: design (RB and OJ), execution (RB and OJ), and review and critique (RB and OJ). Manuscript preparation: writing the first draft (RB), review and critique (RB, NH, TJ, and KC).

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at https://www.frontiersin.org/articles/10.3389/fneur.2018.00360/full#supplementary-material.

REFERENCES

1. Ashburn A, Stack E, Ballinger C, Fazakarley L, Fitton C. The circumstances of falls among people with Parkinson's disease and the use of falls diaries to facilitate reporting. *Disabil Rehabil* (2008) 30(16):1205–12. doi:10.1080/09638280701828930
2. Gazibara T, Pekmezovic T, Tepavcevic DK, Tomic A, Stankovic I, Kostic VS, et al. Circumstances of falls and fall-related injuries among patients with Parkinson's disease in an outpatient setting. *Geriatr Nurs* (2014) 35(5):364–9. doi:10.1016/j.gerinurse.2014.05.001
3. Foongsathaporn C, Panyakaew P, Jitkritsadakul O, Bhidayasiri R. What daily activities increase the risk of falling in Parkinson patients? An analysis of the utility of the ABC-16 scale. *J Neurol Sci* (2016) 364:183–7. doi:10.1016/j.jns.2016.03.037
4. Slaug B, Nilsson MH, Iwarsson S. Characteristics of the personal and environmental components of person-environment fit in very old age: a comparison between people with self-reported Parkinson's disease and matched controls. *Aging Clin Exp Res* (2013) 25(6):667–75. doi:10.1007/s40520-013-0165-z
5. Jonasson SB, Ullen S, Iwarsson S, Lexell J, Nilsson MH. Concerns about falling in Parkinson's disease: associations with disabilities and personal and environmental factors. *J Parkinsons Dis* (2015) 5(2):341–9. doi:10.3233/JPD-140524
6. Bhidayasiri R, Jitkritsadakul O, Boonrod N, Sringean J, Calne SM, Hattori N, et al. What is the evidence to support home environmental adaptation in Parkinson's disease? A call for multidisciplinary interventions. *Parkinsonism Relat Disord* (2015) 21(10):1127–32. doi:10.1016/j.parkreldis.2015.08.025
7. Nilsson MH, Haak M, Iwarsson S. Housing and health: very old people with self-reported Parkinson's disease versus controls. *Parkinsons Dis* (2013) 2013:710839. doi:10.1155/2013/710839
8. Slaug B, Iwarsson S, Ayala JA, Nilsson MH. Housing accessibility problems for people with Parkinson's disease. *Acta Neurol Scand* (2017) 136(5):501–10. doi:10.1111/ane.12763

9. Nikolaus T, Bach M. Preventing falls in community-dwelling frail older people using a home intervention team (HIT): results from the randomized falls-HIT trial. *J Am Geriatr Soc* (2003) 51(3):300–5. doi:10.1046/j.1532-5415.2003.51102.x
10. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord* (2002) 8(3):193–7. doi:10.1016/S1353-8020(01)00015-3
11. Nijkrake MJ, Keus SH, Oostendorp RA, Overeem S, Mulleners W, Bloem BR, et al. Allied health care in Parkinson's disease: referral, consultation, and professional expertise. *Mov Disord* (2009) 24(2):282–6. doi:10.1002/mds.22377
12. Hatano T, Kubo SI, Shimo Y, Nishioka K, Hattori N. Unmet needs of patients with Parkinson's disease: interview survey of patients and caregivers. *J Int Med Res* (2009) 37(3):717–26. doi:10.1177/147323000903700315
13. Bhidayasiri R, Trenkwalder C. Getting a good night sleep? The importance of recognizing and treating nocturnal hypokinesia in Parkinson's disease. *Parkinsonism Relat Disord* (2018) 50:10–8. doi:10.1016/j.parkreldis.2018.01.008
14. Iwarsson S. The Housing Enabler: an objective tool for assessing accessibility. *Br J Occup Ther* (1999) 62(11):491–7. doi:10.1177/030802269906201104
15. Iwarsson S, Stahl A. Accessibility, usability and universal design – positioning and definition of concepts describing person-environment relationships. *Disabil Rehabil* (2003) 25(2):57–66. doi:10.1080/713813473
16. Fange A, Iwarsson S. Physical housing environment: development of a self-assessment instrument. *Can J Occup Ther* (1999) 66(5):250–60. doi:10.1177/000841749906600507
17. Oswald F, Wahl HW, Schilling O, Iwarsson S. Housing-related control beliefs and independence in activities of daily living in very old age. *Scand J Occup Ther* (2007) 14(1):33–43. doi:10.1080/11038120601151615
18. Martinez-Martin P, Gil-Nagel A, Gracia LM, Gomez JB, Martinez-Sarries J, Bermejo F. Unified Parkinson's disease rating scale characteristics and structure. The Cooperative Multicentric Group. *Mov Disord* (1994) 9(1):76–83. doi:10.1002/mds.870090112
19. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. *Mov Disord* (2007) 22(13):1901–11. doi:10.1002/mds.21596
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* (1975) 12(3):189–98. doi:10.1016/0022-3956(75)90026-6
21. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* (1960) 23:56–62. doi:10.1136/jnnp.23.1.56
22. Trenkwalder C, Kohnen R, Hogl B, Metta V, Sixel-Doring F, Frauscher B, et al. Parkinson's disease sleep scale – validation of the revised version PDSS-2. *Mov Disord* (2011) 26(4):644–52. doi:10.1002/mds.23476
23. American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology* (1996) 46(5):1470.
24. Evans JR, Mason SL, Williams-Gray CH, Foltynie T, Brayne C, Robbins TW, et al. The natural history of treated Parkinson's disease in an incident, community based cohort. *J Neurol Neurosurg Psychiatry* (2011) 82(10):1112–8. doi:10.1136/jnnp.2011.240366
25. Nonnekes J, Snijders AH, Nutt JG, Deuschl G, Giladi N, Bloem BR. Freezing of gait: a practical approach to management. *Lancet Neurol* (2015) 14(7):768–78. doi:10.1016/S1474-4422(15)00041-1
26. Iwarsson S, Nygren C, Slaug B. Cross-national and multi-professional inter-rater reliability of the Housing Enabler. *Scand J Occup Ther* (2005) 12(1):29–39. doi:10.1080/11038120510027144
27. Dorsey ER, Vlaanderen FP, Engelen LJ, Kieburtz K, Zhu W, Biglan KM, et al. Moving Parkinson care to the home. *Mov Disord* (2016) 31(9):1258–62. doi:10.1002/mds.26744
28. Bhidayasiri R, Martinez-Martin P. Clinical assessments in Parkinson's disease: scales and monitoring. *Int Rev Neurobiol* (2017) 132:129–82. doi:10.1016/bs.irn.2017.01.001
29. Bhidayasiri R, Mekawichai P, Jitkritsadakul O, Panyakaew P, Kaewwilai L, Boonrod N, et al. Nocturnal journey of body and mind in Parkinson's disease: the manifestations, risk factors and their relationship to daytime symptoms. Evidence from the NIGHT-PD study. *J Neural Transm* (2014) 121(Suppl 1):59–68. doi:10.1007/s00702-014-1199-x
30. Viwattanakulvanid P, Kaewwilai L, Jitkritsadakul O, Brenden NR, Setthawatcharawanich S, Boonrod N, et al. The impact of the nocturnal disabilities of Parkinson's disease on caregivers' burden: implications for interventions. *J Neural Transm* (2014) 121(Suppl 1):15–24. doi:10.1007/s00702-014-1200-8
31. Cianci H, Cloete L, Gardner J, Trail M, Wichmann R. *Activities of Daily Living: Practical Pointers for Parkinson's Disease*. Miami, FL: National Parkinson Foundation (2006).
32. Equipment for Getting In and Out of Bed. *The Parkinson's Disease Society of the United Kingdom [Online]*. UK (2017). Available from: https://www.parkinsons.org.uk/information-and-support/equipment-getting-and-out-bed [accessed January 25, 2018].

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REVIEW
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Accuracy of Rating Scales and Clinical Measures for Screening of Rapid Eye Movement Sleep Behavior Disorder and for Predicting Conversion to Parkinson's Disease and Other Synucleinopathies

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Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by repeated episodes of REM sleep-related vocalizations and/or complex motor behaviors. Definite diagnosis of RBD is based on history and polysomnography, both of which are less accessible due to the lack of trained specialists and high cost. While RBD may be associated with disorders like narcolepsy, focal brain lesions, and encephalitis, idiopathic RBD (iRBD) may convert to Parkinson's disease (PD) and other synucleinopathies in more than 80% of patients and it is to date the most specific clinical prodromal marker of PD. Identification of individuals at high risk for development of PD is becoming one of the most important topics for current PD-related research as well as for future treatment trials targeting prodromal PD. Furthermore, concomitant clinical symptoms, such as subtle motor impairment, hyposmia, autonomic dysfunction, or cognitive difficulties, in subjects with iRBD may herald its phenoconversion to clinically manifest parkinsonism. The assessment of these motor and non-motor symptoms in iRBD may increase the sensitivity and specificity in identifying prodromal PD subjects. This review evaluates the diagnostic accuracy of individual rating scales and validated single items for screening of RBD and the role and accuracy of available clinical, electrophysiological, imaging, and tissue biomarkers in predicting the phenoconversion from iRBD to clinically manifest synucleinopathies.

Keywords: Parkinson's disease, RBD, idiopathic, conversion, imaging, rating scales, non-motor, synuclein

INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) belongs to the parasomnias, which is a group of disorders characterized by paroxysmal motor and behavioral events occurring exclusively during sleep. RBD is defined by dream enactment and complex motor behaviors during REM sleep and loss of normal REM sleep muscle atonia (also known as REM sleep without

atonia—RSWA) as detected by polysomnography (PSG) (1). It is often associated with frightening dreams and may result in sleep-related injuries to the patients as well as to their sleeping partners (2). RBD can also be differentiated as symptomatic and idiopathic. Symptomatic RBD has been previously linked to several etiologies, especially synucleinopathies and narcolepsy, but also to brain lesions, autoimmune, and inflammatory disorders (3–5).

Several reports have shown, that idiopathic RBD (iRBD) may convert to Parkinson's disease (PD) or other synucleinopathies, including multiple system atrophy (MSA) and Dementia with Lewy Bodies (DLB), in more than 80% of patients (6, 7). While specificity of iRBD in identification of prodromal PD subjects seems to be very high, its prevalence in the general population is rather low and was reported in the range of 0.3–1.15% when confirmed by video-PSG in populations older than 60 years (2, 8). This prevalence may, however, be underreported as patients with mild severity of symptoms and those without sleeping partners are less likely to report their symptoms and seek medical care. On the other hand, various sleep disorders, such as severe obstructive sleep apnea (OSA), periodic limb movements (PLM), sleepwalking and others, may mimic RBD symptoms and may result in false-positive screening in questionnaire-based population studies. The definite diagnosis of RBD is based on history and PSG (1), both of which are less accessible due to the lack of trained specialists and cost. Thus, several instruments have been developed to enable large population screening and selection of candidates for more detailed testing in sleep centers. However, their diagnostic accuracy seems to depend on the studied population and instrument used and no clear recommendations have been made to this date regarding their use in routine clinical practice.

Parkinson's disease and other synucleinopathies are complex progressive multiorgan disorders affecting different neurotransmitter systems across the central, peripheral, and autonomic nervous systems, with Lewy bodies, Lewy neurites or glial cytoplasmic inclusions as their pathological hallmark (9, 10). In addition to iRBD, other well-recognized non-motor symptoms (NMS), such as hyposmia, constipation, or mood disorders; subtle motor abnormalities; and/or imaging findings may precede the onset of clinically relevant motor or cognitive symptoms by years or even decades (11). These known risk and prodromal markers have been recently summarized in the International Parkinson and Movement Disorder Society (MDS) research criteria for prodromal PD (11) and other novel biomarkers are still emerging. iRBD seems to be the most specific of these clinical prodromal markers so far and thus an optimal candidate for identifying patients for future disease-modifying and neuroprotective treatments. However, before these criteria can enter routine clinical practice, several key issues need to be addressed. These include the development of efficient tools for screening and identification of RBD subjects in the general population and the identification of other measures enabling accurate prediction and estimation of the time frame of phenoconversion from iRBD to a clinically manifest synucleinopathy.

Thus, the aim of this review is to summarize the current evidence on the diagnostic accuracy of screening instruments for identification of iRBD and to summarize the available data on other symptoms and signs, including presence of subtle motor dysfunction, NMS, neuroimaging findings, electrophysiological and tissue biomarkers, in predicting the phenoconversion of iRBD to PD and other synucleinopathies.

METHODS

We searched PubMed for all relevant articles until October 2017, using main search terms "RBD" or "REM sleep behavior disorder" combined with terms: "idiopathic," "Parkinson*," "DLB," "MSA," "synuclein*," "screen*," "questionnaire," "scale," "inventory," "accuracy," "sensitivity," "specificity," "conversion," "predict*," "motor," "UPDRS," "speech," "gait," "non-motor," "NMS," "olfactory," "hyposmia," "autonomic," "cardial," "urinary," "constipation," "sleepiness," "EDS," "cognit*," "imaging," "DaT," "PET," "MRI," "sonography," "SPECT," "substantia nigra," "serum," "CSF," "cerebrospinal," and "biopsy." Only studies in English language and related to human studies were included. All titles and abstracts were reviewed for relevance. References were supplemented by selection from the reference lists of identified papers, as well as personal knowledge of emerging literature.

ACCURACY OF SCREENING INSTRUMENTS FOR RBD

Definite diagnosis of RBD is based on PSG, which demands specific training, is costly and not widely available. Therefore, several screening instruments have been developed to enable screening for RBD. Four RBD-specific questionnaires, two single item RBD-screening questions, and two generic instruments containing items on RBD were identified and discussed below by order of available clinimetric data. The RBD severity scale was not included in this review, since it is based on rating of PSG recordings, and thus does not qualify as a screening tool for RBD *per se* (12).

REM Sleep Behavior Disorder Questionnaire Hong Kong (RBDQ-HK)

Scale Description

The RBDQ-HK was developed to evaluate the presence, but also the frequency and severity of RBD (13). A modified version with added screening questions on severe OSA (14) and validated language translations are available (15). The scale covers occurrence and frequency of dreams and nightmares, dream content, vocalizations during sleep, motor behaviors during sleep, injuries during sleep, and sleep disruptions. The RBDQ-HK is composed of 13 items, each assessing two dimensions—(a) lifetime occurrence (don't know, no, yes) and (b) recent 1-year frequency (once or few times per year; once or few times per month, 1–2 times per week, 3 times or above per week). Questions are weighted differentially and range from 0 (no RBD symptoms) to 100 (highest severity of RBD symptoms), based on the score for lifetime occurrence (0–20) and recent 1-year frequency (0–80). Factor analysis resulted in a significant two-factor solution, factor 1 being dream related (items 1–5 and 13, score range 0–30) and factor 2 evaluating behavioral manifestations (items 6–12, score

range 0–70). Administration time is typically up to 15–20 min. The scale is of public domain.

Clinimetric Properties

The scale has shown good reliability with Cronbach's alpha of 0.74–0.90 and test–retest intraclass correlation coefficients of 0.80–0.92 (13, 15, 16). Construct validity was good with a value of Kaiser–Meyer–Olkin's measure of sampling adequacy of 0.89–0.91 and Bartlett's test of sphericity which yielded a significance value of less than 0.001, rendering an exploratory factor analysis adequate for the RBDQ-HK questionnaire (13, 15). The RBDQ showed moderate correlation with the RBD-screening questionnaire ($r = 0.51$, $p < 0.01$) and low correlation with the RBD severity scale ($r = 0.35$, $p < 0.01$) (15). Sensitivity to change after treatment was demonstrated in multiple studies (17, 18).

Score Differences in Studied Populations

RBDQ-HK scores did not differ between early- and late-onset RBD (19) and also between subjects with iRBD, symptomatic RBD and RBD-like disorders due to psychotropic medications or psychiatric illness (13). Males were found to have significantly higher scores for behavioral manifestations (factor 2) ($p = 0.019$), with more dream-related movements and falling out of bed compared to females (20). RBDQ-HK scores in subjects with RBD and dementia were found to be significantly higher ($p = 0.029$) compared to RBD patients without dementia (21).

Diagnostic Accuracy

There are four studies that have evaluated the diagnostic accuracy of the RBDQ in PSG-confirmed RBD populations with acceptable to excellent results for diagnostic accuracy in the general RBD population with iRBD, PD-related RBD and RBD-like disorders due to psychotropic medications and psychiatric illness (13–16) (see **Table 1**). The sensitivity and positive predictive value (PPV) of RBDQ-HK were lower in OSA patients. Shen et al. (16) reported superior diagnostic accuracy of Factor 2 score compared to total RBDQ score in their total RBD sample as well as in PD and OSA patients. Also, adding two items related to OSA in the modified RBDQ-Beijing scale (14) resulted in improved specificity and PPV, while excellent sensitivity and negative predictive value (NPV) were retained.

Strengths and Limitations

The RBDQ-HK is a well validated instrument with good psychometric properties and good diagnostic accuracy. Compared to some other RBD-screening instruments it evaluates not only presence, but also frequency and severity of RBD symptoms historically and more recently. On the other hand, due to its relatively longer administration time, it is less suitable for first line screening in large population-based studies. Although the English version of the scale has been published, it seems that it was not translated systematically, was not validated, and thus has some cultural specific phrases (e.g., chased by a ghost) that may not be appropriate in non-Chinese populations (22).

TABLE 1 | Diagnostic accuracy of the rapid eye movement (REM) sleep behavior questionnaire (RBDQ-HK).

Reference	Study population	No of subjects	Mean values	Proposed cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	Comments
Li et al. (13)	Total RBD sample	107	32.1 ± 16.1	18/19	82.2	86.9	86.3	83.0	0.90	*Mostly associated with psychotropic medications and psychiatric illness **RBDQ-HK items 6–12—behavioral manifestations, score range 0–70
	iRBD	51	29.7 ± 15.5	18/19	78.4	86.9	74.1	89.4	0.89	
	sRBD (mostly PD)	29	30.8 ± 17.3	18/19	79.3	86.9	62.2	93.9	0.88	
	RBD-like disorders*	27	38.1 ± 14.9	20/21	92.6	86.9	64.1	98.0	0.94	
	Factor 2 score**	107		7/8	87.9	81.3	82.5	87.0	0.92	
	Controls	107	9.5 ± 10.2							
Sasai et al. (15)	iRBD Controls	122 106	46.4 ± 12.6 5.7 ± 6.8	19/20	97.2	97.5	97.5	97.2	0.99	
Shen et al. (16)	All RBD	115								**RBDQ-HK items 6–12—behavioral manifestations, score range 0–70
	Total score		38.4 ± 21.7	17	84.4	81.0	70.8	90.4	0.89	
	Factor 2 score**			7/8	90.4	82.2	73.8	94.0	0.91	
	PD patients	95	32.6 ± 23.1							
	With RBD	61								
	Total score		42.1 ± 21.5	18	86.9	70.6	81.8	75.8	0.84	
	Factor 2 score**			13	83.6	76.5	87.4	65.6	0.86	
	Without RBD	34	15.7 ± 15.0							
	OSA patients	144	12.0 ± 13.2							
	With RBD	30								
	Total score		26.3 ± 18.1	17	70.0	86.8	52.5	91.4	0.85	
	Factor 2 score**			7	83.3	87.7	64.1	95.2	0.88	
	Without RBD	114	8.2 ± 8.3							
Chang et al. (14)	All RBD	118								***Modified version RBDQ-Beijing includes 2 additional items on OSAS, scores range 0–110
	RBDQ-HK	118		18/19	97.1	83.2	86.4	96.3		
	RBDQ-Beijing***	118		28/29	95.8	94.3	95.0	95.2		
	Controls	106								

PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve; iRBD, idiopathic REM sleep behavior disorder; sRBD, symptomatic REM sleep behavior disorder; PD, Parkinson's disease; OSAS, obstructive sleep apnea syndrome; OSA, obstructive sleep apnea.

REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)

Scale Description

The RBDSQ was developed as a simple screening tool for RBD (23). The scale was originally developed in English and German, but currently several validated language translations are available (24–27). The RBDSQ covers frequency, dream content, nocturnal movements, injuries to self or bed partner, types of motor behaviors during the night, nocturnal awakenings, sleep disruption, and the presence of neurological diseases. It is comprised of 13 yes/no questions. Total scores range from 0 (no symptoms) to 13 (maximum score). Administration time is typically 5 min. The scale is of public domain.

Clinimetric Properties

The scale has shown good reliability with Cronbach's alpha of 0.77–0.89 (23, 25) and test–retest intraclass correlation coefficients of 0.84–0.95 (24, 26). In the original validation cohort, the item test correlations ranged from 0.34 (item 9) to 0.75 (item 6.1) (acceptable if > 0.30). In the Italian version of RBDSQ item 10 had a low item-total correlation (0.14) (27). Regarding convergent validity, the RBDSQ showed moderate correlations with the RBDQ-HK ($r = 0.51$, $p < 0.001$) (15). On the other hand, significant correlations with the PLM index, number of PLM during sleep and PLM during wakefulness was found in a cohort suffering with other sleep disturbances (23). Sensitivity to change after treatment has not been studied. Stefani et al. (28) have shown an increase of RBDSQ score by 1 point ($p < 0.001$) in the general population over 2 years, however, the consistency of score changes over this period was low (Spearmen $r = 0.35$; ICC 0.39).

Score Differences in Studied Populations

RBDSQ scores did not correlate with age (28) or duration of RBD (23). There were no gender differences between RBDSQ total scores, nevertheless, men had more fights, violent behaviors, and awakenings by own movement, while women experienced more disturbed sleep (29). The mean RBDSQ scores of subjects with iRBD were similar to those with symptomatic RBD, but significantly higher compared to patients with other sleep disturbances, PD without RBD or healthy controls (25). The scores of RBDSQ in patients with other sleep disturbances were highest for subjects with sleepwalking and epilepsy, followed by narcolepsy, insomnia, PLM, restless legs (RLS) or hypersomnia. Scores of RBD patients with and without narcolepsy did not differ (23).

Diagnostic Accuracy

There are nine studies that have evaluated the diagnostic accuracy of the RBDSQ in PSG-confirmed RBD populations with sensitivity ranging from moderate to excellent and specificity ranging from low to excellent based on study population and cutoff used (see **Table 2**). While both sensitivity and specificity were good to excellent when comparing RBD subjects with healthy controls, the specificity was generally lower when including other sleep disorders in the control groups. Stiasny-Kolster et al. (30) have shown that administration of the RBDSQ in randomly selected PD patients without prior sleep interviews yielded only moderate sensitivity and specificity as opposed to a PD cohort which was specifically selected for validation of the RBDSQ and included a sleep interview prior to administration of the questionnaire. Mixed specificity was found in studies evaluating diagnostic accuracy of RBDSQ in OSA (24, 26). Using a cutoff value of 5, a recent meta-analysis found pooled sensitivity, specificity, positive likelihood ratio (LR), negative LR, and diagnostic odds ratio (OR) of RBDSQ to be 0.91 (95% confidence interval (CI) 0.85–0.95), 0.77 (95% CI 0.66–0.85), 4.00 (95% CI 2.60–6.10), 0.12 (95% CI 0.07–0.19), and 34 (95% CI 16–71), respectively (31).

Strengths and Limitations

The RBDSQ is currently the most commonly used screening instrument for RBD, with short administration time, good reliability and overall good diagnostic accuracy in the general population. However, different aspects of validity have not been properly studied, sensitivity to change after treatment has not been demonstrated and its diagnostic accuracy in specific populations, such as subjects with other sleep disorders or in randomly selected PD patients without prior interview, was less satisfactory (31).

Mayo Sleep Questionnaire (MSQ)

Scale Description

In 2001, two versions of the MSQ were originally developed, one to be filled out by the patient and the other by his/her bedside partner/informant. Pilot data showed that the informant sleeping in the same room provided information with higher sensitivity and specificity than the patient (regardless of patient cognitive status) when correlated with PSG (35). Thus, the partner/informant version is currently the most widely used. It is a 16-item scale that screens for the presence of RBD but also for periodic leg movements (PLM), RLS, sleep walking, OSA and sleep-related leg cramps. There is one sole screening question for RBD (question 1) which asks about acting out dreams (punching/screaming) and is answered yes or no if the behavior has happened at least three times (time frame is since you remember). If yes, the partner continues to answer the subsequent 5 items (a–e). The questionnaire can be completed in about 2 min and is of public domain.

Clinimetric Properties

Published data on reliability, validity, with exception of criterion validity (see diagnostic accuracy below), and sensitivity to change are not available.

Diagnostic Accuracy

Question 1 of this questionnaire has been found to have an excellent sensitivity and acceptable to excellent specificity for determining the presence of RBD when compared to PSG results (36, 37) (see **Table 3**). Four additional questions on dream enactment leading to patient or partner injuries, dream content and its correlation with movements, improved specificity (36). In further studies, Chahine et al. (33) and Bolitho et al. (38) diagnosed RBD

TABLE 2 | Diagnostic accuracy of the Rapid Eye Movement (REM) sleep behavior screening questionnaire (RBDSQ).

Reference	Study population	No of subjects	Mean values	Proposed cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	Comments
Stiasny-Kolster et al. (23)	RBD	54	9.5 ± 2.8							*Including other sleep-related distrubances
	All controls*	160	4.6 ± 3.0	5	96	56	–	–	0.87	
	Healthy controls	133	2.0 ± 1.8	5	96	92	–	–		
Marelli et al. (27)	All RBD	76	9.8 ± 2.3				–	–	0.89	*Including other sleep-related disturbances **without item 10
	All Controls*	405*	5.2 ± 2.8	8	84	78	–	–		
				5	97	46	–	–	0.90	
	Modified RBDSQ**			8	83	82				
Wang et al. (25)	iRBD	41	8.1 ± 2.7							
	Other sleep abnormalities	78	3.2 ± 1.7	5	90.2	82.1	–	–	0.93	
	Healthy controls	50	2.3 ± 2.0	5	90.2	76.0	–	–	0.95	
	sRBD	22	8.0 ± 2.0	6	90.9	91.9	–	–	0.97	
Miyamoto et al. (24)	iRBD	52	7.5 ± 2.8							
	Healthy controls	65	1.6 ± 1.2	4.5	88.5	96.9	97.9	91.4	0.97	
	OSA	55	1.9 ± 2.3	4.5	88.5	90.9	90.2	89.3	0.93	
Comert et al. (26)	RBD	17	9.4 ± 1.6							
	OSA	28	4.1 ± 2.9	5	100	64	63	100	0.92	
	Healthy controls	78	2.9 ± 2.2	5	100	87	63	100	0.97	
Lee et al. (32)	iRBD	47	9.0 ± 2.0							*Newly diagnosed and untreated, patients with other sleep disturbances excluded
	OSA	213*	2.0 ± 3.0	6.5	85.1	93.4	74.1	96.6	0.92	
				4.5	89.4	77.5	46.7	97.1		
	Healthy controls	58	1.0 ± 3.0	4.5	89.4	98.3	97.7	91.9	0.99	
Chahine et al. (33)	PD with RBD PD without RBD			7	74.2	82.4			0.80	
Nomura et al. (34)	PD with RBD	19	7.2 ± 1.9							All RBD versus non-RBD
	PD without RBD	26	2.9 ± 1.6	6	84.2	96.2				
	iRBD	31	7.9 ± 2.8							
Stiasny-Kolster et al. (30)	PD with RBD (A)	37	7.5 ± 2.4	5	90.0	87.0			0.95	A—PD sample specifically selected to validate RBDSQ including prior interview B—randomly selected PD patients without prior interview
	PD without RBD (A)	15	3.1 ± 1.4	6	78.0	100				
	PD with RBD (B)	56	6.0 ± 3.1	5	68.0	63.0			0.67	
	PD without RBD (B)	19	4.2 ± 2.7	6	64.0	68.0				

PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve; iRBD, idiopathic REM sleep behavior disorder; sRBD, symptomatic REM sleep behavior disorder; PD, Parkinson's disease; OSA, obstructive sleep apnea.

in PD populations based on PSG and contrasted results with several RBD questionnaires, including the MSQ (see **Table 3**), which showed high sensitivity but low specificity.

Score Differences in Studied Populations

This questionnaire has been used by the group that developed it in two studies with aging and predominantly male populations (mean age 71, median age 77, respectively) (36, 37). The earlier publication studied an aging and dementia cohort (controls = 8, MCI = 44, AD = 23, DLB = 74, dementia with parkinsonism other = 27) where 55% had RBD (36). The second studied a community-based cohort with mostly cognitively normal subjects and only 5% were found to have RBD (37).

Strengths and Limitations

The questionnaire is simple and easy to complete. However, it is limited to patients with a partner that sleeps in the same room or has slept in the same room. The MSQ has a single question that screens for RBD, clinimetric properties of the questionnaire and this single question require further study.

Innsbruck RBD Inventory (RBD-I)

Scale Description

The Innsbruck RBD-I (39) is a short screening questionnaire for RBD made up of five questions. The questions are answered yes (1), no (0), or don't know. The RBD symptom score is equal to the number of positive answers divided by the number of answered questions and thus ranges between 0 and 1. The second part of the questionnaire determines frequency of behavior and ranges from never (0) to very frequent (4). RBD frequency score is the sum of all frequency scores divided by the number of questions answered, thus ranging from 0 (minimum) to 4 (maximum) and may give information about severity. It can be completed in a few minutes. There is an English and a German version.

TABLE 3 | Diagnostic accuracy of other RBD rating scales and screening items.

Scale	Reference	Study population	No of subjects	Proposed cutoff	Sensitivity	Specificity	PPV	NPV	AUC	Comments
MSQ	Boeve et al. (36)	Aging dementia cohort	176	Yes (core question 1)	98	74				
MSQ	Boeve et al. (5, 37)	Community based (normal, MCI, AD)	95		100	95				
MSQ	Chahine et al. (33)	PD	75	Yes/no question 1	90.3	54.6			0.7	69.3% correctly classified. 2.0 (1.4–2.8) + LR
MSQ	Bolitho et al. (38)	PD	46/31 with bed partners	Yes (core question 1)	95	64	83	88		vs REM EMG density
					100	36	43	100		vs REM atonia index
RBD-I	Frauscher et al. (39, 40)	RBD (idiopathic, PD, narcolepsy, other) and controls	210	0.25	91.4	85.7			0.886	
IRBDIQ	Frauscher et al. (39, 40)	Same as above	210	Single item	74.3	92.9			0.836	
RBD1Q	Postuma et al. (21, 41, 42)	iRBD Controls—healthy subjects, OSA, RLS, other	242 242	Single item	93.8	87.2	87.9	93.4	0.905	
RBD1Q	Bolitho et al. (38)	PD with/without RBD	46	Single item	100	48	48	100		vs REM atonia index
					93	68	81	87		vs REM EMG density
RBD1Q	Ma et al. (43)	iRBD Controls	14 18	Single item	100	55.6	63.6	100	0.778	

PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve; MSQ, Mayo Sleep Questionnaire; MCI, mild cognitive impairment; AD, Alzheimer disease; PD, Parkinson disease; +LR, positive likelihood ratio; REM, rapid eye movement; EMG, electromyography; RBD-I, Innsbruck RBD inventory; IRBDIQ, Innsbruck RBD Inventory Single Question; RBD1Q, RBD single-question screening; OSA, obstructive sleep apnea; RLS, restless legs syndrome; iRBD, idiopathic RBD.

Clinimetric Properties

Cronbach's alpha for RBD-I was 0.855, test-retest reliability was not assessed (39). Correlation between RBD frequency score and patient global impression was 0.305 ($p = 0.011$) (39). There is no data available on sensitivity to change.

Diagnostic Accuracy

This inventory was validated in a population of 70 RBD subjects and 140 controls. Originally the questionnaire had 7 REM sleep-related questions and 2 non-REM behavior control items (sleep walking, snoring). Only the response patterns to the REM sleep items discriminated between patients and controls ($p < 0.05$). Five of the 9 items had an AUC > 0.7 and were thus included in the final version of the questionnaire (See **Table 3**). The sensitivity and specificity of RBD-I in a single cohort of clinically diagnosed iRBD patients versus healthy controls reporting on diagnostic accuracy was good-excellent (39).

Score Differences in Study Populations

In the validation study, there were no differences in scores between the PD population and the iRBD group nor between patients with or without bed partners (39).

Strengths and Limitations

This simple and easy to complete questionnaire can be used for screening and may give information about RBD severity based on the frequency score. However, the original study was performed on a population that had an RBD diagnosis based on PSG which may have influenced questionnaire completion. Further validation and reliability data and data from other groups beyond the developers are needed.

Single RBD-Screening Questions

REM Sleep Behavior Disorder Single-Question Screening (RBD1Q)

The RBD1Q was developed as a simple screening tool for large-scale epidemiological studies (41) It consists of a single question, answered "yes" or "no," as follows: "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?" This question was initially translated into French, German, Japanese, Italian, Spanish, Czech and Danish, and subsequently also in multiple other languages. The screen was designed to be self-administered, with participation by spouses/caregivers encouraged. If literacy was poor, administration by rater was allowed. The RBD1Q is of the public domain.

Diagnostic Accuracy

The sensitivity and specificity of RBD1Q was found good-excellent compared to controls and OSA in the initial validation study of iRBD patients and the sensitivity and specificity were not significantly altered after excluding patients who lived alone,

were using antidepressants, clonazepam, or melatonin (41). While sensitivity was generally excellent across other studies as well, the specificity of RBD1Q was found low to moderate when evaluating RBD1Q against PSG criteria in other studies (38, 43) (see **Table 3**).

Strengths and Limitations

The RBD1Q is the most commonly used single question screening instrument for RBD with a good-excellent sensitivity across multiple studies, and thus a good candidate for first step screening in large-scale population studies. Nevertheless, it does not screen for sleep talking and sleep yelling, which might be the only manifestations of RBD in a subset of patients and may be, therefore, missed on screening. Also the specificity of the scale was found rather low in multiple studies.

Innsbruck RBD-I Single Question (IRBDIQ)

The same group that developed the RBD-I (39) also assessed the value of a single RBD summary question: "Do you hit or kick because you dream that you have to defend yourself?" Based on this yes or no answer, the patient is classified as probable RBD or not.

Diagnostic Accuracy

This single item showed low sensitivity and high specificity in the original validating study (see **Table 3**).

Strengths and Limitations

The single question asks about violent dream enactment behaviors and thus has a high specificity for RBD. However, it may miss milder cases showing a relatively moderate sensitivity. Therefore, this summary question is not recommended for screening in the general population but may prove useful in population-based neurodegenerative risk-marker studies.

Generic Rating Scales Including RBD-Related Items

The Non-Motor Symptom Questionnaire (NMQuest)

Scale Description

The NMSQuest (44) is a PD-specific global scale to screen for NMS. It is made up of 30 yes/no questions covering 10 domains: cardiovascular (2 items), gastrointestinal (8), urinary (2), sexual (2), sleep/fatigue (5), sudomotor (1), and miscellaneous (10). Two items refer to RBD-related symptoms referring to the presence of vivid or frightening dreams (question 24) and, more specifically, to moving in dreams as if acting them out (question 25). It is a patient reported outcome and can be completed in 5–10 min.

Clinimetric Properties

The original publication demonstrated good validity, feasibility and acceptability with low ceiling and floor effects (44). Further testing showed moderate average sensitivity for all items (63.4%) and high mean specificity for most items (88.5%) (45). As far as RBD, this study used a semi-structured clinical interview for RBD diagnosis and found that item 25 had a 69.7% sensitivity, 91.4% specificity, and PPV of 88.5% and NPV of 76.2%.

Strengths and Limitations

This questionnaire can be recommended for screening NMS in PD and has been proposed to evaluate burden of NMS as a whole (46). The MDS task force recommended or suggested the NMSQuest for screening of some non-motor domains such as gastrointestinal, urinary and orthostatic symptoms (47). The role of the two sleep items on the NMSQuest alluding to possible REM sleep disturbances in screening for RBD requires further testing and comparison to polysomnographic results. Therefore, the diagnostic value of NMSQuest in screening for RBD or for predicting conversion to synucleinopathies is not known at this moment.

The Movement Disorders Non-Motor Symptom Scale (MDS-NMSS)

The MDS-NMSS is currently in the process of validation (48). This revised version of the Non-Motor Symptom Scale (NMSS) is designed to include one item in the sleep wakefulness domain that alludes to RBD symptoms. Supposedly, the clinician will ask the patient and his partner about acting out dreams while asleep, such as shouting, flailing arms, punching, or running movements. As in the original NMSS, the time frame will be the last month and the rater will evaluate for presence of the symptom and its frequency. The addition of this item to the NMSS demonstrates the importance of RBD as a salient NMS in PD.

DIAGNOSTIC ACCURACY OF CLINICAL MEASURES FOR PREDICTING CONVERSION TO PD AND OTHER SYNUCLEINOPATHIES

Subtle Motor Impairment

Among different prodromal markers, subtle motor dysfunction strongly predicts conversion from iRBD to degenerative parkinsonism, regardless of primary diagnosis of PD or DLB (49). However, studies investigating different aspects of subtle motor changes in iRBD are rather scarce. Most evidence is based on a cross-sectional study comparing results of 68 iRBD subjects to 36 controls, 34 PD patients with RBD and 21 PD patients without RBD using clinical scales and quantitative motor testing (50). In addition, a follow-up longitudinal study investigated motor changes in 20 subjects with iRBD who developed parkinsonism and their motor testing results from the preceding 5 years were assessed with regression analysis to determine when clinical markers first deviated from normal values (42). Pilot results regarding instrumental assessment of speech and gait dysfunction in iRBD have also been published (51–54).

Unified Parkinson's Disease Rating Scale (UPDRS)/ Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

Although examination using the UPDRS is rather subjective and requires a well-trained examiner, it still represents the most widely used instrument for measuring severity of parkinsonian symptoms with the motor part allowing assessment of the cardinal manifestations of PD including bradykinesia, rigidity,

resting tremor and gait abnormalities (55). The MDS-UPDRS was developed to address the identified shortcomings of the original UPDRS (56). It discriminates the slight and mild manifestations of the disease making the scale preferable in early stages of disease, provides uniform item scoring and clear instructions to both raters and patients (56). Higher UPDRS part III (motor examination) scores associated with increased risk of parkinsonism were observed in iRBD compared to controls (42, 50). In particular, higher UPDRS part III scores have been estimated to deviate from normal values approximately 4.5 years before diagnosis (42). The diagnostic cutoff value was identified as UPDRS part III >3 points and MDS-UPDRS part III (motor examination) >6 points with removal of action tremor, which is common in non-parkinsonian conditions (11, 42). Such scores on the UPDRS 2 years prior showed a very high specificity of 97% and sensitivity of 94% with overall area under curve (AUC) of 0.99 for conversion to parkinsonism (42),. These cutoffs, however, still need to be validated in more prospective trials, as up to 30% of elderly patients may score >6 points on the MDS-UPDRS part III without including the action tremor items (57).

Hand Motor Speed Tests

Upper limb movements in iRBD possibly present with both rigidity and bradykinesia. Indeed, UPDRS subscores on rigidity and limb bradykinesia deviated from normal values at estimated intervals of 4.4 and 4.2 years before diagnosis, respectively (42). In addition, patients with iRBD showed deteriorated performance in Purdue pegboard and alternate tap tests compared to controls (50). Scores on these hand motor speed tests have been estimated to deviate from normal values at 8.6 and 8.2 years before diagnosis of PD, respectively (42). Using the Purdue pegboard and alternate tap tests, parkinsonism in iRBD patients may be detected 3 years before clinical diagnosis with a 71–82% sensitivity and specificity (AUC = ~0.80) (42). These findings need to be reproduced in an independent population.

Speech Impairment

Based upon UPDRS scores, longitudinal changes in items evaluating voice/face in an iRBD population were estimated as the first motor signs to develop 9.8 years before diagnosis followed by rigidity, gait abnormalities, and limb bradykinesia (42). The assumption that speech impairment in iRBD represents a sensitive prodromal marker of neurodegeneration was consequently confirmed by a pilot cross-sectional study comparing vocal performance in 16 iRBD patients and 16 controls using quantitative and objective acoustic voice analysis (54). Some form of speech impairment was observed in 88% of iRBD subjects, leading to a promising sensitivity of 96% and specificity of 79% (AUC = 0.83) in distinguishing between iRBD and control subjects (54). Subsequently, automated analysis of connected speech revealed similar speech timing deficits in independent cohorts of 50 iRBD and 30 *de novo* PD patients (53). The main speech abnormalities found in iRBD were prolonged duration of pauses, longer length of stop consonants and decreased rate of switching between follow-up speech segments (53). In general, speech disorders were more prominent in iRBD subjects with higher motor scores on the UPDRS (53, 54), suggesting that speech impairment partially parallels increasing motor disability due to the underlying neurodegenerative process. Nevertheless, the potential predictive value of instrumentally assessed vocal abnormalities needs to be established in prospective follow-up studies.

Gait Dysfunction

Gait abnormalities in iRBD deviated from normal values at an estimated interval of 4.4 years based on the UPDRS and 6.3 years using the timed up-and-go test before formal diagnosis of PD (42). Timed up-and-go test statistically separated iRBD from controls (50) and was able to distinguish both groups with a high sensitivity 90% but low specificity 46% (AUC = 0.71) 3 years before conversion of the subject with iRBD to parkinsonism (42). Based on automated gait analysis (GAITRite) collected from 42 probable RBD subjects and 492 controls, presence of RBD was associated with decreased velocity and cadence, increased double limb support variability, and greater stride time variability and swing time variability (51). Furthermore, in a pilot study based on four groups of 10 participants, significant reductions were seen in the posterior shift of the center of pressure during the propulsive phase of gait initiation in the iRBD and PD with freezing of gait patients compared to controls and PD subjects without freezing of gait (52). These reductions negatively correlated with the amount of REM sleep without atonia (52). Longitudinal studies are necessary to estimate reliability of instrumental gait analysis to predict conversion from iRBD into parkinsonism.

Conclusion

Motor abnormalities are very strong predictors of conversion to synucleinopathy with one of the greatest hazard ratios (HR) of 3.9 among available predictive markers to date (49). However, no consensus exists on the ideal method for examination of these subtle motor changes. For example, no agreement has been reached whether to use traditional scales or instrumental devices or whether to focus on movement velocity or amplitude. Several objective quantitative methods for testing motor function are being developed. In particular, assessment of *s*peech and gait dysfunction seem to have potential to provide sensitive motor markers of prodromal neurodegeneration; however, longitudinal studies are necessary to estimate predictive values of these examinations.

Non-Motor Symptoms

Multiple prodromal clinical NMS have been studied in iRBD patients to identify subjects with an increased risk and time frame of conversion to synucleinopathy. Most of these NMS are recognized as risk or prodromal markers for development of PD (11).

Olfactory Loss

Several studies have shown increased prevalence of olfactory impairment in iRBD subjects compared to healthy controls and similar, or slightly lower, prevalence compared to clinically diagnosed PD patients (50, 58–61). In one study (62), 9 of the 34 iRBD patients converted over a 5-year follow-up period, 6 to PD, 3 to DLB, and significantly higher prevalence of olfactory dysfunction was found in converters compared to non-converters. The Sniffin' Sticks test showed a diagnostic accuracy of 82.4% in predicting

conversion after 2.4 ± 1.7 years. Similarly, Fereshtehnejad et al. (63) found a significantly higher prevalence of olfactory dysfunction, measured by the UPSIT-12, in iRBD subjects who converted compared to those who did not convert to synucleinopathy (75.0 vs 46.6%). In this study, prodromal NMS appeared to be largely independent of one another while interaction between hyposmia and quantitative motor testing was found. In this regard, abnormal baseline quantitative motor testing increased conversion only in subjects who also had hyposmia (OR = 10.0; 95% CI: 3.3–30.3; $p < 0.001$), with no predictive value in those with normal olfaction (OR = 1.1; 95% CI: 0.2–6.3; $p = 0.91$) (63). Mean disease-free follow-up in this study was 3.6 years, while total follow-up duration was 5.7 years. On the other hand, in another iRBD cohort, Li et al. (64) in their iRBD cohort found slightly worse olfaction scores in converters compared to non-converters, this was not statistically significant (HR = 1.22; adjusted 95% CI: 0.48–3.11).

Conclusion

Olfactory loss is significantly higher in iRBD subjects compared to healthy controls, severity is reported to be intermediate between controls and PD patients. Olfactory dysfunction may predict early conversion to clinically manifest synucleinopathy and seems to be independent from other NMS. The time frame of conversion needs to be furtherly investigated.

Dysautonomia

Clinical Evaluation and Rating Scales

Neurodegenerative synucleinopathies are frequently accompanied by autonomic dysfunction: constipation, urinary frequency, urinary incontinence, erectile dysfunction, and orthostatic blood pressure drop.

Patients with iRBD experience significantly more gastrointestinal, urinary, and cardiovascular functioning problems in comparison to healthy controls (50, 60, 61, 65) and frequency and severity of constipation were reportedly similar to PD patients in one study (61). Systolic blood pressure drop was found to be significantly higher in PD patients with RBD than in those without RBD in an earlier study (50).

In a prospective observational study comparing 32 converted RBD subjects versus 59 non-converted patients (66), autonomic dysfunction evaluated by the Unified Multiple System Atrophy Rating Scale (UMSARS) was more prominent in patients who had RBD with defined synucleinopathy than in iRBD subjects. Even more systolic drop, erectile dysfunction, and constipation could identify disease conversion up to 5 years in advance, with sensitivity ranging from 50 to 90% (66).

In a multicenter study of iRBD subjects, the 93 convertors scored significantly higher on SCOPA-AUT than the 186 non-convertors (14.1 ± 6.1 vs 12.0 ± 6.9) (67). The differences were primarily related to increases in the gastrointestinal and cardiovascular domains, with an additional statistically non-significant increase in urinary symptoms.

Fereshtehnejad et al. (63) calculated the risk of conversion to PD/DLB in their longitudinal study of iRBD subjects based on MDS research criteria for prodromal PD, including assessment of constipation, erectile dysfunction, urinary dysfunction and orthostatic hypotension (see **Table 4**). The prodromal criteria had 81.3% sensitivity and 67.9% specificity for conversion to PD/DLB at 4-year follow-up, while one year before conversion, sensitivity was 100%. The MDS criteria predicted conversion to DLB with even higher accuracy than to PD without dementia at disease onset.

The recent study by Li et al. (64) confirmed that patients with higher scores on the NMSQuest and SCOPA-AUT were more likely to develop synucleinopathy (see **Table 4**).

Conclusion

Questionnaire-assessed autonomic dysfunction is significantly more frequent and severe in iRBD compared to controls. Orthostatic drop, erectile dysfunction, and constipation independently increase the LR for the conversion to synucleinopathy.

TABLE 4 | Predictive value of autonomic symptoms for phenoconversion in idiopathic RBD subjects.

Study	Study population	AUTONOMIC SYMPTOMS			
Postuma et al. (67)	Non-convertors *n* = 169 vs convertors *n* = 72 (PD = 39, Possible DLB = 47, MSA = 7)		SCOPA – AUT* total 11.97 ± 6.93 vs 14.07 ± 6.05 Adjusted OR (95% CI) 1.13 (1.01–1.25)		
Li et al. (31, 64)	Non-convertors *n* = 25 vs Convertors *n* = 18 (DLB = 2, MSA = 3, PD/mild cognitive impairment = 4, and PD = 9)	CONSTIPATION Response: Yes 56 vs 66.7% HR (95% CI, adjusted) 1.48 (0.55–3.98)	SCOPA – AUT** ≥ 11 20 vs 66.7% HR (95% CI, adjusted) 4.46 (1.64–2.10)	NMSQ ≥ 12 8 vs 33.3% HR (95% CI, adjusted) 3.11 (1.15–8.40)	
Fereshtehnejad et al. (63)	Non-convertors *n* = 73 Convertors *n* = 48 (PD/DLB)	CONSTIPATION* UMSARS score ≥ 2 19.1 vs 31.2% +LR 1.63 (0.87–3.06)	Erectile dysfunction* (only men) UMSARS score ≥ 3 30.4 vs 44.1% +LR 1.45 (0.84–2.51)	Urinary dysfunction UMSARS score ≥ 2 2.7 vs 8.3% +LR 3.04 (0.58–15.96)	Orthostatic hypotension** UMSARS score ≥ 2 23.3 vs 45.8% + LR 1.97 (1.17–3.30)

PD, Parkinson's disease; DLB, dementia with Lewy Body; MSA, multiple system atrophy; SCOPA-AUT, Scale for Outcomes in Parkinson Disease—Autonomic; OR, odds ratio; CI, confidence interval; NMSQ, Non-Motor Symptom Questionnaire; HR. hazard ratio; UMSARS. Unified Multiple System Atrophy Rating Scale; Orthostatic hypotension tested by manual measurement of blood pressure in supine position and after 1-min standing; +LR, positive likelihood ratio.
**p < 0.05; **p < 0.01; ***p < 0.001.*

There is not enough evidence to support the predictive role of urinary dysfunction in iRBD subjects specifically. Severity of autonomic dysfunction in iRBD and PD patients was found comparable in some of the studies.

Electrophysiological Testing and Imaging

Cardiac autonomic testing during wakefulness showed that only 5/14 patients (36%) with RBD (10 iRBD) had normal results in all traditional autonomic tests during wakefulness, and all had reduced heart rate variability (HRV) during sleep (68). While reduced nocturnal HRV generally correlated with impairment while awake, patients with normal autonomic activity during wakefulness showed reduced nocturnal HRV. Another study also (69) found significant differences in HRV between iRBD and healthy control subjects; however, the investigators did not find a difference between those who converted to PD, MSA or DLB and those who did not. Also, RR interval, HRV, and respiratory frequency remained stable in RBD subjects in comparison with healthy controls when evaluated from stage 2 NREM to REM sleep (70). Sorensen et al. (71) found an attenuated sympathetic nervous system activity in RBD patients (11 iRBD, 14 PD patients with RBD) based on HRV evaluation compared to controls. The HRV pathology was even more pronounced in PD patients compared to iRBD. Another study (72) analyzed heart rate response to arousals or to leg movements during sleep in PD patients with RBD or without RBD, iRBD subjects and healthy controls. The heart rate responses for the iRBD group were intermediate with respect to the control and PD groups. Frauscher et al. (40) showed that, in a cohort of 15 iRBD subjects, 15 controls, and 15 PD patients: (a) blood pressure changes in the tilt table examination were similar between iRBD patients and healthy controls, but blood pressure drops were more pronounced in PD; (b) in the orthostatic standing test, iRBD patients had higher blood pressure changes than healthy controls and highest drops were found in the PD group; (c) Valsalva ratio was lower in iRBD and PD compared to healthy controls; and (d) total COMPASS score was higher in iRBD compared to healthy controls, with highest scores found in PD.

Conclusion

Heart rate variability, peripheral sympathetic system activity, autonomic responses to arousal and leg movements in sleep and orthostatic testing show higher prevalence and severity of autonomic dysfunction in iRBD subjects compared to healthy controls. Autonomic evaluation during sleep could identify impaired cardiac dysautonomia in RBD patients earlier than the traditional tests during wakefulness. There is insufficient evidence to calculate diagnostic accuracy of electrophysiological testing in prediction of phenoconversion to manifest synucleinopathy.

Daytime Sleepiness

Excessive daytime sleepiness (EDS) is associated with the later stages of PD and there are studies documenting higher risk of PD in men reporting daily napping (73). Arnulf et al. (74) showed that the 75 patients with iRBD in their study were sleepier (Epsworth Sleepiness Scale (ESS): 7.8 ± 4.6) at the time of RBD diagnosis than 74 age- and sex-matched controls (ESS: 5.0 ± 3.6, $p < 0.0001$). Those who had ESS scores greater than 8 at the time of RBD diagnosis had higher probability to convert to parkinsonism and dementia, both from RBD onset and from RBD diagnosis within the follow-up of 1–15 years (median 3 years) (74). A more recent study investigated 179 patients with iRBD (75). Of these, 45 patients with ESS score ≥ 14 were defined as having EDS. After a mean follow-up of 5.8 years (SD = 4.3 years), 50 (27.9%) patients developed neurodegenerative diseases. There was a significantly higher proportion of conversion in patients with EDS compared to those without EDS (42.2 vs 23.1%, $p = 0.01$). EDS significantly predicted an increased risk of developing neurodegenerative diseases (adjusted HR = 2.56, 95% CI 1.37–4.77) after adjusting for age, sex, body mass index, current depression, OSA, and PLM. Further analyses demonstrated that EDS predicted the conversion to PD (adjusted HR = 3.55, 95% CI 1.59–7.89) but not dementia (adjusted HR = 1.48, 95% CI 0.44–4.97) (75). Similarly, higher HR to phenoconvert has been found in iRBD subjects reporting EDS (HR 2.73, 95% CI 1.06–7.05, $p = 0.038$) based on the non-motor Symptom Questionnaire (64).

On the other hand, a recent study by Postuma et al. (76) did not find sleepiness as a predicting factor for future conversion. The same study did not reveal any difference in subjective rating on the Insomnia Severity Scale in convertors and non-convertors (76).

Conclusion

Excessive daytime sleepiness seems to be more common in iRBD subjects compared to controls. EDS seems to increase the likelihood of phenoconversion to synucleinopathies, although this has not been confirmed in all studies. Further evidence is needed to confirm diagnostic accuracy and time frame of phenoconversion. There is insufficient evidence to consider insomnia as a symptom indicating higher risk of phenoconversion.

Depression, Anxiety

A case–control study (77) showed that patients with iRBD were more likely to report comorbid depression based on questionnaire assessment than controls (OR 2.0, 95% CI 1.3–2.9). Depression was found to be associated with reduced ability to recall enacted dreams (32). No differences in depressive symptomatology were found between iRBD and healthy controls evaluated by the Hospital Anxiety and Depression Scale (78). Also, no differences were found between depressive symptomatology evaluated in two recent studies (63, 64) by the Hamilton Depression Rating Scale and Beck Depression Inventory in the RBD convertors and non-convertors. It was suggested that antidepressants unmask latent RBD rather than cause it, in a study in which medications were modified, RBD symptoms improved, but the RSWA persisted (79).

A prospective cohort study of anxiety predictors showed more symptoms of anxiety at baseline that increased over time in patients with RBD compared to early stage untreated PD (80).

Conclusion

Depressive symptoms do not identify RBD subjects with the risk for conversion to synucleinopathy. There is not enough evidence

for depression and anxiety to be considered risk factors for neurodegeneration in RBD patients.

Color Vision Impairment

The abnormality of color vision is one of the NMS in patients with PD, and the severity of axial motor symptoms is closely related to visual dysfunction (81).

In a 10-year prospective study of an iRBD cohort over the age of 55 years old, color vision deficit (Farnsworth-Munsell 100-hue test) increased the HR of neurodegenerative disease conversion by 3.1-fold (49). Color vision in iRBD was reduced as much as 5 years before synucleinopathy diagnosis, with only slight decline in preclinical stages (82).

Conclusion

Color vision might be helpful in predicting phenoconversion in iRBD subjects. The data are, however, limited and need confirmation in further studies.

Cognitive Impairment

Significant differences in cognitive functioning (memory, executive functions) between iRBD and healthy controls have been found (83–86). The frequency of mild cognitive impairment (MCI) was estimated to be 33–50% in iRBD patients and 63–73% in PD patients with RBD, respectively (87). The high conversion rate of iRBD was interconnected with a 2.2-fold increase in risk of developing MCI in a population-based sample (88). MCI status in subjects with iRBD strongly predicts conversion to dementia related to synucleinopathy (85, 89), but not PD based on a 10-years follow-up study of 89 subjects with iRBD (49). Cognitive tests assessing attention and executive functions strongly predict conversion to dementia in iRBD patients (89), Cross-sectional studies indicate that a proportion of iRBD patients show a pattern of cognitive deficits similar to those typically found in patients with synucleinopathies, especially in LBD or PD with MCI or PD with dementia (85, 89–91). In iRBD selective attention, executive functions and episodic verbal and non-verbal memory are the most affected (83–85, 92). Positive correlation between time-based prospective memory performance and reduced striatal dopamine transport uptake on DaT scan on the more affected side has been found (86), indicating that impaired prospective memory may also be a marker for neurodegeneration associated with dopamine depletion syndromes. However, the presence of visuospatial and visuoconstructional deficits has also been reported in some studies (92–94), especially in those iRBD subgroups that later convert to PD dementia or DLB.

Conclusion

Cognitive impairment is a sign of future phenoconversion but there is not enough evidence to recommend optimal set of neuropsychological examinations for precise estimation of the disease evolution.

Neuroimaging Biomarkers

Presynaptic Dopaminergic Imaging

Imaging of the nigrostriatal dopaminergic pathway typically consists in measuring dopamine transporter (DAT) density (95) and positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are used in this indication.

Presynaptic PET and SPECT have been shown to identify PD and related disorders in very early stages. Striatal DAT uptake has been shown to decrease with expected pattern of disease progression from healthy controls to RSWA on PSG to manifest RBD to PD (96). Compared with controls, iRBD patients had significantly reduced mean (97) I-FP-CIT binding in all four striatal regions at baseline and after 3 years. After adjustment for baseline (97) I-FP-CIT uptake ratios, the decline in Ref. (97) I-FP-CIT binding was significantly greater in patients than in controls in the left putamen. The three subjects displaying the lowest tracer uptake at baseline in this iRBD cohort were subsequently diagnosed with PD (98). The 5-year follow-up study showed that patients with lower DAT uptake (99mTc-TRODAT-1 binding) in the putamen exhibited a shorter progression-free survival time compared to the population with higher DAT uptake (64). PET using the tracer 6-[18 F] fluoro-meta-tyrosine showed that putamen and caudate uptake was significantly lower in iRBD patients than in controls (99). A recent study also revealed that a reduction of FP-CIT uptake in the putamen greater than 25% discriminated patients with DAT deficit who developed synucleinopathy from patients with DAT deficit that remained disease-free after 3-year follow-up (100). At 5-year follow-up, DAT-SPECT had a 75% sensitivity, 51% specificity, 44% PPV, 80% NPV, and a LR of 1.54 in predicting synucleinopathy. The above mentioned studies and other available data indicate that imaging of presynaptic dopaminergic integrity is suitable to monitor disease progression and identify individuals at risk of phenoconversion (101).

Metabolic Imaging

18F-fluorodeoxyglucose PET shows altered RBD-related regional cerebral metabolism. Increased metabolism has been found in the pons, thalamus, medial frontal and sensorimotor areas, hippocampus, supramarginal and inferior temporal gyri, and posterior cerebellum, and decreased activity in occipital and superior temporal regions (102). In another study, elevated metabolism was found in the hippocampus/parahippocampus, cingulate, supplementary motor area, and pons, and decreased metabolism in the occipital cortex/lingual gyrus (103). The above mentioned elevation in iRBD decreased with disease progression (102). Regional metabolic abnormalities were associated with clinical measures such as RBD duration and chin electromyographic activity (103).

An elevated PD-related covariance pattern in resting-state metabolic brain imaging with 18F-fluorodeoxyglucose PET has been found in subjects with iRBD compared to healthy controls. For individual subjects with RBD, final phenoconversion status has been predicted using a logistic regression model based on a PD-related covariance pattern expression and subject age at the time of imaging (104).

Resting-state functional magnetic resonance imaging (rs-fMRI) may detect preclinical alterations in brain network functioning. Connectivity measures within resting-state networks differentiated both iRBD and PD from controls, indicating its

potential as an indicator of early basal ganglia dysfunction. iRBD was indistinguishable from PD on rs-fMRI despite obvious differences on DAT-SPECT. Basal ganglia connectivity is a promising biomarker for the detection of early basal ganglia disturbance and may help to identify patients at risk of developing PD in the future (105).

Transcranial Sonography (TCS)

Hyperechogenicity of the substantia nigra (SN) on TCS is reported in the vast majority of PD patients and only in 10% of healthy subjects. Several studies have applied TCS in iRBD and SN hyperechogenicity was found in about 35–55% of iRBD subjects and in about 70% of iRBD patients with comorbid depression (101).

Longitudinal follow-up studies showed that 36% of iRBD subjects with SN hyperechogenicity at baseline phenoconverted within 2.5 years (106) and 42% converted within 5 years (107). However, 12% iRBD patients with normal SN echogenicity at baseline also developed a neurodegenerative disorder within 2.5 years (106), and 34% within 5 years (107).

Combining TCS with other examinations might increase accuracy of prognosis. Combination of TCS with FP-CIT-SPECT revealed 100% sensitivity and 55% specificity to predict subsequent phenoconversion within 2.5 years (106). Assessment of hyposmia and mild motor impairment may also enhance the predictive value of TCS (59, 108, 109). TSC SN hyperechogenicity might act as a very weak marker for further neurodegeneration. In combination with other markers its predictive value is higher (101).

Cardial Imaging

In an early study by Miyamoto et al., cardiac 123I-MIBG uptake was compared in PSG confirmed iRBD subjects ($N = 31$), PD ($N = 26$), DLB ($N = 6$), and controls (110). The findings were similar among iRBD, PD and DLB, but differed from those with tauopathies and MSA. In PD patients, cardial MIBG uptake as determined by heart-to-mediastinum ratios was reduced in subjects with clinical RBD compared to subclinical RBD and those with normal REM sleep (34).

Conclusion

Among the available imaging methods currently available today, the measurement of presynaptic DAT density is the most informative for synucleinopathy progression evaluation (101). The HR of conversion in iRBD patients with reduced uptake on DAT-SPECTs is 3.2 higher than in subjects with normal DAT Scans.

Electrophysiology

EEG

In iRBD subjects, subtle changes found in EEG during sleep (111) and wakefulness (112–114) suggest abnormalities. EEG slowing, according to a follow-up EEG study in iRBD, seems a promising marker of neurodegeneration in iRBD patients (114).

Polysomnography

A large and long-lasting Montreal follow-up study has found that iRBD convertors had a modest decrease in % of REM sleep (15.8 ± 8.0 vs $19.8 \pm 7.5\%$, $p = 0.005$) at the time of diagnosis. Also, patients who converted had higher tonic REM% (58.4 ± 27.0 vs $46.1 \pm 30.4\%$, $p = 0.019$), without any difference in phasic REM% (35.5 ± 17.0 vs $34.7 \pm 18.0\%$, $p = 0.81$). On Cox regression analysis, adjusting for age and sex, having tonic REM > 50% was associated with a HR of 1.88 for development of neurodegenerative disease ($p = 0.039$) (76).

Conclusion

These electrophysiology results are interesting pathophysiologically but, to date, do not have a role for predicting phenoconversion of an individual subject with iRBD.

Tissue Biomarkers

Genetics

Several gene mutations and single nucleotide polymorphisms (SNPs) have been studied in relation to iRBD. The OR for the GBA p.E326K mutation carriers to have probable RBD (RBDSQ score ≥ 6) was 3.13 in one study ($p = 0.039$) (115), while the difference in GBA mutation frequency between patients with iRBD (PSG proven) and controls showed boarderline significance ($p = 0.05$) in another recent investigation (61). On the other hand, LRRK2 mutations were not found in two iRBD cohorts (61, 116). The APOE ε4 allele frequency was similar among RBD patients and controls and it was not associated with conversion from RBD to DLB or other synucleinopathies (117). Melanoma gene variant MC1R p.R160W and other variants do not increase susceptibility for PD or RBD (118). As far as SNP studies, three SNCA-3′UTR SNPs (rs356165, rs3857053, rs1045722) were found more frequently in PD patients (with or without RBD) than in iRBD subjects ($p = 0.014$, 0.008, and 0.008, respectively) (119). In another study (120) evaluating nine PD-related SNPs, the SCARB2 rs6812193 (OR = 0.67, 95% CI = 0.51–0.88, $p = 0.004$) and the MAPT rs12185268 (OR = 0.43, 95% CI = 0.26–0.72, $p = 0.001$) were associated with RBD in different models. Kaplan–Meier survival analysis in a subset of RBD patients ($n = 56$), demonstrated that homozygous carriers of the USP25 rs2823357 SNP had progressed to synucleinopathies faster than others (log-rank $p = 0.003$, Breslow $p = 0.005$, Tarone-Ware $p = 0.004$).

Conclusion

There is insufficient evidence to support the role of genetic testing in identifying subjects at higher risk of RBD or for predicting phenoconversion to synucleinopathies.

Fluid Biomarkers

Only a limited number of studies evaluating serum and cerebrospinal fluid (CSF) biomarkers in RBD subjects have been published. Anderson et al., (121) found normal hypocretin levels in the CSF of RBD subjects. Elevated expression of prion protein (PrP, both mRNA and protein) in PD patients with RBD, compared to PD patients without sleep problems and healthy controls has been recently reported (122). Although total alpha-synuclein was reportedly lower in early untreated PD patients compared to healthy controls and CSF total tau was slightly higher, the rates of changes were not significant after 24 months of follow-up

and, moreover, these CSF parameters were not studied in iRBD subjects specifically so far (123).

As far as serum biomarkers, hypercholesterolemia is possibly a predictor of lower conversion rate in iRBD according to one follow-up study (67) and higher plasma urate levels have previously been associated with a longer duration of RBD without converting to PD (97).

Conclusion

There is insufficient evidence to support the use of CSF and serum biomarkers as predictors for iRBD conversion to synucleinopathy.

Peripheral Nerve Tissue Biopsies

Parkinson's disease-related Lewy pathology is typically present in several peripheral tissues (124, 125), some of which, like the salivary glands, colon, or skin, are readily accessible for biopsies and histopathological evaluation. Several reports have shown presence of pathological a-synuclein aggregates in peripheral tissues biopsies several years prior to onset of first motor symptoms (126, 127), raising the possibility of using these evaluations for *in vivo* confirmation of Lewy pathology in patients with iRBD. A single study has evaluated the presence of 129-phosphorylated a-synuclein (p-a-syn) in colonic biopsies, with positive findings in 4/17 (24%) iRBD patients and none of the healthy controls, resulting in excellent specificity, but low sensitivity (128). P-a-syn pathology was found only in the colonic submucosa, which is more difficult to obtain with routine colonoscopies compared to colonic mucosa. Significantly higher prevalence of colonic p-a-syn positivity in PD patients with RBD compared to patients without RBD (18/28 vs 2/15, $p < 0.01$) was reported in another study (129). Vilas et al. (130) evaluated the presence of p-a-syn in submandibular glands of 21 iRBD subjects and 26 controls with excellent specificity and good sensitivity when comparing iRBD versus healthy controls (8/9 vs 0/26 with available submandibular gland tissue). However, the needle core biopsies missed the submandibular gland in 12/21 iRBD patients even under ultrasound guidance. Two studies evaluated the presence of p-a-syn in skin with positive findings in 9/12 and 10/18 iRBD patients respectively, while none of the controls had p-a-syn findings (131, 132), thus yielding excellent specificity and moderate-acceptable sensitivity. The presence of pathological p-a-syn aggregates was more common in proximal than distal body segments. Reduced intraepidermal nerve fiber density in patients with iRBD compared to healthy controls has also been reported (133).

Conclusion

Although peripheral tissue biopsies seem to be a promising technique for confirmation of peripheral Lewy pathology in iRBD patients, there are several technical and methodological issues which need to be addressed prior its use in routine practice, including optimal immunostaining methodology, target regions and sampling technique among others. Moreover, there are no longitudinal studies to date evaluating the real rates of phenoconversion from iRBD with, or without, peripheral Lewy pathology to clinically manifest synucleinopathy. Thus the predictive value of this examination is still unknown and needs to be determined.

DISCUSSION AND CONCLUSION

Cumulative evidence strongly supports the role of iRBD as one of the most important clinical markers of synucleinopathies. While the diagnosis is based on expensive and scarcely accessible PSG confirmation, a high need for easily available and accurate identification of RBD at risk subjects in the general population will arise with emerging therapeutic strategies, such as immunization therapies (134) and potential neuroprotective agents, including exenetide (135) and others. Also, in order to initiate this type of trials in iRBD subjects and ensure their accurate evaluation, clinical markers assessing disease progression and estimate of time of conversion to manifest synucleinopathy need to be determined. Several validated questionnaires and screening measures for RBD have been developed to enable easier identification of subjects with RBD in large-scale studies and in individual subjects. Although the diagnostic accuracy of RBD rating scales has been shown acceptable to excellent in most validation studies, caution should be exercised when interpreting these results. Most of the validation studies for RBD scales were performed in patients with a confirmed diagnosis of RBD, who were more likely to recognize and be aware of their RBD symptoms. In fact, diagnostic accuracy depends on the setting in which the questionnaire has been applied. In a study, where RBDSQ was administered to PD patients with a confirmed diagnosis of RBD and to PD patients where RBDSQ was administered as first line screening without prior sleep interview and PSG, the diagnostic accuracy was significantly lower in the latter group with only moderate sensitivity and specificity to identify the RBD subjects (30). Also, uncritical use of RBD-screening instruments may result into false-positive findings, e.g., in patients with other sleep disorders such as OSA or non-REM parasomnias, RLS, or in false negative results, as in patients who lack a bed partner and may not be aware of their RBD symptoms. Up to 16% of patients who are later considered negative on sleep interview and PSG may score positive in RBD questionnaires (136). Moreover, several studies have shown that using different RBD questionnaires in the same population yields a variable prevalence of RBD (137). Therefore, questionnaire-based diagnosis of RBD is insufficient and should be considered as probable only, with necessity of further PSG confirmation. More effective strategies for identification of RBD subjects in large populations may be based on multistep screening approaches (138, 139), using single screening questions, followed by one of the specific RBD rating scales and a more detailed sleep interview. Also, while there is no solid evidence on use of wearable technologies such as smartphones and smartwatch in screening for RBD, with advancing technologies it is likely these may become a reasonable first line screening option for RBD in the future and thus should be explored in more details.

From the clinimetric point of view, the only rating scale which has been shown to be reliable, valid (with exception of convergence validity) and sensitive to change is the RBDQ-HK. The remaining scales were either not studied appropriately from

the clinimetric point or view, or the results were not satisfactory. These limitations mostly regard the validity of the scales and their sensitivity to change.

Several clinical, imaging and electrophysiological progression markers have been identified in iRBD subjects. For some of these markers, like subtle motor impairment, time from deviation of normal values to a diagnosis of synucleinopathy has been estimated in the range of 4.2–9.8 years. Several other promising markers of phenoconversion, such as olfactory loss, autonomic dysfunction, cognitive impairment, imaging markers, including presynaptic dopaminergic nuclear medicine imaging, rs-fMRI or TCS, as well as peripheral nerve tissue biopsies have been identified. Although these markers seem to predict future conversion to synucleinopathies, reported results have not always been uniform, and there is not enough evidence to support a specific set of evaluations or procedures for precise estimation of disease conversion or progression. Moreover, it is very likely that a single marker will not be sufficient to predict future conversion of iRBD to a manifest synucleinopathy and that a combination of different clinical, imaging and other markers, such as confirmation of presence of pathological a-synuclein aggregation in peripheral tissues, will be necessary for accurate estimation of future disease progression. In this regard, the recently published MDS research criteria for prodromal PD (11) have yielded sensitivity of 81.3% and specificity of 67.9% for iRBD conversion to PD/DLB at 4-year follow-up, with a 100% sensitivity 1 year before conversion (63).

Future studies are needed in order to predict conversion of iRBD into specific types of synucleinopathies. Moreover, prospective studies are necessary to confirm and explore the role of individual prodromal markers and their combination in predicting conversion from iRBD to PD, DLB, or MSA.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception of the work, drafted sessions of the manuscript or revised it critically for important intellectual content, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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REFERENCES

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine (2014). 383 p.
2. Chiu HKF, Wing YK, Lam LCW, Li SW, Lum CM, Ho CK, et al. Sleep-related injury in the elderly-an epidemiological study in Hong Kong. *Sleep* (2000) 23:513–7. doi:10.1093/sleep/23.4.1e
3. St. Louis EK, McCarter SJ, Boeve BF, Silber MH, Kantarci K, Benaroch EE, et al. Lesional REM sleep behavior disorder localizes to the dorsomedial pons. *Neurology* (2014) 83:1871–3. doi:10.1212/WNL.0000000000000978
4. Postuma RB, Gagnon JF, Tuineaig M, Bertrand JA, Latreille V, Desjardins C, et al. Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal? *Sleep* (2013) 36:1579–85. doi:10.5665/sleep.3102
5. Boeve BF, Silber MH, Ferman TJ, Lin SC, Benaroch EE, Schmeichel AM, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. *Sleep Med* (2013) 14:754–62. doi:10.1016/j.sleep.2012.10.015
6. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med* (2013) 14:744–8. doi:10.1016/j.sleep.2012.10.009
7. Iranzo A, Fernandez-Arcos A, Tolosa E, Serradell M, Molinuevo JL, Valldeoriola F, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. *PLoS One* (2014) 9:e89741. doi:10.1371/journal.pone.0089741
8. Kang SH, Yoon IY, Lee SD, Han JW, Kim TH, Kim KW. REM sleep behavior disorder in the Korean elderly population: prevalence and clinical characteristics. *Sleep* (2013) 36:1147–52. doi:10.5665/sleep.2874
9. Jellinger K. Neuropathology of Sporadic Parkinson's disease: evaluation and changes of concepts. *Mov Disord* (2012) 27:8–30. doi:10.1002/mds.23795
10. Koga S, Dickson DW. Recent advances in neuropathology, biomarkers and therapeutic approach of multiple system atrophy. *J Neurol Neurosurg Psychiatry* (2018) 89:175–84. doi:10.1136/jnnp-2017-315813
11. Berg D, Postuma R, Adler C, Bloem B, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. *Mov Disord* (2015) 30:1600–9. doi:10.1002/mds.26431
12. Sixel-Doring F, Schweitzer M, Mollenhauer B, Trenkwalder C. Intraindividual variability of REM sleep behavior disorder in Parkinson's disease: a comparative assessment using a new REM sleep behavior disorder severity scale (RBDSS) for clinical routine. *J Clin Sleep Med* (2011) 7:75–80.
13. Li SX, Wing YK, Lam SP, Zhang J, Yu MW, Ho CK, et al. Validation of a new REM sleep behavior disorder questionnaire (RBDQ-HK). *Sleep Med* (2010) 11:43–8. doi:10.1016/j.sleep.2009.06.008
14. Chang Y, Gu Z, Zhan S, Zhang H, Li Y, An J, et al. Validation of the Beijing version of the REM sleep behavior disorder questoinnaire (RBDQ-Beijing) in a mainland chinese cohort. *Tohoku J Exp Med* (2014) 234:7–15. doi:10.1620/tjem.234.7
15. Sasai T, Matsuura M, Wing YK, Inoue Y. Validation of the Japanese version of the REM sleep behavior disorder questionnaire (RBDQ-JP). *Sleep Med* (2012) 13:913–8. doi:10.1016/j.sleep.2012.04.011
16. Shen SS, Shen Y, Xiong KP, Chen J, Mao CJ, Huang JY, et al. Validation study of REM sleep behavior disorder questionnaire – Hong Kong (RBDQ-HK) in East China. *Sleep Med* (2014) 15:952–8. doi:10.1016/j.sleep.2014.03.020
17. Li SX, Lam SP, Zhang J, Yu MW, Chan JW, Liu Y, et al. A prospective, naturalistic follow-up study of treatment outcomes with clonazepam in rapid eye movement sleep behavior disorder. *Sleep Med* (2016) 21:114–20. doi:10.1016/j.sleep.2015.12.020
18. Kashihara K, Nomura T, Maeda T, Tsuboi Y, Mishima T, Takigawa H, et al. Beneficial effects of Ramalteon on rapid eye movement sleep behavior disorder associated with Parkinson's disease – results of a multicenter open trial. *Intern Med* (2016) 55:231–6. doi:10.2169/internalmedicine.55.5464
19. Zhou J, Zhang J, Du L, Li Z, Li Y, Lei F, et al. Characteristics of early- and late-onset rapid eye movement sleep behavior disorder in China: a case-control study. *Sleep Med* (2014) 15:654–60. doi:10.1016/j.sleep.2013.12.020
20. Zhou J, Zhang J, Li Y, Du L, Li Z, Lei F, et al. Gender differences in REM sleep behavior disorder: a clinical and polysomnographic study in China. *Sleep Med* (2015) 16:414–8. doi:10.1016/j.sleep.2014.10.020
21. Postuma RB, Bertrand JA, Montplaisir J, Desjardins C, Vendette M, Rios Romenets S, et al. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. *Mov Disord* (2012) 27:720–6. doi:10.1002/mds.24939
22. Neikrug AB, Anconi-Israel S. Diagnostic tools for REM sleep behavior disorder. *Sleep Med Rev* (2012) 16:415–29. doi:10.1016/j.smrv.2011.08.004
23. Stiasny-Kolster K, Mayer G, Schafer S, Möller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire – a

new diagnostic instrument. *Mov Disord* (2007) 22:2386–93. doi:10.1002/mds.21740
24. Miyamoto T, Miyamoto M, Iwananmi M, Kobayashi M, Nakamura M, Inoue Y, et al. The REM sleep behavior disorder screening questionnaire: validation study of a Japanese version. *Sleep Med* (2009) 10:1151–4. doi:10.1016/j.sleep.2009.05.007
25. Wang Y, Wang ZW, Yang YC, WU HJ, Zhao JY, Zhao ZX. Validation of the rapid eye movement sleep behavior disorder screening questionnaire in China. *J Clin Neurosci* (2015) 22:1420–4. doi:10.1016/j.jocn.2015.03.008
26. Comert IT, Pelin Z, Aricak T, Yapan S. Validation of the Turkish version of the REM sleep behavior disorder screening questionnaire. *Behav Neurol* (2016) 2016:8341651. doi:10.1155/2016/8341651
27. Marelli S, Rancoita PMV, Giarusso F, Galbiati A, Zucconi M, Oldani A, et al. National validation and proposed revision of REM sleep behavior disorder screening questionnaire. *J Neurol* (2016) 263:2470–5. doi:10.1007/s00415-016-8285-y
28. Stefani A, Mahllknecht P, Seppi K, Nocker M, Mair KJ, Hotter A, et al. Consistency of "Probable RBD" diagnosis with the RBD screening questionnaire: a follow-up study. *Mov Disord Clin Pract* (2016) 4:403–5. doi:10.1002/mdc3.12448
29. Bjornara KA, Dietrichs E, Toft M. REM sleep behavior disorder in Parkinson's disease – is there a gender difference? *Parkinsonism Relat Disord* (2013) 19:120–2. doi:10.1016/j.parkreldis.2012.05.027
30. Stiasny-Kolster K, Sixel-Doring F, Trenkwalder K, Heinzel-Gutenbrunner M, Seppi K, Poewe W, et al. Diagnostic value of the REM sleep behavior disorder screening questionnaire in Parkinson's disease. *Sleep Med* (2015) 16:186–9. doi:10.1016/j.sleep.2014.08.014
31. Li K, Li SH, Su W, Chen HB. Diagnostic accuracy of REM sleep behavior disorder screening questionnaire: a meta-analysis. *Neurol Sci* (2017) 38:1039–46. doi:10.1007/s10072-017-2886-9
32. Lee HG, Choi JW, Lee YJ, Jeong DU. Depressed REM sleep behavior disorder patients are less likely to recall enacted dreams than non-depressed ones. *Psychiatry Investig* (2016) 13:227–31. doi:10.4306/pi.2016.13.2.227
33. Chahine LM, Daley J, Horn S, Colcher A, Hurtig H, Cantor C, et al. Questionnaire-based diagnosis of REM sleep behavior disorder in Parkinson's disease. *Mov Disord* (2013) 28:1146–9. doi:10.1002/mds.25438
34. Nomura T, Inoue Y, Hogl B, Uemura Y, Kitayama M, Abe T, et al. Relationship between (123)I-MIBG scintigrams and REM sleep behavior disorder in Parkinson's disease. *Parkinsonism Relat Disord* (2010) 16:683–5. doi:10.1016/j.parkreldis.2010.08.011
35. Boeve B, Silber M, Ferman T, Smith G, Petersen R. Validation of a questionnaire for the diagnosis of REM sleep behavior disorder. *Neurology* (2002) 58:A509.
36. Boeve BF, Molano JR, Ferman TJ, Smith GE, Lin S-C, Bieniek K, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. *Sleep Med* (2011) 12:445–53. doi:10.1016/j.sleep.2010.12.009
37. Boeve BF, Molano JR, Ferman TJ, Lin S-C, Bieniek K, Tippmann-Peikert M, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in a community-based sample. *J Clin Sleep Med* (2013) 9:475–80. doi:10.5664/jcsm.2670
38. Bolitho SJ, Naismith SL, Terpening Z, Grunstein RR, Melehan K, Yee BJ, et al. Investigating rapid eye movement sleep without atonia in Parkinson's disease using the rapid eye movement sleep behavior disorder screening questionnaire. *Mov Disord* (2014) 29:736–42. doi:10.1002/mds.25832
39. Frauscher B, Ehrmann L, Zamarian L, Auer F, Mitterling T, Gabelia D, et al. Validation of the Innsbruck REM sleep behavior disorder inventory. *Mov Disord* (2012) 27:1673–8. doi:10.1002/mds.25223
40. Frauscher B, Nomura T, Duerr S, Ehrmann L, Gschliesser V, Wenning GK, et al. Investigation of autonomic function in idiopathic REM sleep behavior disorder. *J Neurol* (2012) 259:1056–61. doi:10.1007/s00415-011-6298-0
41. Postuma RB, Arnulf I, Hogl B, Iranzo A, Miyamoto T, Dauvilliers Y, et al. A single-question screen for rapid eye movement sleep behavior disorder: a multicenter validation study. *Mov Disord* (2012) 27:913–6. doi:10.1002/mds.25037
42. Postuma RB, Lang AE, Gagnon JF, Pelletier A, Montplaisir JY. How does parkinsonism start? Prodromal parksonism motor changes in idiopathic REM sleep behaviour disorder. *Brain* (2012) 135:1860–70. doi:10.1093/brain/aws093
43. Ma JF, Hou MM, Tang HD, Gao X, Liang L, Zhu LF, et al. REM sleep behavior disorder was associated with Parkinson's disease: a community-based study. *BMC Neurol* (2016) 16:123. doi:10.1186/s12883-016-0640-1
44. Chaudhuri KR, Martinez-Martin P, Schapira AHV, Stocchi F, Sethi K, Odin P, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. *Mov Disord* (2006) 21:916–23. doi:10.1002/mds.20844
45. Romenets S, Wolfson C, Galatas C, Pelletier A, Altman R, Wadup L, et al. Validation of the non-motor symptoms questionnaire (NMS-Quest). *Parkinsonism Relat Disord* (2012) 18:54–8. doi:10.1016/j.parkreldis.2011.08.013
46. Chaudhuri K, Rojo JM, Schapira AHV, Brooks DJ, Stocchi F, Odin P, et al. A proposal for a comprehensive grading of Parkinson's disease severity combining motor and non-motor assessments: meeting an unmet need. *PLoS One* (2013) 8:e0150130. doi:10.1371/journal.pone.0150130
47. Evatt ML, Chaudhuri KR, Chou KL, Cubo E, Hinson V, Kompoliti K, et al. Dysautonomia rating scales in Parkinson's disease: sialorrhea, dysphagia, and constipation – critique and recommendations by movement disorders task force on rating scales for Parkinson's disease. *Mov Disord* (2009) 24:635–46. doi:10.1002/mds.22260
48. Chaudhuri KR, Weintraub D, Schrag A, Martinez-Martin P; On Behalf of EUROPAR, The MDS Non-Motor PD Study Group. The International Parkinson and Movement Disorder Society–Non-Motor Rating Scale (MDS-NMS): results from the cognitive pre-testing and phases 1 and 2 of an international validation. *Mov Disord* (2016) 31:S516.
49. Postuma RB, Gagnon JF, Bertrand JA, Genier Marchand D, Montplaisir J. Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials. *Neurology* (2015) 84:1104–13. doi:10.1212/WNL.0000000000001364
50. Postuma RB, Gagnon JF, Vendette M, Montplaisir JY. Markers of neurodegeneration in idiopathic rapid eye movement sleep behaviour disorder and Parkinson's disease. *Brain* (2009) 132:3298–307. doi:10.1093/brain/awp244
51. McDade EM, Boot BP, Christianson TJH, Pankratz VS, Boeve BF, Ferman TJ, et al. Subtle gait changes in patients with REM sleep behavior disorder. *Mov Disord* (2013) 28:1847–53. doi:10.1002/mds.25653
52. Alibiglou L, Videnovic A, Planetta PJ, Vaillancourt DE, MacKinnon CD. Subliminal gait initiation deficits in rapid eye movement sleep behavior disorder: a harbinger of freezing of gait? *Mov Disord* (2016) 31:1711–9. doi:10.1002/mds.26665
53. Hlavnicka J, Cmejla R, Tykalova T, Sonka K, Ruzicka E, Rusz J. Automated analysis of connected speech reveals early biomarkers of Parkinson's disease in patients with rapid eye movement sleep behaviour disorder. *Sci Rep* (2017) 7:12. doi:10.1038/s41598-017-00047-5
54. Rusz J, Hlavnicka J, Tykalova T, Buskova J, Ulmanova O, Ruzicka E, et al. Quantitative assessment of motor speech abnormalities in idiopathic REM sleep behaviour disorder. *Sleep Med* (2016) 19:141–7. doi:10.1016/j.sleep.2015.07.030
55. Fahn S, Elton RL. Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Lieberman A, editors. *Recent Developments in Parkinson's Disease*. (Vol. 2), Florham Park, NJ: MacMillan Healthcare Information (1987). p. 153–63.
56. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* (2008) 23:2129–70. doi:10.1002/mds.22340
57. Skorvanek M, Ladomirjakova Z, Han V, Lesko N, Feketeova E, Jarcuskova D, et al. Prevalence of prodromal Parkinson's disease as defined by MDS research criteria among elderly patients undergoing colonoscopy. *J Parkinsons Dis* (2017) 7:481–9. doi:10.3233/JPD-161036
58. Fantini ML, Postuma RB, Montplaisir J, Ferini-Strambi L. Olfactory deficit in idiopathic rapid eye movements sleep behavior disorder. *Brain Res Bull* (2006) 70:386–90. doi:10.1016/j.brainresbull.2006.07.008
59. Shin HY, Joo EY, Kim ST, Dhong HJ, Cho JW. Comparison study of olfactory function and substantia nigra hyperechogenicity in idiopathic REM sleep behavior disorder, Parkinson's disease and normal control. *Neurol Sci* (2013) 34(6):935–40. doi:10.1007/s10072-012-1164-0
60. Iranzo A, Stefani A, Serradell M, Martí MJ, Lomeña F, Mahllknecht P, et al. Characterization of patients with longstanding idiopathic REM sleep behavior disorder. *Neurology* (2017) 89:242–8. doi:10.1212/WNL.0000000000004121

61. Barber TR, Lawton M, Rolinski M, Evetts S, Baig F, Ruffmann C, et al. Prodromal Parkinsonism and neurodegenerative risk stratification in REM sleep behavior disorder. *Sleep* (2017) 40(8):zsx071. doi:10.1093/sleep/zsx071
62. Mahlknecht P, Iranzo A, Högl B, Frauscher B, Müller C, Santamaría J, et al. Olfactory dysfunction predicts early transition to a Lewy body disease in idiopathic RBD. *Neurology* (2015) 84:654–8. doi:10.1212/WNL.0000000000001265
63. Fereshtehnejad SM, Montplaisir JY, Pelletier A, Gagnon JF, Berg D, Postuma RB. Validation of the MDS research criteria for prodromal Parkinson's disease: longitudinal assessment in a REM sleep behavior disorder (RBD) cohort. *Mov Disord* (2017) 32:865–73. doi:10.1002/mds.26989
64. Li Y, Kang W, Yang Q, Zhang L, Zhang L, Dong F, et al. Predictive markers for early conversion of iRBD to neurodegenerative synucleinopathy diseases. *Neurology* (2017) 88:1493–500. doi:10.1212/WNL.0000000000003838
65. Ferrini-Strambi L, Oertel W, Dauvilliers Y, Postuma RB, Marelli S, Iranzo A, et al. Autonomic symptoms in idiopathic REM behavior disorder: a multicentre case-control study. *J Neurol* (2014) 261:1112–8. doi:10.1007/s00415-014-7317-8
66. Postuma RB, Gagnon JF, Pelletier A, Montplaisir J. Prodromal autonomic symptoms and signs in Parkinson's disease and dementia with Lewy bodies. *Mov Disord* (2013) 28:597–604. doi:10.1002/mds.25445
67. Postuma RB, Iranzo A, Hogl B, Arnulf I, Ferini-Strambi L, Manni R, et al. Risk factors for neurodegeneration in idiopathic rapid eye movement sleep behavior disorder: a multicenter study. *Ann Neurol* (2015) 77:830–9. doi:10.1002/ana.24385
68. Ferrini-Strambi L, Oldani A, Zucconi M, Smirne S. Cardiac autonomic activity during wakefulness and sleep in REM sleep behavior disorder. *Sleep* (1996) 19:367–9. doi:10.1093/sleep/19.5.367
69. Postuma RB, Lanfranchi PA, Blais H, Gagnon JF, Montplaisir JY. Cardiac autonomic dysfunction in idiopathic REM sleep behavior disorder. *Mov Disord* (2010) 25:2304–10. doi:10.1002/mds.23347
70. Lanfranchi PA, Fradette L, Gagnon JF, Colombo R, Montplaisir J. Cardiac autonomic regulation during sleep in idiopathic REM sleep behavior disorder. *Sleep* (2007) 30:1019–25. doi:10.1093/sleep/30.8.1019
71. Sorensen GL, Mehlsen J, Jennum P. Reduced sympathetic activity in idiopathic rapid-eye-movement sleep behavior disorder and Parkinson's disease. *Auton Neurosci* (2013) 179:138–41. doi:10.1016/j.autneu.2013.08.067
72. Sorensen GL, Kempfner J, Zoetmulder M, Sorensen HB, Jennum P. Attenuated heart rate response in REM sleep behavior disorder and Parkinson's disease. *Mov Disord* (2012) 27:888–94. doi:10.1002/mds.25012
73. Postuma RB, Berg D. Advances in markers of prodromal Parkinson disease. *Nat Rev Neurol* (2016) 12:622–34. doi:10.1038/nrneurol.2016.152
74. Arnulf I, Neutel D, Herlin B, Golmard JL, Leu-Semenescu S, Cochen de Cock V, et al. Sleepiness in idiopathic REM sleep behavior disorder and Parkinson disease. *Sleep* (2015) 38:1529–35. doi:10.5665/sleep.5040
75. Zhou J, Zhang J, Lam SP, Chan JW, Mok V, Chan A, et al. Excessive daytime sleepiness predicts neurodegeneration in idiopathic REM sleep behavior disorder. *Sleep* (2017) 40:zsx041. doi:10.1093/sleep/zsx041
76. Postuma RB, Gagnon JF, Pelletier A, Montplaisir JY. Insomnia and somnolence in idiopathic RBD: a prospective cohort study. *NPJ Parkinsons Dis* (2017) 3:9. doi:10.1038/s41531-017-0011-7
77. Frauscher B, Jennum P, Ju YE, Postuma RB, Arnulf I, Cochen De Cock V, et al. Comorbidity and medication in REM sleep behavior disorder: a multicenter case-control study. *Neurology* (2014) 82:1076–9. doi:10.1212/WNL.0000000000000247
78. Aguirre-Mardones C, Iranzo A, Vilas D, Serradell M, Gaig C, Santamaría J, et al. Prevalence and timeline of nonmotor symptoms in idiopathic rapid eye movement sleep behavior disorder. *J Neurol* (2015) 262:1568–78. doi:10.1007/s00415-015-7742-3
79. Lam SP, Zhang J, Tsoh J, Li SX, Ho CK, Mok V, et al. REM sleep behavior disorder in psychiatric populations. *J Clin Psychiatry* (2010) 71:1101–3. doi:10.4088/JCP.l05877gry
80. Rutten S, van der Ven PM, Weintraub D, Pontone GM, Leentjens AFG, Berendse HW, et al. Predictors of anxiety in early-stage Parkinson's disease – results from the first two years of a prospective cohort study. *Parkinsonism Relat Disord* (2017) 43:49–55. doi:10.1016/j.parkreldis.2017.06.024
81. Oh YS, Kim JS, Chung SW, Song IU, Kim YD, Kim YI, et al. Color vision in Parkinson's disease and essential tremor. *Eur J Neurol* (2011) 18:577–83. doi:10.1111/j.1468-1331.2010.03206.x
82. Postuma RB, Gagnon JF, Vendette M, Desjardins C, Montplaisir JY. Olfaction and color vision identify impending neurodegeneration in rapid eye movement sleep behavior disorder. *Ann Neurol* (2011) 69:811–8. doi:10.1002/ana.22282
83. Ferrini-Strambi L, Di Gioia MR, Castronovo V, Oldani A, Zucconi M, Cappa SF. Neuropsychological assessment in idiopathic REM sleep behavior disorder (RBD): does the idiopathic form of RBD really exist? *Neurology* (2004) 62:41–5. doi:10.1212/01.WNL.0000101726.69701.FA
84. Massicotte-Marquez J, Decary A, Gagnon JF, Vendette M, Mathieu A, Postuma RB, et al. Executive dysfunction and memory impairment in idiopathic REM sleep behavior disorder. *Neurology* (2008) 70:1250–7. doi:10.1212/01.wnl.0000286943.79593.a6
85. Terzaghi M, Zucchella C, Rustioni V, Sinforiani E, Manni R. Cognitive performances and mild cognitive impairment in idiopathic rapid eye movement sleep behavior disorder: results of a longitudinal follow-up study. *Sleep* (2013) 36:1527–32. doi:10.5665/sleep.3050
86. Bezdíček O, Nikolai T, Nepožitek J, Peřinová P, Kemlink D, Dušek P, et al. Prospective memory impairment in idiopathic REM sleep behavior disorder. *Clin Neuropsychol* (2017) 26:1–19. doi:10.1080/13854046.2017.1394493
87. Zhang JR, Chen J, Yang ZJ, Zhang HJ, Fu YT, Shen Y, et al. Rapid eye movement sleep behavior disorder symptoms correlate with domains of cognitive impairment in Parkinson's disease. *Chin Med J (Engl)* (2016) 129:379–85. doi:10.4103/0366-6999.176077
88. Boot BP, Boeve BF, Roberts RO, Ferman TJ, Geda YE, Pankratz VS, et al. Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: a population-based study. *Ann Neurol* (2012) 71:49–56. doi:10.1002/ana.22655
89. Marchand D, Montplaisir J, Postuma RB, Rahayel S, Gagnon JF. Detecting the cognitive prodrome of dementia with lewy bodies: a prospective study of REM sleep behavior disorder. *Sleep* (2017) 40:zsw014. doi:10.1093/sleep/zsw014
90. Manni R, Sinforiani E, Pacchetti C, Zucchella C, Cremascoli R, Terzaghi M. Cognitive dysfunction and REM sleep behavior disorder: key findings in the literature and preliminary longitudinal findings. *Int J Psychophysiol* (2013) 89:213–7. doi:10.1016/j.ijpsycho.2013.04.003
91. Boeve BF, Silber MH, Ferman TJ, Kokmen E, Smith GE, Ivnik RJ, et al. REM sleep behavior disorder and degenerative dementia: an association likely reflecting Lewy body disease. *Neurology* (1998) 51:363–70. doi:10.1212/WNL.51.2.363
92. Fantini ML, Farini E, Ortelli P, Zucconi M, Manconi M, Cappa S, et al. Longitudinal study of cognitive function in idiopathic REM sleep behavior disorder. *Sleep* (2011) 34:619–25.
93. Iranzo A, Molinuevo JL, Santamaria J, Serradell M, Marti MJ, Valldeoriola F, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. *Lancet Neurol* (2006) 5:572–7. doi:10.1016/S1474-4422(06)70476-8
94. Molano J, Boeve B, Ferman T, Smith G, Parisi J, Dickson D, et al. Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study. *Brain* (2010) 133:540–56. doi:10.1093/brain/awp280
95. Shen LH, Liao MH, Tseng YC. Recent advances in imaging of dopaminergic neurons for evaluation of neuropsychiatric disorders. *J Biomed Biotechnol* (2012) 2012:259349. doi:10.1155/2012/259349
96. Eisensehr I, Linke R, Tatsch K, Kharraz B, Gildehaus JF, Wetter CT, et al. Increased muscle activity during rapid eye movement sleep correlates with decrease of striatal presynaptic dopamine transporters. IPT and IBZM SPECT imaging in subclinical and clinically manifest idiopathic REM sleep behavior disorder, Parkinson's disease, and controls. *Sleep* (2003) 26:507–12.
97. Uribe-San Martin R, Venegas Francke P, Lopez Illanes F, Jones Gazmuri A, Salazar Rivera J, Godoy Fernndez J, et al. Plasma urate in REM sleep behavior disorder. *Mov Disord* (2013) 28:1150–1. doi:10.1002/mds.25441
98. Iranzo A, Valldeoriola F, Lomena F, Molinuevo JL, Serradell M, Salamero M, et al. Serial dopamine transporter imaging of nigrostriatal function in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. *Lancet Neurol* (2011) 10:797–805. doi:10.1016/S1474-4422(11)70152-1
99. Miyamoto M, Miyamoto T, Iwanami M, Muramatsu S, Asari S, Nakano I, et al. Preclinical substantia nigra dysfunction in rapid eye movement

sleep behaviour disorder. *Sleep Med* (2012) 13:102–6. doi:10.1016/j.sleep.2011.03.024

100. Iranzo A, Santamaria J, Valldeoriola F, Serradell M, Salamero M, Gaig C, et al. Dopamine transporter imaging deficit predicts early transition to synucleinopathy in idiopathic rapid eye movement sleep behavior disorder. *Ann Neurol* (2017) 82:419–28. doi:10.1002/ana.25026
101. Heller J, Brcina N, Dogan I, Holtbernd F, Romanzetti S, Schulz JB, et al. Brain imaging findings in idiopathic REM sleep behavior disorder (RBD) – a systematic review on potential biomarkers for neurodegeneration. *Sleep Med Rev* (2017) 34:23–33. doi:10.1016/j.smrv.2016.06.006
102. Wu P, Yu H, Peng S, Dauvilliers Y, Wang J, Ge J, et al. Consistent abnormalities in metabolic network activity in idiopathic rapid eye movement sleep behaviour disorder. *Brain* (2014) 137:3122–8. doi:10.1093/brain/awu290
103. Ge J, Wu P, Peng S, Yu H, Zhang H, Guan Y, et al. Assessing cerebral glucose metabolism in patients with idiopathic rapid eye movement sleep behavior disorder. *J Cereb Blood Flow Metab* (2015) 35:2062–9. doi:10.1038/jcbfm.2015.173
104. Holtbernd F, Gagnon JF, Postuma RB, Ma Y, Tang CC, Feigin A, et al. Abnormal metabolic network activity in REM sleep behavior disorder. *Neurology* (2014) 82:620–7. doi:10.1212/WNL.0000000000000130
105. Rolinski M, Griffanti L, Piccini P, Roussakis AA, Szewczyk-Krolikowski K, Menke RA, et al. Basal ganglia dysfunction in idiopathic REM sleep behaviour disorder parallels that in early Parkinson's disease. *Brain* (2016) 139:2224–34. doi:10.1093/brain/aww124
106. Iranzo A, Lomena F, Stockner H, Valldeoriola F, Vilaseca I, Salamero M, et al. Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study [corrected]. *Lancet Neurol* (2010) 9:1070–7. doi:10.1016/S1474-4422(10)70216-7
107. Iranzo A, Stockner H, Serradell M, Seppi K, Valldeoriola F, Frauscher B, et al. Five-year follow-up of substantia nigra echogenicity in idiopathic REM sleep behavior disorder. *Mov Disord* (2014) 29:1774–80. doi:10.1002/mds.26055
108. Rupprecht S, Walther B, Gudziol H, Steenbeck J, Freesmeyer M, Witte OW, et al. Clinical markers of early nigrostriatal neurodegeneration in idiopathic rapid eye movement sleep behavior disorder. *Sleep Med* (2013) 14:1064–70. doi:10.1016/j.sleep.2013.06.008
109. Iwanami M, Miyamoto T, Miyamoto M, Hirata K, Takada E. Relevance of substantia nigra hyperechogenicity and reduced odor identification in idiopathic REM sleep behavior disorder. *Sleep Med* (2010) 11:361–5. doi:10.1016/j.sleep.2009.12.006
110. Miyamoto T, Miyamoto M, Suzuki K, Nishibayashi M, Iwanami M, Hirata K. 123I-MIBG cardiac scintigraphy provides clues to the underlying neurodegenerative disorder in idiopathic REM sleep behavior disorder. *Sleep* (2008) 31:717–23. doi:10.1093/sleep/31.5.717
111. Ferri R, Rundo F, Silvani A, Zucconi M, Bruni O, Ferini-Strambi L, et al. REM sleep EEG instability in REM sleep behavior disorder and clonazepam effects. *Sleep* (2017) 40(8):zsx080. doi:10.1093/sleep/zsx080
112. Bang YR, Jeon HJ, Youn S, Yoon IY. Alterations of awake EEG in idiopathic REM sleep behavior disorder without cognitive impairment. *Neurosci Lett* (2017) 637:64–9. doi:10.1016/j.neulet.2016.11.052
113. Sunwoo JS, Lee S, Kim JH, Lim JA, Kim TJ, Byun JI, et al. Altered functional connectivity in idiopathic rapid eye movement sleep behavior disorder: a resting-state EEG study. *Sleep* (2017) 40(6):zsx058. doi:10.1093/sleep/zsx058
114. Rodrigues Brazete J, Gagnon JF, Postuma RB, Bertrand JA, Petit D, Montplaisir J. Electroencephalogram slowing predicts neurodegeneration in rapid eye movement sleep behavior disorder. *Neurobiol Aging* (2016) 37:74–81. doi:10.1016/j.neurobiolaging.2015.10.007
115. Gan-Or Z, Mirelman A, Postuma RB, Arnulf I, Bar-Shira A, Dauvilliers Y, et al. GBA mutations are associated with rapid eye movement sleep behavior disorder. *Ann Clin Transl Neurol* (2015) 2:941–5. doi:10.1002/acn3.228
116. Fernández-Santiago R, Iranzo A, Gaig C, Serradell M, Fernández M, Tolosa E, et al. Absence of LRRK2 mutations in a cohort of patients with idiopathic REM sleep behavior disorder. *Neurology* (2016) 86:1072–3. doi:10.1212/WNL.0000000000002304
117. Gan-Or Z, Montplaisir JY, Ross JP, Poirier J, Warby SC, Arnulf I, et al. The dementia-associated APOE ε4 allele is not associated with rapid eye movement sleep behavior disorder. *Neurobiol Aging* (2017) 49:218.e13–e15. doi:10.1016/j.neurobiolaging.2016.10.002
118. Gan-Or Z, Mohsin N, Girard SL, Montplaisir JY, Ambalavanan A, Strong S, et al. The role of the melanoma gene MC1R in Parkinson disease and REM sleep behavior disorder. *Neurobiol Aging* (2016) 43:180.e7–13. doi:10.1016/j.neurobiolaging.2016.03.029
119. Toffoli M, Dreussi E, Cecchin E, Valente E, Sanvilli N, Montico M, et al. SNCA 3'UTR genetic variants in patients with Parkinson's disease and REM sleep behavior disorder. *Neurol Sci* (2017) 38:1233–40. doi:10.1007/s10072-017-2945-2
120. Gan-Or Z, Girard SL, Noreau A, Leblond CS, Gagnon JF, Arnulf I, et al. Parkinson's disease genetic loci in rapid eye movement sleep behavior disorder. *J Mol Neurosci* (2015) 56:617–22. doi:10.1007/s12031-015-0569-7
121. Anderson KN, Vincent A, Smith IE, Shneerson JM. Cerebrospinal fluid hypocretin levels are normal in idiopathic REM sleep behavior disorder. *Eur J Neurol* (2010) 17:1105–7. doi:10.1111/j.1468-1331.2010.02954.x
122. Zhang WJ, Shang XL, Peng J, Zhou MH, Sun WJ. Expression of prion protein in the cerebrospinal fluid of patients with Parkinson's disease complicated with rapid eye movement sleep behavior disorder. *Genet Mol Res* (2017) 16:16019022. doi:10.4238/gmr16019022
123. Mollenhauer B, Zimmermann J, Sixel-Doring F, Focke NK, Wicke T, Ebentheuer J, et al. Monitoring of 30 marker candidates in early Parkinson disease as progression markers. *Neurology* (2016) 87:168–77. doi:10.1212/WNL.0000000000002651
124. Beach T, Adler CH, Sue L, Vedders L, Lue L, White III CL, et al. Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders. *Acta Neuropathol* (2010) 119:689–702. doi:10.1007/s00401-010-0664-3
125. Gelpi E, Navarro-Otano J, Tolosa E, Gaig C, Compta Y, Rey MJ, et al. Multiple organ involvement by alpha-synuclein pathology in Lewy body disorders. *Mov Disord* (2014) 29:1010–8. doi:10.1002/mds.25776
126. Shannon KM, Keshavarzian A, Dodiya H, Jakate S, Kordower JH. Is alpha-synuclein in the colon a biomarker for premotor Parkinson disease? Evidence from 3 cases. *Mov Disord* (2012) 27:716–9. doi:10.1002/mds.25020
127. Stockholm MG, Danielsen EH, Hamilton-Dutoit SJ, Borghammer P. Pathological α-synuclein in gastrointestinal tissues from prodromal Parkinson disease patients. *Ann Neurol* (2016) 79:940–9. doi:10.1002/ana.24648
128. Sprenger FS, Stefanova N, Gelpi E, Seppi K, Navarro-Otano J, Offner F, et al. Enteric nervous system alpha-synuclein immunoreactivitiy in idiopathic REM sleep behavior disorders. *Neurology* (2015) 85:1761–8. doi:10.1212/WNL.0000000000002126
129. Leclair-Visonneau L, Clairembault T, Coron E, Le Dily S, Vavasseur F, Dalichampt M, et al. REM sleep behavior disorder is related to enteric neuropathology in Parkinson disease. *Neurology* (2017) 89:1612–8. doi:10.1212/WNL.0000000000004496
130. Vilas D, Iranzo A, Tolosa E, Aldecoa I, Berenguer J, Vilaseca I, et al. Assessment of α-synuclein in submandibular glands of patients with idiopathic rapid-eye-movement sleep behavior disorder: a case-control study. *Lancet Neurol* (2016) 15:708–18. doi:10.1016/S1474-4422(16)00080-6
131. Antelmi E, Donadio V, Incensi A, Plazzi G, Liguori R. Skin nerve phosphorylated a-synclein deposits in idiopathic REM sleep behavior disorder. *Neurology* (2017) 88:2128–31. doi:10.1212/WNL.0000000000003989
132. Doppler K, Jentschke HM, Schulmeyer L, Vadasz D, Janzen A, Luster M, et al. Dermal phospho-alpha-synuclein deposits confirm REM sleep behavior disorder as prodromal Parkinson's disease. *Acta Neuropathol* (2017) 133:535–45. doi:10.1007/s00401-017-1684-z
133. Schrempf W, Katona I, Dogan I, Felbert VV, Wienecke M, Heller J, et al. Reduced nerve fiber density in patients with REM sleep behavior disorder. *Parkinsonism Relat Disord* (2016) 29:10–6. doi:10.1016/j.parkreldis.2016.06.003
134. Braczynski AK, Schulz JB, Bach JP. Vaccination strategies in tauopathies and synucleinopathies. *J Neurochem* (2017) 143:467–88. doi:10.1111/jnc.14207
135. Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet* (2017) 390:1664–75. doi:10.1016/S0140-6736(17)31585-4
136. Frauscher B, Mitterling T, Bode A, Ehrmann L, Gabelia D, Biermayr M, et al. A prospective questionnaire study in 100 healthy sleepers: non-bothersome

forms of recognizable sleep disorders are still present. *J Clin Sleep Med* (2014) 10:623–9. doi:10.5664/jcsm.3784

137. Mahlknecht P, Seppi K, Frauscher B, Kiechl S, Willeit J, Stockner H, et al. Probable RBD and association with neurodegenerative disease markers: a population-based study. *Mov Disord* (2015) 30:1417–21. doi:10.1002/mds.26350
138. Postuma R, Pelletier A, Berg D, Gagnon JF, Escudier F, Montplaisir J. Screening for prodromal Parkinson's disease in the general community: a sleep-based approach. *Sleep Med* (2016) 21:101–5. doi:10.1016/j.sleep.2015.12.016
139. Buskova J, Ibarburu V, Sonka K, Ruzicka E. Screening for REM sleep behavior disorder in the general population. *Sleep Med* (2016) 24:147. doi:10.1016/j.sleep.2016.07.003

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REVIEW
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A Review of Scales to Evaluate Sleep Disturbances in Movement Disorders

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Patients with movement disorders have a high prevalence of sleep disturbances that can be classified as (1) nocturnal sleep symptoms, such as insomnia, nocturia, restless legs syndrome (RLS), periodic limb movements (PLM), obstructive sleep apnea (OSA), and REM sleep behavior disorder; and (2) diurnal problems that include excessive daytime sleepiness (EDS) and sleep attacks. The objective of this review is to provide a practical overview of the most relevant scales that assess these disturbances to guide the choice of the most useful instrument/s depending on the line of research or clinical focus. For each scale, the reader will find a brief description of practicalities and psychometric properties, use in movement disorder cohorts and analyzed strengths and limitations. To assess insomnia, the Pittsburgh Sleep Quality Index, a generic scale, and three disease-specific scales: the Parkinson Disease Sleep Scale (PDSS), the PDSS-2, and Scales for outcomes in Parkinson's disease (PD)-Sleep-Nocturnal Sleep subscale are discussed. To evaluate nocturia, there are no specific tools, but some extensively validated generic urinary symptom scales (the Overall Bladder Questionnaire and the Overactive Bladder Symptom Score) and some PD-specific scales that include a nocturia item are available. To measure RLS severity, there are currently four domain-specific generic scales: The International Restless Legs Scale, the Johns Hopkins Restless Legs Severity Scale, the Restless Legs Syndrome-6 measure, a Pediatric RLS Severity Scale, and the Augmentation Severity Rating Scale (a scale to evaluate augmentation under treatment) and several instruments that assess impact on quality of sleep and health-related quality of life. To evaluate the presence of PLM, no clinical scales have been developed to date. As far as OSA, commonly used instruments such as the Sleep Apnea Scale of the Sleep Disorders Questionnaire, the STOP-Bang questionnaire, and the Berlin Questionnaire are reviewed. Three scales have been extensively used to assess EDS: the generic Epworth Sleepiness Scale, the Stanford Sleepiness Scale, and the PD-specific Scales for outcomes in PD-Sleep-Daytime sleepiness subscale. To date, only the Inappropriate Sleep Composite Score specifically evaluates propensity to sleep attacks.

Keywords: Parkinson's disease, Parkinsonism, chorea, dystonia, insomnia, nocturia, restless legs, sleep apnea

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INTRODUCTION

Sleep problems such as insomnia, nocturia, restless legs syndrome (RLS), periodic limb movements (PLMs), REM sleep behavior disorder (RBD), obstructive sleep apnea (OSA), and excessive daytime sleepiness (EDS) are prevalent in the general population and in movement disorder patients. Insomnia, for example, is a salient problem in Parkinson's disease (PD) (1), multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration (2), but also in patients with hyperkinetic disorders such as Huntington's chorea, neuroacantocytosis, and Tourette syndrome (3). Daytime sleepiness (DS) is one of the main features of Lewy body dementia and is also problematic in PD (4) and may be particularly influenced by treatment with dopamine agonists as well as levodopa.

Sleep disturbances affect quality of rest and health-related quality of life (HRQoL) and may lead to problems during the waking hours, such as EDS, fatigue, and memory and attention difficulties. Nocturnal disturbances alter blood pressure, oxygen, and carbon dioxide blood levels and are thus well-established risk factors for cardio-cerebrovascular diseases. On the other hand, DS and sleep attacks impair social and working function and are highly dangerous if subjects are driving a vehicle, with evident implications beyond the patient.

Therefore, diagnosis and treatment of sleep disorders is a priority for clinicians but also for health policy makers. Diagnosis of insomnia is based on the subject's perception of sleep quality while diagnosis of nocturia, and RLS is based on careful clinical history and evaluation. Many instruments have been designed to detect these problems, measure their severity, evaluate their effect on quality of life, and assess their change in time or after intervention. The diagnostic criteria of other sleep disturbances, such as PLMs, RBD, and OSA, are defined by polysomnographic (PSG) data. For EDS and sleep attacks, objective tests such as the Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT) are used. PSG is not a useful ancillary test to diagnose EDS, although it can be useful to identify underlying sleep disorders (5). However, these laboratory tests are highly demanding in terms of cost, human resources, and other logistics required; therefore, questionnaires and scales have been developed for screening patients and thus make recommendations for further testing.

Questionnaires are patient-based instruments that allow for the evaluation of signs and symptoms that cannot be observed in the clinic (i.e., insomnia or nocturia) and may include subjective features based on the patient's perception and judgment of the symptom and its impact on his/her life. As such, they are considered patient-related outcomes and have the advantage of shifting the focus to the patient, a requirement in the current biopsychosocial model of patient-centered medicine.

The objective of this review is to provide the clinician and researcher with an overview of the scales that are currently available to screen and measure the severity of these sleep disturbances (except RBD, which is the focus of another article in this issue). All the reviewed scales are questionnaires and are organized by type (generic, disease-specific, and HRQoL) and chronologically by year of publication. After a practical description of each scale including diagnostic accuracy (for screening instruments, where available), the psychometric properties and application in different movement disorder cohorts are discussed, along with the instruments' advantages and disadvantages.

METHODS

The literature search was based on the pubmed database and included articles published before January 31, 2018 and written in English, Italian, French or Spanish. The combined MeSH search terms used were: ("insomnia" OR "nocturia" OR "restless legs" OR "periodic leg movements" OR "obstructive sleep apnea" OR "excessive daytime sleepiness" OR "sleep attacks" OR "sleep disturbance") AND ("Parkinson's disease"). A similar search strategy was performed with the following terms: "multiple system atrophy," "dementia with lewy bodies," "progressive supranuclear palsy," "corticobasal degeneration," "dystonia," "chorea," "Huntington's chorea," "tics," "Tourette." The identified articles were perused for the use of scales or questionnaires for screening or diagnosis of the sleep disturbances under review, and their references were also searched for other sleep disturbance scales. For each identified measuring instrument, psychometric properties were noted from the original developers of the instrument and completed with further clinimetric investigations when available. With all identified generic scales, a similar search strategy was used to identify their use in the different movement disorder populations mentioned above. The extracted information was initially discussed and agreed by two authors (Mónica M. Kurtis and Roberta Balestrino), and their consensus was reviewed by the other authors to obtain a final agreement of the most relevant scales.

NOCTURNAL SLEEP (NS) DISTURBANCES

Insomnia

The diagnostic criteria of "insomnia syndrome" include the following: (1) difficulty falling asleep, awakenings during the night or waking up too early, (2) despite adequate sleep circumstances, and (3) symptoms during wakefulness, such as attention problems or fatigue, due to the lack of sleep (6). Thus, the diagnosis depends on self-reported outcomes, not on a specific amount of sleep or other objective sleep measures. Insomnia can be classified as primary or secondary; however, it is often hard to establish the cause, effect, or coexistence of conditions that are associated with insomnia such as psychiatric disorders. Thus, the term "comorbid" is preferable to "secondary." Insomnia is a frequent complaint in movement disorder patients and has been extensively studied in PD, chorea, and antibody-mediated encephalopathies manifesting with movement disorders.

Pittsburgh Sleep Quality Index (PSQI)

Scale Description

The PSQI is a generic, 19 items self-rated scale designed to measure overall sleep problems (7). A score above 5 distinguishes between "good" and "poor" sleepers with a high sensitivity and specificity (7, 8) (**Table 1**).

TABLE 1 | Scales that evaluate insomnia in movement disorders.

Scale	Overview	Scoring	Cut off Diagnostic accuracy	Time frame	Administration	Languages
PSQI (7)	Generic Assesses overall sleep quality	19 items are combined to form seven component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction). Items are scored from 0 to 3 (no difficulty to severe difficulty). Total scores range from 0 to 21, where higher scores indicating more severe difficulties in the different areas	>5 "bad sleepers" Sensitivity 90–98% Specificity 84–86% (7, 8)	Previous month	Self-rated 10 min	Public domain English Spanish
PDSS (17)	PD specific Measures nocturnal problems and daytime sleepiness	15 items rated on visual analog scale (0–10). Range 0–150, where higher scores indicate more severe sleep problems. Weighted toward severity	>82 AUC: 0.85 (95% CI 0.78–0.91) Sensitivity 75% Specificity 80% (18)	Previous week	Self-rated 10 min	Public domain English Japanese Spanish Portuguese
PDSS-2 (21)	PD specific NS problems	15 items scored from 0 (never) to 4 (very frequent). Range 0–60, where higher scores indicate more sleep problems	≥15 Sensitivity 72.1% Specificity 72.9% (21)	Previous week	Self-rated 10 min	Public domain English Spanish
SCOPA-Sleep-NS (11)	PD specific Measures NS problems and sleep quality	The NS subscale has 5 items scored from 0 (not at all) to 3 (very much). Range 0–15. Higher scores indicate more severity. One item on sleep quality is rated on 7-point scale, 0 (very well) to 7 (badly)	>7 AUC 0.96 (CI 0.93–0.98) Sensitivity 97% Specificity 80–88% (11, 18)	Previous month	Self-rated 5 min	Public domain Dutch English Spanish Thai

AUC, area under the curve; CI confidence interval; NS, nocturnal sleep; PDSS, Parkinson Disease Sleep Scale; PSQI, Pittsburg Sleep Quality Index; SCOPA, Scales for outcomes in PD; PD, Parkinson's disease.

Psychometric Properties

The scale has shown high internal consistency and homogeneity (Cronbach's alpha = 0.80–0.83) (7, 9). A factor scoring model based on three different domains (sleep efficiency, perceived sleep quality, and daily disturbances) is suggested (10). This scale shows strong correlation with SCOPA-Sleep but not with PSG, except for sleep latency (7, 11).

Use in Different Movement Disorder Populations

The scale has been extensively used in primary insomnia, dementia, depression and anxiety but also in movement disorders such as PD (12), MSA, PSP (13), and Huntington's disease (14). It has shown sensitivity to change in PD cohorts after interventions such as deep brain stimulation (15) and pharmacological treatment (16).

Strengths and Limitations

The PSQI is a generic scale with strong psychometric attributes that has been used in different movement disorders populations and reliably measures overall sleep problems. The scale was "recommended" by the MDS Task Force that reviewed clinical scales assessing sleep in PD as a screening tool and a measure of severity for overall sleep problems (10). The PSQI has the limitations of a self-rated scale (unreliable in dementia populations), although it does include 5 items to be filled out by the caregiver that are not included in the total score. It is heavily weighted toward sleep habits and does not adequately cover other sleep disturbances such as motor problems at bedtime (akinesia, dystonia, or chorea), RLS, REM Sleep Behavior Disorder (RBD) or DS. Furthermore, questions addressing respiratory disturbances and awakening may be confounders since they may be secondary to different problems, and scoring is complex.

Parkinson Disease Sleep Scale (PDSS)

Scale Description

The PDSS (17) is a PD-specific, 15 item self-rated scale that preferentially evaluates NS problems, with only one item pertaining to DS [see Nocturnal Sleep (NS) Disturbances]. Each item is rated on a 0–10 visual analog scale (VAS), total score ranging from 0 to 150. A cutoff score above 82 indicates the presence of NS problems with acceptable sensitivity and specificity (18) (**Table 1**).

Use in Different Movement Disorder Populations

The PDSS has been extensively used in PD and there is some experience in a dystonia cohort including patients with generalized, segmental, and focal dystonia (19).

Psychometric Properties

The PDSS has been validated in PD patients in all stages (20). Internal consistency and test–retest reliability are high [Cronbach's alpha = 0.77 and intraclass correlation coefficient (ICC) = 0.94, respectively] (17). Floor and ceiling effects are low, and there is significant correlation between 11 of the 15 items (20). The PDSS has shown strong correlation with the SCOPA-Sleep-NS (18).

Data From Different Populations

The PDSS has been widely used in different PD populations and distinguishes between PD patients and controls and drug naïve, mild and long-standing PD patients.

Strengths and Limitations

The PDSS has demonstrated good psychometric characteristics. The scale is "recommended" by the MDS Task Force as a screening tool and severity measure for sleep symptoms in PD as it includes most of the patient's possible disturbances (10). However, patients require explanation on how to score the VAS, and the scale does not include information from the caregiver. It does not address respiratory difficulties such as sleep apnea and specific sleep disturbances such as RBD and RLS are partially addressed but wording is ambiguous. Finally, the scale only has one item regarding DS and thus is not recommended to assess diurnal sleep problems in PD.

Parkinson Disease Sleep Scale-2

Scale Description

The PDSS-2 (21) is the second version of the PDSS and has two main differences with the first version of the PDSS (see above): items are scored on a Likert scale (from 0 = never to 4 = very frequent), and all 15 items evaluate NS problems. Total scores range from 0 to 60, and higher scores indicate higher severity. A cut of score above or equal to 15 distinguishes "bad" sleepers from good sleepers with acceptable diagnostic accuracy (21) (**Table 1**).

Psychometric Properties

The scale has shown acceptable inter-item correlations (>0.30) and internal consistency (Cronbach's alpha, 0.73). Test–retest reliability is also satisfactory (ICC = 0.80). Factor analysis resulted in a strong main factor that justifies summing all the items into a total scale, but also a three factors solution explaining 42.75% of variance, which suggested a hierarchical scale structure. The three subscales are night-time motor problems, PD-specific symptoms, and sleep-specific symptoms (21).

Strengths and Limitations

Like the previous version, the PDSS-2 has shown good psychometric characteristics and has been extensively used in PD and is thus recommendable for screening and measuring severity of sleep disturbances in PD. This Likert scaling is easier for patients to understand, although scoring in item 1 is inverted which may be confusing.

SCOPA-Sleep (NS Subscale)

Scale Description

The Scales for Outcomes in PD-Sleep (SCOPA-Sleep) (11) is a PD-specific scale that includes 12 items to measure sleep quality, NS disturbances, and DS. The NS subscale includes 5 items on insomnia, multiple awakenings, sleep efficiency, and duration plus one single item on overall sleep quality. A cutoff score of 7 has demonstrated excellent sensitivity and satisfactory specificity (11, 18) (**Table 1**).

Psychometric Properties

The internal consistency of the NS subscale is high (Cronbach's alpha = 0.88–0.84), and test–retest reliability is excellent (ICC = 0.94) (11). Factor analysis revealed one factor accounting for 68.1% of the variance, thus demonstrating that this subscale measures a single construct (11). The SCOPA-Sleep-NS has shown strong correlations with other instruments such as the PSQI ($r = 0.83$) (11) and the PDSS ($r = 0.60$) (18).

Strengths and Limitations

The NS subscale of the SCOPA-Sleep has shown strong psychometric properties and has been extensively used, discriminating between subjects and controls and PD patients in different stages. The subscale is a "recommended" tool for screening and for measuring severity of overall sleep problems in PD (10). However, sensitivity to change has not been investigated and, similarly to the PDSS, the scale lacks specific items addressing RLS and RBD.

Multidomain Scales

Some multidomain PD-specific scales, such as the Non-Motor Symptom Questionnaire (NMSQuest) (22), the Non-Motor Symptom Scale (NMSS) (23), and the Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS UPDRS) part 1B (24) include a single item that evaluates insomnia. The NMSS is a rater-based scale that evaluates both severity and frequency of thirty different non-motor symptoms seen in PD, considering the past month. Item 5 has been used to evaluate difficulty falling asleep or staying asleep in other hypokinetic disorders such as MSA and PSP (25). The NMSQuest and the MDS UPDRS part 1B are both self-rated questionnaires. Question 23 on the NMSQuest evaluates difficulty falling asleep or maintaining sleep while item 1.7 of the MDS UPDRS asks the patient to give an overall score on sleep quality in the past 7 days. Another disease-specific scale for another parkinsonism, the Progressive Supranuclear Palsy Rating Scale (26) includes one item on sleep difficulty, rated from 0 to 4, in the activities of daily living part. These scales have demonstrated excellent psychometric characteristics, although the validity and reliability of single items has not been tested yet.

Conclusion

Only the PSQI can be recommended for screening and assessing severity of insomnia in any type of movement disorders since it is a generic scale with satisfactory psychometric properties and extensive use. There are three PD-specific scales that can be recommended in patients with this disease. There are single items on PD-specific multidomain scales that assess insomnia, but these single items have insufficient psychometric data on validity and reliability.

Nocturia

Nocturia is defined as "waking up to pass urine during the main sleep period," and it is a common phenomenon although patients tend to under-report this symptom (27). Nocturia can be due to different causes, such as renal, urological, vascular, or neurological diseases and medications, and etiology ranges widely by gender and age group. Similarly to other sleep disturbances, consequences of nocturia include lower sleep quality with eventual daytime consequences. Furthermore, nocturia is associated with falls and bone fractures, therefore increasing morbidity and, in elderly populations, mortality (27). Nocturia is highly frequent in patients with PD and can exacerbate sleep fragmentation among this population (28).

Overactive Bladder Questionnaire (OAB-q)

Scale Description

The OAB-q (29) is a generic, self-rated, 33 items scale developed to measure symptoms of overactive bladder (OAB), which include urinary frequency, nocturia, and urgency, with or without incontinence. The scale is made up of two subscales: a symptom bother scale (8 items), rated 1 (not at all) to 6 (a very great deal) and an HRQoL scale (HRQoL) (25 items), rated 1 (none of the time) to 6 (all the time). Two items of the symptom bother scale assess nocturia, and five of the HRQoL scale are related to sleep. The time frame is the past 4 weeks. It takes about 20–25 min to complete. A shorter form, the OAB-q SF, made up of 19 items (6 symptom bother items and 13 HRQoL items) was developed by the original authors and includes nocturia (1 item) and impact on sleep quality (2 items) (30).

Psychometric Properties

Factor analysis provided a four factors solution for the HRQoL items (one of them being sleep) (29). Internal consistency is high with subscale Cronbach's alpha-values ranging from 0.86 to 0.94 (29). The questionnaire has also demonstrated adequate test–retest reliability (31) and satisfactory responsiveness (32). The shorter form has also shown appropriate convergent validity, discriminant validity, internal reliability, reproducibility, and responsiveness to change (30).

Scale Use in Movement Disorders

In PD, the OAB-q has been used to evaluate the correlation of bladder dysfunction and motor impairment (33), while its short form has been used to evaluate the effect of percutaneous posterior nerve stimulation on detrusor (34) but no published experience in other movement disorder cohorts was found.

Strengths and Limitations

The OAB-q has been extensively used due to its robust psychometric characteristics and because it assesses severity of symptoms and impact on quality of life. It can be found in several languages and a short form is available. However, studies demonstrating sensitivity to change of the OAB-q are lacking. The psychometric properties of the items on nocturia have not been investigated nor their impact on sleep quality. Finally, data in movement disorders patients are only available for PD patients.

Overactive Bladder Symptom Score (OABSS)

Scale Description

The OABSS (35) is another generic, self-rated scale with 4 items that include: daytime urinary frequency (scored 0–2), nocturia (from 0, never wake up to urinate, to 3, wake up ≥3 times to urinate), urgency (0–5), and incontinence (0–5). Thus, the total score ranges from 0 to 15, where higher scores indicate more severity. The time frame is the past week, and the questionnaire takes about 3–4 min to complete.

Psychometric Properties

In patients with OAB, each symptom score correlated positively with the total OABSS ($r_S = 0.10–0.78$), and the scale showed good internal consistency (Cronbach's alpha = 0.74) and high test–retest reliability (weighted kappa coefficients were 0.80–1.0 for each symptom score and 0.86 for OABSS). The OABSS showed moderated correlations with quality of life scores assessed by the King's Health Questionnaire ($r = 0.20–0.49$). The OABSS discriminated patients with OAB from controls and showed sensitivity to change after therapeutic intervention (35).

Use in Movement Disorders

The OABSS has been recently used in two PD cohorts to evaluate urinary symptoms, including nocturia. Mito et al investigated PD patients without treatment and found moderate correlations between OABSS and the UPDRS motor scores ($r_S = 0.39$), particularly with the akinetic-rigid subscore ($r_S = 0.47$) (36). Another study investigated the correlation between urinary disturbances and falls in 90 patients with PD and did not find a relationship between nocturia and falling (37). To the best of our knowledge, the scale has not been used in other movement disorders.

Strengths and Limitations

The OABSS is a fast and easy to use scale that has demonstrated content and construct validity and internal consistency in measuring urinary disturbances in OAB syndrome. However, the psychometric properties of the single item on nocturia have not been sufficiently investigated, and data for movement disorders populations are limited to PD.

Urinary Symptom Profile (USP)

Scale Description

The USP is a 13 item, self-rated scale that evaluates three dimensions of urinary disturbances: stress urinary incontinence, OAB, and low stream symptoms (38). The OAB domain includes two items on nocturnal urinary symptoms. The time frame includes symptoms in the past 4 weeks.

Psychometric Properties

The scale has demonstrated robust psychometric qualities with good internal consistency, convergent validity, and test–retest reproducibility. In the validation study, USP dimension scores were good predictors of urinary disorder presence and identification and correlated with micturition diaries (38).

Use in Movement Disorders

To the best of our knowledge, the scale has only been used in a population of functional movement disorders patients who reported lower urinary tract symptoms (39).

Strengths and Limitations

Although this is the first scale to comprehensively assess the main dimensions of urinary disturbances in both sexes and the psychometric properties are more than adequate, the UPS has scarcely been studied in movement disorders patients. The nocturia items have not been investigated separately to evaluate their psychometric properties.

Other Generic Urinary Symptom Scales

There are four generic questionnaires designed to assess lower urinary tract symptoms associated with benign prostatic enlargement in men that have excellent psychometric properties (validity and reliability) and include an item on nocturia.

Of these, the most extensively used, probably due to simplicity and fast completion, is the American Urological Association symptom score (40), also known as the International Prostate Symptom Score. The Danish Prostate Symptom Score (41) and the International Continence Society (ICS) ICSmale questionnaire (42) are very complete but requires more time and harder to score. The shortened version of the latter, the ICSmale Short Form (43), provides a good alternative and has been used in a Huntington's disease population (44).

PD-Specific Multidomain Scales

The NMSQuest (22), the NMSS (23), and the SCOPA-Autonomic (45) include an item on nocturia. Item 24 on the NMSS and item 9 on the NMSQuest evaluate whether the patient has to get up during the night to urinate. The SCOPA-Autonomic is a tool that evaluates the range of dysautonomic symptoms that most affect PD patients and item 13 evaluates the frequency of nocturia. These single items have not been properly investigated to establish their psychometric properties and reliability to screen for and measure severity of nocturia in PD.

Conclusion

There is no scale designed solely for the evaluation of nocturia and its effect on sleep. The available measurements include generic scales that measure lower urinary tract dysfunction, including nocturia, and PD-specific scales that address a range of non-motor symptoms that are prevalent in this movement disorder, including nocturia.

Restless Legs Syndrome

Restless legs syndrome is a neurological disorder characterized by the presence of unpleasant sensations that patients describe as creeping, crawling, itching, tingling, pulling, or painful sensations, more commonly, but not exclusively, in the lower limbs. Moving the interested limb or standing up, walking or stretching can release these sensations, thus the name of the disease. RLS is relatively common, with prevalence rates ranging from 3.9 to 15% in the general population; is more common among Caucasians and older people, although it can affect children as well (46). Approximately 10% of patients seek medical help, and the most common complaints are difficulty in sleeping/daytime activities and an overall lower HRQoL (47). The diagnostic criteria have been recently revised by the International Restless Legs Syndrome Study Group (48).

There are three scales to assess the severity of RLS, one scale to assess the augmentation phenomenon, three scales that assess HRQoL and two scales that assess the impact of RLS on sleeping and on daily functioning, although just one has been validated (**Table 2**). One pediatric scale has been designed but has not been validated. Two PD multidomain scales have an item to assess symptoms that are compatible with RLS.

Johns Hopkins Restless Legs Severity Scale (JHRLSS)

Scale Description

The JHRLSS is a short scale used to assess the usual time of onset and severity of symptoms of RLS and consists one sole item (49) (**Table 2**).

Psychometric Properties

This scale showed a strong correlation with sleep efficiency, as assessed by an all-night polysomnogram ($r_S = 0.60$) and moderate correlation with Periodic Limb Movements (PLMs) per hour of sleep ($r_S = 0.45$). The JHRLSS inter-rater reliability was excellent: Spearman's rank coefficient was 0.91, and Cramer's *V* for inter-rater agreement was 0.87 (49).

Data From Different Populations

It has been validated in an adult population of RLS patients, with symptoms at least 5 days/week (50). We did not find any data regarding its use on other populations.

Strengths and Limitations

The JHRLSS is an easy and fast instrument to administer to obtain additional information on RLS. It showed correlation with objective measures of the disease. In a revision of instruments to assess the severity of RLS performed by the MDS Task Force (50), this scale was rated as "suggested" for RLS patients with frequent symptoms (5 days a week or more) since no data on its responsiveness were available. There are no published data on populations other than adults with RLS. Importantly, the demarcation point for "evening" (6:00 p.m.) might need to be adjusted based on geographic and cultural characteristics of the population. It does not provide information on other important aspects of the disease such as severity, impact on sleep, or HRQoL.

International Restless Legs Scale (IRLS)

Scale Description

The IRLS (51) is a 10-item questionnaire with two subscales, one assessing symptoms and one evaluating how bothersome they are to the patient. It is probably the most widely used tool to evaluate severity and impact on quality of life of RLS (**Table 2**).

Psychometric Properties

Factor analysis showed two factors, "Severity of symptoms" and "Life Impact," with a total of 64.3% of the variance explained. Internal consistency was satisfactory (Cronbach's alpha = 0.93–0.95) and corrected item-total correlations acceptable (>0.40). Reliability was adequate: after 2 weeks, the ICC was 0.87, and inter-rater reliability was 0.93–0.97. It showed strong correlation with other scales such as the Clinician's Global Impression of Severity (CGIS) (0.73–0.74) and the Patient Global Impression (0.78–0.82). The IRLS differentiates a group of RLS patients from a normal control group and a sleep-disorder control group (51). The scale has demonstrated responsiveness (52).

Data From Different Populations

The scale was originally validated in an adult population of RLS patients. It has been used to study prevalence of RLS in PD and controls (53) and to compare the prevalence or RLS in different movement disorders: PD, PSP, and MSA (13). The scale has also been recently used in Huntington's disease (54).

Strengths and Limitations

This scale was rated as "recommended" by the MDS Task Force (50). It is the primary instrument used to determine RLS severity,

TABLE 2 | Scales that evaluate restless legs syndrome.

Scale	Overview	Scoring	Cut off Diagnostic accuracy	Time frame	Administration	Languages
JHRLSS (49)	RLS specific Assesses the usual time of onset/severity of symptoms	1 question on what time of day the RLS appears, with answers ranging from 0 (no symptoms) to 3 (day and night symptoms)	No established cutoff	Lifetime (50% of days)	Clinician rated 1 min	English
IRLS (51)	RLS specific Most used scale to assess severity of RLS	10 items in total. Answers range from "no RLS or impact (0)" to "very severe RLS or impact (4)" 2 subscales: symptoms and symptoms impact Total score that ranges from 0 to 40	No established cutoff	Previous week	Clinician rated 10 min	English, Japanese, Hindi, Brazilian Portuguese, and translations performed by MAPI Research Trust[a]
RLS-6 (55, 56)	RLS specific Assess severity of RLS at different times of a 24 h period	6 items, scored on a 0–10 scale (0 = no symptom, 10 = very severe). No total score, separate scores for 4 domains: sleep quality (items 1 + 6); RLS at night time (items 2 + 3); daytime manifestations during relaxation (item 4); and during activity ("RLS mimics") (item 5)	No established cutoff	Previous week	Clinician rated 10 min	English
ASRS (57)	RLS specific Measures RLS before and after dopaminergic treatment	3 items cover where symptoms begin and the onset. Each item is scored "0" (improvement after treatment), worsening score ranges between 1 ("mild") and 8 ("severe"). Total score ranges from 0 to 24 following an algorithm	≥5 Sensitivity 82% Specificity 92% (57)	Previous week	Clinician rated 10 min for the scale and 5 min to calculate the score	English and translations performed by MAPI Research Trust[b]
RLS-QLI (58)	RLS specific Measures impact of RLS on HRQoL	17 items in 4 domains: daily function, social function, sleep quality, and emotional well-being. Scores for each domain can be calculated as explained in the scale. Total scores range between 0 and 100 (lower scores mean lower HRQoL)	No established cutoff	Previous month	Self-rated 15 min for the scale and 5 min for the score	English
ARLSQoL (60)	RLS specific Measures impact of RLS on daily life, emotional well-being, social life and work	18 items. 10 items are scored on a 5-point scale, and form a single summary score, the overall life impact score (lower scores indicate worse HRQoL). The remaining 8 items are recorded as either a numerical value or a dichotomous response and concern daily activities (one question), sexual interest (two questions) and work (five questions)	No established cutoff	Previous 4 weeks	Self-rated 10 min	Dutch, Finnish, French, German, Greek, Hungarian, Italian, Hindi, and Japanese
KRLS-QoL (62)	RLS specific Measures impact of RLS on HRQoL	12 items, 5 domains (effects of RLS symptoms; disturbed sleep and its effects; effects of other features; handling the RLS symptoms; overall impact on QoL). First 11 items are scored from 0 (no impairment at all) to 5 (extreme impairment). Item 12 summarizes the impact on quality of life	No established cutoff	Previous 4 weeks	Self-rated 10 min	English
PSQ-RLS (63)	RLS specific Assesses impact of RLS on sleeping and on daily functioning	5 single item domains (overall quality of sleep, ability to function during the day, frequency of RLS symptoms, awakening at night due to RLS, length of awakening in the night due to RLS symptoms). 4 Items are assessed with a Likert scale (1–4 or 1–5); one Item is an open-ended question on the number of nights per week with RLS symptoms	No established cutoff	Previous week	Self-rated 5 min	English

IRLS, International Restless Legs Scale; JHRLSS, Johns Hopkins Restless Legs Severity Scale; ASRS, Augmentation Severity Rating Scale; ARLSQoL, Restless Legs Syndrome Quality of Life Questionnaire/Abetz; RLS-QLI, Restless Legs Syndrome Quality of Life Instrument; KRLS-QoL, Kohnen Restless Legs Syndrome Quality of Life Questionnaire; PSQ-RLS, Post-Sleep Questionnaire for RLS; RLS-6, Restless Legs Syndrome-6; HRQoL, health related quality of life; RLS, restless legs syndrome.

[a]*Translations: Afrikaans for South Africa, Arabic for Saudi Arabia, Cebuano for the Philippines, Czech for Czech Republic, Danish for Denmark, Dutch for Belgium (Flemish), Dutch for the Netherlands, English for Canada, English for the Philippines, English for the UK, Farsi for Iran, Finnish for Finland, French for Belgium, French for Canada, French for France, French for Switzerland, German for Austria, German for Germany, German for Switzerland, Greek for Greece, Hungarian for Hungary, Italian for Italy, Italian for Switzerland, Japanese for Japan, Korean for Korea, Mandarin for China, Mandarin for Taiwan, Norwegian for Norway, Polish for Poland, Portuguese for Portugal, Russian for Russia, Serbian for Serbia, Slovak for Slovakia, Spanish for Spain, Spanish for the USA, Swedish for Sweden, Tagalog for the Philippines, and Turkish for Turkey.*

[b]*Translations: Czech for Czech Republic, Dutch for the Netherlands, Finnish for Finland, German for Austria, German for Germany, Italian for Italy, Polish for Poland, Spanish for Spain, Swedish for Finland, and Swedish for Sweden.*

applied in different populations including movement disorder patients. It is available and validated in many different languages. However, the scale does not provide information on RLS symptom severity during different times of the day or under different circumstances.

Restless Legs Syndrome-6 (RLS-6)

Scale Description

The RLS-6 is a specific measure to assess the severity of RLS that was developed more than a decade ago (55) and has been recently validated (56). This 6 items scale is divided into four domains assessing RLS symptoms during different times and situation of the day (**Table 2**).

Psychometric Properties

The RLS-6 has adequate internal consistency (Cronbach's alpha = 0.79). The factor analysis showed one factor explaining 55% of the variance (item 5 excluded). Moderate to high correlations were obtained between RLS-6 domains and IRLS subscores (0.25–0.70) and between RLS-6 domains and IRLS total score (0.35–0.74). The RLS-6 displayed a satisfactory ability to discriminate between patients in different severity categories as assessed by the IRLS and CGIS, and was responsive to treatment, with responsiveness coefficients ranging from 0.38 to 0.49, except for the RLS mimics domain (56).

Data From Different Populations

The RLS-6 has been validated in adults of both genders with RLS. To the best of our knowledge, there are no data on other populations, and this scale has not yet been used in movement disorders patients.

Strengths and Limitations

In a revision of instruments to assess the severity of RLS performed by the MDS Task Force (50), this scale was rated as "suggested," since validation data had not been published. However, validation data are currently available, demonstrating good psychometric properties and good responsiveness (56). It is a complementary scale to be used with the IRLS as it provides information on symptom severity at different times of the day and night and during activities. However, there are no data on its reproducibility and stability.

Augmentation Severity Rating Scale (ASRS)

Scale Description

The ASRS was designed as a quantitative measure of the severity of augmentation (a paradoxical worsening of RLS symptoms from dopaminergic therapy) during clinical studies (57). It consists of 3 items that evaluate where (body part) and when RLS symptoms start and should be administered at baseline (before treatment) and after treatment. The scale has satisfactory sensitivity and specificity values (57) (**Table 2**).

Psychometric Properties

The ASRS showed acceptable internal consistency (Cronbach's alpha of 0.62). Factor analysis showed only one factor. The worst augmentation score under treatment showed a strong correlation with the independent rating of an expert (0.72), and the ASRS scores were significantly different between subjects with and without augmentation according to experts' opinion. The correlation between the CGIS for augmentation and the ASRS total score was moderate (0.53). Test–retest reliability was satisfactory (0.72); the inter-rater reliability analysis was excellent (0.94) (57).

Data From Different Populations

It has been validated in an adult population of RLS patients of both genders. No data on patients with other movement disorder and associated RLS are available.

Strengths and Limitations

The ASRS is a specific tool to measure augmentation in RLS patients who have been treated with dopaminergic agents. In the MDS Task Force review (50), this scale was rated as "recommended" to measure augmentation. The scale must be administered before and after the start of dopaminergic therapy. The main disadvantage is that it has not been correlated with objective measures of augmentation.

Restless Legs Syndrome Quality of Life Instrument (RLS-QLI)

Scale Description

The RLS-QLI is another self-administered questionnaire designed to measures the impact of RLS on HRQoL (58). This 17-item questionnaire is divided into four domains considering impact on daily activities and sleep (**Table 2**).

Psychometric Properties

Factor analysis showed 4 factors. The RLS-QLI has satisfactory internal consistency and reliability: for the subscales, Cronbach's alpha was 0.85–0.91 test–retest reliability coefficients ranged 0.81–0.93. It showed weak to moderate correlations with SF-36 subscales (0.26–0.62) and moderate-to-strong correlations with the total IRLS score (−0.71, −0.62) (58).

Data From Different Populations

The RLS-QLI has been validated in adult patients of both genders, without a confirmed diagnosis of RLS. We did not find data regarding its use in other populations.

Strengths and Limitations

The MDS Task Force (59) rated this scale as "suggested." It showed good psychometric properties; however, it has only been tested in a population without a confirmed diagnosis of RLS, and its responsiveness has not been assessed.

Restless Legs Syndrome Quality of Life Questionnaire/Abetz (ARLSQoL)

Scale Description

ARLSQoL (60) is a self-administered scale to measure the impact of RLS on HRQoL. This 18-item questionnaire is made up of two subscales, one evaluating overall impact and the other assessing different spheres of patients' life (i.e., work, sexual, and social) (**Table 2**).

Psychometric Properties

There is one factor for the 10 items that are grouped in the summary score. The ARLSQoL showed excellent internal consistency (Cronbach's alpha = 0.82–0.92) (60, 61) and satisfactory stability, with ICCs of 0.79, −0.84 (60). Correlation coefficients were moderate between the scale summary score and the Mental Component Score of the SF-36 ($r = 0.50$) and with the IRLS ($r = -0.67$ to -0.68). The ARLSQoL was able to distinguish between patients with mild, moderate or severe symptoms according to their reports, between levels of sleep problems assessed by the MOS Sleep Scale and between levels of global health status determined by a CGIS (60, 61).

Data From Different Populations

It has been validated in an adult population of RLS patients of both genders. To the best of our knowledge, no data on other populations are available.

Strengths and Limitations

This is a quick, easy and self-administered instrument to evaluate HRQoL in RLS. It has shown acceptable psychometric properties. However, its responsiveness has not been evaluated. In the MDS Task Force revision of scales to assess HRQoL in RLS (59), this scale was rated as "recommended."

Kohnen Restless Legs Syndrome Quality of Life Questionnaire (KRLS-QOL)

Scale Description

The Kohnen Restless Legs Syndrome Quality of Life Questionnaire (KRLS-QOL) is a self-administered questionnaire to assess the HRQoL in patients with RLS. This 12-item questionnaire is divided into five domains evaluating the effect of RLS, how they are handled and overall impact (Domain 5) (**Table 2**) (62).

Psychometric Properties

The exploratory factor analysis identified two factors explaining 56.85% of the variance ("Impaired health by symptoms" and "Burden of symptoms"), but the parallel factor analysis advised to consider only one dimension in the scale.

This scale showed acceptable internal consistency and reproducibility (Cronbach's alpha = 0.88). For test–retest reliability, kappa values were 0.43–0.64 (item 4), and the ICC for the KRLS-QoL Index was 0.73. The KRLS-QoL showed moderate-to-strong correlations with the IRLS total score (0.68) and its subscores (0.50–0.73), moderate to low correlations with the RLS-6 (0.33–0.57), and with the CGI (0.42). KRLS-QoL-Domain 5 had moderate to high correlations with the IRLS total score (0.60) and subscores (0.49–0.59), moderate to low with the RLS-6 (0.26–0.49), and CGIS (0.37). KRLS-QoL Index and Domain 5 significantly increased their scores with increasing RLS severity levels based on the IRLS and CGIS scores (62). Responsiveness parameters (effect size) showed large effect with an effective treatment, and strong correlations with change in other scales (62).

Data From Different Populations

The KRLS-QoL has been validated in an adult population of RLS patients of both genders. No data on other populations are available.

Strengths and Limitations

In the review by the MDS Task Force (59), this scale was rated as "suggested" since the validation study had not been published. However, the KRLS-QoL has now been validated and demonstrated good psychometric properties (62), therefore it can be considered a "recommended" instrument to assess the impact of RLS on HRQoL and to measure responsiveness to therapy.

Post-Sleep Questionnaire for RLS (PSQ-RLS)

Scale Description

The PSQ-RLS is a self-administered questionnaire to assess the impact of RLS on sleep and daily functioning (63). This 5-item questionnaire considers number and length of night-time interruptions of sleep due to RLS (**Table 2**).

Psychometric Properties

The PSQ-RLS showed a weak to moderate convergent validity with the following related scales: the IRLS (51), the RLSQoL (61), the Profile of Mood States (64), and sleep domains of the MOS Scale (65). In a study, PSQ-RLS scores did not include systematic measurement errors associated with personal attributes (race, gender, and ethnicity), had adequate discriminate validity across RLS severity groups, and showed satisfactory responsiveness in a 3-month treatment period (63).

Data From Different Populations

The PSQ-RLS has been validated in an adult population of RLS patients of both genders. No data on other populations are available.

Strengths and Limitations

The PSQ-RLS is an instrument that can be used to assess the impact of RLS on quality of sleep. A review of instruments that assesses HRQoL in RLS (59) noted that the scale had not been used by other investigators beyond its designers and its internal consistency and stability had not been explored, which justified the scale's rating as "listed." Subsequently, the scale has been used by other investigators, but the missing psychometric properties have yet to be published.

Restless Legs Syndrome-Next Day Impact Questionnaire (RLS-NDI)

The RLS-NDI is a self-administered questionnaire to assess the impact of RLS on sleep and daily functioning. The RLS-NDI is composed of 14 items rated on an 11-point Likert-type scale. It is designed to be administered in the evening with a 12-h recall, to assess the impact of RLS on the same day. It has shown a good content validity, but no further data on its psychometric properties are available (66).

Pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS)

The P-RLS-SS was designed to measure RLS severity in children (67). This scale is composed of 41 items (17 morning and 24 evening items) and a parent questionnaire composed of 20 items. Its importance relies in being the only instrument to assess RLS severity in children; however it has not been validated, and no data on its psychometric properties are available.

Multidomain Scales That Assess RLS

For PD, there are two multidomain scales that assess the range of non-motor symptoms that are prevalent in this disease, the NMSS (23) and the NMSQuest (68). Both instruments include one item for RLS assessment when the patient is lying down or inactive: item 6 of the NMSS and item 26 of the NMSQuest.

Conclusion

There are two scales (IRLS and RLS-6) that can be recommended to assess the severity of RLS, since they have the appropriate psychometric properties and have been extensively used. There is a recommended scale (ASRS) to assess the augmentation phenomenon. Two scales (KRLS-QoL and ARLSQoL) can be recommended to assess HRQoL in RLS. There is currently no recommended scale to evaluate RLS in the pediatric population. There are single items on PD-specific multidomain scales that assess RLS but there is insufficient evidence to evaluate their psychometric reliability or clinical applicability. Just one of the discussed scales (IRLS) has been used in several movement disorders.

Periodic Leg Movements (PLMs)

PLMs are sleep-related movements characterized by a stereotyped and periodic pattern. They are relatively common in the general population, particularly in the elderly (69) and can occur in isolation or be associated with RLS or other movement disorders (70). The golden standard to diagnose PLMs is overnight PSG, and two sets of standards for recording and scoring are available: one by the International Restless Legs Syndrome Study group and the World Association of Sleep Medicine (71); the other by the American Academy of Sleep Medicine (72). As PSG is a cumbersome and costly test, alternative assessment tools are currently under evaluation: leg-worn actigraphy (73), contactless devices to measure movement and respiration during sleep (74) and analysis of electrocardiographic data (75) among others. Currently, there is no available questionnaire or scale to measure PLMs.

Obstructive Sleep Apnea

Obstructive sleep apnea is a common sleep-related disorder characterized by repetitive episodes of complete or partial collapse of the upper airway which cause breath cessation. Despite being frequently underdiagnosed, its prevalence is reported to be 6–17%, varying according to age, sex, and body mass index (BMI). The gold standard for diagnosis is based on PSG recording of events of apnea (breathing pauses lasting 10 s or more) and hypopnea (reduction in respiratory airflow, without apnea, associated with oxygen desaturation or arousal from sleep). The apnea-hypopnea index (AHI) per hour is calculated to determine the presence and severity of OSA (based on standard scoring: AHI > 5 mild, AHI > 15 moderate, AHI > 30 severe) (76).

There are three questionnaires that have been designed as screening tools for OSA. The severity of OSA can be assessed by two extensively used generic scales for sleep disorders, and two specific scales have been developed to assess HRQoL in OSA. Scales that assess OSA are summarized in **Table 3**.

Wisconsin Sleep Questionnaire (WSQ)

Scale Description

The WSQ is a generic questionnaire to investigate snoring, obstructive apnea, and sleeping problems in general (**Table 3**) (77, 78). It is one of the most cited questionnaires for OSA (79). It has a high sensitivity and a low specificity, especially for diagnosing moderate OSA, and an excellent negative predictive value (**Table 3**) (80).

Psychometric Properties

The internal consistency in each domain of the scale was satisfactory (Cronbach's alpha = 0.67–0.81), reliability was acceptable: at retest after 3 months, the kappa values were 0.28–0.60, the Cohen kappa was >0.60 (81).

Data From Different Populations

This scale has been used in the general population and in a sleep disorders population. It has not been used in movement disorders to the best of our knowledge.

Strengths and Limitations

This is a widely used scale for assessing different aspects of OSA. It has demonstrated robust psychometric properties with a high sensitivity. However, its specificity is low, and it has not been used in movement disorders patients.

Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ)

Scale Description

The SA-SDQ is part of a generic questionnaire on sleep disorders, the Sleep Disorders Questionnaire. This subscale includes questions about sleep disturbances and demographic data. The sensitivity and specificity of this scale are acceptable, the negative predictive value was high (**Table 3**) (82).

Psychometric Properties

The scale has shown good internal consistency: Cronbach's alpha was 0.85, and the item-total correlation ranged from 0.19 to 0.71. The intercorrelations with other subscales from the SDQ were weak (<0.35), and the scale could distinguish patients with sleep apnea from patients with other sleep disorders (narcolepsy, periodic limb movements, and psychiatric sleep disorder). The test–retest reliability after 4 months was acceptable (0.84) (82).

Data From Different Populations

The SA-SDQ has been validated in both genders, in patients with sleep disorders and with epilepsy (83). To the best of our knowledge, there are currently no studies that report its use in movement disorders populations.

Strengths and Limitations

This scale has satisfactory psychometric properties. It accurately diagnoses patients with sleep apnea events and sleep apnea related conditions. However, no data were found on the responsiveness of this scale and its use in movement disorders.

Multivariable Apnea Prediction (MAP) Index

Scale Description

The MAP index is a specific instrument used for screening sleep apnea (84) (see **Table 3** for details). There is also an objective MAP index, only based on symptom frequency. The index showed acceptable sensitivity with lower specificity for detecting any OSA, and good specificity with poorer sensitivity for detecting severe OSA (85) (**Table 3**).

Psychometric Properties

The MAP index showed a moderate correlation with the AHI ($r = 0.59$). The objective MAP showed a strong correlation

TABLE 3 | Scales that evaluate obstructive sleep apnea.

Scale	Overview	Scoring	Cut off Diagnostic accuracy	Time frame	Administration	Languages
WSQ (77)	Generic on sleep disorders Investigates snoring, obstructive apnea, and sleeping problems	32 items. 10 questions on sleep disorders due to breathing, 5 questions on sleep disorders, 5 questions on medical history, and 12 questions on life habits. Multiple-choice responses with different scoring based on the question	Score of >3 point for snoring or choking (78) In general population *Any OSA stage* Sensitivity 79–95% Specificity 46–64% PPV 46–28% NPV 89–97% *Moderate OSA* Sensitivity 87% Specificity 40% PPV 11% NPV 97% (80)	3 months (81)	Self-rated 30 min	French, English, and Polish Scoring instructions provided by authors (81)
SA-SDQ (82)	Generic scale subscale Assesses sleep disturbances due to sleep apnea and sleep apnea risk factors	8 questions about sleep disturbances and 4 other items related to weight, smoking status, age, and body mass index (BMI). Each question is scored on a scale 0–5 (0 = never, 5 = always); the total score ranges 0–60	In sleep clinic patients 36 for men 32 for women Sensitivity 85–88% Specificity 76–81% PPV 31–72% NPV 87–99% (82)	Lifetime	Self-rated 8 min	English and Dutch
MAP index (84)	OSA specific Screening questionnaire for OSA	3 frequency questions (loud snoring, snoring or gasping, cessation of breathing, or struggle for breath) and gender, age, and BMI are calculated. Formulas are explained in the reference. MAP index ranges between 0 and 1	In sleep clinic patients *Mild OSA [apnea-hypopnea index (AHI) = 5]* Cutoff 0.46 Sensitivity 76.8% Specificity 71.8% *Moderate OSA (AHI = 15)* Cutoff 0.48 Sensitivity 83.3% Specificity 64.3% *Severe OSA (AHI = 30)* Cutoff 0.65 Sensitivity 61.8% Specificity 79.2% (85)	Last month and lifetime risk factors	Self-rated 5 min for the scale and 5 min for scoring	English
Berlin questionnaire (87)	OSA specific Screening questionnaire for OSAS	10 items, 3 domains: snoring severity, excessive daytime sleepiness, history of high blood pressure or obesity. Multiple-choice questions, for each question there is different scoring. Categories 1 and 2 are positive if total score is ≥2; Category 3 is positive if high blood pressure or if BMI > 30 kg/m^2. Scoring: high risk: ≥2 categories with positive score; low risk: 1 or no categories with positive score	High risk score in sleep clinic patients Sensitivity 79–82% Specificity 32–39% (88)	Lifetime	Self-rated 10 min	English Arabic, Chinese, Dutch, French, Greek, Indian, Korean, Malay, Persian, Portuguese, Serbian, Thai, and Turkish

(*Continued*)

TABLE 3 | Continued

Scale	Overview	Scoring	Cut off Diagnostic accuracy	Time frame	Administration	Languages
STOP-BANG questionnaire (94)	OSA specific Screening questionnaire for OSAS	There are four items on symptoms (STOP: *S*noring, *T*iredness, *O*bserved apnea, and high blood *P*ressure) and four demographic items (Bang: *B*MI, *a*ge, *n*eck circumference > 17″/43 cm in male or >16″/41 cm in female, *g*ender) *Yes/no format. Scoring* – Low risk of OSA if "Yes" to 0–2 questions – Intermediate risk if "Yes" to 3–4 questions – High risk if "Yes" to 5–8 questions or "Yes" to 2 or more of 4 STOP questions + male gender/ BMI > 35 kg/m^2/neck circumference	>3 In sleep clinic patients *For any OSA* Sensitivity 90% Specificity 49% NPV 46% PPV 91% *For moderate OSA* Sensitivity 94% Specificity 34% NPV 75% PPV 72% *For severe OSA* Sensitivity 96% Specificity 25% NPV 90% PPV 48% (99)	Lifetime	Self-rated 5 min	English and[a]
SAQLI (101)	OSA specific Measures impact on HRQoL of OSA	40 or 45 items and 4 or 5 domains: daily functioning (11 items), social interactions (13 items), emotional functioning (11 items), symptoms (five items). The 5th domain, treatment-related symptoms (5 items), can be added for adverse events of treatment. Items are scored with a Likert scale 0- to 7-point scale: "all the time" to "not at all." Score ranges from 0 to 280/315	No established cutoff	4 weeks	Clinician rated 40–45 min	English, Spanish, Persian Portuguese, and Japanese
QSQ (104)	OSA specific Measures impact on HRQoL of OSA	32 items; five domains: (1) hypersomnolence; (2) diurnal symptoms; (3) nocturnal symptoms; (4) emotions; and (5) social interactions. Each item is scored on a 0–7 scale. Mean score per item within each domain, equal weighting	No established cutoff	Not specified	Self-rated 30 min	English, French, Chinese, Spanish, Brazilian, and Portuguese

SA-SDQ, Sleep Apnea Scale of the Sleep Disorders Questionnaire; WSQ, Wisconsin Sleep Questionnaire; MAP, Multivariable Apnea Prediction; SAQLI, Calgary Sleep Apnea Quality of Life Index; QSQ, Quebec Sleep Questionnaire; HRQoL, health related quality of life.
[a]Chinese, Persian, Portuguese, Greek, French, Spanish, Afrikaans, Arabic, Bulgarian, Chinese, Czech, Dutch, Filipino, German, Hungarian, Italian, Korean, Malay, Polish, Romanian, Sami, Taiwanese, Turkish, and Arabic.

with the MAP index, but a poorer correlation with the AHI (85). The MAP index showed good internal consistency (Cronbach's alpha = 0.88–0.93), and satisfactory test–retest reliability (84).

Data From Different Populations

This scale has been used in adults of both genders in a sleep disorder population. To the best of our knowledge, it has not been used in movement disorders.

Strengths and Limitations

This is a quantitative index to assess the risk of OSA. It has shown good psychometric properties. However, its use is limited since it is not useful in patients with a BMI > 40 or with mild cognitive impairment (84, 86), and there is no experience in movement disorder populations.

Berlin Questionnaire

Scale Description

The Berlin questionnaire (87) is a specific self-administered measure used to screen for sleep apnea that includes 10 items that can be divided into 3 domains. This instrument has shown adequate sensitivity but very low specificity (88) (**Table 3**).

Psychometric Properties

This questionnaire has shown satisfactory internal consistency in validation studies for different languages and populations (Cronbach's alpha = 0.68–0.98) and acceptable test–retest reliability 0.74–0.98 (89–92). In the original validation study, the internal consistency was adequate (Cronbach's alpha = 0.86–0.92) (87).

Data From Different Populations

The Berlin questionnaire has been validated in different populations including sleep clinic patients, patients before surgery, patients with cerebrovascular diseases/risk factors, multiple sclerosis patients, general population and others (89, 91, 93). It has also been used in movement disorders populations, in particular: PD, PSP, MSA (13), and Huntington's disease (54).

Strengths and Limitations

The Berlin questionnaire is an easy and short instrument to screen for OSA. It has been widely used in different populations, including movement disorders populations. It has been translated into different languages. Its limitations include low specificity.

STOP-Bang Questionnaire

Scale Description

The STOP-Bang questionnaire is a specific self-administered questionnaire for screening OSA that includes questions about four symptoms and demographic data (94) (**Table 3**). Other versions of this scale are available: there is a shorter version (4-item STOP Questionnaire), a weighted version (wSTOP-Bang) and a continuous version (cSTOP-Bang) (95).

Psychometric Properties

In the original validation of the questionnaire, internal consistency was not assessed because the four questions STOP reflected four different dimensions of OSA morbidity (94). However, other investigators validating language version found moderate internal consistency (Cronbach's alpha ranging from 0.62 to 0.7) (96, 97). Test–retest reliability has been adequate (97) and high (94, 98). The STOP-Bang questionnaire has an excellent sensitivity, but a low specificity; showing high positive and negative predictive values (99) (**Table 3**).

Data From Different Populations

The STOP-Bang questionnaire has been validated in adult patients in both genders; it has been used to screen for OSA in preoperative clinics, sleep clinics, workers at risk, kidney failure patients and in the general population (99), but, to the best our knowledge, not in movement disorders.

Strengths and Limitations

The STOP-Bang questionnaire is an easy and short measure to screen for OSA. It has been extensively used in different populations and has been translated into numerous languages. It is highly sensitive, but not specific; specificity can be raised using the continuous version (cSTOP-Bang), adding more variables (e.g., serum bicarbonate level) or modifying the cutoff; however, in the latter case, sensitivity drops drastically (95, 99, 100).

Calgary Sleep Apnea Quality of Life Index (SAQLI)

Scale Description

The Calgary SAQLI is a specific, self-administered scale used to measure HRQoL in patients affected by sleep apnea (101). It is a long questionnaire (40 or 45 items, if the examiner wants to assess treatment-related symptoms) (**Table 3**).

Psychometric Properties

The scale has satisfactory internal consistency (Cronbach's alpha = 0.88–0.92 for the total scale and 0.70–91 for the subscales) and high reliability (ICC after 2 weeks = 0.92). The SAQLI showed no correlation with the respiratory disturbance index, a measure of severity of OSA, a weak correlation (−0.26) with the Epworth Sleepiness Scale (ESS), and moderate-to-strong correlations (0.39–0.71) with the sleep domains of the SF-36 (102). The SAQLI showed satisfactory responsiveness (103).

Data From Different Populations

This scale has been used in adults of both genders in a sleep disorder population. It has not been used in movement disorders, to the best of our knowledge.

Strengths and Limitations

This is a specific scale for assessing HRQoL in OSA. It offers a global evaluation of aspects of life on which OSA can impact, it has good psychometric properties, and it has been translated into different languages. However, this scale showed poor correlation with other measures of sleep apnea, sleep, and quality of life.

Quebec Sleep Questionnaire (QSQ)

Scale Description

The QSQ (104) is a specific, self-administered questionnaire that evaluates HRQoL in patients with OSA through 32 questions (**Table 3**).

Psychometric Properties

Internal consistency and reliability were satisfactory: Cronbach's alpha was 0.76–0.94, and the ICC after 7 months ranged from 0.82 to 0.91 in the domains. It showed moderate-to-strong convergent validity with the following scales: Functional Outcomes in Sleep Questionnaire (FOSQ), Symptom Checklist-90, and ESS (−0.64). There was a high correlation with the Beck Depression Inventory (BDI) (104). The scale responsiveness has been assessed in an OSA population undergoing CPAP treatment (104).

Data From Different Populations

The QSQ was validated in a sleep clinic population, in adult patients of both genders. It has not been used in movement disorders to the best of our knowledge.

Strengths and Limitations

The QSQ is a fast and specific tool to assess HRQoL in OSA; it showed satisfactory psychometric properties and responsiveness. However, it showed a high correlation with the BDI, which can be a confounding factor. It has not been used in movement disorder patients.

Multidomain Scales That Assess OSA

The PSQI is a self-rated scale designed to measure generic sleep disturbances (7); items 5d and 5e of the PSQI assess, respectively, the inability to breathe comfortably and the occurrence of loud coughs or snores during sleep in the past month.

Conclusion

The Berlin questionnaire is the only scale that has been used in movement disorders populations. This questionnaire has been validated, has shown good psychometric properties, and has been widely used. The STOP-Bang questionnaire has similar characteristics but has not been used in movement disorders. Good psychometric properties have also been identified in another screening questionnaire (MAP index) and severity assessment tools such as the WSQ, SA-SDQ. Both the SAQLI and the QSQ are validated specific questionnaires to assess HRQoL in OSA, but they have not been used in movement disorders.

DIURNAL SLEEP DISORDERS: EDS AND SLEEP ATTACKS

Other sleep disturbances found in movement disorders affect the waking hours, such as EDS and sleep attacks. EDS is a symptom rather than a primary disease and can be the consequence of sleep deprivation, sleep disturbances as discussed above, medications or substance abuse, metabolic, neurological and psychiatric diseases or, more rarely, narcolepsy. In PD, for example, the pathophysiology of EDS is multifactorial and related to NS disturbances, other causes of sleep fragmentation (motor symptoms, painful dystonia, and dyskinesias), the neurodegenerative process itself and to medications. In fact, dopaminergic agents can disrupt sleep and induce somnolence, and sedation and drowsiness have been reported as adverse events of dopamine agonists (105).

Excessive daytime sleepiness and sleep attacks can be reported by patients or their relatives and can be assessed with self-reported scales or with objective tests such as the MSLT and the MWT. Since these laboratory tests are time consuming and costly, scales have been developed to detect and evaluate the severity of EDS and sleep attacks.

Stanford Sleepiness Scale (SSS)

Scale Description

The SSS is a generic scale that measures the current state of sleepiness (106, 107). It is based on a single item rated on a Likert-type scale from 0 to 7, with higher scores indicating more subjective sleepiness.

Psychometric Characteristics

Data on the validity and reliability of the scale are sparse (108). The original publication claims high reliability (106). In healthy subjects, sensitivity to change has been reported (109, 110). The scale shows no correlation with the ESS which may be expected as the measured constructs are different.

Scale Use in Movement Disorders

The scale has been used to assess the induction of sleep by levodopa in PD versus MSA (111) and diminished homeostatic sleep drive in PSP (112). To the best of our knowledge, there are no available data in other movement disorders.

Strengths and Limitations

The SSS is an extensively used scale due to its availability in many languages and simplicity. It is useful for rating the sleepiness state of the individual at the time of testing. The MDS Task Force on sleep disturbances in PD concluded that the SSS is a "suggested" scale for rating sleepiness and to measure severity at a specific moment (10). However, an obvious limitation is the lack of data on psychometric characteristics of the scale.

Epworth Sleepiness Scale

Scale Description

The ESS (113) is a generic scale that measures the risk of falling asleep during daily activities. This scale evaluates the possibility of dozing off in 8 every-day situations. Several cutoff scores with different sensitivities and specificities have been proposed to indicate subjects at higher risk of falling asleep involuntarily (114) (**Table 4**).

Psychometric Properties

Internal consistency of the ESS is high (Cronbach's alpha = 0.88), and the scale has demonstrated acceptable reliability ($r = 0.56$). Floor and ceiling effects are practically absent (115). ESS shows adequate convergent validity with sleep latency measured during the MSLT and during overnight PSG (115), as well as SCOPA-Sleep Daytime Sleepiness (SCOPA-Sleep-DS) subscale scores in the PD patients (11).

Scale Use in Movement Disorders

The ESS has been extensively used in populations with diverse sleep disorders, such as sleep apnea, narcolepsy, and idiopathic hypersomnia (113, 115) and idiopathic RBD (116). It also has been widely used in PD (10) and in other hypokinetic disorders such as MSA (117, 118). In addition, there is experience with this scale in hyperkinetic disorders such as Huntington's disease (14, 119, 120), dystonia (19, 121, 122), and essential tremor (123–125).

Strengths and Limitations

The ESS has adequate psychometric properties and has been extensively used by many groups in diverse movement disorder cohorts to evaluate sleep propensity. It is recommended for screening and evaluating severity of DS in the PD population (10). It has also shown sensitivity to change after intervention. However, the scale does not include information from a caregiver, partner or other outside source; and thus, the information provided may be limited, possibly underestimating risk, since the patient may often be unaware of dozing off. The item "while in the car" is ambiguous since it does not specify whether the person is in the driver or passenger's seat. The EES does not include an item on risk of falling asleep while driving nor does it screen for the risk of sudden sleep attacks.

Inappropriate Sleep Composite Score (ISCS)

Scale Description

Two modified versions of the ESS were proposed by the Canadian Movement Disorders Group to fill the gaps of the previous scale, thus developing the ISCS (114). This scale is made up of 6 items, two from the ESS and four additional new items. If sleepiness

TABLE 4 | Scales that evaluate excessive daytime sleepiness in movement disorders.

Scale	Overview	Scoring	Cut off Diagnostic accuracy	Time frame	Administration	Languages
SSS (106)	Generic Measures current state of sleepiness	1 item. Seven point Likert-type scale	No established cutoff	At this time	Self-rated	Public English French Spanish
ESS (113)	Generic Measures sleep propensity in daily situations	8 items, rated 0 (would never doze) to 3 (high chance of dosing). Range of total score 0–24	>7 Sensitivity 75% Specificity 50% >10 Sensitivity 52% Specificity 72% (115)	Recent times (1–4 weeks)	Self-rated 8 min	Public English German Spanish Chinese
ISCS (114)	Generic Measures sleep propensity and sleep attacks in active tasks	6 items, rated 0 (would never doze) to 3 (high chance of dosing). Range 0–18. Two additional questions regarding sudden sleep onset and blank spells	>1	Since disease onset	Externally rated 10 min	English
SCOPA-Sleep-DS (11)	PD specific Measures sleepiness and possibility of sleep attacks in daily activities	DS includes 6 items scored from 0 (never) to 3 (often). Range 0–18	>4 Sensitivity 90% Specificity 82%	Previous month	Self-rated	Public Dutch English Spanish

DS, daytime sleepiness; ESS, Epworth Sleepiness Scale; ISCS, Inappropriate Sleep Composite Score; SCOPA, Scales for outcomes in PD; SSS Stanford Sleepiness Scale; SCOPA-Sleep-DS, SCOPA-Sleep Daytime Sleepiness; PD, Parkinson's disease.

is present, the patient is asked if dozing off occurs gradually or unpredictably and about the incidence of blank spells.

Psychometric Properties

The scale was developed with the objective of evaluating the predictors for sudden-onset sleep, particularly while driving, among patients with PD. It was tested in 638 mild PD patients of whom 420 were currently drivers. There was a high floor and no ceiling effect. Unfortunately, the original article does not provide any validation or reliability data and the scale has not been investigated (although has been used) by other groups.

Strengths and Limitations

The ISCS assesses the propensity of falling asleep during clearly active situations, such as talking or driving. The MDS Task Force reviewing sleep scales in PD gave this scale the rank of "suggested" to evaluate DS and sleep attacks and recommends its use in conjunction with the ESS (10). The scale has no published psychometric analysis, and terminology may lead to confounders since "sudden blank spells" may be due to sleep attacks, but also to syncope or partial seizures.

SCOPA-Sleep-Daytime Sleepiness subscale

Scale Description

The DS subscale of the SCOPA-Sleep scale (11) includes 6 items on unexpected sleep attacks, dozing off in daily situations and difficulty staying awake. Items are scored from 0 to 3, with total scores ranging from 0 to 18 points where higher scores indicate more severe problems.

Psychometric Properties

The internal consistency of the SCOPA-Sleep-DS subscale is good (Cronbach's alpha = 0.91–0.75) (11, 18). The subscale showed robust test–retest scores (ICC = 0.89) (11). Factor analysis revealed that one factor explains 69.1% of the variance for this subscale. Scores of the SCOPA-Sleep-DS have shown high correlations with the ESS ($r = 0.81$, $p < 0.001$) (11).

Strengths and Limitations

The DS subscale of the SCOPA-Sleep has strong psychometric properties and has been extensively used, discriminating between subjects and controls and PD patients in different stages. The subscale is a "recommended" tool for screening and for measuring severity of DS and sleep attacks in PD (10). However, sensitivity to change has not been investigated.

PDSS Item 15

Scale Description

The PDSS (17) is a PD-specific, 15-item scale that preferentially evaluates NS problems, with one item pertaining to DS: item 15 (**Table 1**).

Use in Different Movement Disorder Populations

Besides being extensively used in PD patients, there are also some available data in dystonia patients (19).

Psychometric Properties

Item 15 on the PDSS considers DS. This single item has shown a strong correlation with SCOPA-Sleep-DS (18) and the ESS in one study (17) and a moderate correlation (0.23) in another study

(20). Patients scoring low on this item (mean 4.7) have shown abnormal sleep patterns in overnight PSG results (126).

Strengths and Limitations

This single item has shown strong correlations with longer DS questionnaires and may thus be useful for screening for DS. However, other psychometric properties and diagnostic accuracy have not been tested.

Multidomain Scales to Assess DS

Some multidomain scales such as the NMSQuest (22), the NMSS (23), and the MDS UPDRS part 1B (24) include a single item that evaluates DS. Item 3 on the NMSS, similarly to item 22 on the NMSQuest, evaluates if the patient dozes off unintentionally during daytime activities such as during meals or watching TV. Item 1.8 is the second item of part 1B on the MDS UPDRS considering non-motor symptoms of daily life. The patient indicates whether he/she has had trouble staying awake during the day in the last week. The limitations to the use of these single items are due to unknown psychometric properties, including lack of data regarding correlation with other scales and sensitivity to change.

DISCUSSION

Sleep disorders are receiving increased attention in movement disorders due to the high impact on patient HRQoL and caregiver burden as well as the growing knowledge of the underlying pathophysiological mechanisms. There are currently multiple questionnaires that can be used to screen and measure the severity of the most frequent sleep problems that affect movement disorder patients, and they have been summarized in this review. Selection of the most appropriate instrument for assessment of insomnia, nocturia, RLS, OSA, and EDS should be guided by the appropriateness of the scale for the objective of the study, availability, psychometric attributes, responsiveness, and previous experience in similar populations. In interpreting the results of questionnaires, the clinician should consider the presence of psychological factors like fatigue, impulsivity or depression that may influence completion, the timing of administration of the scale (for example, on or off state for PD patients) and cognitive impairment (127).

Several gaps have been identified that need to be addressed to adequately research the incidence, prevalence, and severity and impact of sleep disorders in populations with movement disorders.

The majority of available questionnaires are generic instruments with established psychometric properties in the general population but no validity or reliability data available in different movement disorder populations. Generic scales have the disadvantage of potentially not assessing areas of specific interest and may lack sensitivity to detect change in a given disease (128). For example, in evaluating insomnia, the well-established PSQI is currently the best option for patients with movement disorders other than PD (where disease-specific scales are available). However, it does not consider any motor symptoms, such as chorea, dystonia, tics, and other hyperkinetic movements, as well as sensitivity disturbances, such as akathisia, or RLS, that may prevent patients from falling asleep. The paucity of data available in different movement disorders populations for these generic scales is striking. For example, the prevalence of RLS in PD is still controversial due to confounders and overlap of symptoms such as dystonia, akathisia, and sensory symptoms. Validation data of the RLS scales in PD, and other forms of parkinsonism, would be helpful to decide if the current instruments are valid tools or additional measures need to be designed taking into account disease-specific symptoms that may mimic RLS. RLS is probably more frequent in ET (129) and cranio-cervical dystonia (130) than controls; however, none of the current scales have been validated in these populations.

Even in sleep disorders such as insomnia, where there are disease-specific scales for PD that are recommendable, none of them appropriately evaluate common disturbances associated with this disease such as PLMs, or sleep apnea, nor do they address motor akinesia or motor fluctuations during sleep. Most of the available scales do not consider the input of a witness, which is highly valuable in sleep disturbances, since self-perception has been reported to differ from laboratory evidence (131) and neuropsychiatric difficulties may make the patient unreliable.

For RLS evaluation, several unmet needs should be considered. To date, none of the scales that measure severity are self-administered (unlike those that consider impact on HRQoL), and the scale designed to evaluate the pediatric population still lacks psychometric data, and validity data in different movement disorders are sparse.

Currently, there are no questionnaires or scales designed to address some common sleep disorders in movement disorders such as sun-down confusion, disordered breathing and PLM. Nocturia is one of the most prevalent and bothersome symptoms for patients, yet it is only considered by 1–2 items in multidomain scales that have not been individually analyzed for their psychometric properties. Similarly, psychometric data on the scales that screen or evaluate the severity of sleep attacks, which can be potentially lethal if the person is driving, manipulating machinery or using a cutting tool, are lacking.

CONCLUSION

To advance in the research of sleep and movement disorders, scientific methodology based on adequate diagnosis is of key importance. This review covers a number of questionnaires that can aid in the screening and appraisal of the most frequent nocturnal and diurnal sleep disturbances that affect movement disorder patients. However, disease-specific scales are only available for PD and even in this "best case scenario," some prevalent symptoms such as sleep apnea or nocturia are insufficiently addressed. Thus, we recommend the development of movement disorder, condition-specific scales addressing the most important and characteristic sleep disturbances and their correlates as well as the revision of existing movement disorder scales, such as the Unified Multiple System Atrophy Rating Scale or the Unified Huntington's Disease Rating Scale, to add a sleep domain. We also advocate for the development of guidelines to steer adequate

application of existing instruments, including interpretation of results and significant change due to treatment or other causes, with the objective of improving the management of sleep disturbances in each movement disorder entity. They should include a recommended combination of assessments using different raters (health professional, patient, and caregiver) as well as advice for when further laboratory testing (PSG or MSLT) should be performed.

AUTHOR CONTRIBUTIONS

MK: conception and design, drafting of manuscript, interpretation of data, and revision of the manuscript. RB: drafting of manuscript and interpretation of data. CR-B and MF: interpretation of data and critical revision of the manuscript. PM-M: conception and design, interpretation of data, and critical revision of the manuscript.

REFERENCES

1. Gros P, Videnovic A. Sleep and Circadin rythm disorders in Parkinson's disease. *Curr Sleep Med Rep* (2017) 3:222–34. doi:10.1007/s40675-017-0079-y
2. Abbott SM, Videnovic A. Sleep disorders in atypical Parkinsonism. *Mov Disord Clin Pract* (2014) 1:89–96. doi:10.1002/mdc3.12025
3. Driver-Dunckley ED, Adler CH. Movement disorders and sleep. *Neurol Clin* (2012) 30:1345–58. doi:10.1016/j.ncl.2012.08.019
4. Pillai JA, Leverenz JB. Sleep and neurodegeneration. *Chest* (2017) 151:1375–86. doi:10.1016/j.chest.2017.01.002
5. Coelho FMS, Narayansingh M, Murray BJ. Testing sleepiness and vigilance in the sleep laboratory. *Curr Opin Pulm Med* (2011) 17:406–11. doi:10.1097/MCP.0b013e32834b7e04
6. Buysse DJ. Insomnia. *JAMA* (2013) 309:706–16. doi:10.1001/jama.2013.193
7. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* (1989) 28:193–213. doi:10.1016/0165-1781(89)90047-4
8. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. *J Psychosom Res* (2002) 53:737–40. doi:10.1016/S0022-3999(02)00330-6
9. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. *J Psychosom Res* (1998) 45:5–13. doi:10.1016/S0022-3999(97)00298-5
10. Högl B, Arnulf I, Comella C, Ferreira J, Iranzo A, Tilley B, et al. Scales to assess sleep impairment in Parkinson's disease: critique and recommendations. *Mov Disord* (2010) 25:2704–16. doi:10.1002/mds.23190
11. Marinus J, Visser M, van Hilten JJ, Lammers GJ, Stiggelbout AM. Assessment of sleep and sleepiness in Parkinson disease. *Sleep* (2003) 26:1049–54. doi:10.1093/sleep/26.8.1049
12. Mahale R, Yadav R, Pal PK. Quality of sleep in young onset Parkinson's disease: any difference from older onset Parkinson's disease. *Parkinsonism Relat Disord* (2015) 21:461–4. doi:10.1016/j.parkreldis.2015.02.007
13. Gama RL, Távora DG, Bomfim RC, Silva CE, de Bruin VM, de Bruin PFC. Sleep disturbances and brain MRI morphometry in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy – a comparative study. *Parkinsonism Relat Disord* (2010) 16:275–9. doi:10.1016/j.parkreldis.2010.01.002
14. Lazar AS, Panin F, Goodman AOG, Lazic SE, Lazar ZI, Mason SL, et al. Sleep deficits but no metabolic deficits in premanifest Huntington's disease. *Ann Neurol* (2015) 78:630–48. doi:10.1002/ana.24495
15. Iranzo A, Valldeoriola F, Santamaría J, Tolosa E, Rumià J. Sleep symptoms and polysomnographic architecture in advanced Parkinson's disease after chronic bilateral subthalamic stimulation. *J Neurol Neurosurg Psychiatry* (2002) 72:661–4. doi:10.1136/jnnp.72.5.661
16. Menza M, Dobkin RD, Marin H, Mark MH, Gara M, Buyske S, et al. A controlled trial of antidepressants in patients with Parkinson disease and depression. *Neurology* (2009) 72:886–92. doi:10.1212/01.wnl.0000336340.89821.b3
17. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2002) 73:629–35. doi:10.1136/jnnp.73.6.629
18. Martinez-Martin P, Visser M, Rodriguez-Blazquez C, Marinus J, Chaudhuri KR, van Hilten JJ, et al. SCOPA-sleep and PDSS: two scales for assessment of sleep disorder in Parkinson's disease. *Mov Disord* (2008) 23:1681–8. doi:10.1002/mds.22110
19. Wagle Shukla A, Brown R, Heese K, Jones J, Rodriguez RL, Malaty IM, et al. High rates of fatigue and sleep disturbances in dystonia. *Int J Neurosci* (2016) 126:928–35. doi:10.3109/00207454.2015.1085035
20. Martínez-Martín P, Salvador C, Menéndez-Guisasola L, González S, Tobías A, Almazán J, et al. Parkinson's disease sleep scale: validation study of a Spanish version. *Mov Disord* (2004) 19:1226–32. doi:10.1002/mds.20144
21. Trenkwalder C, Kohnen R, Högl B, Metta V, Sixel-Döring F, Frauscher B, et al. Parkinson's disease sleep scale-validation of the revised version PDSS-2. *Mov Disord* (2011) 26:644–52. doi:10.1002/mds.23476
22. Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. *Mov Disord* (2006) 21:916–23. doi:10.1002/mds.20844
23. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. *Mov Disord* (2007) 22:1901–11. doi:10.1002/mds.21596
24. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* (2008) 23:2129–70. doi:10.1002/mds.22340
25. Lee C-N, Kim M, Lee HM, Jang J-W, Lee S-M, Kwon D-Y, et al. The interrelationship between non-motor symptoms in atypical Parkinsonism. *J Neurol Sci* (2013) 327:15–21. doi:10.1016/j.jns.2013.01.034
26. Hall DA, Forjaz MJ, Golbe LI, Litvan I, Payan CAM, Goetz CG, et al. Scales to assess clinical features of progressive supranuclear palsy: MDS task force report. *Mov Disord Clin Pract* (2015) 2:127–34. doi:10.1002/mdc3.12130
27. Fine ND, Weiss JP, Wein AJ. Nocturia: consequences, classification, and management. *F1000Res* (2017) 6:1627. doi:10.12688/f1000research.11979.1
28. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. *Nat Rev Neurosci* (2017) 18:435–50. doi:10.1038/nrn.2017.62
29. Coyne K, Revicki D, Hunt T, Corey R, Stewart W, Bentkover J, et al. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. *Qual Life Res* (2002) 11:563–74. doi:10.1023/A:1016370925601
30. Coyne KS, Thompson CL, Lai J-S, Sexton CC. An overactive bladder symptom and health-related quality of life short-form: validation of the OAB-q SF. *Neurourol Urodyn* (2015) 34:255–63. doi:10.1002/nau.22559
31. Matza LS, Thompson CL, Krasnow J, Brewster-Jordan J, Zyczynski T, Coyne KS. Test-retest reliability of four questionnaires for patients with overactive bladder: the overactive bladder questionnaire (OAB-q), patient perception of bladder condition (PPBC), urgency questionnaire (UQ), and the primary OAB symptom questionnaire (POSQ). *Neurourol Urodyn* (2005) 24:215–25. doi:10.1002/nau.20110
32. Coyne KS, Matza LS, Thompson CL. The responsiveness of the overactive bladder questionnaire (OAB-q). *Qual Life Res* (2005) 14:849–55. doi:10.1007/s11136-004-0706-1
33. Iacovelli E, Gilio F, Meco G, Fattapposta F, Vanacore N, Brusa L, et al. Bladder symptoms assessed with overactive bladder questionnaire in Parkinson's disease. *Mov Disord* (2010) 25:1203–9. doi:10.1002/mds.23093
34. Kabay S, Canbaz Kabay S, Cetiner M, Mestan E, Sevim M, Ayas S, et al. The clinical and urodynamic results of percutaneous posterior tibial nerve

stimulation on neurogenic detrusor overactivity in patients with Parkinson's disease. *Urology* (2016) 87:76–81. doi:10.1016/j.urology.2015.09.026
35. Homma Y, Yoshida M, Seki N, Yokoyama O, Kakizaki H, Gotoh M, et al. Symptom assessment tool for overactive bladder syndrome – overactive bladder symptom score. *Urology* (2006) 68:318–23. doi:10.1016/j.urology.2006.02.042
36. Mito Y, Yabe I, Yaguchi H, Tajima Y. Urinary dysfunction and motor symptoms in untreated Parkinson's disease. *J Neurol Sci* (2016) 365:147–50. doi:10.1016/j.jns.2016.04.031
37. Sakushima K, Yamazaki S, Fukuma S, Hayashino Y, Yabe I, Fukuhara S, et al. Influence of urinary urgency and other urinary disturbances on falls in Parkinson's disease. *J Neurol Sci* (2016) 360:153–7. doi:10.1016/j.jns.2015.11.055
38. Haab F, Richard F, Amarenco G, Coloby P, Arnould B, Benmedjahed K, et al. Prostatic diseases and male voiding dysfunction comprehensive evaluation of bladder and urethral dysfunction symptoms: development and psychometric validation of the Urinary Symptom Profile (USP) questionnaire. *Urology* (2008) 71:646–56. doi:10.1016/j.urology.2007.11.100
39. Batla A, Pareés I, Edwards MJ, Stamelou M, Bhatia KP, Panicker JN. Lower urinary tract dysfunction in patients with functional movement disorders. *J Neurol Sci* (2016) 361:192–4. doi:10.1016/j.jns.2015.12.048
40. Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* (1992) 148:1549–57; discussion 1564. doi:10.1016/S0022-5347(17)36966-5
41. Hald T, Nordling J, Andersen JT, Bilde T, Meyhoff HH, Walter S. A patient weighted symptom score system in the evaluation of uncomplicated benign prostatic hyperplasia. *Scand J Urol Nephrol Suppl* (1991) 138:59–62.
42. Donovan JL, Abrams P, Peters TJ, Kay HE, Reynard J, Chapple C, et al. The ICS-'BPH' Study: the psychometric validity and reliability of the ICSmale questionnaire. *Br J Urol* (1996) 77:554–62. doi:10.1046/j.1464-410X.1996.93013.x
43. Donovan JL, Peters TJ, Abrams P, Brookes ST, de aa Rosette JJ, Schäfer W. Scoring the short form ICSmaleSF questionnaire. International Continence Society. *J Urol* (2000) 164:1948–55. doi:10.1016/S0022-5347(05)66926-1
44. Kolenc M, Moharić M, Kobal J, Podnar S. Bladder dysfunction in presymptomatic gene carriers and patients with Huntington's disease. *J Neurol* (2014) 261:2360–9. doi:10.1007/s00415-014-7494-5
45. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. *Mov Disord* (2004) 19:1306–12. doi:10.1002/mds.20153
46. Picchietti MA, Picchietti DL. Restless legs syndrome and periodic limb movement disorder in children and adolescents. *Semin Pediatr Neurol* (2008) 15:91–9. doi:10.1016/j.spen.2008.03.005
47. Stevens MS. Restless legs syndrome/Willis-Ekbom disease morbidity: burden, quality of life, cardiovascular aspects, and sleep. *Sleep Med Clin* (2015) 10:369–73. doi:10.1016/j.jsmc.2015.05.017
48. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria – history, rationale, description, and significance. *Sleep Med* (2014) 15:860–73. doi:10.1016/j.sleep.2014.03.025
49. Allen RP, Earley CJ. Validation of the Johns Hopkins restless legs severity scale. *Sleep Med* (2001) 2:239–42. doi:10.1016/S1389-9457(00)00080-0
50. Walters AS, Frauscher B, Allen R, Benes H, Chaudhuri KR, Garcia-Borreguero D, et al. Review of severity rating scales for restless legs syndrome: critique and recommendations. *Mov Disord Clin Pract* (2014) 1:317–24. doi:10.1002/mdc3.12088
51. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med* (2003) 4:121–32. doi:10.1016/S1389-9457(02)00258-7
52. Abetz L, Arbuckle R, Allen RP, Garcia-Borreguero D, Hening W, Walters AS, et al. The reliability, validity and responsiveness of the International Restless Legs Syndrome Study Group rating scale and subscales in a clinical-trial setting. *Sleep Med* (2006) 7:340–9. doi:10.1016/j.sleep.2005.12.011
53. Bhalsing K, Suresh K, Muthane UB, Pal PK. Prevalence and profile of restless legs syndrome in Parkinson's disease and other neurodegenerative disorders: a case-control study. *Parkinsonism Relat Disord* (2013) 19:426–30. doi:10.1016/j.parkreldis.2012.12.005
54. Piano C, Della Marca G, Losurdo A, Imperatori C, Solito M, Calandra-Buonaura G, et al. Subjective assessment of sleep in Huntington disease: reliability of sleep questionnaires compared to polysomnography. *Neurodegener Dis* (2017) 17:330–7. doi:10.1159/000480701
55. Kohnen R, Oertel W, Stiasny-Kolster K, Benes H, Trenkwalder C. Severity rating of restless legs syndrome: validation of the RLS-6 [abstract suppl]. *Sleep* (2004) 27:A304.
56. Kohnen R, Martinez-Martin P, Benes H, Trenkwalder C, Högl B, Dunkl E, et al. Rating of daytime and nighttime symptoms in RLS: validation of the RLS-6 scale of restless legs syndrome/Willis-Ekbom disease. *Sleep Med* (2016) 20:116–22. doi:10.1016/j.sleep.2015.10.014
57. García-Borreguero D, Kohnen R, Högl B, Ferini-Strambi L, Hadjigeorgiou GM, Hornyak M, et al. Validation of the Augmentation Severity Rating Scale (ASRS): a multicentric, prospective study with levodopa on restless legs syndrome. *Sleep Med* (2007) 8:455–63. doi:10.1016/j.sleep.2007.03.023
58. Atkinson MJ, Allen RP, DuChane J, Murray C, Kushida C, Roth T, et al. Validation of the restless legs syndrome quality of life instrument (RLS-QLI): findings of a Consortium of National Experts and the RLS Foundation. *Qual Life Res* (2004) 13:679–93. doi:10.1023/B:QURE.0000021322.22011.d0
59. Walters AS, Frauscher B, Allen R, Benes H, Chaudhuri KR, Garcia-Borreguero D, et al. Review of quality of life instruments for the restless legs syndrome/Willis-Ekbom Disease (RLS/WED): critique and recommendations. *J Clin Sleep Med* (2014) 10:1351–7. doi:10.5664/jcsm.4300
60. Abetz L, Arbuckle R, Allen RP, Mavraki E, Kirsch J. The reliability, validity and responsiveness of the restless legs syndrome quality of life questionnaire (RLSQoL) in a trial population. *Health Qual Life Outcomes* (2005) 3:79. doi:10.1186/1477-7525-3-79
61. Abetz L, Vallow SM, Kirsch J, Allen RP, Washburn T, Earley CJ. Validation of the restless legs syndrome quality of life questionnaire. *Value Health* (2005) 8:157–67. doi:10.1111/j.1524-4733.2005.03010.x
62. Kohnen R, Martinez-Martin P, Benes H, Trenkwalder C, Högl B, Dunkl E, et al. Validation of the Kohnen restless legs syndrome-quality of life instrument. *Sleep Med* (2016) 24:10–7. doi:10.1016/j.sleep.2016.04.019
63. Canafax DM, Bhanegaonkar A, Bharmal M, Calloway M. Validation of the post sleep questionnaire for assessing subjects with restless legs syndrome: results from two double-blind, multicenter, placebo-controlled clinical trials. *BMC Neurol* (2011) 11:48. doi:10.1186/1471-2377-11-48
64. Curran LS, Michael AA, Jamie SL. Short form of the Profile of Mood States (POMS-SF): psychometric information. *Psychol Assess* (1995) 7:80–3. doi:10.1037/1040-3590.7.1.80
65. Allen RP, Kosinski M, Hill-Zabala CE, Calloway MO. Psychometric evaluation and tests of validity of the Medical Outcomes Study 12-item Sleep Scale (MOS sleep). *Sleep Med* (2009) 10:531–9. doi:10.1016/j.sleep.2008.06.003
66. Lasch KE, Abraham L, Patrick J, Piault EC, Tully SE, Treglia M. Development of a next day functioning measure to assess the impact of sleep disturbance due to restless legs syndrome: the restless legs syndrome-next day impact questionnaire. *Sleep Med* (2011) 12:754–61. doi:10.1016/j.sleep.2011.03.015
67. Arbuckle R, Abetz L, Durmer JS, Ivanenko A, Owens JA, Croenlein J, et al. Development of the Pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS)©: a patient-reported outcome measure of pediatric RLS symptoms and impact. *Sleep Med* (2010) 11:897–906. doi:10.1016/j.sleep.2010.03.016
68. Chaudhuri KR, Healy DG, Schapira AH; National Institute for Clinical Excellence. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol* (2006) 5:235–45. doi:10.1016/S1474-4422(06)70373-8
69. Figorilli M, Puligheddu M, Congiu P, Ferri R. The clinical importance of periodic leg movements in sleep. *Curr Treat Options Neurol* (2017) 19:10. doi:10.1007/s11940-017-0446-5
70. Högl B, Stefani A. Restless legs syndrome and periodic leg movements in patients with movement disorders: specific considerations. *Mov Disord* (2017) 32:669–81. doi:10.1002/mds.26929
71. Ferri R, Fulda S, Allen RP, Zucconi M, Bruni O, Chokroverty S, et al. World Association of Sleep Medicine (WASM) 2016 standards for recording and scoring leg movements in polysomnograms developed by a joint Task Force from the International and the European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG). *Sleep Med* (2016) 26:86–95. doi:10.1016/j.sleep.2016.10.010

72. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. *J Clin Sleep Med* (2012) 8:597–619. doi:10.5664/jcsm.2172
73. Plante DT. Leg actigraphy to quantify periodic limb movements of sleep: a systematic review and meta-analysis. *Sleep Med Rev* (2014) 18:425–34. doi:10.1016/j.smrv.2014.02.004
74. Weinreich G, Terjung S, Wang Y, Werther S, Zaffaroni A, Teschler H. Validation of a non-contact screening device for the combination of sleep-disordered breathing and periodic limb movements in sleep. *Sleep Breath* (2017) 22(1):131–8. doi:10.1007/s11325-017-1546-x
75. Kolappan S, Krishnan S, Murray BJ, Boulos MI. A low-cost approach for wide-spread screening of periodic leg movements related to sleep disorders. *2017 IEEE Canada International Humanitarian Technology Conference (IHTC)*. Toronto, ON (2017). p. 105–8.
76. Mannarino MR, Di Filippo F, Pirro M. Obstructive sleep apnea syndrome. *Eur J Intern Med* (2012) 23:586–93. doi:10.1016/j.ejim.2012.05.013
77. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* (1993) 328:1230–5. doi:10.1056/NEJM199304293281704
78. Sharma SK, Kumpawat S, Banga A, Goel A. Prevalence and risk factors of obstructive sleep apnea syndrome in a population of Delhi, India. *Chest* (2006) 130:149–56. doi:10.1378/chest.130.1.149
79. Fedson AC, Pack AI, Gislason T. Frequently used sleep questionnaires in epidemiological and genetic research for obstructive sleep apnea: a review. *Sleep Med Rev* (2012) 16:529–37. doi:10.1016/j.smrv.2011.12.002
80. Abrishami A, Khajehdehi A, Chung F. A systematic review of screening questionnaires for obstructive sleep apnea. *Can J Anesth* (2010) 57:423–38. doi:10.1007/s12630-010-9280-x
81. Teculescu D, Guillemin F, Virion J-M, Aubry C, Hannhart B, Michaely J-P, et al. Reliability of the Wisconsin Sleep Questionnaire: a French contribution to international validation. *J Clin Epidemiol* (2003) 56:436–40. doi:10.1016/S0895-4356(03)00029-5
82. Douglass AB, Bornstein R, Nino-Murcia G, Keenan S, Miles L, Zarcone VP, et al. The Sleep Disorders Questionnaire. I: creation and multivariate structure of SDQ. *Sleep* (1994) 17:160–7. doi:10.1093/sleep/17.2.160
83. Weatherwax KJ, Lin X, Marzec ML, Malow BA. Obstructive sleep apnea in epilepsy patients: the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) is a useful screening instrument for obstructive sleep apnea in a disease-specific population. *Sleep Med* (2003) 4:517–21. doi:10.1016/j.sleep.2003.07.004
84. Maislin G, Pack AI, Kribbs NB, Smith PL, Schwartz AR, Kline LR, et al. A survey screen for prediction of apnea. *Sleep* (1995) 18:158–66. doi:10.1093/sleep/18.3.158
85. Khajeh-Mehrizi A, Aminian O. Diagnostic accuracy of the multivariable apnea prediction (MAP) index as a screening tool for obstructive sleep apnea. *J Sleep Sci* (2015) 1(1):8–12.
86. Wilson G, Terpening Z, Wong K, Grunstein R, Norrie L, Lewis SJG, et al. Screening for sleep apnea in mild cognitive impairment: the utility of the multivariable apnoea prediction index. *Sleep Disord* (2014) 2014:945287. doi:10.1155/2014/945287
87. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* (1999) 131:485–91. doi:10.7326/0003-4819-131-7-199910050-00002
88. Senaratna CV, Perret JL, Matheson MC, Lodge CJ, Lowe AJ, Cassim R, et al. Validity of the Berlin questionnaire in detecting obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev* (2017) 36:116–24. doi:10.1016/j.smrv.2017.04.001
89. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, et al. Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients. *Anesthesiology* (2008) 108:822–30. doi:10.1097/ALN.0b013e31816d91b5
90. Popević MB, Milovanović AAPS, Nagorni-Obradović L, Nešić D, Milovanović J, Milovanović AAPS. Screening commercial drivers for obstructive sleep apnea: translation and validation of Serbian version of Berlin questionnaire. *Qual Life Res* (2016) 25:343–9. doi:10.1007/s11136-015-1087-3
91. Saengsuwan JJ, Ungtrakul N, Saengsuwan JJ, Sawanyawisuth K. Preliminary validity and reliability of a Thai Berlin questionnaire in stroke patients. *BMC Res Notes* (2014) 7:348. doi:10.1186/1756-0500-7-348
92. Suksakorn S, Rattanaumpawan P, Banhiran W, Cherakul N, Chotinaiwattarakul W. Reliability and validity of a Thai version of the Berlin questionnaire in patients with sleep disordered breathing. *J Med Assoc Thai* (2014) 97(Suppl 3): S46–56.
93. Nociti V, Losavio FA, Gnoni V, Losurdo A, Testani E, Vollono C, et al. Sleep and fatigue in multiple sclerosis: a questionnaire-based, cross-sectional, cohort study. *J Neurol Sci* (2017) 372:387–92. doi:10.1016/j.jns.2016.10.040
94. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology* (2008) 108:812–21. doi:10.1097/ALN.0b013e31816d83e4
95. Nahapetian R, Silva GE, Vana KD, Parthasarathy S, Quan SF. Weighted STOP-Bang and screening for sleep-disordered breathing. *Sleep Breath* (2016) 20:597–603. doi:10.1007/s11325-015-1255-2
96. Fonseca LB, Silveira EA, Lima NM, Rabahi MF. STOP-Bang Questionnaire: translation to Portuguese and cross-cultural adaptation for use in Brazil. *J Bras Pneumol* (2016) 42:266–72. doi:10.1590/s1806-37562015000000243
97. BaHammam AS, Al-Aqeel AM, Alhedyani AA, Al-Obaid GI, Al-Owais MM, Olaish AH. The validity and reliability of an Arabic version of the STOP-Bang Questionnaire for identifying obstructive sleep apnea. *Open Respir Med J* (2015) 9:22–9. doi:10.2174/1874306401509010022
98. Popević MB, Milovanović AAPS, Nagorni-Obradović L, Nešić D, Milovanović J, Milovanović AAPS. Screening commercial drivers for obstructive sleep apnea: validation of STOP-Bang Questionnaire. *Int J Occup Med Environ Health* (2017) 30:751–61. doi:10.13075/ijomeh.1896.00906
99. Nagappa M, Liao P, Wong J, Auckley D, Ramachandran SK, Memtsoudis S, et al. Validation of the STOP-Bang Questionnaire as a screening tool for obstructive sleep apnea among different populations: a systematic review and meta-analysis. *PLoS One* (2015) 10:e0143697. doi:10.1371/journal.pone.0143697
100. Chung F, Chau E, Yang Y, Liao P, Hall R, Mokhlesi B. Serum bicarbonate level improves specificity of STOP-Bang screening for obstructive sleep apnea. *Chest* (2013) 143:1284–93. doi:10.1378/chest.12-1132
101. Flemons WW, Reimer MA. Development of a disease-specific health-related quality of life questionnaire for sleep apnea. *Am J Respir Crit Care Med* (1998) 158:494–503. doi:10.1164/ajrccm.158.2.9712036
102. Flemons WW, Reimer MA. Measurement properties of the Calgary sleep apnea quality of life index. *Am J Respir Crit Care Med* (2002) 165:159–64. doi:10.1164/ajrccm.165.2.2010008
103. Billings ME, Rosen CL, Auckley D, Benca R, Foldvary-Schaefer N, Iber C, et al. Psychometric performance and responsiveness of the functional outcomes of sleep questionnaire and sleep apnea quality of life index in a randomized trial: the HomePAP study. *Sleep* (2014) 37:2017–24. doi:10.5665/sleep.4262
104. Lacasse Y, Bureau M, Series F. A new standardised and self-administered quality of life questionnaire specific to obstructive sleep apnoea. *Thorax* (2004) 59:494–9. doi:10.1136/thx.2003.011205
105. Rye DB. Excessive daytime sleepiness and unintended sleep in Parkinson's disease. *Curr Neurol Neurosci Rep* (2006) 6:169–76. doi:10.1007/s11910-996-0041-8
106. Hoddes E, Dement W, Zarcone V. The development and use of the Stanford Sleepiness Scale (SSS). *Psychophysiology* (1972) 9:150.
107. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. *Psychophysiology* (1973) 10:431–6. doi:10.1111/j.1469-8986.1973.tb00801.x
108. Maclean AW, Fekken GC, Saskin P, Knowles JB. Psychometric evaluation of the Stanford Sleepiness Scale. *J Sleep Res* (1992) 1:35–9. doi:10.1111/j.1365-2869.1992.tb00006.x
109. Herscovitch J, Broughton R. Sensitivity of the stanford sleepiness scale to the effects of cumulative partial sleep deprivation and recovery oversleeping. *Sleep* (1981) 4:83–91. doi:10.1093/sleep/4.1.83
110. Slanger TE, Gross JV, Pinger A, Morfeld P, Bellinger M, Duhme A-L, et al. Person-directed, non-pharmacological interventions for sleepiness at work and sleep disturbances caused by shift work. *Cochrane Database Syst Rev* (2016) 8:CD010641. doi:10.1002/14651858.CD010641.pub2

111. Seppi K, Högl B, Diem A, Peralta C, Wenning GK, Poewe W. Levodopa-induced sleepiness in the Parkinson variant of multiple system atrophy. *Mov Disord* (2006) 21:1281–3. doi:10.1002/mds.20898
112. Walsh CM, Ruoff L, Walker K, Emery A, Varbel J, Karageorgiou E, et al. Sleepless night and day, the plight of progressive supranuclear palsy. *Sleep* (2017) 40. doi:10.1093/sleep/zsx154
113. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* (1991) 14:540–5. doi:10.1093/sleep/14.6.540
114. Hobson DE, Lang AE, Martin WRW, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. *JAMA* (2002) 287:455–63. doi:10.1001/jama.287.4.455
115. Johns MW. Sleepiness in different situations measured by the Epworth Sleepiness Scale. *Sleep* (1994) 17:703–10. doi:10.1093/sleep/17.8.703
116. Arnulf I, Neutel D, Herlin B, Golmard J-L, Leu-Semenescu S, Cochen de Cock V, et al. Sleepiness in idiopathic REM sleep behavior disorder and Parkinson disease. *Sleep* (2015) 38:1529–35. doi:10.5665/sleep.5040
117. Moreno-López C, Santamaría J, Salamero M, Del Sorbo F, Albanese A, Pellecchia MT, et al. Excessive daytime sleepiness in multiple system atrophy (SLEEMSA Study). *Arch Neurol* (2011) 68:223–30. doi:10.1001/archneurol.2010.359
118. Shimohata T, Nakayama H, Tomita M, Ozawa T, Nishizawa M. Daytime sleepiness in Japanese patients with multiple system atrophy: prevalence and determinants. *BMC Neurol* (2012) 12:130. doi:10.1186/1471-2377-12-130
119. Piano C, Losurdo A, Della Marca G, Solito M, Calandra-Buonaura G, Provini F, et al. Polysomnographic findings and clinical correlates in Huntington disease: a cross-sectional cohort study. *Sleep* (2015) 38:1489–95. doi:10.5665/sleep.4996
120. Hurelbrink CB, Lewis SJG, Barker RA. The use of the Actiwatch-Neurologica® system to objectively assess the involuntary movements and sleep-wake activity in patients with mild-moderate Huntington's disease. *J Neurol* (2005) 252:642–7. doi:10.1007/s00415-005-0709-z
121. Avanzino L, Martino D, Marchese R, Aniello MS, Minafra B, Superbo M, et al. Quality of sleep in primary focal dystonia: a case-control study. *Eur J Neurol* (2010) 17:576–81. doi:10.1111/j.1468-1331.2009.02884.x
122. Trotti LM, Esper CD, Feustel PJ, Bliwise DL, Factor SA. Excessive daytime sleepiness in cervical dystonia. *Parkinsonism Relat Disord* (2009) 15:784–6. doi:10.1016/j.parkreldis.2009.04.007
123. Gerbin M, Viner AS, Louis ED. Sleep in essential tremor: a comparison with normal controls and Parkinson's disease patients. *Parkinsonism Relat Disord* (2012) 18:279–84. doi:10.1016/j.parkreldis.2011.11.004
124. Rohl B, Collins K, Morgan S, Cosentino S, Huey ED, Louis ED. Daytime sleepiness and nighttime sleep quality across the full spectrum of cognitive presentations in essential tremor. *J Neurol Sci* (2016) 371:24–31. doi:10.1016/j.jns.2016.10.006
125. Chandran V, Pal PK, Reddy JYC, Thennarasu K, Yadav R, Shivashankar N. Non-motor features in essential tremor. *Acta Neurol Scand* (2012) 125:332–7. doi:10.1111/j.1600-0404.2011.01573.x
126. Dhawan V, Dhoat S, Williams AJ, Dimarco A, Pal S, Forbes A, et al. The range and nature of sleep dysfunction in untreated Parkinson's disease (PD). A comparative controlled clinical study using the Parkinson's disease sleep scale and selective polysomnography. *J Neurol Sci* (2006) 248:158–62. doi:10.1016/j.jns.2006.05.004
127. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ, Kurtis MM, Skorvanek M. Measurement of nonmotor symptoms in clinical practice. *Int Rev Neurobiol* (2017) 133:291–345. doi:10.1016/bs.irn.2017.04.001
128. Martinez-Martin P, Kurtis MM. Health-related quality of life as an outcome variable in Parkinson's disease. *Ther Adv Neurol Disord* (2012) 105–17. doi:10.1177/1756285611431974
129. Ondo WG, Lai D. Association between restless legs syndrome and essential tremor. *Mov Disord* (2006) 21:515–8. doi:10.1002/mds.20746
130. Paus S, Gross J, Moll-Müller M, Hentschel F, Spottke A, Wabbels B, et al. Impaired sleep quality and restless legs syndrome in idiopathic focal dystonia: a controlled study. *J Neurol* (2011) 258:1835–40. doi:10.1007/s00415-011-6029-6
131. Kumru H, Santamaria J, Belcher R. Variability in the Epworth sleepiness scale score between the patient and the partner. *Sleep Med* (2004) 5:369–71. doi:10.1016/j.sleep.2004.03.003

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REVIEW
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Rating Scales for Movement Disorders With Sleep Disturbances: A Narrative Review

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Introduction: In recent years, a wide variety of rating scales and questionnaires for movement disorders have been developed and published, making reviews on their contents, and attributes convenient for the potential users. Sleep disorders are frequently present in movement disorders, and some movement disorders are accompanied by specific sleep difficulties.

Aim: The aim of this study is to perform a narrative review of the most frequently used rating scales for movement disorders with sleep problems, with special attention to those recommended by the International Parkinson and Movement Disorders Society.

Methods: Online databases (PubMed, SCOPUS, Web of Science, Google Scholar), related references from papers and websites and personal files were searched for information on comprehensive or global rating scales which assessed sleep disturbances in the following movement disorders: akathisia, chorea, dystonia, essential tremor, myoclonus, multiple system atrophy, Parkinson's disease, progressive supranuclear palsy, and tics and Tourette syndrome. For each rating scale, its objective and characteristics, as well as a summary of its psychometric properties and recommendations of use are described.

Results: From 22 rating scales identified for the selected movement disorders, only 5 included specific questions on sleep problems. Movement Disorders Society-Unified Parkinson's Disease Rating scale (MDS-UPDRS), Non-Motor Symptoms Scale and Questionnaire (NMSS and NMSQuest), Scales for Outcomes in Parkinson's Disease (SCOPA)-Autonomic and Progressive Supranuclear Palsy Rating Scale (PSPRS) were the only rating scales that included items for assessing sleep disturbances.

Conclusions: Despite sleep problems are frequent in movement disorders, very few of the rating scales addresses these specific symptoms. This may contribute to an infra diagnosis and mistreatment of the sleep problems in patients with movement disorders.

Keywords: movement disorders, sleep disorders, rating scales, Parkinson's disease, progressive supranuclear palsy

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INTRODUCTION

A wide variety of rating scales and questionnaires for the wide range of movement disorders that can affect patients have been developed and are currently available for clinical practice and research. These instruments may be classified as "rater-based," which are applied by a health professional or trained person, and "patient-based," which are directly completed by patients themselves. Rater-based scales (clinician-reported outcomes measures) are used to evaluate observable signs of the disorder (e.g., tremor, rigidity, instability, myoclonus, tics) by means of clinical examination, and other non-observable aspects through interview with the patient and/or caregiver. Patient-based instruments (patient-reported outcomes measures) allow the assessment of non-observable, subjective features, and perceptions (e.g., pain, fatigue, sensations, feelings, hallucinations, health state) (1). Some effects caused by the health disorder (e.g., disability, symptoms) can be appraised by both methods.

Their simplicity of use, as well as the amount and quality of information the rating scales provide, justify why rating scales and questionnaires are widely used in clinical and research settings.

Sleep disorders are frequently present in movement disorders, as they can share pathophysiological mechanisms and damage to brain structures (2). Insomnia and sleep fragmentation are common in Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) (3), and different choreic disorders. REM-sleep behavior disorder appears associated to α-synucleinopathies, such as PD, Lewy body dementia, and MSA, and can be an early marker of the disease (4). Impaired sleep architecture is frequent in Tourette syndrome (5). PD and essential tremor (ET) are often associated with restless legs and nocturnal periodic limb movements (6, 7). The relevance of sleep problems in movement disorders has been acknowledged in the recent years and specific rating scales for assessing sleep have been developed and validated. However, these scales are only available for PD, and specific symptoms are not sufficiently addressed (8). Simultaneously, global rating scales for the assessment of specific movement disorders have been developed, such as the Unified Huntington's Disease Rating Scale (UHDRS), Unified Dystonia Rating Scale (UDRS), or the Unified Multiple System Atrophy Rating Scale (UMSARS), with the aim of providing a comprehensive appraisal of the clinical manifestations (motor and non-motor symptoms) of these disorders.

The aim of this study is to perform a narrative review of most frequently used rating scales for those movement disorders that comprise sleep dysfunction among their primary manifestations or sleep problems secondary to the movement disorder, with special attention to the scales recommended by the International Parkinson and Movement Disorders Society (IPMDS) Task Force (9).

METHODS

Authors made a list of the movement disorders that can course with sleep symptoms that included akathisia, chore, dystonia, essential tremor, multiple system atrophy, myoclonus, Parkinson's Disease, progressive supranuclear palsy, and tics and Tourette syndrome. The literature search, carried out using PubMed, Web of Science and Scopus, included these terms plus "sleep" and "rating scales." In addition, the reviews published by IPMDS on these movement disorders (9) and related references from papers and personal files were examined. The IPMDS Task force classifies a scale as "recommended" if it has been used in PD, shows adequate psychometric properties, and has been used by investigators other than the original developers; as "suggested" if it has been used in PD and fulfills only one other criterion; and as "listed" if it has been used in PD but does not meet the other criteria.

The main rating scales for Parkinson's disease (PD), such as the Movement Disorders Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the Non-Motor Symptoms Scale (NMSS), are also included. **Table 1** lists the scales incorporated to this review. Specific instruments assessing sleep disorders in movement disorders, such as the Parkinson's Disease Sleep Scale (PDSS) and the Scales for Outcomes in PD (SCOPA)-Sleep, are reviewed in another article in this issue (8). For each rating scale, its objective, characteristics, psychometric properties, and recommendations of use are described.

MOVEMENT DISORDERS AND RATING SCALES

Akathisia

Akathisia has been associated to nocturnal periodic limb movements and increased number of awakenings (35). However, the main rating scale for akathisia, the Barnes Akathisia Rating Scale (BARS) does not include sleep assessment (10). The BARS is a 4-item scale for rating the presence and severity of the drug-induced akathisia. It shows adequate reliability, validity, and responsiveness (11).

Chorea

Results of an online survey of juvenile Huntington's disease (HD) suggests that disrupted sleep is the most prevalent common, unrecognized symptom (87%), followed by periodic limb movements, tics, and pain (36, 37). HD gene carriers complain about sleep problems, both in terms of sleep quality as well as excessive daytime sleepiness (38, 39). Sleep complaints seem to be associated with neuropathology and neuropsychiatric symptoms in HD (40). However, ratings scales for chorea or HD do not assess sleep difficulties.

The Universidade Federal de Minas Gerais Sydenham's Chorea Rating Scale (USCRS) assesses signs and symptoms of children and adults with Sydenham's Chorea and related disorders (12). It is formed by 27 items organized into three sections (behavior, activities of daily living, and motor assessment). Items are scored on a 0–4 rating scale, with higher values indicating higher severity of disability or signs. Although the scale presented a two-factor structure (motor function and ADL; behavioral) (12), a total sum score is used in most studies (41–44). Published in 2005 (12), the scale is rater-based and it is owned by the IPMDS. It has shown adequate inter-rater reliability and internal consistency (12), as well as discriminative validity by

TABLE 1 | Rating scales for movement disorders with sleep disturbances included in this review.

Movement disorder	Rating scale	References	Includes sleep assessment?
Akathisia	Barnes Akathisia Rating Scale, BARS	(10, 11)	No
Chorea	Universidade Federal de Minas Gerais Sydenham's Chorea Rating Scale, USCRS	(12)	No
	Unified Huntington's Disease Rating Scale, UHDRS	(13)	No
Dystonia	Unified Dystonia Rating Scale, UDRS	(14)	No
	Fahn-Marsden Dystonia Rating Scale, F-M Scale	(15)	No
	Toronto Western Spasmodic Torticollis Rating Scale, TWSTRS	(16)	No
Essential tremor	Fahn-Tolosa-Marin Tremor Rating Scale	(17)	No
	Bain and Findley Clinical Tremor Rating Scale	(18)	No
	Bain and Findley Spirography Scale	(19)	No
	Washington Heights -Inwood Genetic Study of Essential Tremor Rating Scale, WHIGET	(20)	No
	Tremor Research Group Essential Tremor Rating Assessment Scale, TETRAS	(21)	No
Multiple system atrophy	Unified Multiple System Atrophy Rating Scale, UMSARS	(22)	No
Myoclonus	Unified Myoclonus Rating Scale, UMRS	(23)	No
Parkinson's Disease	Movement Disorders Society–Unified Parkinson's Disease Rating Scale, MDS-UPDRS	(24)	Yes (2 items, validated as screening tool)
	Non-Motor Symptoms Scale, NMSS	(25)	Yes (3 items)
	Non-Motor Symptoms Questionnaire, NMSQuest	(26)	Yes (5 items, validated as screening tool)
	Scales for Outcomes in Parkinson's Disease (SCOPA)-Motor	(27)	No
	Scales for Outcomes in Parkinson's Disease (SCOPA)-Autonomic	(28)	Yes (2 items)
Progressive supranuclear palsy	Progressive Supranuclear Palsy Rating Scale, PSPRS	(29)	Yes (1 item)
Tics and Tourette syndrome	Yale Global Tic Severity Scale, YGTSS	(30)	No
	Shapiro Tourette Syndrome Severity Scale, STSSS	(31)	No
	Tourette Syndrome Clinical Global Impressions scale, TS-CGI	(32)	No
	Tourette's Disorder Scale, TODS	(33)	No
	Premonitory Urge for Tic Disorders Scale, PUTS	(34)	No

disease stage (44). The USCRS has been used in Brazil (12, 43, 44), Italy (42), and Israel (41).

The UHDRS was developed by the Huntington Study Group as a research tool, and it has been used as an outcome measure in clinical trials (13). It is formed by the following components: motor, with 15 items (45); cognitive (formed by Verbal Fluency Test; Symbol Digit Modalities Test; Stroop Interference Test), behavioral (10 items) and functional (5 items) assessments, independence scale (1 item, from 10, totally dependent, to 100, totally independent), and total functional capacity (TFC, 25 items). Internal consistency is high and the UHDRS shows satisfactory inter-rater reliability and sensitivity to change. Although it was published as annex of an article (13), it is actually owned by the Huntington Study Group and permission for use is required.

A IPMDS task force rated the UHDRS behavioral section (UHDRS-b) as a "suggested" scale for assessing severity of and screening for behavioral symptoms in patients with HD (46). The UHDRS also has a version for advanced patients (UHDRS-FAP), with satisfactory internal consistency and inter-rater reliability (47).

Dystonia

There is a growing interest on non-motor symptoms of dystonia patients, including sleep problems (48). Sleep impairment may be a primary effect of dystonia or secondary effects of pain and medications (49). Different types of dystonia may be associated to specific sleep disorders: poor sleep quality has been described in blepharospasm, cervical dystonia patients report more daytime sleepiness than controls (50), and impaired sleep efficiency and decreased rapid eye movement (REM) sleep has been reported in blepharospasm and oromandibular dystonia (51).

On the basis of their psychometric properties and clinical and research application, a review commissioned by the IPMDS qualified five disease-specific scales as "recommended," and two scales as "listed" for laryngeal dystonia (52). None of them assesses sleep disorders.

The UDRS (14), a rating scale for generalized dystonia, was "suggested" for use in dystonia and did not reach a "recommended" rating due to insufficient psychometric studies about responsiveness (52). The clinician assesses 14 body locations, rated for both duration (0–4 score, including half-scores) and severity (0–4 scale) of dystonia. The total score is the sum of the duration and severity ratings. Internal consistency

is high, and the scale shows good inter-rater reliability and convergent validity with other dystonia rating scales (14). The UDRS is owned by the IPMDS and license for use is needed.

The Fahn-Marsden Dystonia Rating Scale (F-M Scale), a predecessor of the UDRS, was initially developed to assess primary torsion dystonia in 9 body parts (15). It has two factors, one for severity (each body part is rated from 0, no dystonia, to 4, severe dystonia) and the other for the precipitation or provoking factor (from 0, no dystonia, to 4, dystonia at rest). The scores for eyes, mouth, and neck are multiplied by 0.5 when calculating the total score, which is then obtained by summing the product of the severity, provoking, and weighting factors. The F-M Scale also includes a disability scale based on the patient's report that evaluates the impact of dystonia on seven activities of daily living. The walking item is rated on a 7-point scale and the rest of the disability items on a 0–4 point scale. The F-M scale has shown good internal consistency, inter-rater agreement, and convergent validity with other dystonia rating scales (14), as well as adequate responsiveness (52). Despite criticisms of the low contribution of some body parts to the overall score, this scale is "recommended" to assess the severity of the dystonia (52) and has been used for evaluating dystonia in many conditions and clinical trials.

The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) (16) is a "recommended" rating scale that was designed to assess a specific condition, cervical dystonia, in clinical trials (52). It is formed by three subscales assessing motor severity (11 items), disability (6 items), and pain (3 items). The first subscale is rated by the clinician whereas the other two are patient-rated. The scoring system is not uniform and a videotape for training is available for the severity section. This scale, available in English, has been frequently used in clinical trials. Its psychometric properties are satisfactory and well-documented, including internal consistency, inter-rater agreement for the severity subscale, internal, and convergent validity, as well as responsiveness. The TWSTRS has been criticized for its complexity for clinical practice (52). Excessive daytime sleepiness in cervical dystonia was not associated with TWSTRS scores (50).

Essential Tremor

Besides motor features, essential tremor also includes non-motor symptoms such as sleep problems (53–55), which have a negative effect on quality of life (56). Excessive daytime sleepiness, shorter sleep duration (57), and restless legs complaints are more frequent in essential tremor patients than in healthy controls (8).

Despite increasing evidence of sleep problems in essential tremor, none of the currently available rating scales to assess tremor include items about sleep. The IPMDS Task Force recommends several rating scales for evaluating tremor severity.

The Fahn-Tolosa-Marin Tremor Rating Scale provides a comprehensive assessment of tremor, rated by the clinician and the patient (17). It is formed by 3 parts: tremor in 9 body parts and orthostatic tremor; action tremor in 3 tasks; and patient-reported functional disability. In addition, both clinical and patient rate a global assessment item. Items are rated on a 0–4 point scale. The scale presents good intra and inter-rater reliability (18), but there is a lack of data on other psychometric parameters (58). It has been used in many clinical trials.

The Bain and Findley Clinical Tremor Rating Scale assesses tremor severity (59) and impact on activities of daily living. For each body part (head, voice, and limbs), the clinician rates the severity of several tremor components: rest, postural, and kinetic/intention tremor. The initial 0–10 response scale was simplified to a 5-point scale with intermediate values. Inter-rater reliability was satisfactory as a whole, especially for upper limb postural and head tremor, but not for voice tremor (59). The severity scale shows good convergent validity with other tremor measures, and it was sensitive to change in clinical trials (58). With a scoring system based on subjective impression, the Bain and Findley Clinical Tremor Rating Scale is easy to apply in a diversity of conditions and circumstances, including bedside.

In the Bain and Findley Spirography Scale, action tremor is assessed through Archimedes spirals. Rating are on a 0–10 scale, and rating examples are provided (19, 59). Its reliability is good provided that raters are trained (58). This scale has been criticized for its high floor and ceiling effects; however, it shows adequate face and construct validity (58).

The Washington Heights -Inwood Genetic Study of Essential Tremor (WHIGET) Rating Scale is aimed at assessing the severity of essential tremor during the performance of several tasks (20). The clinician rates the following tremor parameters: intensity, amplitude, oscillation prevalence, and persistency of rest, kinetic and postural tremor. There are 26 items rated on a 0–3 scale. A revised version rates kinetic tremor from 0 to 4 (60). A training videotape is available (60). Test-retest and inter-rater reliability are satisfactory, as well as convergent validity with other measures of tremor (61). Some studies support the scale's sensitivity to change (62, 63). The WHIGET limits assessment to upper extremity tremor.

The Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) is formed by two subscales (21). The performance subscale, with 9 items, rates action tremor in head, face, voice, limbs, and trunk. The activities of daily living section if formed by 12 items. Both sections use a 0–4 point scale, but performance items admit half-point scores. This short, easy to apply scale has appropriate reliability, validity, and sensitivity to change for the performance section (64–66). More psychometric studies are needed for the activities of daily living subscale.

Multiple System Atrophy (MSA)

MSA affects sleep in several ways: sleep-disordered breathing (67), sleep fragmentation, REM sleep behavior disorder, insomnia, and excessive daytime sleepiness (68). In addition, sleep study (polysomnography) are included in a list of useful tools for differential diagnosis of MSA (69). Despite this, specific rating scales for this movement disorder do not include items for assessment of sleep disturbances.

The most used scale for MSA is the UMSARS developed by the European MSA Study Group (22). It comprises four parts: Part I, historical (functional status), with 12 items; Part II, motor examination, with 14 items; Part III, autonomic examination, with items assessing blood pressure, heart rate and orthostatic symptoms; and Part IV, global disability scale. In Parts I and II, scores range from 0 to 4, and in Part IV, the scale ranges from 1 (completely independent) to 5 (totally independent).

The UMSARS psychometric properties are adequate, showing high internal consistency in Parts I and II, satisfactory inter and intra-rater reliability and sensitivity to change over time (22, 70). The UMSARS can distinguish between different subtypes (parkinsonism- vs cerebellar ataxia-predominant) of MSA (71) and has been used as reference in the validation of other scales for MSA (72). It is owned and licensed by the IPMDS. A comparative review of the longitudinal performance of the UMSARS and other scales for MSA can be found in Matsushima et al. (73).

Myoclonus

Clinical presentations of myoclonus are divided into physiological, essential, epileptic, and symptomatic (74). While physiological myoclonus can occur as jerks during sleep or sleep transitions in healthy individuals, other myoclonic sleep disorders (e.g., propriospinal myoclonus) can be identified (75) and some types of myoclonic epilepsy, characterized by abnormal sleep electroencephalogram and an activation of the paroxysms during non-REM sleep and on waking up (76).

The main tool for assessing myoclonus is the Unified Myoclonus Rating Scale (UMRS) (23). It assesses the severity and characteristics of the disorder and the associated disability. The UMRS has 73 items, grouped into five sections: patient's questionnaire (12 items, scored from 1 to 5); myoclonus at rest (8 items for frequency and amplitude, scored from 0 to 4); stimulus sensitivity (17 items, dichotomous); myoclonus with action (10 items, scored for frequency and amplitude on a 5-point scale); and functional tests (5 items, scored from 0 to 4). It also includes a global disability scale, scored from 0 (normal) to 4 (severe), and two items assessing presence (yes/no) and severity (from 0 to 3) of negative myoclonus. Components for evaluation of myoclonus-related sleep disorders are not included in this scale. The UMRS has satisfactory internal consistency and inter-rater reliability (23, 77) and is responsive to changes due to treatment (78).

Parkinson's Disease (PD)

Sleep disorders are common in PD: they can affect up to 60–90% of PD patients, with increasing prevalence as the disease progresses (7). Insomnia and sleep fragmentation, excessive daytime sleepiness, restless legs and REM-sleep behavior disorder are frequently present in PD (79). Some specific rating scales for sleep disorders in PD are currently available, but they are the object of another article in this issue. Sleep problems are included in the main multi-domain, comprehensive rating scales for PD, the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (24), and the Non-Motor Symptoms Scale (NMSS) (25).

The MDS-UPDRS is the revised version of the widely used UPDRS (80). It has four sections: Part I, non-motor experiences of daily living; Part II, motor experiences of daily living; Part III, motor examination; and Part IV, motor complications. In Part I, with 6 rater-based items and 7 self-assessed items, two questions rating nighttime sleep problems and daytime sleepiness can be used as screening tool for sleep disturbances (81). All items are scored from 0 (normal) to 4 (severe). The MDS-UPDRS has good psychometric properties and is responsive to changes due to treatment (82, 83). The minimal clinically important difference of the Part III has been calculated (84).

The NMSS, which is administered by interview, was designed to assess the burden (frequency and severity) of non-motor symptoms (NMS). It is composed of 30 items, grouped in nine domains: cardiovascular (2 items), sleep/fatigue (4 items), mood/cognition (6 items), perceptual problems/hallucinations (3 items), attention/memory (3 items), gastrointestinal tract (3 items), urinary (3 items), sexual function (2 items), and miscellaneous (4 items). In the domain sleep/fatigue, there are three questions to rate daytime sleepiness, problems falling or staying asleep and restless legs syndrome, while in the urinary domain, one item assesses nocturia. All items are scored 0–3 for severity and 1–4 for frequency. The total item score is obtained by multiplication of both aspects and domain and scale score by sum of the respective items scores. The scale, validated, and available in several languages, has good psychometric properties, including responsiveness (85–87).

An instrument related with the NMSS is the Non-Motor Symptoms Questionnaire (NMSQuest) (26), which was developed as a self-assessment of non-motor symptoms. It is composed by 30 yes/no questions, of which six address sleep disturbances: nocturia, daytime sleepiness, insomnia, vivid dreams, acting out while dreaming, and restless legs. These items have been validated and resulted useful as a screening tool for sleep difficulties in PD patients (88). The NMSQuest has good feasibility, acceptability and validity, resulting suitable for patients to flag symptoms that may be undeclared and remain untreated (89). A NMSQuest-based grading system for NMS burden has also been published (90).

Another recommended rating scale (91) is the Scales for Outcomes in Parkinson's Disease (SCOPA)-Motor (27) for assessing motor functioning and disability in PD. It is composed by 21 items, scored from 0 (normal) to 3 (severe), and grouped into three sections: motor examination (10 items), activities of daily living (7 items), and motor complications (4 items). It does not include sleep problems. Satisfactory internal consistency, inter-rater and test-retest reliability and construct validity have been reported (92). It is also responsive to changes over time (93) and can predict an increase in PD-related costs (94).

The SCOPA-Autonomic (28), the first validated rating scale specifically designed for assessing autonomic symptoms in PD, includes two items on symptoms that can cause sleep disturbances: nicturia and excessive sweating during the night. This scale, composed by 25 items grouped in 6 domains (cardiovascular, gastrointestinal, urinary, thermoregulatory, pupillomotor, and sexual), meets criteria for "recommended" (95, 96).

A wide set of other rating scales for assessing specific symptoms and manifestations of PD are recommended by the IPMDS (9), but they are out of the scope of this review.

Progressive Supranuclear Palsy (PSP)

Insomnia and impaired sleep architecture are the most common sleep abnormalities in PSP, and are more frequently described in PSP than in other atypical parkinsonisms (4). In particular,

PSP patients can show a shorter total sleep time, a lower sleep efficiency and a lower percentage of REM sleep than controls (97).

The Progressive Supranuclear Palsy Rating Scale (PSPRS) (29) is the IPMDS Task Force recommended rating scale for assessing symptoms and associated disability of the PSP (98). It has 28 items, scored on a 3- or 5-point scale, and grouped into six dimensions: history (with an item on sleep difficulty), mental, bulbar, supranuclear ocular motor, and limb and gait/mildline examinations. The item named "Sleep difficulty" focused on insomnia and rated from 0 to 4 is included in the "History/Daily activities" section. The total scale score ranges from 0 to 100. The scale shows good inter-rater reliability and satisfactory predictive validity in relation to survival. The minimal clinically important worsening has been established in 5.7 points (99).

Tics and Tourette Syndrome (TS)

Tics and TS can be associated with sleep disturbances such as insomnia and abnormal behaviors during sleep (100). Specific sleep architecture abnormalities, such as shorter REM latency and increased percentage of REM sleep, have also been reported in patients with TS (6). However, none of the IPMDS-recommended scales for tics and TS assesses sleep problems.

Five rating scales have been recommended for the IPMDS Task Force for assessment of tics and Tourette syndrome (101). The most widely used rating scale for motor and phonic tics is the Yale Global Tic Severity Scale (YGTSS) (30). It is a complex, rater-based tool, composed by items rating number, frequency, intensity, complexity, and interference of symptoms in a scoring scale from 0 (none/absent) to 5 (severe/always). The YGTSS yields total motor and phonic scores, an overall impairment rating and a global severity score. Its psychometric properties are satisfactory and thresholds of score changes due to clinical treatment are available (102, 103).

The Shapiro Tourette Syndrome Severity Scale (STSSS) (31) rates intensity of symptoms and interference with functioning, and it is reliable, valid, brief, and easy to administer. The Tourette Syndrome Clinical Global Impressions scale (TS-CGI) (32), also a brief scale, scores the overall adverse impact of tics. These two scales are less comprehensive than the YGTSS, as they do not include some aspects such as frequency, complexity, and distribution of tics. The Tourette's Disorder Scale (TODS) (33) rates overall tics severity but also assess comorbid behavioral symptoms: inattention, hyperactivity, obsessions, compulsions, aggression, and emotional symptoms. It shows excellent internal consistency and excellent inter-rater agreement and convergent and divergent validity (104).

Finally, the Premonitory Urge for Tic Disorders Scale (PUTS), the only specific scale for tic-related premonitory urges, presented satisfactory psychometric properties only for patients older than 10 years (34).

DISCUSSION

Several conditions, toxic agents, and metabolic dysfunctions can produce effects on brain structures and functional circuits in such a way that movement disorders and sleep disorders are manifested simultaneously. On the other hand, some movement disorders are associated with disturbed physiological sleep patterns, adding to the distress, and quality of life deterioration these patients suffer. Correct management of both types of disorders is mandatory and thus requires close evaluation and monitoring. However, as frequently occurs in the realm of movement disorders, the existence of non-motor symptoms and, specifically, sleep disturbances may remain undeclared (89) and underdiagnosed, missing the opportunity of appropriate treatment to improve the patient's health state.

Objective methods, based on wearable devices and technological developments, can be used for the appraisal of severity of movement disorders, sleep disturbances, and both types of conditions simultaneously when they are present in combination. Objective methods are also used for the diagnosis of several sleep disorders according to sleep disorder diagnostic criteria (periodic limb movement, obstructive sleep apneas, etc.), and particularly when the sleep dysfunction is due to several different causes as in atypical Parkinsonism or HD.

Polysomnography is very useful for this objective, but due to the complexity and costs of the sleep laboratories, this resource can be applied usually to a limited proportion of patients (105). Inertial sensors for capturing and recording movement during sleep are increasingly used and this is a rapidly growing field because progress in technology continuously offers easier to manage and portable devices that provide great amounts of information. The great advantage of these objective methods is that they furnish genuine measures providing real numbers based on physical phenomena.

The main disadvantages of rating scales are the influence of subjectivity in score assignment and the ordinal level of measurement (representing an ordered classification rather than real numerical values) adopted for the huge majority of them. Nonetheless, rating scales have the advantage of low cost, simplicity of application without need of special circumstances and settings, long time frame evaluation, and the multitude of facets they can assess. These characteristics have favored the wide use of these instruments in clinical daily practice and research.

Many of the rating scales described in this review are focused on the specific abnormal movement they evaluate and, therefore, do not include other elements for sleep assessment. However, the fact that several comprehensive scales that were designed to gather those components representing the most relevant aspects of the corresponding disorder, do not include sleep evaluations even when sleep disorders are frequently present in such condition, is striking. In general, it seems that the field of motor disorders has difficulty recognizing the presence of non-motor manifestations as disturbances causing important health problems to patients. The existence of similar non-motor symptoms in the general population (e.g., insomnia), although usually with lower prevalence and severity, may explain why these symptoms remained hidden to the attention of clinicians interested in movement disorders. In turn, the lack of systematic screening of these non-motor problems, has possibly led to the infradiagnosis and treatment of these disorders.

CONCLUSIONS

The present review offers a rapid and pragmatic vision of the properties of the most used rating scales in those movement disorders with related sleep disorders and reflects how most scales do not cover the simultaneous evaluation of sleep disturbances. The inclusion of instruments for screening and appraisal of sleep disorders in the assessment of patients with, for example, essential tremor or chronic tics, and the development of new rating scales including items and domains for evaluation of sleep disorders in movement disorders will help to recognize the magnitude of the problem this combination represents.

AUTHOR CONTRIBUTIONS

CR-B and MF conception and design of the study and wrote the first draft of the manuscript. MK, RB, and PM-M revised the work critically for important intellectual content. All authors contributed to manuscript revision, read, and approved the submitted version.

REFERENCES

1. Hobart JC, Cano SJ, Zajicek JP, Thompson AJ. Rating scales as outcome measures for clinical trials in neurology: problems, solutions, and recommendations. *Lancet Neurol.* (2007) **6**:1094–105. doi: 10.1016/S1474-4422(07)70290-9
2. Giannoccaro MP, Antelmi E, Plazzi G. Sleep and movement disorders. *Curr Opin Neurol.* (2013) **26**:428–34. doi: 10.1097/WCO.0b013e3283632cef
3. Abbott SM, Videnovic A. Sleep disorders in atypical Parkinsonism. *Mov Disord Clin Pract.* (2014) **1**:89–96. doi: 10.1002/mdc3.12025
4. Iranzo A, Molinuevo JL, Santamaría J, Serradell M, Martí MJ, Valldeoriola F, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. *Lancet Neurol.* (2006) **5**:572–7. doi: 10.1016/S1474-4422(06)70476-8
5. Martino D, Ganos C, Pringsheim TM. Tourette syndrome and chronic tic disorders: the clinical spectrum beyond tics. *Int Rev Neurobiol.* (2017) **134**:1461–90. doi: 10.1016/bs.irn.2017.05.006
6. Zoccolella S, Savarese M, Lamberti P, Manni R, Pacchetti C, Logroscino G. Sleep disorders and the natural history of Parkinson's disease: the contribution of epidemiological studies. *Sleep Med Rev.* (2011) **15**:41–50. doi: 10.1016/j.smrv.2010.02.004
7. Wu Y, Wang X, Wang C, Sun Q, Song N, Zhou Y, et al. Prevalence and clinical features of non-motor symptoms of essential tremor in Shanghai rural area. *Parkinsonism Relat Disord.* (2016) **22**:15–20. doi: 10.1016/j.parkreldis.2015.10.617
8. Kurtis MM, Balestrino R, Rodriguez-Blazquez C, Forjaz MJ, Martinez-Martin P. A review of scales to evaluate sleep disturbances in movement disorders. *Front Neurol.* (2018) **9**:369. doi: 10.3389/fneur.2018.00369
9. Movement Disorders Society. *MDS Rating Scales [Internet].* Available online at: http://www.movementdisorders.org/MDS/Education/Rating-Scales.htm (Cited November 10, 2017).
10. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry.* (1989) **154**:672–6.
11. Barnes TRE. The barnes akathisia rating scale–revisited. *J Psychopharmacol.* (2003) **17**:365–70. doi: 10.1177/0269881103174013
12. Teixeira AL, Maia DP, Cardoso F. UFMG Sydenham's chorea rating scale (USCRS): reliability and consistency. *Mov Disord.* (2005) **20**:585–91. doi: 10.1002/mds.20377
13. Unified Huntington's disease rating scale: reliability and consistency. *Mov Disord.* (1996) **11**:136–42. doi: 10.1002/mds.870110204
14. Comella CL, Leurgans S, Wuu J, Stebbins GT, Chmura T, Dystonia study group. rating scales for dystonia: a multicenter assessment. *Mov Disord.* (2003) **18**:303–12. doi: 10.1002/mds.10377
15. Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. *Neurology* (1985) 35:73–7.
16. Consky E, Lang A. Clinical assessments of patients with cervical dystonia. In: Jankovic J, Hallett M, editors. *Therapy with Botulinum Toxin*. New York, NY: Marcel Dekker (1994). p. 221–37.
17. Fahn S, Tolosa E, Marín C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, editors. *Parkinson's Disease and Movement Disorders*. Baltimore, MD: Williams and Wilkins (1993). p. 271–80.
18. Stacy MA, Elble RJ, Ondo WG, Wu S-C, Hulihan J, TRS study group. Assessment of interrater and intrarater reliability of the Fahn-Tolosa-Marin Tremor Rating Scale in essential tremor. *Mov Disord.* (2007) **22**:833–8. doi: 10.1002/mds.21412
19. Bain PG, Findley LJ. *Assessing Tremor Severity: A Clinical Handbook*. London: Gordon-Smith (1993).
20. Louis ED, Ottman R, Ford B, Pullman S, Martinez M, Fahn S, et al. The Washington heights-inwood genetic study of essential tremor: methodologic issues in essential-tremor research. *Neuroepidemiology* (1997) **16**:124–33.
21. Elble R, Comella C, Fahn S, Hallett M, Jankovic J, Juncos JL, et al. Reliability of a new scale for essential tremor. *Mov Disord.* (2012) **27**:1567–9. doi: 10.1002/mds.25162
22. Wenning GK, Tison F, Seppi K, Sampaio C, Diem A, Yekhlef F, et al. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). *Mov Disord.* (2004) **19**:1391–402. doi: 10.1002/mds.20255
23. Frucht SJ, Leurgans SE, Hallett M, Fahn S. The unified myoclonus rating scale. *Adv Neurol.* (2002) **89:**361–76.
24. Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): process, format, and clinimetric testing plan. *Mov Disord.* (2007) **22**:41–7. doi: 10.1002/mds.21198
25. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. *Mov Disord.* (2007) **22**:1901–11. doi: 10.1002/mds.21596
26. Chaudhuri KR, Martinez-Martin P, Schapira AHV, Stocchi F, Sethi K, Odin P, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. *Mov Disord.* (2006) **21**:916–23. doi: 10.1002/mds.20844
27. Marinus J, Visser M, Stiggelbout AM, Rabey JM, Martínez-Martín P, Bonuccelli U, et al. A short scale for the assessment of motor impairments and disabilities in Parkinson's disease: the SPES/SCOPA. *J Neurol Neurosurg Psychiatry* (2004) **75**:388–95. doi: 10.1136/jnnp.2003.017509
28. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. *Mov Disord.* (2004) **19**:1306–12. doi: 10.1002/mds.20153
29. Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. *Brain* (2007) **130**:1552–65. doi: 10.1093/brain/awm032
30. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The yale global tic severity scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry.* (1989) **28**:566–73.
31. Shapiro AK, Shapiro E. Controlled study of pimozide vs. placebo in Tourette's syndrome. *J Am Acad Child Psychiatry* (1984) **23**:161–73.
32. Leckman JF, Towbin KE, Ort SI, Cohen DJ. Clinical assessment of tic disorders severity. In: Cohen DJ, Bruun RD, Leckman JF, editors. *Tourette's Syndrome and Tic Disorders: Clinical Understanding and Treatment*. New York, NY: John Wiley & Sons (1988).
33. Shytle RD, Silver AA, Sheehan KH, Wilkinson BJ, Newman M, Sanberg PR, et al. The Tourette's Disorder Scale (TODS): development, reliability, and validity. *Assessment* (2003) **10**:273–87. doi: 10.1177/1073191103255497
34. Woods DW, Piacentini J, Himle MB, Chang S. Premonitory Urge for Tics Scale (PUTS): initial psychometric results and examination of the

premonitory urge phenomenon in youths with Tic disorders. *J Dev Behav Pediatr.* (2005) **26**:397–403.
35. Walters AS, Hening W, Rubinstein M, Chokroverty S. A clinical and polysomnographic comparison of neuroleptic-induced akathisia and the idiopathic restless legs syndrome. *Sleep* (1991) **14**:339–45.
36. Moser AD, Epping E, Espe-Pfeifer P, Martin E, Zhorne L, Mathews K, et al. A survey-based study identifies common but unrecognized symptoms in a large series of juvenile Huntington's disease. *Neurodegener Dis Manag.* (2017) **7**:307–15. doi: 10.2217/nmt-2017-0019
37. Piano C, Losurdo A, Della Marca G, Solito M, Calandra-Buonaura G, Provini F, et al. Polysomnographic findings and clinical correlates in huntington disease: a cross-sectional cohort study. *Sleep* (2015) **38**:1489–95. doi: 10.5665/sleep.4996
38. Maskevich S, Jumabhoy R, Dao PDM, Stout JC, Drummond SPA. Pilot validation of ambulatory activity monitors for sleep measurement in Huntington's disease gene carriers. *J Huntingt Dis.* (2017) **6**:249–53. doi: 10.3233/JHD-170251
39. Bellosta Diago E, Pérez Pérez J, Santos Lasaosa S, Viloria Alebesque A, Martínez Horta S, Kulisevsky J, et al. Circadian rhythm and autonomic dysfunction in presymptomatic and early Huntington's disease. *Parkinsonism Relat Disord.* (2017) **44**:95–100. doi: 10.1016/j.parkreldis.2017.09.013
40. Baker CR, Domínguez D JF, Stout JC, Gabery S, Churchyard A, Chua P, et al. Subjective sleep problems in Huntington's disease: a pilot investigation of the relationship to brain structure, neurocognitive, and neuropsychiatric function. *J Neurol Sci.* (2016) **364**:148–53. doi: 10.1016/j.jns.2016.03.021
41. Ben-Pazi H, Stoner JA, Cunningham MW. Dopamine receptor autoantibodies correlate with symptoms in Sydenham's chorea. *PLoS ONE* (2013) **8**:e73516. doi: 10.1371/journal.pone.0073516
42. Fusco C, Ucchino V, Frattini D, Pisani F, Della Giustina E. Acute and chronic corticosteroid treatment of ten patients with paralytic form of Sydenham's chorea. *Eur J Paediatr Neurol.* (2012) **16**:373–8. doi: 10.1016/j.ejpn.2011.12.005
43. Barreto LB, Maciel ROH, Maia DP, Teixeira AL, Cardoso F. Parkinsonian signs and symptoms in adults with a history of Sydenham's chorea. *Parkinsonism Relat Disord.* (2012) **18**:595–7. doi: 10.1016/j.parkreldis.2011.11.002
44. Teixeira AL, Maia DP, Cardoso F. The initial testing and the discrimination property of the UFMG Sydenham's Chorea Rating Scale (USCRS). *Arq Neuropsiquiatr.* (2005) **63**:825–7. doi: 10.1590/S0004-282X2005000500019
45. Siesling S, Zwinderman AH, van Vugt JP, Kieburtz K, Roos RA. A shortened version of the motor section of the Unified Huntington's disease rating scale. *Mov Disord.* (1997) **12**:229–34. doi: 10.1002/mds.870120214
46. Mestre TA, van Duijn E, Davis AM, Bachoud-Lévi A-C, Busse M, Anderson KE, et al. Rating scales for behavioral symptoms in Huntington's disease: critique and recommendations. *Mov Disord.* (2016) **31**:1466–78. doi: 10.1002/mds.26675
47. Youssov K, Dolbeau G, Maison P, Boissé M-F, Cleret De Langavant L, Roos R, et al. Unified Huntington's disease rating scale for advanced patients: validation and follow-up study. *Mov Disord.* (2013) **28**:1717–23. doi: 10.1002/mds.25654
48. Torres JAKL, Rosales RL. Nonmotor symptoms in dystonia. *Int Rev Neurobiol.* (2017) **134**:1335–71. doi: 10.1016/bs.irn.2017.05.003
49. Kuyper DJ, Parra V, Aerts S, Okun MS, Kluger BM. The non-motor manifestations of dystonia: a systematic review. *Mov Disord.* (2011) **26**:1206–17. doi: 10.1002/mds.23709
50. Trotti LM, Esper CD, Feustel PJ, Bliwise DL, Factor SA. Excessive daytime sleepiness in cervical dystonia. *Parkinsonism Relat Disord.* (2009) **15**:784–6. doi: 10.1016/j.parkreldis.2009.04.007
51. Sforza E, Montagna P, Defazio G, Lugaresi E. Sleep and cranial dystonia. *Electroencephalogr Clin Neurophysiol.* (1991) 79:166–9.
52. Albanese A, Sorbo FD, Comella C, Jinnah HA, Mink JW, Post B, et al. Dystonia rating scales: critique and recommendations. *Mov Disord.* (2013) **28**:874–83. doi: 10.1002/mds.25579
53. Rohl B, Collins K, Morgan S, Cosentino S, Huey ED, Louis ED. Daytime sleepiness and nighttime sleep quality across the full spectrum of cognitive presentations in essential tremor. *J Neurol Sci.* (2016) **371**:24–31. doi: 10.1016/j.jns.2016.10.006
54. Chunling W, Zheng X. Review on clinical update of essential tremor. *Neurol Sci.* (2016) **37**:495–502. doi: 10.1007/s10072-015-2380-1
55. Louis ED. Non-motor symptoms in essential tremor: a review of the current data and state of the field. *Parkinsonism Relat Disord.* (2016) **22**:S115–118. doi: 10.1016/j.parkreldis.2015.08.034
56. Sengul Y, Sengul HS, Yucekaya SK, Yucel S, Bakim B, Pazarci NK, et al. Cognitive functions, fatigue, depression, anxiety, and sleep disturbances: assessment of nonmotor features in young patients with essential tremor. *Acta Neurol Belg.* (2015) **115**:281–7. doi: 10.1007/s13760-014-0396-6
57. Lenka A, Benito-León J, Louis ED. Is there a Premotor Phase of Essential Tremor? *Tremor Other Hyperkinetic Mov.* (2017) **7**:498. doi: 10.7916/D80S01VK
58. Elble R, Bain P, Forjaz MJ, Haubenberger D, Testa C, Goetz CG, et al. Task force report: scales for screening and evaluating tremor: critique and recommendations. *Mov Disord.* (2013) **28**:1793–800. doi: 10.1002/mds.25648
59. Bain PG, Findley LJ, Atchison P, Behari M, Vidailhet M, Gresty M, et al. Assessing tremor severity. *J Neurol Neurosurg Psychiatry* (1993) **56**:868–73.
60. Louis ED, Barnes L, Wendt KJ, Ford B, Sangiorgio M, Tabbal S, et al. A teaching videotape for the assessment of essential tremor. *Mov Disord.* (2001) **16**:89–93.
61. Louis ED, Ford B, Bismuth B. Reliability between two observers using a protocol for diagnosing essential tremor. *Mov Disord.* (1998) **13**:287–93.
62. Louis ED, Agnew A, Gillman A, Gerbin M, Viner AS. Estimating annual rate of decline: prospective, longitudinal data on arm tremor severity in two groups of essential tremor cases. *J Neurol Neurosurg Psychiatry* (2011) **82**:761–5. doi: 10.1136/jnnp.2010.229740
63. Frucht SJ, Bordelon Y, Houghton WH, Reardan D. A pilot tolerability and efficacy trial of sodium oxybate in ethanol-responsive movement disorders. *Mov Disord.* (2005) **20**:1330–7. doi: 10.1002/mds.20605
64. Voller B, Lines E, McCrossin G, Artiles A, Tinaz S, Lungu C, et al. Alcohol challenge and sensitivity to change of the essential tremor rating assessment scale. *Mov Disord.* (2014) **29**:555–8. doi: 10.1002/mds.25667
65. Chang WS, Chung JC, Kim JP, Chang JW. Simultaneous thalamic and posterior subthalamic electrode insertion with single deep brain stimulation electrode for essential tremor. *Neuromodulation Technol Neural Interface* (2013) **16**:236–43. doi: 10.1111/j.1525-1403.2012.00503.x
66. Mostile G, Fekete R, Giuffrida JP, Yaltho T, Davidson A, Nicoletti A, et al. Amplitude fluctuations in essential tremor. *Parkinsonism Relat Disord.* (2012) **18**:859–63. doi: 10.1016/j.parkreldis.2012.04.019
67. Ohshima Y, Nakayama H, Matsuyama N, Hokari S, Sakagami T, Sato T, et al. Natural course and potential prognostic factors for sleep-disordered breathing in multiple system atrophy. *Sleep Med.* (2017) **34**:13–7. doi: 10.1016/j.sleep.2017.01.020
68. Videnovic A. Management of sleep disorders in Parkinson's disease and multiple system atrophy. *Mov Disord.* (2017) **32**:659–68. doi: 10.1002/mds.26918
69. Palma J-A, Norcliffe-Kaufmann L, Kaufmann H. Diagnosis of multiple system atrophy. *Auton Neurosci Basic Clin.* (2017). **211**:15–25. doi: 10.1016/j.autneu.2017.10.007
70. Krismer F, Seppi K, Tison F, Sampaio C, Zangerl A, Peralta C, et al. The unified multiple system atrophy rating scale: intrarater reliability. *Mov Disord.* (2012) **27**:1683–5. doi: 10.1002/mds.25181
71. Guo XY, Cao B, Lei F, Huang L, Chen K, Song W, et al. Clinical and polysomnographic features of patients with multiple system atrophy in Southwest China. *Sleep Breath* (2013) **17**:1301–7. doi: 10.1007/s11325-013-0839-y
72. Matsushima M, Yabe I, Takahashi I, Hirotani M, Kano T, Horiuchi K, et al. Validity and reliability of a pilot scale for assessment of multiple system atrophy symptoms. *Cereb Ataxias* (2017) **4**:11. doi: 10.1186/s40673-017-0067-5
73. Matsushima M, Yabe I, Oba K, Sakushima K, Mito Y, Takei A, et al. Comparison of Different symptom assessment scales for multiple system atrophy. *Cerebellum* (2016) **15**:190–200. doi: 10.1007/s12311-015-0686-4
74. Caviness JN, Brown P. Myoclonus: current concepts and recent advances. *Lancet Neurol.* (2004) **3**:598–607. doi: 10.1016/S1474-4422(04)00880-4

75. Montagna P, Provini F, Vetrugno R. Propriospinal myoclonus at sleep onset. *Neurophysiol Clin*. (2006) **36**(5–6):351–5. doi: 10.1016/j.neucli.2006.12.004
76. Salas Puig J, Tuñón A, Vidal JA, Mateos V, Guisasola LM, Lahoz CH. [Janz's juvenile myoclonic epilepsy: a little-known frequent syndrome. A study of 85 patients]. *Med Clin*. (1994) **103**:684–9.
77. van Zijl JC, Beudel M, Elting J-WJ, de Jong BM, van der Naalt J, van den Bergh WM, et al. The inter-rater variability of clinical assessment in post-anoxic myoclonus. *Tremor Other Hyperkinetic Mov*. (2017) **7**:470. doi: 10.7916/D81R6XBV
78. Hainque E, Vidailhet M, Cozic N, Charbonnier-Beaupel F, Thobois S, Tranchant C, et al. A randomized, controlled, double-blind, crossover trial of zonisamide in myoclonus-dystonia. *Neurology* (2016) **86**:1729–35. doi: 10.1212/WNL.0000000000002631
79. Schrempf W, Brandt MD, Storch A, Reichmann H. Sleep disorders in Parkinson's disease. *J Park Dis*. (2014) **4**:211–21. doi: 10.3233/JPD-130301
80. Fahn S, Elton R, UPDRS program members. Unified Parkinson's disease rating scale. In: Fahn S, Marsden C, Goldstein M, Calne D, editors. *Recent Developments in Parkinson's Disease*. Florham Park, NJ: Macmillan Healthcare Information (1987), p. 153–163.
81. Horváth K, Aschermann Z, Acs P, Bosnyák E, Deli G, Pál E, et al. Is the MDS-UPDRS a good screening tool for detecting sleep problems and daytime sleepiness in Parkinson's disease? *Park Dis*. (2014) **2014**:806169. doi: 10.1155/2014/806169
82. Poewe W, Hauser RA, Lang A, ADAGIO Investigators. Effects of rasagiline on the progression of nonmotor scores of the MDS-UPDRS. *Mov Disord*. (2015) **30**:589–92. doi: 10.1002/mds.26124
83. Jafari N, Pahwa R, Nazzaro JM, Arnold PM, Lyons KE. MDS-UPDRS to assess non-motor symptoms after STN DBS for Parkinson's disease. *Int J Neurosci*. (2016) **126**:25–9. doi: 10.3109/00207454.2015.1065257
84. Horváth K, Aschermann Z, Ács P, Deli G, Janszky J, Komoly S, et al. Minimal clinically important difference on the Motor Examination part of MDS-UPDRS. *Parkinsonism Relat Disord*. (2015) **21**:1421–6. doi: 10.1016/j.parkreldis.2015
85. Martinez-Martin P, Rodriguez-Blazquez C, Abe K, Bhattacharyya KB, Bloem BR, Carod-Artal FJ, et al. International study on the psychometric attributes of the non-motor symptoms scale in Parkinson disease. *Neurology* (2009) **73**:1584–91. doi: 10.1212/WNL.0b013e3181c0d416
86. Chaudhuri KR, Martinez-Martin P, Antonini A, Brown RG, Friedman JH, Onofrj M, et al. Rotigotine and specific non-motor symptoms of Parkinson's disease: *post hoc* analysis of RECOVER. *Parkinsonism Relat Disord*. (2013) **19**:660–5. doi: 10.1016/j.parkreldis.2013.02.018
87. Martinez-Martin P, Reddy P, Katzenschlager R, Antonini A, Todorova A, Odin P, et al. EuroInf: a multicenter comparative observational study of apomorphine and levodopa infusion in Parkinson's disease. *Mov Disord*. (2015) **30**:510–6. doi: 10.1002/mds.26067
88. Perez Lloret S, Rossi M, Cardinali DP, Merello M. Validation of the sleep related items of the Non-motor Symptoms Questionnaire for Parkinson's disease (NMSQuest). *Parkinsonism Relat Disord*. (2008) **14**:641–5. doi: 10.1016/j.parkreldis.2008.01.004
89. Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, Mitra T, Frades-Payo B, Tluk S, et al. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. *Mov Disord*. (2010) **25**:704–9. doi: 10.1002/mds.22868
90. Chaudhuri KR, Sauerbier A, Rojo JM, Sethi K, Schapira AHV, Brown RG, et al. The burden of non-motor symptoms in Parkinson's disease using a self-completed non-motor questionnaire: a simple grading system. *Parkinsonism Relat Disord*. (2015) **21**:287–91. doi: 10.1016/j.parkreldis.2014.12.031
91. Shulman LM, Armstrong M, Ellis T, Gruber-Baldini A, Horak F, Nieuwboer A, et al. Disability rating scales in Parkinson's disease: critique and recommendations. *Mov Disord*. (2016) **31**:1455–65. doi: 10.1002/mds.26649
92. Martínez-Martín P, Benito-León J, Burguera JA, Castro A, Linazasoro G, Martínez-Castrillo JC, et al. The SCOPA-Motor Scale for assessment of Parkinson's disease is a consistent and valid measure. *J Clin Epidemiol*. (2005) 58:674–9. doi: 10.1016/j.jclinepi.2004.09.014
93. Marinus J, van der Heeden JF, van Hilten JJ. Calculating clinical progression rates in Parkinson's disease: methods matter. *Parkinsonism Relat Disord*. (2014) **20**:1263–7. doi: 10.1016/j.parkreldis.2014.08.009
94. Martinez-Martín P, Rodriguez-Blazquez C, Paz S, Forjaz MJ, Frades-Payo B, Cubo E, et al. Parkinson symptoms and health related quality of life as predictors of costs: a longitudinal observational study with linear mixed model analysis. *PLoS ONE* (2015) **10**:e0145310. doi: 10.1371/journal.pone.0145310
95. Evatt ML, Chaudhuri KR, Chou KL, Cubo E, Hinson V, Kompoliti K, et al. Dysautonomia rating scales in Parkinson's disease: sialorrhea, dysphagia, and constipation–critique and recommendations by movement disorders task force on rating scales for Parkinson's disease. *Mov Disord*. (2009) **24**:635–46. doi: 10.1002/mds.22260
96. Pavy-Le Traon A, Amarenco G, Duerr S, Kaufmann H, Lahrmann H, Shaftman SR, et al. The Movement Disorders task force review of dysautonomia rating scales in Parkinson's disease with regard to symptoms of orthostatic hypotension. *Mov Disord*. (2011) **26**:1985–992. doi: 10.1002/mds.23742
97. Montplaisir J, Petit D, Décary A, Masson H, Bédard MA, Panisset M, et al. Sleep and quantitative EEG in patients with progressive supranuclear palsy. *Neurology* (1997) **49**:999–1003.
98. Hall DA, Forjaz MJ, Golbe LI, Litvan I, Payan CAM, Goetz CG, et al. Scales to assess clinical features of progressive supranuclear palsy: MDS task force report. *Mov Disord Clin Pract*. (2015) **2**:127–34. doi: 10.1002/mdc3.12130
99. Hewer S, Varley S, Boxer AL, Paul E, Williams DR. AL-108-231 Investigators. Minimal clinically important worsening on the progressive supranuclear Palsy Rating Scale. *Mov Disord*. (2016) **31**:1574–7. doi: 10.1002/mds.26694
100. Ghosh D, Rajan PV, Das D, Datta P, Rothner AD, Erenberg G. Sleep disorders in children with Tourette syndrome. *Pediatr Neurol*. (2014) **51**:31–5. doi: 10.1016/j.pediatrneurol.2014.03.017
101. Martino D, Pringsheim TM, Cavanna AE, Colosimo C, Hartmann A, Leckman JF, et al. Systematic review of severity scales and screening instruments for tics: critique and recommendations. *Mov Disord*. (2017) **32**:467–73. doi: 10.1002/mds.26891
102. Storch EA, De Nadai AS, Lewin AB, McGuire JF, Jones AM, Mutch PJ, et al. Defining treatment response in pediatric tic disorders: a signal detection analysis of the Yale global tic severity scale. *J Child Adolesc Psychopharmacol*. (2011) **21**:621–7. doi: 10.1089/cap.2010.0149
103. Jeon S, Walkup JT, Woods DW, Peterson A, Piacentini J, Wilhelm S, et al. Detecting a clinically meaningful change in tic severity in Tourette syndrome: a comparison of three methods. *Contemp Clin Trials* (2013) **36**:414–20. doi: 10.1016/j.cct.2013.08.012
104. Storch EA, Merlo LJ, Lehmkuhl H, Grabill KM, Geffken GR, Goodman WK, et al. Further psychometric examination of the Tourette's Disorder Scales. *Child Psychiatry Hum Dev*. (2007) **38**:89–98. doi: 10.1007/s10578-006-0043-4
105. Bhidayasiri R, Martinez-Martin P. Clinical Assessments in Parkinson's disease: scales and monitoring. *Int Rev Neurobiol*. (2017) **132**:129–82. doi: 10.1016/bs.irn.2017.01.001

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Microstructural Changes in Patients With Parkinson's Disease Comorbid With REM Sleep Behaviour Disorder and Depressive Symptoms

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The diagnosis of Parkinson's disease (PD) is currently anchored on clinical motor symptoms, which appear more than 20 years after initiation of the neurotoxicity. Extra-nigral involvement in the onset of PD with probable nonmotor manifestations before the development of motor signs, lead us to the preclinical (asymptomatic) or prodromal stages of the disease (various nonmotor or subtle motor signs). REM sleep behavior disorder (RBD) and depression are established prodromal clinical markers of PD and predict worse motor and cognitive outcomes. Nevertheless, taken by themselves, these markers are not yet claimed to be practical in identifying high-risk individuals. Combining promising markers may be helpful in a reliable diagnosis of early PD. Therefore, we aimed to detect neural correlates of RBD and depression in 93 treatment-naïve and non-demented early PD by means of diffusion MRI connectometry. Comparing four groups of PD patients with or without comorbid RBD and/or depressive symptoms with each other and with 31 healthy controls, we found that these two non-motor symptoms are associated with lower connectivity in several white matter tracts including the cerebellar peduncles, corpus callosum and long association fibers such as cingulum, fornix, and inferior longitudinal fasciculus. For the first time, we were able to detect the involvement of short association fibers (U-fibers) in PD neurodegenerative process. Longitudinal studies on larger sample groups are needed to further investigate the reported associations.

Keywords: Parkinson's disease, REM sleep behavior disorder, depression, connectometry, diffusion MRI

INTRODUCTION

Parkinson's disease (PD), a form of α-synucleinopathy neurodegeneration (1), is manifested by a heterogeneous combination of motor and non-motor symptoms (NMS) (2). PD is classically diagnosed based on its cardinal motor symptoms relatively late in the course of the disease, years or even decades after the initiation of neurotoxicity. Thus, the golden time to halt the disease progression is missed. Searching for markers to diagnose PD in the early stage of the disease, a critical opportunity for neuroprotective interventions remains a hot topic (3).

Rapid Eye movement (REM) sleep behavior disorder (RBD), characterized by unpleasant dreams and loss of normal muscle atonia (4), has by far proved to be the strongest precursor of upcoming PD (3) and with more than 75% conversion rate, is considered as an evolving synucleinopathy (5–7). With an estimated prevalence of 15–60% in PD patients (8), baseline RBD is attributed to more aggressive clinical subtype with worse motor and non-motor symptoms, especially depressive disorders and cognitive decline (9). Besides high specificity and prognostic value, its low predictive sensitivity and long lead time to the development of parkinsonism bring challenges in practice. Combining RBD with another prodromal symptom may solve this task by increasing the risk of conversion (10).

Depression is another established clinical prodromal marker (3, 7) and is the main culprit in a lower quality of life in PD patients (11). Depression together with RBD play as potential interactive risk factors for the development of dementia in PD which is associated with more advanced disease and poorer prognosis (12–14). Depression has multitude neural and clinical correlates with RBD. Depressed mood is often associated with disrupted REM sleep structure such as decreased latency, longer duration and more rapid eye movements, which may precede the onset of depressive episodes or even persist after complete remission with an increased rate of relapse or recurrence and poor treatment response (15–18). Furthermore, studies on healthy relatives of depressed patients have shown that REM sleep disturbances can predict the development of depressive episodes (19–22). This indicates that REM sleep dysregulation is not merely secondary but rather share underlying pathologies with depression (23–25). The frequency of Depression and its severity are also shown to be related to RBD and other sleep disturbances in PD (9, 26, 27). Some studies on depressed patients with idiopathic RBD (iRBD) have supported the assumption that this comorbidity might underpin and accelerate the neurodegenerative process (28–30). Interestingly, Wing et al. proved depression as a potential predictor of upcoming PD in following a cohort of iRBD patients (31). Remarked subcortical Lewy bodies in late-life depression (32) further supports this proposed link between depression and RBD.

Accumulating evidence suggests that white matter damage underlies the heterogenous manifestation of PD symptomatology (33). Although the pathogenesis of PD is still unclear, it is speculated that α-synuclein species spread as a prion-like pattern through axons and cause disruption in the white matter integrity via mitochondrial damage and glial activation (34). In this regard, diffusion MRI (dMRI) is a promising tool to measure white matter microstructure *in vivo* and has shed light through the knowledge of involved neural networks in PD in association with its distinct features. DMRI connectomery is a powerful analytical method that probes significant between-group differences within subcomponents of a neural pathway, rather than the entire pathway. Conventional diffusion tensor approaches track the entire pathway, which will inevitably contain fibers not strongly associated with study variables. This will result in higher sensitivity and lower type II error using connectometry approach by focusing only on significant variabilities (35). Furthermore, connectometry relies on Spin Distribution Function (SDF) to measure the density of water diffusion for any direction of a voxel and reveals the so-called "local connectome fingerprint" which is highly specific to each individual (36). Ability to quantify the degree of connectivity between adjacent voxels within a neural fascicle, local connectome, has opened a new door to investigate pathological insults on the unique configuration of white matter microstructure.

In two previous studies, we have tried to discover whether RBD and depression can lead us to white matter degeneration signature of early PD, comparing two groups of depressed (dPD) and non-depressed PD patients (ndPD) with comorbid RBD (37) and comparing two groups of dPD and ndPD without comorbid RBD (38) through dMRI connectometry. RBD and depressive symptoms both have been proposed as markers of prodromal PD and with possible cumulative effect on progression to PD and its severe subtypes and each can predict worse outcomes in PD or the other. In this study, which is an extension of two previous mentioned studies, we aimed to track differences in white matter connectivity in four groups of treatment-naïve early PD patients with and without comorbid RBD and/or depressive symptoms compared to healthy controls (HC) with added within PD subgroups comparisons.

MATERIALS AND METHODS

Participants

Participants, PD patients and HC, involved in this research were recruited from Parkinson's Progression Markers Initiative (PPMI, http://www.ppmi-info.org/). The study was approved by the institutional review board of all participating sites. Written informed consent was obtained from all participants before study enrolment. The study was performed in accordance with relevant guidelines and regulations (39). These participants were tested and confirmed negative for any neurological disorders apart from PD. The participants' PD status was confirmed by Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), and the loss of dopaminergic neurons was observed on DAT scans.

We analyzed only drug-naïve cases with available diffusion weighted imaging (DWI) in baseline visit after performing automated quality-control steps expressed by Fang-Chen Yeh, using q-space diffeomorphic reconstruction (QSDR) (40). This method is based on checking how compatible the quantitative anisotropy (QA) value of each voxel is with the reconstructed QA map. Subjects were excluded if imaging failed specific quality control criteria. Finally, a total of 93 drug-naïve early PD patients and 31 age-matched and sex-matched HC with good imaging quality were enrolled in this study. Clinical measures included disease duration, motor section (III) of UPDRS, Hoehn and Yahr (H&Y staging), Montreal Cognitive Assessment (MoCA), Epworth Sleepiness Scale (ESS) for daytime sleepiness, and the University of Pennsylvania Smell Identification Test (UPSIT) for olfaction function. Depression was assessed using the Geriatric Depression Scale (GDS), with a cut-off score of 5 or more indicating clinically significant symptoms (41). GDS is an easy to use, self-report screening and diagnostic tool with good reliability and validity to discriminate minor and major depressive disorders from non-depressive disorder in PD patients of all ages, particularly

elders (41). It is recommended for use by the Movement Disorders Society to screen for symptoms of depression in PD individuals (www.movementdisorders.org/MDS/Education/Rating-Scales.htm). RBD was assessed using REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), with a cut-off score of 5 or above to detect probable RBD (42, 43). Based on GDS and RBDSQ, PD patients were divided into four groups of 14 patients with depression and RBD (DEP+/RBD+), 16 without depression and with RBD (DEP-/RBD+), 43 with depression and without RBD (DEP+/RBD-), and 20 without depression and without RBD (DEP-/RBD-).

Data Acquisition

Data used in the preparation of this article were obtained from PPMI database (www.ppmiinfo.org/data) (39). This dataset was acquired on 3 Tesla Siemens scanners, producing 64 diffusion MRI (repetition time = 7748 MS, echo time = 86 ms; voxel size: 2.0 × 2.0 × 2.0 mm3; field of view = 224 × 224 mm) at b = 1,000 s/mm^2 and one b0 image along with 3D T1-weighted structural scans (repetition time = 8.2 ms, echo time = 3.7 ms; flip angle = 8°, voxel size: 1.0 × 1.0 × 1.0 mm^3; field of view = 240 mm, acquisition matrix = 240 × 240).

Diffusion MRI Processing

The diffusion MRI data were corrected for subject motion, eddy current distortions, and susceptibility artifacts due to the magnetic field inhomogeneity using Explore DTI toolbox (44). We performed quality control analysis on the subject's signals based on the goodness-of-fit value given in QSDR reconstruction of fibers. Each QSDR reconstruction file has a goodness-of-fit value quantified by R2. For example, an R82 indicates a goodness-of-fit between of the subject and template of 0.82 total. We excluded cases in which the R2 value did not reach a threshold of 0.6 otherwise.

Diffusion MRI Connectometry

The diffusion data were reconstructed in the Montreal Neurological Institute (MNI) space using QSDR to obtain the SDF (45), to detect the differences between groups. Quantitative anisotropy (QA) is one of the several diffusion indices derived from spin density, i.e., SDF (46). QA of each fiber orientation gives the peak value of water density in that direction. More precisely, in contrast to tensor-derived measures such as fractional anisotropy (FA) which are defined for each voxel and rely on diffusivity, QA is defined for each fiber orientation and is based on density. Therefore, diffusivity measures reflect the intactness of fibers, while QA quantifies the total diffusing water or "connectivity." As a result, QA has successfully overcome the shortage of conventional tensor measures on crossing fibers. Another advantage of QA over diffusivity metrics is that it is not affected by partial volume defect, as it is derived from spin density (47). We used diffusion MRI connectometry to identify white matter tracts in which QA was significantly different between two groups of PD patients with different degrees of depression and RBD, and comparing each PD group to HC. Resulting uncorrected output was corrected for multiple comparisons by false discovery rate (FDR). A deterministic fiber tracking algorithm was conducted along the core pathway of the fiber bundle to connect the selected local connectomes (48). Tracts with QA > 0.1, angle threshold lesser than 40° and tract length >40 mm were included. To estimate the false discovery rate, a total of 2,000 randomized permutations were applied to the group label to obtain the null distribution of the track length. A T-score threshold of 2.5 was assigned to select local connectomes, and the local connectomes were tracked using a deterministic fiber tracking algorithm. Permutation testing allows for estimating and correcting the FDR of Type-I error inflation due to multiple comparisons. The analysis was conducted using publicly available software DSI Studio (http://dsi-studio.labsolver.org), released in 5th April 2018.

Statistical Analysis

IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA) was used to analyse the demographic and clinical data. Probability graphics and Shapiro–Wilk test were used to check the compliance of variables with normal distribution. For normally distributed variables, one-way analysis of variance (ANOVA) was used to assess differences of means between groups. Kruskal–Wallis test was used to determine whether there are any statistically significant differences within continuous variables without normal distribution. Pearson's chi-square was used to test nominal variables across groups. Finally, $P < 0.05$ were considered statistically significant.

RESULTS

Demographic and Clinical Measures

PD patients in four groups were matched in their age, sex, disease duration and years of education. Patients were also comparable based on their degree of motor impairment (UDPRS-III and H&Y) after controlling for age, sex, and disease duration. The cognitive state (MoCA), olfaction function (UPSIT), and daytime sleepiness (ESS) did not differ between four PD groups (**Table 1**). There are few discrepancies between PD patients enrolled in this study and those investigated in our two previous studies, as we attempted to include patients matched in their demographic, motor and other non-motor symptoms other than depression and RBD in the present study. Eleven patients in the DEP+/RBD+ group, eight patients in the DEP-/RBD+ group, 19 patients in the DEP+/RBD- group, and 14 patients in the DEP-/RBD- group were at their stage 2 of H&Y, indicative of bilateral involvement without disturbance in balance. The rest of the patients were all in stage 1 of H&Y scaling compatible with mild symptoms of unilateral involvement. None of the patients in any group were demented as they all scored above the cut-off score of 21 on the MoCA. HC were matched with PD patients regarding age, sex, handedness, education years, MoCA, and ESS scores, while performed better than PD patients on GDS, RBD, and UPSIT.

PD Groups vs. HC Imaging Analysis

As outlined in **Table 2**, all four groups of PD patients showed lower connectivity in superior longitudinal fasciculus and U-fibers of parietal lobe and motor and pre-motor areas of the

TABLE 1 | Demographic and baseline clinical information of healthy controls and patients with Parkinson's disease with or without comorbid RBD and/or depression.

Groups	Healthy controls ($n = 31$)	DEP+RBD+ ($n = 14$)	DEP-RBD+ ($n = 16$)	DEP+RBD- ($n = 43$)	DEP-RBD- ($n = 20$)	*p*-Value**	*p*-Value (between PD groups)**
Age (mean ± *sd*)	58.0 ± 12.1	58.8 ± 9.8	59.2 ± 11.6	58.5 ± 8.7	58.4 ± 9.4	0.997	0.997
Female/Male no.	18/13	11/3	12/4	24/19	13/7	0.441	0.441
Handedness (L/R)	3/28	0/14	2/14	4/36	3/17	0.717	0.716
Education years (mean ± *sd*)	15.0 ± 2.8	15.1 ± 2.4	16.2 ± 2.6	15.0 ± 3.0	14.8. ± 3.1	0.611	0.611
Duration of disease in years (mean ± *sd*)	–	7.5 ± 7.5	8.5 ± 7.5	6.2 ± 6.7	6.3 ± 6.8	–	0.738
Hoehn & Yahr stage (mean ± *sd*)	–	1.8 ± 0.4	1.5 ± 0.5	1.4 ± 0.5	1.7 ± 0.5	–	0.146
UPDRS III* (mean ± *sd*)	–	21.7 ± 8.3	21.8 ± 11.4	19.3 ± 7.3	24.7 ± .8.7	–	0.163
MOCA* score (mean ± *sd*)	28.4 ± 1.1	27.4 ± 2.2	27.5 ± 1.8	27.6 ± 1.8	27.6 ± 2.4	0.324	0.955
RBD* score (mean ± *sd*)	3.4 ± 2.1	7.4 ± 2.0	7.1 ± 1.4	2.5 ± 1.1	2.3 ± 1.1	**<0.001**	**<0.001**
GDS* score (mean ± *sd*)	4.4 ± 1.1	5.1 ± 0.9	3.2 ± 1.1	5.2 ± 0.4	3.3 ± 1.1	**<0.001**	**<0.001**
ESS* scale (mean ± *sd*)	6.7 ± 4.3	7.4 ± 3.1	7.5 ± 3.8	5.5 ± 3.2	6.2 ± 3.0	0.263	0.126
UPSIT (mean ± *sd*)	33.1 ± 4.3	21.6 ± 9.9	19.6 ± 8.4	24.8 ± 8.1	24.3 ± 6.8	**<0.001**	0.145

**UPDRS III, Unified Parkinson's Disease Rating Scale part III; ESS, Epworth Sleepiness Scale; MoCA, Montreal Cognitive Assessment; RBD, REM sleep Behaviour Disorder Screening Questionnaire; GDS, Geriatric Depression Scale; UPSIT, the University of Pennsylvania Smell Identification Test (UPSIT). **p-value of one-way ANOVA analysis for age, education years, disease duration, and UPSIT; Pearson Chi-square for gender, handedness, and H&Y stage; and Kruskal–Wallis test for ESS, UPRDS part III, GDS scale, MoCA score, and RBDSQ. P < 0.05 are considered statistically significant.*

TABLE 2 | Regions with significantly reduced quantitative anisotropy comparing each group of PD patients with healthy controls.

PD RBD+/DEP+ vs. HC (FDR = 0.01)	PD Dep–/RBD+ vs. HC (FDR = 0.02)	Dep+/RBD–vs. HC (FDR = 0.001)	DEP-/RBD-vs. HC (FDR = 0.036)
B-SLF	B-SLF	B-SLF	B-SLF
B-U-fiber	B-U-fiber	L-U-fiber	R-U-fiber
L-ILF	B-cingulum	L-ILF	R-cingulum
body of CC		B-cingulum	

B, bilateral; L, left; R, right; SLF, superior longitudinal fasciculus; ILF, inferior longitudinal fasciculus; CC, corpus callosum; FDR, false discovery rate.

frontal lobe. Left inferior longitudinal fasciculus (ILF) was only disrupted in the PD groups with comorbid depression, i.e., DEP+/RBD- and DEP+/RBD+. Cingulum had lower connectivity in all PD patients except RBD+/DEP+. This group instead showed lower connectivity in the body of corpus callosum (CC).

Between-Group Imaging Analyses of PD Patients

Compared with PD DEP-/RBD+ patients, PD DEP+/RBD+ patients showed decreased connectivity in the right cingulum, left ILF, splenium, and body of the CC (FDR = 0.03) (**Figure 1**). As shown in **Figure 2**, the PD DEP+/RBD+ group demonstrated decreased connectivity in the genu, splenium, and body of CC, left ILF, left fornix, and right superior cerebellar peduncle (SCP) in contrast to PD DEP+/RBD- (FDR = 0.02). The group differences between PD DEP+/RBD+ patients and PD DEP-/RBD- were that connectivity in PD DEP-/RBD- was higher than that in PD DEP+/RBD+ patients in the genu, splenium and body of CC, bilateral cingulum, left ILF, left fornix, right SCP, and right inferior fronto-occipital fasciculus (IFOF) (FDR = 0.01).

Compared with PD DEP-/RBD- patients, PD DEP–/RBD+ patients showed decreased connectivity in the bilateral cingulum, bilateral fornix, left ILF, genu, and body of CC, middle cerebellar peduncle (MCP), bilateral SCP, right uncinate fasciculus (UF), and left cerebro-cortical pathway (CST) (FDR = 0.03). These were almost the same results of comparison between PD DEP+/RBD- with the DEP-/RBD+, except for the right fornix, left cingulum, and left ILF (FDR = 0.006).

Finally, PD DEP+/RBD- patients showed decreased connectivity in the bilateral cingulum, bilateral fornix, bilateral ILF, left UF, right CST and genu, splenium, and body of CC compared to PD DEP-/RBD- (FDR = 0.02). **Table 3** summarizes the significant regions of lower connectivity in between-group analyses.

DISCUSSION

In this study, we investigated the neural underpinnings of RBD and depression as clinical PD prodromal markers with more severe outcome mainly of the motor and cognitive function. RBD not only predicts upcoming PD but also warns the development of non-tremor dominant motor subtype with a diversity of other NMS such as depression and dementia (49). Recent evidence has exposed the role of widespread white matter disruption underlying heterogenous symptoms of PD, including commissural, projection and long association fibers (33). Previous studies have mostly relied on diffusion tensor imaging (DTI), which has major limitations in detecting pathologies in areas of high crossing fibers such as near cortical structures. Using connectometry analysis, which successfully overcomes this pitfall (50), we were able to capture the novel contribution of U-fibers in PD. U-fibers are short association fibers which run between white matter and cortex and connect adjacent gyri and participate in higher functions of the brain. As these particular fibers have low metabolic rate and high blood supply, they are relatively spared in vascular disorders such as stroke. In contrast, pathologies with glial insult, such as multiple sclerosis, are shown to result in early involvement of U-fibers

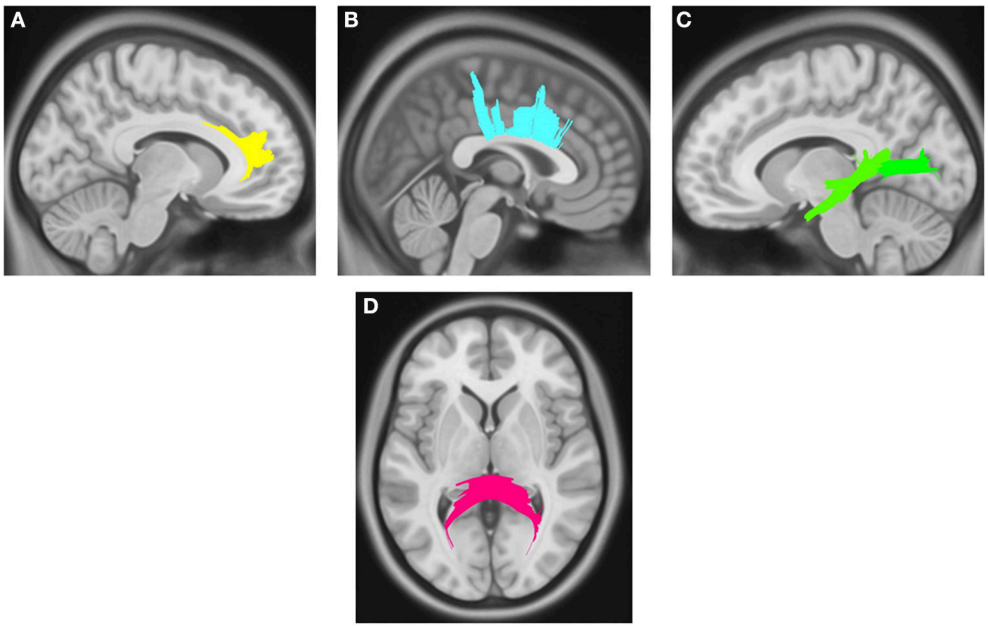

FIGURE 1 | White matter pathways with significantly reduced quantitative anisotropy in PD DEP+RBD+ vs. PD DEP-RBD+ (FDR = 0.03). **(A)** right cingulum, **(B)** body of the corpus callosum, **(C)** left inferior longitudinal fasciculus, **(D)** splenium. The results are overlaid on ICBM152 (mni_icbm152_t1) from the McConnell Brain Imaging Centre using DSI-STUDIO software.

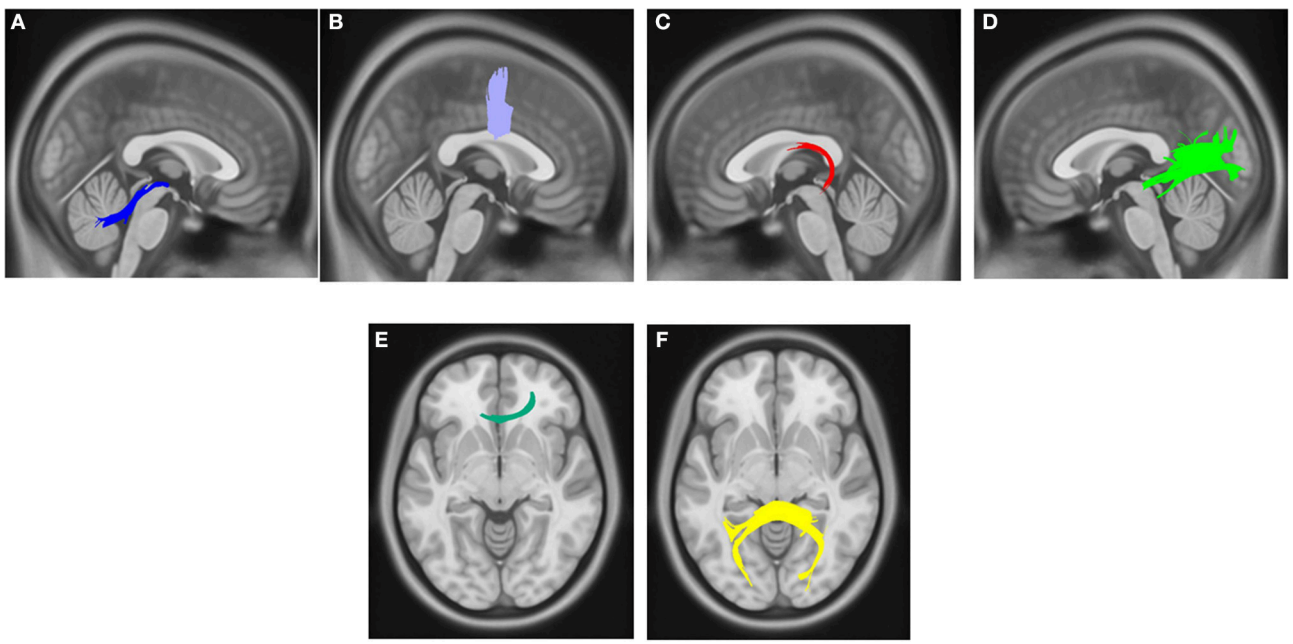

FIGURE 2 | White matter pathways with significantly reduced quantitative anisotropy in PD DEP+RBD+ vs. PD DEP+RBD- (FDR = 0.02). **(A)** right superior cerebellar peduncle, **(B)** body of the corpus callosum, **(C)** left fornix, **(D)** left inferior longitudinal fasciculus, **(E)** genu, **(F)** splenium. The results are overlaid on ICBM152 (mni_icbm152_t1) from the McConnell Brain Imaging Centre using DSI-STUDIO software.

and the subsequent cognitive malperformance in such patients (51). Glial dysfunction is one of the key events in initiation and progression of neurodegenerative processes as well (52–54). Therefore, it seems that U-fibers can be potentially affected in PD. This is a thought-provoking result that should be addressed in future research.

TABLE 3 | Regions with significantly different connectivity in between group comparing of PD patients with or without comorbid RBD and/or depression.

***PD DEP+/RBD+* vs. *PD DEP-/RBD–* (FDR = 0.01)**	***PD DEP+/RBD+* vs. *PD DEP–/RBD+* (FDR = 0.03)**	***PD DEP+/RBD+* vs. *PD DEP+/RBD–* (FDR = 0.02)**
R-SCP B-cingulum L-fornix L-ILF R-IFOF Genu, body and splenium of CC	R-Cingulum L-ILF Splenium and body of CC (previous study: Fornix, genu, L-MCP, R-CST, R-cing, L-ILF)	R-SCP L-ILF L-fornix Genu, body and splenium of CC
***PD DEP–/RBD+* vs. *PD DEP-/RBD–* (FDR = 0.03)**	***PD DEP+/RBD–* vs. PD *DEP-/RBD-* (FDR = 0.02)**	***PD DEP–/RBD+* vs. *PD DEP+/RBD–* (FDR = 0.006)**
B-SCP MCP B-cingulum B-fornix L-ILF Genu and body of CC R-UF L-CST	B-cingulum B-fornix B-ILF Genu, body and splenium of CC L-UF R-CST (Previous study: R-IFOF, MCP Genu, UF, L-ILF, R-CST, Fornix)	B-SCP MCP R-cingulum L-fornix Genu and body of CC L-external capsule L-CST

The left groups vs. the right groups showed lower quantitative anisotropy in the areas listed. B, bilateral; R, right; L, left; SCP, superior cerebellar peduncle; MCP, middle cerebellar peduncle; ILF, inferior longitudinal fasciculus; UF, uncinate fasciculus; CST, cerebrospinal tract; IFOF, inferior fronto-occipital fasciculus; CC, corpus callosum; FDR, false discovery rate.

Among other fibers with lower connectivity, like U-fibers, SLF also consistently differed between PD patients and HC regardless of the comorbid RBD or depression. Previous studies have specified the lower integrity of SLF associated with several domains of cognitive decline from mild cognitive impairment to dementia (55–58), and also in non-tremor motor phenotypes of PD such as freezing of gait (59, 60), bradykinesia (61), and postural instability (62), which have poor prognostic implications. SLF is a long association fiber that originates from posterior regions of the brain and projects to the frontal lobe. However, among few studies which have investigated DTI findings in relation to depression, lower FA in the left SLF near the midline and superior frontal lobe is reported in dPD versus ndPD in one whole brain study (63). The authors have discussed this finding through the cognitive aspect of depression. A meta-analysis has also implicated the disruption of SLF in major depressive disorder (MDD) (64). However, within-patients analysis of our cohort did not reveal any subgroup-differences in SLF, which would indirectly point toward to non-contribution of this tract with depression and RBD. This is in agreement with our previous studies on dPD (37, 38, 65).

ILF was only disrupted in the PD groups with comorbid depression compared to HC. ILF fast and directly integrates visual categorization and recognition data between extrastriate visual cortex and temporal gyri which subsequently project to the limbic structures (66). High-order visual problems such as visually evoked memory and emotional impairments are linked to ILF disruptions, as a key component of the visual-limbic pathway (67, 68). ILF is among the main fibers involved in the major depressive disorder, proved by the mentioned meta-analysis of whole brain voxel-based DTI studies (64). The same association was also demonstrated in dPD (63, 69) and mild cognitive impairment and dementia in PD (55, 58) based on whole brain tract-based spatial statistics studies. This finding may signal the higher risk of cognitive impairment in terms of executive and visuospatial dysfunction in dPD. ILF disruption most consistently observed in the left hemisphere is in agreement with the perception that depression is a result of left hemispheric dysfunction (70). Interestingly, it is revealed that right-onset PD predict more severe depressive symptoms in the course of the disease (71). These may explain our finding of ILF lateralization in comorbid depression in PD. Apart from ILF alterations in dPD, our results are also indicative of reduced connectivity in left ILF in DEP-/RBD+ compared to DEP-/RBD-, which is in line with the study by Ford et al. (72). However, few other studies comparing PD-RBD patients with PD-non-RBD have not reached to this association. May longitudinal follow-up of these patients reveal subsequent depressive symptoms followed by ILF disruption, should be investigated in well-designed cohorts.

Cingulate, the prominent limbic structure and the well-known structure of emotion and cognition activates during REM sleep (73). Cingulum injury has been shown in abnormalities in attention, memory and emotional processing (74). Existing literature is already enriched with cingulum associations in depression and its pathognomonic REM sleep dysregulations (75, 76) and also depression, apathy, impulse control deficit and dementia in PD (77–80). More severe lesions of this tract predispose to poorer treatment response in late-life depression (81) and is a stimulating target to treat resistant depression (82). This area is also attributed to comorbid RBD in PD patients recruited from PPMI database (83, 84). Overall, it is not surprising that disrupted cingulum bundle is correlated with depressive symptoms and RBD in PD patients.

CC with more than 200 million axonal projections, is the largest fiber bundle in the central nervous system, which actively transfers information between homologous areas of two cerebral hemispheres (85). This commissure has a major role in the regulation of cognitive and emotional function and bilateral limb movement (86). Extensive corpus callosal damage is described in early PD (87), which becomes more severe with motor worsening (88). Reduction of callosal integrity is implicated in the freezing of gait and postural instability in non-tremor dominant PD (89). This phenotype is more often accompanied by cognitive decline and mood disorders (33, 90). In line with these observations, diffusion MRI connectometry has revealed reduced integrity in CC in the neuropathology of comorbid RBD (84) and depression (65) in PD. Same association is shown regarding cognitive decline and its severity in PD (33).

The results of between PD subgroups evaluation showed that superior and middle cerebellar peduncles have lower connectivity consistently comparing PD patients with RBD compared to those without RBD. Cerebellum has heavy connections to the cerebral cortex via brainstem structures. Disruptions of this circuitry

and asynchronization of cerebral and cerebellar functions are related to sleep-wake state abnormalities (91, 92). As a result, cerebellar pathology is often present in sleep disorders (93), and its cortical volume reduction has been shown in RBD (83, 94), although the exact contributed pathways are yet to be elucidated. It is now well documented that sleep has a major role in memory consolidation (95). Cerebellar increased activity during sleep in order to integrate learned motor skills is well-documented (96), and gray matter reductions of the cerebellum have resulted in the impaired consolidation of action memories (97). The interconnected sleep and cerebellar cognitive and motor-related functions may point toward the more severe motor and cognitive impairments associated with PD-RBD (9). Metabolic imaging studies have interestingly proposed cerebellum as a PD prodromal biomarker, as a part of a metabolic network associated with the severe motor subtype of PD (98). Idiopathic RBD patients with altered cerebellar metabolism are also at higher risk of photoconverting to neurodegeneration (99). Our consistent results of significant altered white matter in cerebellar peduncles is in line with disturbed cortico-cerebellar connections in PD-RBD patients in contrast to PD patients without RBD. Another DWI connectometry analysis also has manifested middle cerebellar peduncle as a discriminative indicator between these two groups of patients recruited from PPMI (84). Recent neuroanatomical studies have shown the important role of the cerebellum in emotional regulation and high-order cognitive coordination through extensive networks with the cerebral cortex, limbic system and thalamus via superior and middle cerebellar peduncles (100–105). There is a tendency to lateralization in the cerebellum in processing cognition and affection. Lesions of the right cerebellum, in connection to the left cerebral cortex, result in cognitive dysfunctions and positive or approach related emotional disturbances (103, 106). A diffusional kurtosis study has found disrupted superior and middle cerebellar peduncles in related to depression, with a particular relationship between disease duration and right SCP (107). The right posterior cerebellar white matter was also associated with treatment resistance in depression in a voxel-based DTI study (105). Functional brain studies have shown the involvement of cerebellar abnormality in depressed PD and also severe PD (108, 109). While connectivity of superior and middle cerebellar peduncles was significantly lower in related to comorbid RBD without depression in this study, reduced connectivity is seen only in right SCP, the main output route from the cerebellum to the left prefrontal cortex, in depressed PD patients with comorbid RBD and there is no such association with depressed PD without concomitant RBD. This may be a result of a small number of patients or may point to the specific patterns of comorbidity of depression and RBD in PD. Future studies with a larger number of patients are needed to investigate the generalizability of these results.

Another white matter structure with consistently differed connectivity in between-patients' subgroups comparison was fornix. Fornix, a limbic structure, is the main output tract of the hippocampus to diencephalon and basal forebrain. This structure is an important component of both episodic memory and emotional circuits (110–112). Fornix degeneration is proposed as a strong predictor of upcoming cognitive impairment, as it precedes hippocampal atrophy (113). Comorbid mild cognitive impairment and late-life depression, a possible representation of neurodegenerative disorders, has been related to reduced FA in fornix (114). This result has also been linked to treatment-refractory major depressive disorder (115). In another DTI studies, higher mean diffusivity (MD) in fornix has been revealed in PD patients (116) and with association with short-term nonverbal memory impairment in these patients (117). Experimental studies on animal models have demonstrated that so-called hypocretin neurons in perifornical region regulate sleep/wake cycle (118, 119) and neuronal loss may cause increased REM sleep portion (120, 121) and sleep disorders such as narcolepsy (122, 123). Interestingly, hypocretin neurotransmission system is shown to be affected in a post-mortem study of PD patients (124). Anatomical disruptions are also reported in iRBD (125) and the generation of excessive daytime sleepiness in PD patients (126). Our previous studies and the current study are the first to directly attribute fornix to comorbid depression and RBD in early PD. Left fornix disruption, resulted in disconnection of the left or verbal sphere of the hippocampus may contribute to memory deficits for verbal stimuli, in contrast to visuospatial input processed in the right side (127). Although executive dysfunction is considered as the hallmark cognitive deficit in PD, it has been cleared that verbal memory impairment has the greatest impact of all cognitive domains in PD (128–132). Poor performance on verbal memory tasks is also shown to be associated with sleep problems such as RBD in PD patients (133). Unsurprisingly, depressive disorders are accompanied by impairment in verbal memory as well (134).

There are some discrepancies in results from the current study and our two previous studies (**Table 3**). In order to control for the effect of the motor and other non-motor symptoms, we attempted to include patients with matched scores on other tests in the current study. This resulted in overlap in our patient selection from PPMI cohort. Using a new version of DSI studio may have also imposed more precise outcomes. Not using gold-standard diagnostic assessments for RBD and depression, polysomnography and clinically approved depression using DSM criteria, may be a source of error that should be kept in mind in interpreting our results. Despite GDS and RBDSQ scores, PD patients had worse olfaction function compared to HC and this would have contributed to the observed connectivity differences in the first part of the analysis. Longitudinal studies on larger subgroups of PD patients will address the accuracy of these results and better specify the role of each tract disruption in emergence of comorbid symptoms in heterogenous PD. In other words, tracts with differed connectivity in only within PD patients' comparison, such as cerebellar peduncles which most consistently were attributed to PD-RBD, and fornix in dPD-RBD may serve as markers useful for PD subtyping, which would be helpful in establishing better prognostic evaluation and more individualized treatment strategies. Needless to mention that these are preliminary findings that should be approved by future research.

CONCLUSION

The results of this study support the entangled pathophysiology of depression and RBD which both predict poor outcomes regarding motor symptoms and cognitive decline in PD patients. As discussed above, specific commissural (CC), projection (CST, SCP, MCP) and long association fibers (cingulum, fornix, ILF, UF, IFOF) have been previously shown to serve as neural underpinnings of malignant subtypes of PD besides reputable associations with RBD and depression. So, disruption in these tracts may serve as an underlying pathology of REM sleep and mood dysregulations in early PD which also warn the emergence of debilitating motor and cognitive symptoms. A novel result of this study is the disruption of short association fibers (commonly known as U-fibers) in PD neurodegeneration that should be addressed in future research. A small number of patients in each group and not using gold standard tools to diagnose NMS in PPMI database should raise suspicion as multiple sources of error in this study. Shared neural substrates in RBD and depression in early PD is promising to discover high-risk individuals for future PD. Follow-up studies with larger number of patients will clear whether small regional diversities observed in between-patients-groups comparisons are linked to a specific pattern of RBD and depression in PD or may be justified by small sample sizes.

ETHICS STATEMENT

All procedures performed here, including human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

AUTHOR CONTRIBUTIONS

FG and MA contributed to the conception and design of the study; AA-G, HS, FG, and MA contributed to data collection and analysis; FG, YR, MMZ and MA contributed to writing and revising the manuscript.

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REFERENCES

1. Goedert M. Alpha-synuclein and neurodegenerative diseases. *Nat Rev Neurosci.* (2001) 2:492–501. doi: 10.1038/35081564
2. Berg D, Postuma RB, Bloem B, Chan P, Dubois B, Gasser T, et al. Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. *Mov Disord.* (2014) 29:454–62. doi: 10.1002/mds.25844
3. Postuma RB, Berg D. Advances in markers of prodromal Parkinson disease. *Nat Rev Neurol.* (2016) 12:622–34. doi: 10.1038/nrneurol.2016.152
4. Mahowald MW, Schenck CH. REM sleep parasomnias. In: Kryger MH, Roth T, Dement C, editors. *Principles and Practice of Sleep Medicine*, 3rd ed. Philadelphia, PA: W.B. Saunders (2000), p. 724–41.
5. Boeve BF, Silber MH, Ferman TJ, Lucas JA, Parisi JE. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. *Mov Disord.* (2001) 16:622–30. doi: 10.1002/mds.1120
6. Boeve BF, Silber M, Ferman TJ, Lin S, Benarroch E, Schmeichel A, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. *Sleep Med.* (2013) 14:754–62. doi: 10.1016/j.sleep.2012.10.015
7. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. *Mov Disord.* (2015) 30:1600–11. doi: 10.1002/mds.26431
8. Kim Y, Kim YE, Park EO, Shin CW, Kim HJ, Jeon B. REM sleep behavior disorder portends poor prognosis in Parkinson's disease: a systematic review. *J Clin Neurosci.* (2017) 47:6–13. doi: 10.1016/j.jocn.2017.09.019
9. Fereshtehnejad SM, Romenets SR, Anang JB, Latreille V, Gagnon JF, Postuma RB. New clinical subtypes of Parkinson disease and their longitudinal progression: a prospective cohort comparison with other phenotypes. *JAMA Neurol.* (2015) 72:863–73. doi: 10.1001/jamaneurol.2015.0703
10. Jin H, Zhang JR, Shen Y, Liu CF. Clinical significance of REM sleep behavior disorders and other non-motor symptoms of Parkinsonism. *Neurosci Bull.* (2017) 33:576–84. doi: 10.1007/s12264-017-0164-8
11. van Uem JM, Marinus J, Canning C, van Lummel R, Dodel R, Liepelt-Scarfone I, et al. Health-related quality of life in patients with Parkinson's disease—a systematic review based on the ICF model. *Neurosci Biobehav Rev.* (2016) 61:26–34. doi: 10.1016/j.neubiorev.2015.11.014
12. Aarsland D, Andersen K, Larsen J, Lolk A, Nielsen H, Kragh–Sørensen P. Risk of dementia in Parkinson's disease a community-based, prospective study. *Neurology* (2001) 56:730–6. doi: 10.1212/WNL.56.6.730
13. Postuma RB, Bertrand JA, Montplaisir J, Desjardins C, Vendette M, Rios Romenets S, et al. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. *Mov Disord.* (2012) 27:720–6. doi: 10.1002/mds.24939
14. Zhu K, van Hilten JJ, Marinus J. Predictors of dementia in Parkinson's disease; findings from a 5-year prospective study using the SCOPA-COG. *Parkinsonism Relat Disord.* (2014) 20:980–5. doi: 10.1016/j.parkreldis.2014.06.006
15. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders: a meta-analysis. *Arch Gen Psychiatry* (1992) 49:651–68.
16. Clark C, Dupont R, Golshan S, Gillin JC, Rapaport MH, Kelsoe JR. Preliminary evidence of an association between increased REM density and poor antidepressant response to partial sleep deprivation. *J Affect Disord.* (2000) 59:77–83. doi: 10.1016/S0165-0327(99)00135-4

17. Peterson MJ, Benca RM. Sleep in mood disorders. *Sleep Med Clin.* (2008) 3:231–49. doi: 10.1016/j.psc.2006.09.003
18. Murphy MJ, Peterson MJ. Sleep disturbances in depression. *Sleep Med Clin.* (2015) 10:17–23. doi: 10.1016/j.jsmc.2014.11.009
19. Giles DE, Roffwarg HP, Rush AJ. REM latency concordance in depressed family members. *Biol Psychiatry* (1987) 22:910–4.
20. Giles DE, Biggs MM, Rush AJ, Roffwarg HP. Risk factors in families of unipolar depression. I. psychiatric illness and reduced REM latency. *J Affect Disord.* (1988) 14:51–9.
21. Giles DE, Kupfer DJ, Roffwarg HP, Rush AJ, Biggs MM, Etzel BA. Polysomnographic parameters in first-degree relatives of unipolar probands. *Psychiatry Res.* (1989) 27:127–36.
22. Giles DE, Roffwarg HP, Rush AJ. A cross-sectional study of the effects of depression on REM latency. *Biol Psychiatry* (1990) 28:697–704.
23. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. *Neuropsychopharmacology* (2004) 29:1765. doi: 10.1038/sj.npp.1300506
24. Gottesmann C, Gottesman I. The neurobiological characteristics of rapid eye movement (REM) sleep are candidate endophenotypes of depression, schizophrenia, mental retardation and dementia. *Prog Neurobiol.* (2007) 81:237–50. doi: 10.1016/j.pneurobio.2007.01.004
25. Modell S, Lauer CJ. Rapid eye movement (REM) sleep: an endophenotype for depression. *Curr Psychiatry Rep.* (2007) 9:480–5. doi: 10.1007/s11920-007-0065-z
26. Borek LL, Kohn R, Friedman JH. Mood and sleep in Parkinson's disease. *J Clin Psychiatry* (2006) 67:958–63.
27. Rolinski M, Szewczyk-Krolikowski K, Tomlinson PR, Nithi K, Talbot K, Ben-Shlomo Y, et al. REM sleep behaviour disorder is associated with worse quality of life and other non-motor features in early Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2014) 85:560–6. doi: 10.1136/jnnp-2013-306104
28. Vilas D, Iranzo A, Pont-Sunyer C, Serradell M, Gaig C, Santamaria J, et al. Brainstem raphe and substantia nigra echogenicity in idiopathic REM sleep behavior disorder with comorbid depression. *J Neurol.* (2015) 262:1665–72. doi: 10.1007/s00415-015-7745-0
29. Wing YK, Lam SP, Zhang J, Leung E, Ho CL, Chen S, et al. Reduced striatal dopamine transmission in REM sleep behavior disorder comorbid with depression. *Neurology* (2015) 84:516–22. doi: 10.1212/WNL.0000000000001215
30. Fujishiro H, Okuda M, Iwamoto K, Miyata S, Otake H, Noda A, et al. REM sleep without atonia in middle-aged and older psychiatric patients and Lewy body disease: a case series. *Int J Geriatr Psychiatry* (2017) 32:397–406. doi: 10.1002/gps.4477
31. Wing YK, Li SX, Mok V, Lam SP, Tsoh J, Chan A, et al. Prospective outcome of rapid eye movement sleep behaviour disorder: psychiatric disorders as a potential early marker of Parkinson's disease. *J Neurol Neurosurg Psychiatr.* (2012) 83:470–2. doi: 10.1136/jnnp-2011-301232
32. Tsopelas C, Stewart R, Savva GM, Brayne C, Ince P, Thomas A, et al. Neuropathological correlates of late-life depression in older people. *Br J Psychiatry* (2011) 198:109–14. doi: 10.1192/bjp.bp.110.078816
33. Hall JM, Ehgoetz Martens KA, Walton CC, O'Callaghan C, Keller PE, Lewis SJ, et al. Diffusion alterations associated with Parkinson's disease symptomatology: A review of the literature. *Parkinsonism Relat. Disord.* (2016) 33:12–26. doi: 10.1016/j.parkreldis.2016.09.026
34. Lamberts JT, Hildebrandt EN, Brundin P. Spreading of α-synuclein in the face of axonal transport deficits in Parkinson's disease: a speculative synthesis. *Neurobiol Dis.* (2015) 77:276–83. doi: 10.1016/j.nbd.2014.07.002
35. Yeh FC, Badre D, Verstynen T. Connectometry: a statistical approach harnessing the analytical potential of the local connectome. *Neuroimage* (2016) 125:162–71. doi: 10.1016/j.neuroimage.2015.10.053
36. Yeh FC, Vettel JM, Singh A, Poczos B, Grafton ST, Erickson KI, et al. Quantifying differences and similarities in whole-brain white matter architecture using local connectome fingerprints. *PLoS Comput Biol.* (2016) 12:e1005203. doi: 10.1371/journal.pcbi.1005203
37. Ghazi Sherbaf F, Rahmani F, Jooyandeh SM, Aarabi MH. Microstructural changes in patients with Parkinson disease and REM sleep behavior disorder: depressive symptoms versus non-depressed. *Acta Neurol Belg.* (2018). doi: 10.1007/s13760-018-0896-x.. [Epub ahead of print].
38. Ansari M, Adib Moradi S, Ghazi Sherbaf F, Hedayatnia A, Aarabi M. Comparison of structural connectivity in Parkinson's disease with depressive symptoms versus non-depressed: a diffusion MRI connectometry study. *Int Psychogeriatr.* (2018) doi: 10.1017/S1041610218000170. [Epub ahead of print].
39. Marek K, Jennings D, Lasch S, Siderowf A, Tanner C, Simuni T, et al. The parkinson progression marker initiative (PPMI). *Prog Neurobiol.* (2011) 95:629–35. doi: 10.1016/j.pneurobio.2011.09.005
40. Zhang Y, Wu IW, Tosun D, Foster E, Schuff N. Progression of regional microstructural degeneration in Parkinson's disease: a multicenter diffusion tensor imaging study. *PLoS ONE* (2016) 11:e0165540. doi: 10.1371/journal.pone.0165540
41. Torbey E, Pachana NA, Dissanayaka NN. Depression rating scales in Parkinson's disease: A critical review updating recent literature. *J Affect Disord.* (2015) 184:216–24. doi: 10.1016/j.jad.2015.05.059
42. Stiasny-Kolster K, Mayer G, Schafer S, Moller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire–a new diagnostic instrument. *Mov Disord.* (2007) 22:2386–93. doi: 10.1002/mds.21740.
43. Mahajan A, Rosenthal LS, Gamaldo C, Salas RE, Pontone GM, McCoy A, et al. REM sleep behavior and motor findings in Parkinson's disease: a cross-sectional analysis. *Tremor Other Hyperkinet. Mov.* (2014) 4:245. doi: 10.7916/d84b2zdf
44. Leemans A, Jeurissen B, Sijbers J, Jones D. (2009). ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. In: *17th Annual Meeting of Intl Soc Mag Reson Med* (Hawaii), p. 3537.
45. Yeh FC, Tseng WY. NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. *Neuroimage* (2011) 58:91–9. doi: 10.1016/j.neuroimage.2011.06.021
46. Yeh FC, Tang PF, Tseng WYI. Diffusion MRI connectometry automatically reveals affected fiber pathways in individuals with chronic stroke. *Neuroimage Clin.* (2013) 2:912–21. doi: 10.1016/j.nicl.2013.06.014
47. Yeh FC, Tseng WYI. Sparse solution of fiber orientation distribution function by diffusion decomposition. *PLoS ONE* (2013) 8:e75747. doi: 10.1371/journal.pone.0075747
48. Yeh FC, Verstynen TD, Wang Y, Fernández-Miranda JC, Tseng WYI. Deterministic diffusion fiber tracking improved by quantitative anisotropy. *PLoS ONE* (2013) 8:e80713. doi: 10.1371/journal.pone.0080713
49. Slow EJ, Postuma RB, Lang AE. Implications of nocturnal symptoms towards the early diagnosis of Parkinson's disease. *J Neural Transm.* (2014) 121:49–57. doi: 10.1007/s00702-014-1168-4
50. Wedeen VJ, Wang R, Schmahmann JD, Benner T, Tseng W, Dai G, et al. Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. *Neuroimage* (2008) 41:1267–77. doi: 10.1016/j.neuroimage.2008.03.036
51. Reiser MF, Semmler W, Hricak H. editors. *Magnetic Resonance Tomography*. Springer Science & Business Media (2007).
52. Verkhratsky A, Parpura V, Pekna M, Pekny M, Sofroniew M. (2014). Glia in the pathogenesis of neurodegenerative diseases. *Biochem Soc Trans*. (2014) 42:1291–301. doi: 10.1042/BST20140107
53. Brück D, Wenning GK, Stefanova N, Fellner L. Glia and alpha-synuclein in neurodegeneration: a complex interaction. *Neurobiol Dis.* (2016) 85:262–74. doi: 10.1016/j.nbd.2015.03.003
54. Liu B, Jau-Shyong H. Roles of microglia in inflammation-mediated neurodegeneration: models, mechanisms, and therapeutic interventions for Parkinson's disease. *J Pharmacol Exp Therapeut*. (2003) 304:1–7. doi: 10.1124/jpet.102.035048
55. Hattori T, Orimo S, Aoki S, Ito K, Abe O, Amano A, et al. Cognitive status correlates with white matter alteration in Parkinson's disease. *Hum Brain Mapp.* (2012) 33:727–39. doi: 10.1002/hbm.21245
56. Melzer TR, Watts R, MacAskill MR, Pitcher TL, Livingston L, Keenan RJ, et al. White matter microstructure deteriorates across cognitive stages in Parkinson disease. *Neurology* (2013) 80:1841–9. doi: 10.1212/WNL.0b013e3182929f62
57. Koshimori Y, Segura B, Christopher L, Lobaugh N, Duff-Canning S, Mizrahi R, et al. Imaging changes associated with cognitive abnormalities in Parkinson's disease. *Brain Struct Funct.* (2015) 220:2249–61. doi: 10.1007/s00429-014-0785-x

58. Duncan GW, Firbank MJ, Yarnall AJ, Khoo TK, Brooks DJ, Barker RA, et al. Gray and white matter imaging: A biomarker for cognitive impairment in early Parkinson's disease? *Mov Disord.* (2016) 31:103–10. doi: 10.1002/mds.26312
59. Canu E, Agosta F, Sarasso E, Volontè MA, Basaia S, Stojkovic T, et al. Brain structural and functional connectivity in Parkinson's disease with freezing of gait. *Hum Brain Mapp.* (2015) 36:5064–78. doi: 10.1002/hbm.22994
60. Vercruysse S, Leunissen I, Vervoort G, Vandenberghe W, Swinnen S, Nieuwboer A. Microstructural changes in white matter associated with freezing of gait in Parkinson's disease. *Mov Disord.* (2015) 30:567–76. doi: 10.1002/mds.26130
61. Lee E, Lee JE, Yoo K, Hong JY., Oh J, Sunwoo MK, et al. Neural correlates of progressive reduction of bradykinesia in de novo Parkinson's disease. *Parkinsonism Relat Disord.* (2014) 20:1376–81. doi: 10.1016/j.parkreldis.2014.09.027
62. Gu Q, Huang P, Xuan M, Xu X, Li D, Sun J, et al. Greater loss of white matter integrity in postural instability and gait difficulty subtype of Parkinson's disease. *Can J Neurol Sci.* (2014) 41:763–8. doi: 10.1017/cjn.2014.34
63. Huang P, Xu X, Gu Q, Xuan M, Yu X, Luo W, et al. Disrupted white matter integrity in depressed versus non-depressed Parkinson's disease patients: a tract-based spatial statistics study. *J Neurol Sci.* (2014) 346:145–8. doi: 10.1016/j.jns.2014.08.011
64. Liao Y, Huang X, Wu Q, Yang C, Kuang W, Du M, et al. Is depression a disconnection syndrome? Meta-analysis of diffusion tensor imaging studies in patients with MDD. *J Psychiatry Neurosci.* (2013) 38:49–56. doi: 10.1503/jpn.110180
65. Ghazi Sherbaf F, Same K, Aarabi MH. High angular resolution diffusion imaging correlates of depression in Parkinson's disease: a connectometry study. *Acta Neurol Belg.* (2018) doi: 10.1007/s13760-018-0937-5. [Epub ahead of print].
66. Catani M, Jones DK, Donato R, Ffytche DH. Occipito-temporal connections in the human brain. *Brain* (2003) 126:2093–107. doi: 10.1093/brain/awg203
67. Ross ED. Sensory-specific and fractional disorders of recent memory in man: I. isolated loss of visual recent memory. *Arch Neurol.* (1980) 37:193–200. doi: 10.1001/archneur.1980.00500530031001
68. Bauer RM. Visual hypoemotionality as a symptom of visual-limbic disconnection in man. *Arch Neurol.* (1982) 39:702–8. doi: 10.1001/archneur.1982.00510230028009
69. Wu JY, Zhang Y, Wu WB, Hu G, Xu Y. Impaired long contact white matter fibers integrity is related to depression in Parkinson's disease. *CNS Neurosci Ther* (2017) 24:108–14. doi: 10.1111/cns.12778
70. Hama S, Yamashita H, Shigenobu M, Watanabe A, Kurisu K, Yamawaki S, et al. Post-stroke affective or apathetic depression and lesion location: left frontal lobe and bilateral basal ganglia. *Eur Arch Psychiatry Clin Neurosci.* (2007) 257:149–52. doi: 10.1007/s00406-006-0698-7
71. Foster PS, Drago V, Crucian GP, Sullivan WK, Rhodes RD, Shenal BV, et al. Anxiety and depression severity are related to right but not left onset Parkinson's disease duration. *J Neurol Sci.* (2011) 305:131–5. doi: 10.1016/j.jns.2011.02.023
72. Ford AH, Duncan GW, Firbank MJ, Yarnall AJ, Khoo TK, Burn DJ, et al. Rapid eye movement sleep behavior disorder in Parkinson's disease: magnetic resonance imaging study. *Mov Disord.* (2013) 28:832–6. doi: 10.1002/mds.25367
73. Nofzinger EA, Mintun MA, Wiseman M, Kupfer DJ, Moore RY. Forebrain activation in REM sleep: an FDG PET study. *Brain Res.* (1997) 770:192–201. doi: 10.1016/S0006-8993(97)00807-X
74. Vogt BA, Laureys S. Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. *Prog Brain Res.* (2005) 150:205–17. doi: 10.1016/S0079-6123(05)50015-3
75. Ebert D, Ebmeier KP. The role of the cingulate gyrus in depression: from functional anatomy to neurochemistry. *Biol Psychiatry* (1996) 39:1044–50. doi: 10.1016/0006-3223(95)00320-7
76. Scherfler C, Frauscher B, Schocke M, Iranzo A, Gschliesser V, Seppi K, et al. White and gray matter abnormalities in idiopathic rapid eye movement sleep behavior disorder: a diffusion-tensor imaging and voxel-based morphometry study. *Ann Neurol.* (2011) 69:400–7. doi: 10.1002/ana.22245
77. Zgaljardic DJ, Borod JC, Foldi NS, Mattis P. A review of the cognitive and behavioral sequelae of Parkinson's disease: relationship to frontostriatal circuitry. *Cogn Behav Neurol.* (2003) 16:193–210. doi: 10.1097/00146965-200312000-00001
78. Matsui H, Nishinaka K, Oda M, Niikawa H, Komatsu K, Kubori T, et al. Depression in Parkinson's disease. *J Neurol.* (2007) 254:1170–3. doi: 10.1007/s00415-006-0236-6
79. Kostić VS, Filippi M. Neuroanatomical correlates of depression and apathy in Parkinson's disease: magnetic resonance imaging studies. *J Neurol Sci.* (2011) 310:61–3. doi: 10.1016/j.jns.2011.05.036
80. Wen MC, Chan L, Tan L, Tan E. Depression, anxiety, and apathy in Parkinson's disease: insights from neuroimaging studies. *Eur J Neurol.* (2016) 23:1001–19. doi: 10.1111/ene.13002
81. Taylor WD, Kudra K, Zhao Z, Steffens DC, MacFall JR. Cingulum bundle white matter lesions influence antidepressant response in late-life depression: a pilot study. *J Affect Disord.* (2014) 162:8–11. doi: 10.1016/j.jad.2014.03.031
82. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biol Psychiatry* (2012) 72:595–603. doi: 10.1016/j.biopsych.2012.04.028
83. Boucetta S, Salimi A, Dadar M, Jones BE, Collins DL, Dang-Vu TT. Structural brain alterations associated with rapid eye movement sleep behavior disorder in Parkinson's disease. *Sci Rep.* (2016) 6:srep26782. doi: 10.1038/srep26782
84. Ansari M, Rahmani F, Dolatshahi M, Pooyan A, Aarabi MH. Brain pathway differences between Parkinson's disease patients with and without REM sleep behavior disorder. *Sleep Breath.* (2017) 21:155–61. doi: 10.1007/s11325-016-1435-8
85. Funnell MG, Corballis PM, Gazzaniga MS. Insights into the functional specificity of the human corpus callosum. *Brain* (2000) 123:920–6. doi: 10.1093/brain/123.5.920
86. Bloom JS, Hynd GW. The role of the corpus callosum in interhemispheric transfer of information: excitation or inhibition? *Neuropsychol Rev.* (2005) 15:59–71. doi: 10.1007/s11065-005-6252-y
87. Li XR, Ren YD, Cao B, Huang XL. Analysis of white matter characteristics with tract-based spatial statistics according to diffusion tensor imaging in early Parkinson's disease. *Neurosci Lett.* (2017) 675:127–32. doi: 10.1016/j.neulet.2017.11.064
88. Galantucci S, Agosta F, Stankovic I, Petrovic I, Stojkovic T, Kostic V, et al. Corpus callosum damage and motor function in Parkinson's disease", in: European Journal of Neurology: WILEY-BLACKWELL 111 RIVER ST, HOBOKEN 07030-5774, NJ *USA)*, 120–120. (2014).
89. Chan LL, Ng KM, Rumpel H, Fook-Chong S, Li HH, Tan EK. Transcallosal diffusion tensor abnormalities in predominant gait disorder parkinsonism. *Parkinsonism Relat Disord.* (2014) 20:53–9. doi: 10.1016/j.parkreldis.2013.09.017
90. Lewis S, Foltynie T, Blackwell A, Robbins T, Owen A, Barker R. Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. *J Neurol Neurosurg Psychiatry* (2005) 76:343–8. doi: 10.1136/jnnp.2003.033530
91. Andre P, Arrighi P. Hipnic modulation of cerebellar information processing: implications for the cerebro-cerebellar dialogue. *Cerebellum* (2003) 2:84–95. doi: 10.1080/14734220309403
92. Popa D, Spolidoro M, Proville RD, Guyon N, Belliveau L, Léna C. Functional role of the cerebellum in gamma-band synchronization of the sensory and motor cortices. *J Neurosci.* (2013) 33:6552–6. doi: 10.1523/JNEUROSCI.5521-12.2013
93. Canto CB, Onuki Y, Bruinsma B, van der Werf YD, De Zeeuw CI. The Sleeping Cerebellum. *Trends Neurosci.* (2017) 40:309–23. doi: 10.1016/j.tins.2017.03.001
94. Hanyu H, Inoue Y, Sakurai H, Kanetaka H, Nakamura M, Miyamoto T, et al. Voxel-based magnetic resonance imaging study of structural brain changes in patients with idiopathic REM sleep behavior disorder. *Parkinsonism Relat Disord.* (2012) 18:136–9. doi: 10.1016/j.parkreldis.2011.08.023
95. Diekelmann S. Sleep for cognitive enhancement. *Front Syst Neurosci.* (2014) 8:46. doi: 10.3389/fnsys.2014.00046
96. Cousins JN, El-Deredy W, Parkes LM, Hennies N, Lewis PA. Cued reactivation of motor learning during sleep leads to overnight changes in functional brain activity and connectivity. *PLoS Biol.* (2016) 14:e1002451. doi: 10.1371/journal.pbio.1002451

97. Fogel S, Vien C, Karni A, Benali H, Carrier J, Doyon J. Sleep spindles: a physiological marker of age-related changes in gray matter in brain regions supporting motor skill memory consolidation. *Neurobiol Aging* (2017) 49:154–64. doi: 10.1016/j.neurobiolaging.2016.10.009
98. Heller J, Brcina N, Dogan I, Holtbernd F, Romanzetti S, Schulz JB, et al. Brain imaging findings in idiopathic REM sleep behavior disorder (RBD)–a systematic review on potential biomarkers for neurodegeneration. *Sleep Med Rev*. (2017) 34:23–33. doi: 10.1016/j.smrv.2016.06.006
99. Holtbernd F, Gagnon JF, Postuma RB, Ma Y, Tang CC, Feigin A, et al. Abnormal metabolic network activity in REM sleep behavior disorder. *Neurology* (2014) 82:620–7. doi: 10.1212/WNL.0000000000000130
100. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. *Brain* (1998) 121:561–79. doi: 10.1093/brain/121.4.561
101. Lekeu F, Marczewski P, Van der Linden M, Collette F, Degueldre C, Del Fiore G, et al. Effects of incidental and intentional feature binding on recognition: a behavioural and PET activation study. *Neuropsychologia* (2002) 40:131–44. doi: 10.1016/S0028-3932(01)00088-4
102. Smith KA, Ploghaus A, Cowen PJ, McCleery JM, Goodwin, GM, Smith S, et al. Cerebellar responses during anticipation of noxious stimuli in subjects recovered from depression. *Br J Psychiatry* (2002) 181:411–5. doi: 10.1192/bjp.181.5.411
103. Baillieux H, De Smet HJ, Dobbeleir A, Paquier PF, De Deyn PP, Mariën P. Cognitive and affective disturbances following focal cerebellar damage in adults: a neuropsychological and SPECT study. *Cortex* (2010) 46:869–79. doi: 10.1016/j.cortex.2009.09.002
104. Doron KW, Funk CM, Glickstein M. Fronto-cerebellar circuits and eye movement control: a diffusion imaging tractography study of human cortico-pontine projections. *Brain Res.* (2010) 1307:63–71. doi: 10.1016/j.brainres.2009.10.029
105. Peng HJ, Zheng HR, Ning YP, Zhang Y, Shan BC, Zhang L, et al. Abnormalities of cortical-limbic-cerebellar white matter networks may contribute to treatment-resistant depression: a diffusion tensor imaging study. *BMC Psychiatry* (2013) 13:72. doi: 10.1186/1471-244X-13-72
106. Lee GP, Meador KJ, Loring DW, Allison JD, Brown WS, Paul LK, et al. Neural substrates of emotion as revealed by functional magnetic resonance imaging. *Cogn Behav Neurol.* (2004) 17:9–17. doi: 10.1097/00146965-200403000-00002
107. Zhao L, Wang Y, Jia Y, Zhong S, Sun Y, Zhou Z, et al. Cerebellar microstructural abnormalities in bipolar depression and unipolar depression: a diffusion kurtosis and perfusion imaging study. *J Affect Disord*. (2016) 195:21–31. doi: 10.1016/j.jad.2016.01.042
108. Skidmore F, Yang M, Baxter L, Von Deneen K, Collingwood J, He G, et al. Apathy, depression, and motor symptoms have distinct and separable resting activity patterns in idiopathic Parkinson disease. *Neuroimage* (2013) 81:484–95. doi: 10.1016/j.neuroimage.2011.07.012
109. Wen X, Wu X, Liu J, Li K, Yao L. Abnormal baseline brain activity in non-depressed Parkinson's disease and depressed Parkinson's disease: a resting-state functional magnetic resonance imaging study. *PLoS ONE* (2013) 8:e63691. doi: 10.1371/journal.pone.0063691
110. Lee DY, Fletcher E, Carmichael OT, Singh B, Mungas D, Reed B, et al. Sub-regional hippocampal injury is associated with fornix degeneration in Alzheimer's disease. *Front Aging Neurosci.* (2012) 4:1. doi: 10.3389/fnagi.2012.00001
111. Hescham S, Lim LW, Jahanshahi A, Steinbusch HW, Prickaerts J, Blokland A, et al. Deep brain stimulation of the forniceal area enhances memory functions in experimental dementia: the role of stimulation parameters. *Brain Stimul.* (2013) 6:72–7. doi: 10.1016/j.brs.2012.01.008
112. Douet V, Chang L. Fornix as an imaging marker for episodic memory deficits in healthy aging and in various neurological disorders. *Front Aging Neurosci.* (2015) 6:343. doi: 10.3389/fnagi.2014.00343
113. Fletcher E, Raman M, Huebner P, Liu A, Mungas D, Carmichael O, et al. Loss of fornix white matter volume as a predictor of cognitive impairment in cognitively normal elderly individuals. *JAMA Neurol.* (2013) 70:1389–95. doi: 10.1001/jamaneurol.2013.3263
114. Duffy SL, Paradise M, Hickie IB, Lewis SJ, Naismith SL, Lagopoulos J. Cognitive impairment with and without depression history: an analysis of white matter microstructure. *J Psychiatry Neurosci.* (2014) 39:135–43. doi: 10.1503/jpn.130079
115. Hoogenboom WS, Perlis RH, Smoller JW, Zeng-Treitler Q, Gainer VS, Murphy SN, et al. Limbic system white matter microstructure and long-term treatment outcome in major depressive disorder: a diffusion tensor imaging study using legacy data. *World J Biol Psychiatry* (2014) 15:122–34. doi: 10.3109/15622975.2012.669499
116. Kim HJ, Kim SJ, Kim HS, Choi CG, Kim N, Han S, et al. Alterations of mean diffusivity in brain white matter and deep gray matter in Parkinson's disease. *Neurosci Lett* (2013) 550:64–8. doi: 10.1016/j.neulet.2013.06.050
117. Zheng Z, Shemmassian S, Wijekoon C, Kim W, Bookheimer SY, Pouratian N. DTI correlates of distinct cognitive impairments in Parkinson's disease. *Hum Brain Mapp*. (2014) 35:1325–33. doi: 10.1002/hbm.22256
118. Koyama Y, Takahashi K, Kodama T, Kayama, Y. State-dependent activity of neurons in the perifornical hypothalamic area during sleep and waking. *Neuroscience* (2003) 119:1209–19. doi: 10.1016/S0306-4522(03)00173-8
119. Lu JW, Fenik VB, Branconi JL, Mann GL, Rukhadze I, Kubin L. Disinhibition of perifornical hypothalamic neurones activates noradrenergic neurones and blocks pontine carbachol-induced REM sleep-like episodes in rats. *J Physiol.* (2007) 582:553–67. doi: 10.1113/jphysiol.2007.127613
120. Gerashchenko D, Murillo-Rodriguez E, Lin L, Xu M, Hallett L, Nishino S, et al. Relationship between CSF hypocretin levels and hypocretin neuronal loss. *Exp Neurol*. (2003). 184:1010–6. doi: 10.1016/S0014-4886(03)00388-1
121. Chen L, Thakkar MM, Winston S, Bolortuya Y, Basheer R, McCarley RW. REM sleep changes in rats induced by siRNA-mediated orexin knockdown. *Eur J Neurosci.* (2006) 24:2039–48. doi: 10.1111/j.1460-9568.2006.05058.x
122. Peyron C, Faraco J, Rogers W, Ripley, B, Overeem, S, Charnay, Y, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med*. (2000) 6:991–7. doi: 10.1038/79690
123. Kiyashchenko LI, Mileykovskiy BY, Maidment N, Lam HA, Wu MF, John J, et al. Release of hypocretin (orexin) during waking and sleep states. *J Neurosci.* (2002) 22:5282–6. doi: 10.1523/JNEUROSCI.22-13-05282.2002
124. Fronczek R, Overeem S, Lee SY, Hegeman IM, Van Pelt J, Van Duinen SG, et al. Hypocretin (orexin) loss in Parkinson's disease. *Brain* (2002) 130:1577–85. doi: 10.1093/brain/awm090
125. Unger MM, Belke M, Menzler K, Heverhagen JT, Keil B, Stiasny-Kolster K, et al. Diffusion tensor imaging in idiopathic REM sleep behavior disorder reveals microstructural changes in the brainstem, substantia nigra, olfactory region, and other brain regions. *Sleep* (2010) 33:767–73. doi: 10.1093/sleep/33.6.767
126. Matsui H, Nishinaka K, Oda M, Niikawa H, Komatsu K, Kubori T, et al. Disruptions of the fornix fiber in Parkinsonian patients with excessive daytime sleepiness. *Parkinsonism Relat Disord*. (2006) 12:319–22. doi: 10.1016/j.parkreldis.2006.01.007
127. Cruz-Gómez Á, Belenguer-Benavides A, Martinez-Bronchal B, Fittipaldi-Márquez M, Forn C. Structural and functional changes of the hippocampus in patients with multiple sclerosis and their relationship with memory processes. *Rev Neurol*. (2016) 62:6–12. doi: 10.1148/radiol.10091433
128. Bohlhalter S, Abela E, Weniger D, Weder B. Impaired verbal memory in Parkinson disease: relationship to prefrontal dysfunction and somatosensory discrimination. *Behav Brain Funct.* (2009) 5:49. doi: 10.1186/1744-9081-5-49
129. Beyer MK, Bronnick KS, Hwang KS, Bergsland N, Tysnes OB, Larsen JP, et al. Verbal memory is associated with structural hippocampal changes in newly diagnosed Parkinson9s disease. *J Neurol Neurosurg Psychiatr*. (2013) 84:23–8. doi: 10.1136/jnnp-2012-303054
130. Segura B, Ibarretxe-Bilbao N, Sala-Llonch R, Baggio HC, Martí MJ, Valldeoriola F, et al. Progressive changes in a recognition memory network in Parkinson's disease. *J Neurol Neurosurg Psychiatr*. (2013) 84:370–8. doi: 10.1136/jnnp-2012-302822
131. Chiaravalloti ND, Ibarretxe-Bilbao N, DeLuca J, Rusu O, Pena J, García-Gorostiaga I, et al. The source of the memory impairment in Parkinson's disease: acquisition versus retrieval. *Mov Disord.* (2014) 29:765–71. doi: 10.1002/mds.25842

132. Lucas-Jiménez O, Díez-Cirarda M, Ojeda N, Pe-a J, Cabrera-Zubizarreta A, Ibarretxe-Bilbao N. Verbal memory in parkinson's disease: a combined DTI and fMRI study. *J Parkinsons Dis.* (2015) 5:793–804. doi: 10.3233/JPD-150623
133. Pushpanathan ME, Loftus AM, Thomas MG, Gasson N, Bucks, RS. The relationship between sleep and cognition in Parkinson's disease: a meta-analysis. *Sleep Med Rev*. (2016) 26:21–32. doi: 10.1016/j.smrv.2015.04.003
134. Sankar A, Adams TM, Costafreda SG, Marangell LB, Fu CH. Effects of antidepressant therapy on neural components of verbal working memory in depression. *J Psychopharmacol.* (2017) 31:1176–83. doi: 10.1177/0269881117724594

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REVIEW
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Restless Legs Syndrome and Parkinson Disease: A Causal Relationship Between the Two Disorders?

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Restless Legs Syndrome/Willis-Ekbom Disease (RLS/WED) is a common sleep related movement disorder that can be idiopathic or occurs in comorbidity with other medical conditions such as polyneuropathy, iron deficiency anemia, multiple sclerosis, hypertension and cardiovascular diseases. In recent years, a growing body of literature investigated the association between RLS/WED and Parkinson's Disease (PD). Several questions regarding the comorbidity between these two disorders are still unanswered. If the insurgence of RLS/WED may precede the onset of PD, or if RLS/WED could represent a secondary condition of PD and if impaired dopaminergic pathway may represent a bridge between these two conditions are still debatable issues. In this review, we critically discuss the relationship between RLS/WED and PD by reviewing cross sectional and longitudinal studies, as well as the role of dopamine in these disorders. A twofold interpretation have to be taken into account: dopaminergic therapy may have a crucial role in the development of RLS/WED in PD patients or RLS/WED can be conceived as an early manifestation of PD rather than a risk factor. Several studies showed a high prevalence of RLS/WED in PD patients and several findings related to dopaminergic and iron alterations in both disorders, however up to now it is difficult to find a point of agreement between studies. A greater number of systematic and strongly controlled longitudinal studies as well as basic pathophysiological investigations particularly in RLS/WED are needed to clarify this complex relationship.

Keywords: RLS/WED, PD, dopamine, iron, dopamine agonists

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INTRODUCTION

Restless Legs Syndrome/Willis-Ekbom Disease (RLS/WED) is a common sleep related movement disorder characterized by an urge to move the limbs frequently accompanied by uncomfortable and unpleasant sensations that are difficult to describe. Patients define their symptoms as burning, twitching, or pain in their lower limbs. However, in the most severe cases the symptomatology can be perceived also in the upper limbs (1). Onset of symptoms is frequent during period of rest or inactivity and an exacerbation of unpleasant sensations is reported in those situations where immobility is forced such as driving, flying long distance, watching movies in theater, and attending business meetings. Movement and motor activity typically relieved symptoms and patients may employ different strategies

to alleviate the discomfort (2). RLS/WED has a clear circadian trend with a peak in the evening or at the night that can severely compromise nocturnal sleep quality and quantity. In accordance, patients commonly report insomnia symptoms characterized by difficulty to fall asleep or/and frequent nocturnal awakenings that disrupt sleep continuity. Therefore, daytime consequences such as irritability, fatigue, drowsiness, and cognitive impairments are usually reported (3). Remarkably, despite sleep macrostructure and microstructure is significantly altered by the presence of Periodic Limb Movements (PLM) sleepiness is not universally reported by these patients (4). In accordance, it has been argued that RLS/WED subjects may display a daytime hyperarousal state useful to compensate the negative effects of nocturnal impairments (5).

By employing minimal diagnostic criteria of the international restless legs syndrome study group (IRLSSG) the prevalence of this disorder has been estimated between 3.9% and 14.3% with women more affected than men and an increase with age (6). Notably, RLS/WED seems to have different prevalence linked to geographic areas: highest in European populations (5% to 12%), intermediate in Asian countries (1% to 8%), and lowest in African countries (<1%) (7).

RLS/WED is typically a chronic condition and requires a treatment in the long term. Different drugs have shown a good efficacy. In particular, dopamine agonists are effective in reducing patients' symptomatology and are considered first line treatment whereas Alpha-2-delta agonists are recognized as a valid alternative (8). However, after an initial amelioration, worsening, and re-emergence of symptoms are frequently reported. A well known iatrogenic side effect caused mostly by dopaminergic compounds is augmentation that can be defined as a worsening of symptomatology characterized by earlier onset of symptoms, shorter latency to symptom occurrence at rest, and spreading to other parts of the body. In this case the medication should be suspended or changed with an agent with minor probability of augmentation (9).

RLS/WED can be idiopathic but can also occur in comorbidity with other medical conditions. Genetic risk factors seem to be particularly related to the primary form of the disease, underlined by a high familiarity and the identification of some risk loci (10). Secondary form is described in several studies reporting its relationship with polyneuropathy (11), iron deficiency anemia (12), multiple sclerosis (13), hypertension, and cardiovascular diseases (14). However, in recent years a growing body of literature investigated the association between RLS/WED and Parkinson's Disease (PD). Several questions regarding the comorbidity between these two disorders are still unanswered. If the insurgence of RLS/WED may precede the onset of PD, or if RLS/WED could represent a secondary condition of PD and if impaired dopaminergic pathway may represent a bridge between these two conditions (15) are still debated topics. Jagota et al. (16) suggested that RLS/WED and PD may have similar impaired groups of neurons but a different pathophysiology. They argued that both types of patients respond to different therapies, except for the dopaminergic one. For example RLS/WED symptomatology improve with opioids and anticonvulsants while PD symptomatology has a good response to anticholinergic therapy. Thus, they supported the idea of an involvement of systems diverse than the dopaminergic one.

The aim of this paper is to critically discuss the relationship between RLS/WED and PD by reviewing cross-sectional and longitudinal studies, as well the role of dopamine in these disorders.

CROSS-SECTIONAL STUDIES

The literature regarding the prevalence of RLS/WED in PD patients presents conflictual findings leading to an open debate regarding this issue. Cross-sectional studies show a variable prevalence of RLS/WED in PD patients ranging approximately from 0 to 50% (**Table 1**). The evaluation of the prevalence of RLS/WED in PD patients can be useful to improve the knowledge of the relationship between these two diseases. RLS/WED and PD respond to dopaminergic therapy (8, 51, 52): this evidence suggest that the dopaminergic system may play a crucial role in both disorders. However, not all cross-sectional studies support this hypothesis (16, 20, 26, 27, 34, 36, 37, 45). The main hypotheses addressed by cross-sectional studies reported in this review are the following: (1) two diseases may share the same pathophysiological mechanism, (2) RLS/WED in PD has a different pathophysiology from the idiopathic RLS/WED (iRLS/WED) and (3) these two diseases are different entities (**Figure 1**).

Several studies supported the hypothesis that RLS/WED and PD may share a common neuropathology (17, 19, 21, 23–25, 32, 34, 38–42, 45, 46). Some surveys reported an increased RLS/WED prevalence in PD patients suggesting a possible relationship between the two disorders, but without supporting any specific pathophysiological bridge (19, 21). For example, Kumar et al. (19) investigated sleep disorders in PD. They found that RLS/WED had a significant higher occurrence in PD patients (14.9%) than in controls (1%). Krishann et al. (21) performed a case-control study showing that RLS/WED prevalence was higher in PD patients (7.9%) than in healthy controls (HC) (0.8%), but the authors did not provide a specific pathophysiological hypothesis. Notably, Nomura et al. (24) found that RLS/WED was more frequent in PD Japanese patients than in Japanese HC, emphasizing an etiological link between RLS/WED and PD beyond the ethnic differences.

Only few studies investigated PD occurrence in a RLS/WED sample. Gao et al. (53) assessed weather RLS/WED can be a preclinical marker of PD by using the Health Professional Follow-up study which evaluated a large sample of men (51,529 males). They employed a sample of RLS/WED patients assessed in according the IRLSSG criteria (22). By considering for analyses only patients who had symptoms at least 5–14 times per month. Among 944 RLS/WED patients 13 also presented PD, while among 22,175 without RLS/WED patients 132 exhibited PD. Thus, the frequency of PD was higher in RLS/WED patients. Furthermore the authors found that patients with more severe RLS/WED symptoms showed higher prevalence of PD. These results were consistent with those of Walters et al. (54), who found that 4.7% of their RLS/WED sample showed also PD

TABLE 1 | Cross-sectional study assessing the prevalence of RLS/WED in PD patients and general population.

Article	Sample country	% RLS/WED in PD patients (n°)	% RLS/WED in controls (n°)	RLS/WED criteria
(17)	USA	20.8 (63 out of 303)	N.A	IRLSSG diagnostic criteria of RLS/WED (1995) (18)
(19)	India	14.9 (21 out of 149)	1 (1 out of 115)	RLS/WED was referred to by a question
(20)	Singapore	0 (0 out of 125)	N.A	IRLSSG diagnostic criteria of RLS/WED (1995) (18)
(21)	India	7.9 (10 out of 126)	0.8 (1 out of 128)	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(23)	Brazil	52.3 (45 out of 86)	N.A	Irresistible desire to move the legs, particularly at night, aggravated by rest and ameliorated after movement.
(24)	Japan	12 (20 out of 165)	2.3 (3 out of 131)	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(25)	Spain	21.9 (25 out of 114)	N.A	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(26)	Singapore	3 (3 out of 200)	0.5 (1 out of 200)	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(27)	Italy	3.3 (4 out of 118)	2.7 (3 out of 110)	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(28)	Korea	16.3 (73 out of 447)	N.A	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(29)	France	0 (0 out of 11)	N.A	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(30)	Austria	24 (28 out of 113)	N.A	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(31)	Brazil	50 (8 out of 16)	0 (0 out of 12)	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(32)	Brazil	18.75 (9 out of 48)	N.A	IRLSSG diagnostic criteria of RLS/WED (1995) (18)
(34)	Netherlands	11 (29 out of 269)	N.A	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(16)	Thailand	1.6 (3 out of 183)	N.A	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(35)	Italy	2.75 (3 out of 109)	2.58 (3 out of 116)	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(36)	Norway	12.5 (21 out of 200)	6.9 (12 out of 173)	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(37)	Japan	5.5 (5 out of 93)	2.2 (2 out of 93)	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(38)	Norway	27 (47 out of 176)	N.A	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(39)	Malaysia	9.7 (11 out of 113)	N.A	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(40)	India	11.9 (16 out of 134)	2.9 (5 out of 172)	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(41)	Canada (diverse ethnic background)	21.3 (27 out of 127)	4.7 (6 out of 127)	RLS/WED diagnostic criteria (not specify)
(42)	UK	16.2 (6 out of 37)	10.8 (4 out of 37)	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(43)	South Korea	16.5 (25 out of 151)	N.A	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(44)	South Korea	16 (36 out of 225)	N.A	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(45)	Iran	14.8 (16 out of 108)	7.5 (32 out of 424)	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(46)	Finland	20.3 (117 out of 577)	N.A	IRLSSG diagnostic criteria of RLS/WED (2003) (22)
(47)	China	10.7 (28 out of 262)	N.A	IRLSSG diagnostic criteria of RLS/WED (2014) (2)
(48)	Canada	20 (25 out of 123)	5 (6 out of 123)	RLS/WED diagnostic criteria (not specify)
(49)	Brazil	28.4 (25 out of 88)	N.A	IRLSSG diagnostic criteria of RLS/WED (2014) (2)
(50)	Japan	3.4 (15 out of 436)	2.7 (11 out of 401)	IRLSSG diagnostic criteria of RLS/WED (2003) (22)

RLS/WED, Restless Legs Syndrome/Willis-Ekbom Disease; PD, Parkinson's disease; N.A, not available; IRLSSG, International Restless Legs Syndrome Study Group.

in comparison to 1% displayed by general population over 60 years. Dragan et al. (55) collected iRLS/WED patients before the onset of PD. They performed a comparison between RLS/WED with PD group and PD patients without RLS/WED and they found that the former group had a later onset of PD and reduced dyskinesia occurrence. The authors speculated about the possibility that iRLS/WED may reduce the progression of PD.

Other studies evaluated the importance of the duration of the disease and the possible role of the progressive depletion

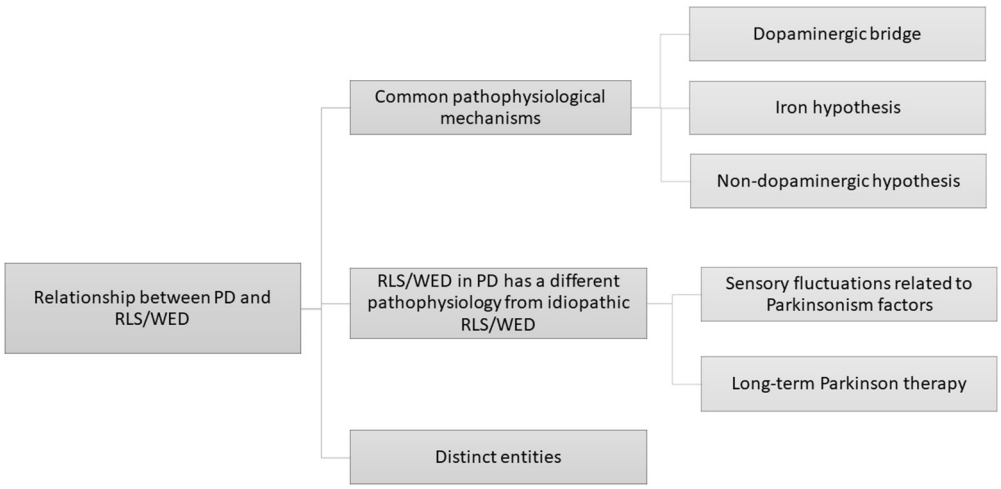

FIGURE 1 | A graphical representation of several pathophysiological hypotheses proposed in literature regarding the relationship between PD and RLS/WED.

of dopaminergic system. Braga-Neto et al. (23) in a sample of 86 PD patients found that 49.9% of patients exhibited RLS/WED. They highlighted that RLS/WED was more frequent in patients with longer disease duration. Since the occurrence of RLS/WED frequently arose after a mean of 5 years from PD onset, the authors suggested a role of progressive depletion of dopamine system and its occurrence in PD. This hypothesis was supported also by Bhalsing et al. (40) who proposed a possible degeneration of dopaminergic diencephalo-spinal pathway (A11) in the hypothalamus, along with nigrostriatal neurons in PD, that may lead to manifestation of RLS/WED.

Some cross-sectional studies considered RLS/WED as a secondary symptom induced by PD symptomatology and therapy (28, 30, 35, 43, 44, 50). Most of the studies explained the occurrence of RLS/WED as a consequence of dopaminergic therapies. Moreover, the association of RLS/WED with clinical features of PD, especially motor fluctuations have been investigated. Peralta et al. (30) found that 61% of PD patients who met clinical criteria for RLS/WED showed wearing-off. Thus, the authors suggested that the RLS/WED may be part of sensory-motor spectrum of wearing off (RLS/WED-like symptoms). Previously, Fereshtehnejad et al. (45) found similar results. They showed that unpredictability of the off periods was correlated with the higher prevalence of RLS/WED symptoms in patients with PD. Studies conducted in different populations suggest that the antiparkinsonian therapy may explain the occurrence of RLS/WED in PD patients. Lee et al. (28) by a logistic regression showed that the duration of dopaminergic therapy was the factor that better explained the development of RLS/WED in PD patients. Angelini et al. (35) assessed the prevalence of RLS/WED in untreated PD patients excluding secondary forms of RLS/WED and they found no significant differences between patients and controls. Thus, they suggested that RLS/WED occurring in PD patients may be due to dopaminergic therapy.

However, Verbaan et al. (34) studied the prevalence of RLS/WED in 269 PD patients and found a value of 11% that is slightly higher than the frequency reported in general population (56–60) but lower than PD populations of others studies (17, 25, 30), suggesting a possible masking effect of dopaminergic therapy in their sample. They also found that among PD patients RLS/WED severity was positively associated with PD severity, motor fluctuations, depressive symptoms, daytime sleepiness, cognitive problems, autonomic symptoms, and psychotic ones. On the basis of their results, they proposed a non-dopaminergic hypothesis to explain the relationship between PD and RLS/WED. In particular, they emphasized the possible role of adrenergic system in both disorders. The involvement of locus coeruleus and its projections to the central nervous system in both PD and RLS/WED pathologies is supported by some studies (33, 61, 62). In particular, in PD pathology the impairment of serotonergic, cholinergic, and noradrenergic systems in addition to dopaminergic one has been showed (62). Instead the literature regarding this issue in RLS/WED disease is still unclear (33, 61). Thus, the adrenergic hypothesis needs to be more investigated in order to clarify its role in explaining the relationship between PD and RLS/WED.

Other authors explained the higher prevalence of RLS/WED in PD patients with low ferritin levels (17). It is well known that iron has a role in biosynthesis and transmission of dopamine (63). The authors found that 20.8% of their PD patients presented RLS/WED and these patients had lower serum ferritin levels. Thus, they suggested that PD may be a risk factor to develop RLS/WED in combination with low ferritin levels. Interestingly, Fereshtehnejad et al. (45) showed a worse nutritional status associated to RLS/WED in PD patients. They suggested that a worse nutritional status may lead to an iron deficiency in PD patients who exhibited RLS/WED. However, several studies did not show iron deficiency anemia in PD patients with RLS/WED (16, 24, 26, 32, 42, 43).

Shin et al. (43) assessing 151 drug-naïve early-stage PD patients found that 16.5% of PD patients had RLS/WED and presented different characteristics in comparison to RLS/WED of

the general population. Indeed, PD patients with RLS/WED tend to perceive symptoms in limb more affected by extrapyramidal symptomatology, while traditional RSL/WED patients have a bilateral involvement. Thus, the authors suggested that RLS/WED in PD patients may have a different underling pathophysiology. Moreover, a significant number of studies reported absence or weak association between the two disorders (16, 20, 26, 27, 36, 37).

Tan et al. (20) reported that none of 125 PD patients recruited met all the clinical IRLSSG criteria for RLS/WED. Loo et al. (26) with a case-control study showed a week association between RLS/WED and PD. Calzetti et al. (27) found that 12.7% of PD and 6.3% of controls suffered from iRLS/WED, but the difference was not statistically significant. Gjertstad et al. (36) evaluated 200 drug-naïve PD patients and 173 healthy controls and found that 15.5% of PD patients and 9.2% of controls had RLS/WED. The difference of prevalence of RLS/WED in the two groups was not statistically significant. The authors also assessed the presence of leg motor restlessness (LMR). LMR was described as an urge to move the legs without met all clinical criteria for RLS/WED. They found that 25% of PD patients and 8.7% HC had a concurrent LMR with a relative risk of 3.1. After the exclusion of the patients with potential confounders the relative risk for LMR was 2.84. These findings supported the notion that RLS/WED and PD may be different entities, but on the other hand opened a debate on whether also LMR and RLS/WED may be considered as such. In relation to this aspect some authors proposed LMR as a bridge between RLS/WED and PD (42). The authors showed that RLS/WED have a similar frequency in patients and controls, but LMR was a more common complaint in PD patients. In addition, no correlation between RLS/WED or LMR and all the possible causes of a secondary RLS/WED evaluated in the study (e.g., neuropathies) has been found.

In conclusion, the literature has not yet been able to give a clear framework of the issue because of the contrasting results. These heterogeneous results may be due to methodological issues. The main problem is the composition of the sample, since different exclusion criteria has been employed among the various studies (e.g., cases of secondary form of RLS/WED like radiculopathies or patients with L-dopa related motor complications). Also the modality of RLS/WED assessment was different across studies (e.g., interviews, neurological evaluation, retrospective use of clinical criteria). Dopaminergic treatment is another remarkable confounding factor. The RLS/WED usually benefits from dopaminergic medication at lower doses than those used for PD treatment (51, 52). Thus, the use of dopaminergic drugs in PD patients may lead to an underestimation of RLS/WED. On the other side, the antiparkinsonian treatment, in particular L-dopa, may produce an increased frequency of sensory-motor disorders in PD (9), giving rise to "mimics" conditions of RLS/WED or augmentation. Notably, considering only studies performed on untreated patients (35, 36, 43) the prevalence range of RLS/WED in PD decreases from 0–50% to 5.5–16.5%.

Moreover, a crucial issue is the time of RLS/WED occurrence in relation to PD onset. Krishnan et al. (21) showed that PD patients with RLS/WED were older than those who did not present the co-occurrence of these diseases. However, other studies found an earlier age at the time of investigation and an earlier onset of PD in patients with RLS/WED (24, 26, 30, 39). Some authors reported a higher prevalence of RLS/WED in female PD patients (25, 26, 34), but others did not find gender differences in PD patients with RLS/WED (21, 40, 43). There is a general agreement in literature considering PD patients with RLS/WED less likely to have a family history of RLS/WED (17, 21, 24, 25, 40, 47). RLS/WED clinical manifestations in PD patients seem to be less severe (24, 25, 46) and RLS/WED symptoms in PD are often transient and irregular (17, 24, 40). However, it must be noted that the studies included treated PD patients, hence the dopaminergic therapy may improve the RLS/WED symptomatology.

LONGITUDINAL STUDIES

In order to evaluate the causal link between two conditions, longitudinal studies are an essential first step for establishing at least a temporal relationship. However, in literature there are few studies evaluating the incidence of PD in RLS/WED patients, or the appearance of RLS/WED symptomatology in PD patients. Calzetti et al. (64) performed a long-term prospective study to assess the incidence of RLS/WED in newly diagnosed PD patients under dopaminergic therapy. The authors analyzed 106 PD patients with a follow-up ranging from 6 to 96 months. 15 out of 106 (14.15%) patients developed RLS/WED with 3 of them being affected by a secondary form of the disorder: two cases with a chronic polyneuropathy and one case with a bilateral radiculopathy. These prevalence indices are higher in comparison to those reported in a study conducted in general German population in the age ranges of 55–64 and 45–74 years. The median time from starting medication treatment to the development of RLS/WED was 12.5 years with 10 out of 12 patients that developed this condition within 24 months. These findings suggest that dopaminergic medication may be crucial for the development of RLS/WED in PD patients. The same authors reported an updated cumulative incidence and clinical course study in the same cohort of patients after a 3-year follow-up (65). This study confirmed that RLS/WED prevalence is increased in PD patients under treatment in comparison to general population and drug naïve PD patients. The authors demonstrate that clinical course in these patients was prevalently remittent. Accordingly, during an observational period of 12 months after the emergence of RLS/WED, the mean rate of the episodes decreased from 8.9 ± 7.5 in the first 6 months to 3.3 ± 3.2 in the second 6 months. Notably, this time course suggests the absence of augmentation phenomenon in these patients.

More recently, Moccia et al. (66) investigated the presence of RLS/WED patients in a cohort of newly diagnosed PD patients and its incidence after a 4-year follow-up in 109 newly diagnosed PD patients with 10 of them lost during the follow-up. Results showed that RLS/WED is present since the time of PD diagnosis with a prevalence of 4.6% (5 patients out of 109), that rose to 6.5% (7 out of 108), and 16.3% (16 out of 99) after 2 and 4 years. Incidence rate was

5.7% at 2 years and 10.2% at 4 years, with a cumulative incidence of 6.8%. However, no significant association was found between dopaminergic therapy and RLS/WED. Interestingly, this study investigated also dopamine transporter by means of single photon emission computed tomography (FP-CIT SPECT). Findings demonstrate that PD patients with RLS/WED showed a preserved nigrostriatal dopaminergic pathway in comparison to patients without RLS/WED. This result seems to suggest the involvement of neurotransmitters diverse from dopamine.

Up to now only two longitudinal studies evaluated the presence of RLS/WED as an early manifestation or risk factor of PD. In 2014, Wong and Li (67) performed a prospective longitudinal study assessing 22,999 health professional men aged 40–75 without PD, diabetes, arthritis and common mimics of RLS/WED with an 8-year follow-up. At baseline evaluation 931 subjects affected by RLS/WED were identified. Among these, 7 out of 8 incident PD cases were observed during the first 4 years of follow-up. Furthermore, a significant risk for developing PD in subjects affected by a severe form of RLS/WED (RLS/WED symptoms 15+ times/month) in comparison to subjects without RLS/WED was found during the same time period, but not in the full 8-year follow-up. According to the authors' interpretation of the results, these data suggest that RLS/WED might be an early manifestation of PD rather than a risk factors, since a longer follow-up period was not associated with an increased risk of PD development. Therefore, they speculate a different pathogenesis for these two disorders.

More recently, Szatmari et al. (68) evaluated the association of RLS/WED with the development of incident PD in a large cohort of US veterans. Out of 3.5 million of US veterans, 58,475 had a prevalent RLS/WED. After a mean follow-up of 8.1 years, 68 incident PD were identified in the no-RLS/WED group in comparison to 185 PD in the RLS/WED group. Therefore, a two-fold increased risk for PD was found in RLS/WED patients. The authors argued that since the uncertainty regarding the pathophysiological mechanism of RLS/WED and the low incidence of PD in this condition, it is very difficult to speculate regarding a common ethiopathogenesis between the two disorders.

The increased incidence of RLS/WED in PD patients is supported by all three longitudinal studies (64–66), however the possible influence of dopaminergic therapy in inducing RLS/WED is reported in two out of three (64, 65). Furthermore, neuroimaging showed a preserved dopaminergic pathway in PD+RLS/WED in comparison to PD alone. On the other hand, the two studies investigating the development of PD in these patients seem to indicate that RLS/WED might be an early manifestation rather than a risk factor of the neurodegenerative disease.

Alongside with the paucity of longitudinal studies investigating this association, several limitations have to be taken into account interpreting these results. When considering studies investigating the insurgence of RLS/WED in PD patients, the most striking weakness common to all three longitudinal studies (64–66) was the lack of a control group. Furthermore, a possible underestimation of the disorder due to the presence of dopaminergic treatment, that likely permit to identify only those patients affected by a severe form or those who did not respond to this therapy, might be considered. In the two studies examining the incidence of PD in RLS/WED patients (67, 68) the main concern regards the assessment of RLS/WED. In one study (67) the presence of the disorder was assessed throughout a questionnaire, whereas in the other (68) it was retrospectively extracted from a database through the codes of the International Classification of Diseases (Ninth Revision). For these methodological issues, results should be cautiously interpreted.

DIRECTING GLANCE ON DOPAMINERGIC SYSTEM PHYSIOLOGY: CAN THE DOPAMINE BE A RELIABLE BRIDGE BETWEEN RLS/WED AND PD?

Dopamine (DA) is the most common catecholamine in the central nervous system that can modulate different functions, like movement, cognition, reward and motivation (69, 70). DA derived from the conversion of 2,3-dihydroxyphenylalanine (DOPA) by the enzyme DOPA decarboxylase (DDC). Tyrosine hydroxylase (TH) is the enzyme responsible for converting the amino acid tyrosine to DOPA, monitoring the DA amount.

It is known that there are three groups of dopaminergic cells that give rise to three different axonal pathways with different functions: nigrostriatal, mesocorticolimbic, and tuberoinfundibular system. The latter is the smallest in terms of brain DA content and controls the pituitary system. Nigrostriatal DA pathway controls voluntary movement, and dysfunction in this pathway has been implicated in movement disorder like PD. Mesocorticolimbic systems DA modulate various cognitive/emotive functions, and their degeneration may lead to some psychiatric disorders. Several studies have pointed out that mesocorticolimbic system can also modulate thalamocortical arousal state (71–73). Studies from the effect of psychomotor stimulant with a molecular structure similar to DA, like amphetamine, (74), has demonstrated that endogenous DA is involved in promoting wakefulness (75, 76).

It is also known that DA release has a circadian fluctuation, and his effects on the DA receptors are different during the day and the night, with a high-affinity for D2-like receptor during the night whereas the effect on D1 receptor can overwhelm the actions of D2-like receptors during the day (15). The sleep/wake effects of exogenous dopaminomimetics, drugs typically used in diseases such as PD but also RLS/WED, are dose and receptor dependent. Sleep is promoted by low dopaminomimetic dose via D2-like receptors (77, 78), whereas higher dose enhances wakefulness via D1-like postsynaptic receptors (79–81).

Take into consideration his contribution to sleep-wake state in addition to other waking behaviors like movement, DA has been considered the "bridge" that underlying PD and RLS/WED (15).

Depletion of DA in basal ganglia as pathophysiology basis of PD is known from 1960s. DA deficiency in the nigriostriatal pathway causes denervation hypersensitivity of D1 and D2 receptors, highly concentrated in the dorsal striatum (82). On the contrary, D3 receptors, more abundant in the mesolimbic pathway (83), are decrease by 40 to 45 percent in PD patients (84) and this can explain the hypersensitivity of D2 nigrostriatal receptors observed in PD. The pathogenesis of neuronal cell degeneration in the basal ganglia is still debated. Numerous theories have been suggested (85).

The dopaminergic pathology has been proposed also among the pathophysiological mechanisms of RLS/WED, as confirmed by the efficacy of the therapy with L-Dopa and DA agonists in the clinical and polysomnographic improvement of patients with RLS/WED (86).

Unlike PD, in RLS/WED anatomopathological studies (87, 88) and some Cerebral Spinal Fluid (CSF) studies (89–91) have failed to provide a consistent pattern indicating a DA deficit.

More recently, a human postmortem study had demonstrated significant decrease in D2 receptors in the putamen and a significant increase in TH in the SN, showing no differences for D1 receptors, DA transporter or vesicular monoamine transporter (VMAT), as in animal models of iron depletion, confirming a clear DA pathology in RLS/WED patients with an increased DA production and DA receptors downregulation, secondary to a primary iron insufficiency (92).

The hypothesis of a hyperdopaminergic state is supported by another study that showed increased levels of the DA metabolite 3-ortho-methyldopa (3-OMD) in CSF of patients with RLS/WED compared to controls (93). In particular, 3-OMD levels are increased during the day but reduced at night, suggesting that in RLS/WED patients there may be a relative DA deficiency during the night on a hyperdopaminergic state on the background (91). Hyperdopaminergic state leads to a downregulation of DA receptors, but due to the circadian profile of DA activity, there is a relative hypofunctioning in the evening and during the night, explaining the relief of RLS/WED symptoms after supplying additional DA with dopaminomimetic drugs (94). Clinical phenomenon of augmentation confirms this theory. DA-based medicines can cause further downregulation or desensitization of DA receptors, increasing the DA requirements while DA deficiency during the night becomes more severe and tends to occur for longer periods with a worsening of RLS/WED symptoms (95).

Interestingly all CSF studies have consistently shown iron insufficiency in RLS/WED (96–99), and autopsy analysis demonstrated alteration iron regulatory protein 1 in neuromelanin cells indicating iron deficiency (100).

Imaging studies in RLS/WED patients have tried to demonstrate the physiopathology of this disease, but with some discordances (101). Regarding the dopaminergic hypothesis Positron Emission Tomography (PET) and Single-photon emission computed tomography (SPECT) studies support a dysfunction in both nigrostriatal and mesolimbic pathways (102–107). D2 receptors and DA transporters in the striatum appear decreased, and these findings are compatible with an increase in synaptic DA (102–105, 107–109).

Using Magnetic Resonance Imaging (MRI) iron-sensitive sequences, numerous evidence has shown iron deficiency in RLS/WED patients (110–116) supporting the iron-dopamine bridge hypothesis (117).

Regarding the principal clinical manifestation of RLS/WED, functional Magnetic Resonance Imaging (fMRI) studies have demonstrated connectivity changes in cerebral areas implicated in the limbic/nociceptive network and the sensorimotor network (118–123). Also, SPECT studies have demonstrated an involvement of the limbic structures, as medial thalamus and anterior cingulate cortex (124, 125).

Latest evidence supports the notion that RLS/WED represents a complex network disorder, with the crucial node localized in the thalamus, which appears to have dopaminergic dysfunction (126), lower iron content (114, 115), and changes in activation and functional connectivity (112, 118, 120).

IRON AND ITS RELATION TO THE DOPAMINE SYSTEM

Iron is an important cofactor in several DA metabolisms and can also produce neurotoxic species.

Usually iron accumulates in the normal aging brain, in particular in the putamen, globus pallidus, red nucleus, and substantia nigra (SN) (127). Elemental iron plays a critical role in oxidative metabolism and it also serves as a cofactor in the synthesis of neurotransmitters (128).

In PD, neurodegeneration occurs mainly in SNc (129), while other iron-rich areas remain unaffected. In early stages of the disease the identification through the use of transcranial ultrasonography of a hyperechogenicity of the SNc (130) correlates positively with the increase of iron and ferritin evaluated in post-mortem analysis (131), allowing an early identification of patients at risk for PD (132).

The increase in neuronal iron may be secondary to an increase in influx, facilitated by transferrin receptor-2/divalent metal transporter-1 endocytosis or the diffusion of ferric citrate (133), an increase in efflux, due to alteration of the activity of ceruloplasmin, or a dysregulation of iron homeostasis, mediated mainly by the iron storage protein ferritin (134).

Some studies have shown reduced ferritin concentrations in the SN from Parkinson's disease brain, suggesting an alteration of this storage mechanism and a consequent increase in the level of free and potentially harmful iron (135).

Also, neuromelanin, a final product of DA, can be implicated in the dysregulation of iron metabolism (136). Quantitative imaging showed in PD patients a significant elevation in iron levels in SNc neuromelanin-positive cells compared with locus coeruleus (137). It is not clear if the association of iron with neuromelanin can play a role in the degeneration of SN cells, but it is hypothesized that when this pigment becomes saturated, an excess of iron can be released into the cytoplasm (138).

DA metabolism through oxidation by iron and oxygen can form o-quinones and 6-hydroxydopamine (6-OHDA) (139). These quinones can form neurotoxic intermediates in iron-facilitated reactions, resulting in alteration of cell

membrane integrity and, eventually, cell death (140). 6-OHDA induces mitochondrial dysfunction (141) and can liberate iron from ferritin (142) that in high concentrations overwhelms compensatory antioxidant mechanisms (143) and facilitates the production of further neurotoxic species.

In PD patients iron is increased by about 50 percent in SN compared to controls (144), and this finding supports the hypothesis that abnormal iron metabolism plays a pathologic role in the development of PD (145, 146).

On the other hand, there is some evidence that links RLS/WED to iron deficiency states. High prevalence of RLS/WED was found in specific condition implicating a reduction in the availability of iron such as pregnancy, iron deficiency anemia or renal pathologies (147–149). However, iron levels in blood sample of most RLS/WED patients are normal (117), suggesting that a state of low iron in the brain could be implicated in the RLS/WED pathophysiology.

MRI study have demonstrated a significant low concentration in specific brain regions as SN, and these decreases were correlated to RLS/WED symptom severity (110). Other imaging studies found iron decrease in other brain regions, like thalamus, caudate, putamen, and white matter (114).

Immunohistochemistry postmortem RLS/WED brain samples have shown a significant reduction of iron and ferritin in the SN (150), as subsequently confirmed in CSF analysis of RLS/WED patients (97, 99, 151).

Iron deficiency may lead to an increase of TH in the basal ganglia (92) and elevated extracellular DA levels (152). Also, DA receptor density may be modified by iron deficiency, with a reduction in caudate and putamen D1 and D2 receptors (87).

Several studies have implicated both the dopaminergic system and the iron in PD and RLS/WED, thus suggesting a common physiopathological basis, however the data are inconsistent with this theory, showing in particular a depletion of DA in PD and a hyperdopaminergic state in RLS/WED.

CONCLUSION

The relationship between RLS/WED and PD has been largely investigated by cross-sectional and longitudinal studies. Among the different pathophysiological hypotheses emerged by cross-sectional studies two of them are confirmed also by longitudinal investigations. In particular, a twofold interpretation regarding the association between these two conditions has to be taken into account: dopaminergic therapy may have a crucial role in the development of RLS/WED in PD patients (28, 35, 64, 65) and on the other hand RLS/WED can be conceived as an early manifestation of PD rather than a risk factor (42, 64, 65). Therefore, it is plausible that these two hypotheses differ in etiopathogenetic mechanisms. However, the literature regarding the pathophysiology of the two diseases showed different results struggling to give a clear message on the possible bridge between RLS/WED and PD. Despite numerous studies showing a higher prevalence of RLS/WED in PD patients and several findings related to dopaminergic and iron alterations in both disorders, up to now it is difficult to find a point of agreement between studies.

Conflicting results may be explained by methodological and theoretical issues. Confounding variables, such as therapy, mimic conditions, time course, symptoms' features, diagnostic criteria, and disease duration should be seriously considered and controlled when investigating the incidence or the prevalence of RLS/WED in PD. Furthermore, whereas there is a certain degree of accordance regarding PD pathophysiology, physiological mechanisms underlying RLS/WED are poorly understood and still matter of debate.

The presence of RLS/WED in PD patients may be partially covered by the presence of dopaminergic therapy or represents a minor sensorimotor complaint among those already present in PD. Furthermore, in both published literature and clinical experience, the long-term observation of RLS/WED patients does not provide evidence regarding a frequent incidence of PD.

In order to better understand this relationship, a greater number of systematic and strongly controlled longitudinal studies are needed. At the same time, it is necessary to improve the knowledge on the pathophysiology of RLS/WED in order to fill the gap regarding putative common etiopathogenetic mechanisms shared with PD.

AUTHOR CONTRIBUTIONS

Conception of the work, literature search and interpretation: LF-S, GC, FC and AG. Drafting and revising the work critically for content: LF-S, GC, FC and AG. Final approval of the version to be published: LF-S, GC, FC and AG.

REFERENCES

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd edn. Darien, IL: American Academy of Sleep Medicine (2014).
2. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. International Restless Legs Syndrome Study Group., Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. *Sleep Med.* (2014) 15:860–73. doi: 10.1016/j.sleep.2014.03.025
3. Galbiati A, Marelli S, Giora E, Zucconi M, Oldani A, Ferini-Strambi L. Neurocognitive function in patients with idiopathic restless legs syndrome before and after treatment with dopamine-agonist. *Int J Psychophysiol.* (2015) 95:304–9. doi: 10.1016/j.ijpsycho.2014.12.005
4. Kallweit U, Siccoli MM, Poryazova R, Werth E, Bassetti CL. Excessive Daytime sleepiness in idiopathic restless legs syndrome: characteristics and evolution under dopaminergic treatment. *Eur Neurol.* (2009) 62:176–9. doi: 10.1159/000228261
5. Ferri R, Cosentino FI, Manconi M, Rundo F, Bruni O, Zucconi M. Increased electroencephalographic high frequencies during the sleep onset period in patients with restless legs syndrome. *Sleep* (2014) 37:1375–81. doi: 10.5665/sleep.3934
6. Ohayon MM, O'hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. *Sleep Med Rev.* (2012) 16: 283–95. doi: 10.1016/j.smrv.2011.05.002

7. Koo BB. Restless leg syndrome across the globe: epidemiology of the restless legs syndrome/Willis-Ekbom disease. *Sleep Med Clin*. (2015) 10:189–205. doi: 10.1016/j.jsmc.2015.05.004
8. Rinaldi F, Galbiati A, Marelli S, Ferini Strambi L, Zucconi M., Treatment Options in Intractable Restless Legs Syndrome/Willis-Ekbom Disease (RLS/WED). *Curr Treat Options Neurol*. (2016) 18:7. doi: 10.1007/s11940-015-0390-1
9. Garcia-Borreguero D, Silber MH, Winkelman JW, Högl B, Bainbridge J, Buchfuhrer M, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. *Sleep Med*. (2016) 21:1–11. doi: 10.1016/j.sleep.2016.01.017
10. Schormair B, Zhao C, Bell S, Tilch E, Salminen AV, Pütz B, et al. Identification of novel risk loci for restless legs syndrome in genome-wide association studies in individuals of European ancestry: a meta-analysis. *Lancet Neurol*. (2017) 16:898–907. doi: 10.1016/S1474-4422(17)30327-7
11. Hattan E, Chalk C, Postuma RB. Is there a higher risk of restless legs syndrome in peripheral neuropathy? *Neurology* (2009) 72:955–60. doi: 10.1212/01.wnl.0000336341.72621.db
12. Earley CJ, Connor J, Garcia-Borreguero D, Jenner P, Winkelman J, Zee PC, et al. Altered brain iron homeostasis and dopaminergic function in restless legs syndrome (Willis-Ekbom disease). *Sleep Med*. (2014) 15:1288–301. doi: 10.1016/j.sleep.2014.05.009
13. Gomez-Choco MJ, Iranzo A, Blanco Y, Graus F, Santamaria J, Saiz A. Prevalence of restless legs syndrome and REM sleep behavior disorder in multiple sclerosis. *Mult Scler*. (2007) 13:805–08. doi: 10.1177/1352458506074644
14. Ferini-Strambi L, Walters AS, Sica D. The relationship among restless legs syndrome (Willis-Ekbom disease), hypertension, cardiovascular disease, and cerebrovascular disease. *J Neurol*. (2014) 261:1051–68. doi: 10.1007/s00415-013-7065-1
15. Rye DB. Parkinson's disease and RLS: the dopaminergic bridge. *Sleep Med*. (2004) 5:317–28. doi: 10.1016/j.sleep.2004.01.016
16. Jagota P, Asawavichienjinda T, Bhidayasiri R. The low prevalence of primary restless legs syndrome in Thai Parkinson's disease patients at Chulalongkorn University Hospital. *J Med Assoc Thai*. (2012) 95:175–80.
17. Ondo WG, Vuong KD, Jankovic J. Exploring the relationship between Parkinson disease and restless legs syndrome. *Arch Neurol*. (2002) 3:421–4. doi: 10.1001/archneur.59.3.421
18. Walters AS. Toward a better definition of the restless legs syndrome. The international restless legs syndrome study group. *Mov Disord*. (1995) 10:634–42. doi: 10.1002/mds.870100517
19. Kumar S, Bhatia M, Behari M. Sleep disorders in Parkinson's disease. *Mov Disord*. (2002) 4:775–8. doi: 10.1002/mds.10167
20. Tan EK, Lum SY, Wong MC. Wong Restless legs syndrome in Parkinson's disease. *J Neurol Sci*. (2002) 196:33–6. doi: 10.1016/S0022-510X(02)00020-5
21. Krishnan PR, Bhatia M, Behari M. Restless legs syndrome in Parkinson's disease: a case-controlled study. *Mov Disord*. (2003) 18:181–5. doi: 10.1002/mds.10307
22. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome diagnosis and epidemiology workshop at the national institutes of health; international restless legs syndrome study group. restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med*. (2003) 4:101–19. doi: 10.1016/S1389-9457(03)00010-8
23. Braga-Neto P, da Silva-Júnior FP, Sueli Monte F, de Bruin PF, de Bruin VM. Snoring and excessive daytime sleepiness in Parkinson's disease. *J Neurol Sci*. (2004) 217:41–5. doi: 10.1016/j.jns.2003.08.010
24. Nomura T, Inoue Y, Miyake M, Yasui K, Nakashima K. Prevalence and clinical characteristics of restless legs syndrome in japanese patients with Parkinson's Disease. *Mov Disord*. (2006) 21:380–4. doi: 10.1002/mds.20734
25. Gómez-Esteban JC, Zarranz JJ, Tijero B, Velasco F, Barcena J, Rouco I, et al. Restless legs syndrome in Parkinson's disease. *Mov Disord*. (2007) 22:1912–6. doi: 10.1002/mds.21624
26. Loo HV, Tan EK. Case-control study of restless legs syndrome and quality of sleep in Parkinson's disease. *J Neurol Sci*. (2008) 266:145–9. doi: 10.1016/j.jns.2007.09.033
27. Calzetti S, Negrotti A, Bonavina G, Angelini M, Marchesi E. Absence of co-morbidity of Parkinson disease and restless legs syndrome: a case-control study in patients attending a movement disorders clinic. *Neurol Sci*. (2009) 30:119–22. doi: 10.1007/s10072-009-0037-7
28. Lee JE, Shin HW, Kim KS, Sohn YH. Factors contributing to the development of restless legs syndrome in patients with Parkinson disease. *Mov Disord*. (2009) 24:579–82. doi: 10.1002/mds.22410
29. Limousin N, Konofal E, Karroum E, Lohmann E, Theodorou I, Dürr A, et al. Restless legs syndrome, rapid eye movement sleep behavior disorder, and hypersomnia in patients with two parkin mutations. *Mov Disord*. (2009) 24:1970–6. doi: 10.1002/mds.22711
30. Peralta CM, Frauscher B, Seppi K, Wolf E, Wenning GK, Högl B, et al. Restless legs syndrome in Parkinson's Disease. *Mov Disord*. (2009) 14:2076–80. doi: 10.1002/mds.22694
31. Gama RL, Távora DG, Bomfim RC, Silva CE, de Bruin VM, de Bruin PF. Sleep disturbances and brain MRI morphometry in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy - a comparative study. *Parkinsonism Relat Disord*. (2010) 16:275–9. doi: 10.1016/j.parkreldis.2010.01.002
32. Guerreiro TM, Nishikawa DR, Ferreira LC, Melo HA, Prado RC. Restless legs syndrome in Parkinson's disease: clinical characteristics and biochemical correlations. *Arq Neuropsiquiatr*. (2010) 68:869–72. doi: 10.1590/S0004-282X2010000600007
33. Walters AS, Ondo WG, Zhu W, et al. Does the endogenous opiate system play a role in the restless legs syndrome? A pilot post-mortem study. *J Neurol Sci*. (2009) 279:62–5. doi: 10.1016/j.jns.2008.12.022
34. Verbaan D, van Rooden SM, van Hilten JJ, Rijsman RM. Prevalence and clinical profile of restless legs syndrome in Parkinson's Disease. *Mov Disord*. (2010) 25:2142–7. doi: 10.1002/mds.23241
35. Angelini M, Negrotti A, Marchesi E, Bonavina G, Calzetti S. A study of the prevalence of restless legs syndrome in previously untreated Parkinson's disease patients: absence of co-morbid association. *J Neurol Sci*. (2011) 310:286–8. doi: 10.1016/j.jns.2011.08.012
36. Gjerstad MD1, Tysnes OB, Larsen JP. Increased risk of leg motor restlessness but not RLS in early Parkinson disease. *Neurology* (2011) 77:1941–6. doi: 10.1212/WNL.0b013e31823a0cc8
37. Suzuki K, Miyamoto M, Miyamoto T, Tatsumoto M, Watanabe Y, Suzuki S, et al. Nocturnal disturbances and restlessness in Parkinson's disease: using the Japanese version of the Parkinson's disease sleep scale-2. *J Neurol Sci*. (2012) 318:76–181. doi: 10.1016/j.jns.2012.03.022
38. Svensson E, Beiske AG, Loge JH, Beiske KK, Sivertsen B. Sleep problems in Parkinson's disease: a community-based study in Norway. *BMC Neurol*. (2012) 12:71. doi: 10.1186/1471-2377-12-71
39. Azmin S, Khairul Anuar AM, Nafisah WY, Tan HJ, Raymond AA, Hanita O. Restless legs syndrome and its associated risk factors in Parkinson's disease. *Parkinsons Dis*. (2013) 2013:535613. doi: 10.1155/2013/535613
40. Bhalsing K, Suresh K, Muthane UB, Pal PK. Prevalence and profile of restless legs syndrome in Parkinson's disease and other neurodegenerative disorders: a case-control study. *Parkinsonism Relat Disord*. (2013) 19:426–30. doi: 10.1016/j.parkreldis.2012.12.005
41. Rana AQ, Siddiqui I, Mosabbir A, Athar A, Syed O, Jesudasan M, et al. Association of pain, Parkinson's disease, and restless legs syndrome. *J Neurol Sci*. (2013) 327:32–4. doi: 10.1016/j.jns.2013.01.039
42. Rajabally YA1, Martey J. No association between neuropathy and restless legs in Parkinson's disease. *Acta Neurol Scand*. (2013) 127:216–20. doi: 10.1111/ane.12011
43. Shin HY, Youn J, Yoon WT, Kim JS, Cho JW. Restless legs syndrome in Korean patients with drug-naïve Parkinson's disease: a nation-wide study. *Parkinsonism Relat Disord*. (2013) 19:355–8. doi: 10.1016/j.parkreldis.2012.09.009
44. Oh YS, Kim JS, Park IS, Song IU, Son YM, Park JW, et al. Association between nocturnal/supine hypertension and restless legs syndrome in patients with Parkinson's disease. *J Neurol Sci*. (2014) 344:186–9. doi: 10.1016/j.jns.2014.06.056
45. Fereshtehnejad SM, Shafieesabet M, Shahidi GA, Delbari A, Lökk J. Restless legs syndrome in patients with Parkinson's disease: a comparative study on prevalence, clinical characteristics, quality of life and nutritional status. *Acta Neurol Scand*. (2015) 131:211–8. doi: 10.1111/ane.12307

46. Ylikoski A, Martikainen K, Partinen M. Parkinson's disease and restless legs syndrome. *Eur Neurol.* (2015) 73:212–9. doi: 10.1159/000375493
47. Zhu XY, Liu Y, Zhang XJ, Yang WH, Feng Y, Ondo WG, et al. Clinical characteristics of leg restlessness in Parkinson's disease compared with idiopathic Restless Legs Syndrome. *J Neurol Sci.* (2015) 357:109–14. doi: 10.1016/j.jns.2015.07.008
48. Rana AQ, Qureshi AR, Rahman L, Jesudasan A, Hafez KK, Rana MA. Association of restless legs syndrome, pain, and mood disorders in Parkinson's disease. *Int J Neurosci.* (2016) 126:116–20. doi: 10.3109/00207454.2014.994208
49. Sobreira-Neto MA, Pena-Pereira MA, Sobreira EST, Chagas MHN, Fernandes RMF, Tumas V. High frequency of sleep disorders in parkinson's disease and its relationship with quality of life. *Eur Neurol.* (2017) 78:330–7. doi: 10.1159/000481939
50. Suzuki K, Okuma Y, Uchiyama T, Miyamoto M, Sakakibara R, Shimo Y, et al. Characterizing restless legs syndrome and leg motor restlessness in patients with Parkinson's disease: a multicenter case-controlled study. *Parkinsonism Relat Disord.* (2017) 44:18–22. doi: 10.1016/j.parkreldis.2017.08.007
51. Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. *Neurology* (2006) 67:125–30. doi: 10.1212/01.wnl.0000223316.53428.c9
52. Oertel WH, Trenkwalder C, Zucconi M, Benes H, Borreguero DG, Bassetti C. State of the art in restless legs syndrome therapy: practice recommendations for treating restless legs syndrome. *Mov Disord.* (2007) 22 (Suppl. 18):S466–75. doi: 10.1002/mds.21545
53. Gao X, Schwarzschild MA, O'Reilly EJ, Wang H, Ascherio A. Restless legs syndrome and Parkinson's disease in men. *Mov Disord.* (2010) 25:2654–7. doi: 10.1002/mds.23256
54. Walters AS, LeBrocq C, Passi V, Patel S, Hanna PA, Cohen B. A preliminary look at the percentage of patients with restless legs syndrome who also have parkinson disease, essential tremor or tourette syndrome in a single practice. *J Sleep Res.* (2003) 12:343–5. doi: 10.1046/j.0962-1105.2003.00368.x
55. Dragan EM, Chen Z, Ondo WG. Does idiopathic restless legs syndrome delay onset and reduce severity of Parkinson's disease: a pilot study. *Int J Neurosci.* (2015) 125:526–30. doi: 10.3109/00207454.2014.987771
56. Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and Morbidity in Augsburg Elderly. *Neurology* (2000) 54:1064–8. doi: 10.1212/WNL.54.5.1064
57. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. *Arch Intern Med.* (2004) 164:196–202. doi: 10.1001/archinte.164.2.196
58. Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med.* (2004) 5:237–46. doi: 10.1016/j.sleep.2004.03.006
59. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med.* (2005) 165:1286–92. doi: 10.1001/archinte.165.11.1286
60. Phillips B, Hening W, Britz P, Mannino D. Prevalence and correlates of restless legs syndrome: results from the 2005 National Sleep Foundation Poll. *Chest* (2006) 129:76–80. doi: 10.1378/chest.129.1.76
61. Weil-Fugazza J, Godefroy F. Dorsal and ventral dopaminergic innervation of the spinal cord: functional implications. *Brain Res Bull.* (1993) 30:319–24. doi: 10.1016/0361-9230(93)90259-E
62. Lim SY, Fox SH, Lang AE. Overview of the extranigral aspects of Parkinson disease. *Arch Neurol.* (2009) 66:167–72. doi: 10.1001/archneurol.2008.561
63. Youdim MB, Ben-Shachar D, Ashkenazi R, Yehuda S. Brain iron and dopamine receptor function. *Adv Biochem Psychopharmacol.* (1983) 37:309–2.
64. Calzetti S, Angelini M, Negrotti A, Marchesi E, Goldoni M. A long-term prospective follow-up study of incident RLS in the course of chronic DAergic therapy in newly diagnosed untreated patients with Parkinson's disease. *J Neural Transm.* (2014) 121:499–506. doi: 10.1007/s00702-013-1132-8
65. Marchesi E, Negrotti A, Angelini M, Goldoni M, Abrignani G, Calzetti S. A prospective study of the cumulative incidence and course of restless legs syndrome in de novo patients with Parkinson's disease during chronic dopaminergic therapy. *J Neurol.* (2016) 263:441–7. doi: 10.1007/s00415-015-7937-7
66. Moccia M, Erro R, Picillo M, Santangelo G, Spina E, Allocca R, et al. A Four-year longitudinal study on restless legs syndrome in Parkinson Disease. *Sleep* (2016) 39:405–12. doi: 10.5665/sleep.5452
67. Wong JC, Li Y, Schwarzschild MA, Ascherio A, Gao X. Restless legs syndrome: an early clinical feature of Parkinson disease in men. *Sleep* (2014) 37:369–72. doi: 10.5665/sleep.3416
68. Szatmari S Jr, Bereczki D, Fornadi K, Kalantar-Zadeh K, Kovesdy CP, Molnar MZ. Association of Restless Legs Syndrome With Incident Parkinson's Disease. *Sleep* (2017) 40:zsw065. doi: 10.1093/sleep/zsw065
69. Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron* (2010) 68:815–34. doi: 10.1016/j.neuron.2010.11.022
70. Gepshtein S, Li X, Snider J, Plank M, Lee D, Poizner H. Dopamine function and the efficiency of human movement. *J Cogn Neurosci.* (2014) 26:645–57. doi: 10.1162/jocn_a_00503
71. Dauvilliers Y, Tafti M, Landolt HP. Catechol-O-methyltransferase, dopamine, and sleep-wake regulation. *Sleep Med Rev.* (2015) 22:47–53. doi: 10.1016/j.smrv.2014.10.006
72. Oishi Y, Lazarus M. The control of sleep and wakefulness by mesolimbic dopamine systems. *Neurosci Res.* (2017) 118:66–73. doi: 10.1016/j.neures.2017.04.008
73. Herrera-Solis A, Herrera-Morales W, Nunez-Jaramillo L, Arias-Carrion O. Dopaminergic modulation of sleep-wake states. *CNS Neurol Disord Drug Targets* (2017) 16:380–6. doi: 10.2174/1871527316666170320145429
74. Hardman J, Limbird L, Goodman A. *Goodman and Gilman's the Pharmacological Basis of Therapeutics.* 10th edn. New York, NY: McGraw-Hill Professional (2001). p. 1825.
75. Edgar DM, Seidel WF. Modafinil induces wakefulness without intensifying motor activity or subsequent rebound hypersomnolence in the rat. *J Pharmacol Exp Ther.* (1997) 283:757–69.
76. Nishino S, Mao J, Sampathkumaran R, Shelton J. Increased dopaminergic transmission mediates the wake-promoting effects of CNS stimulants. *Sleep Res Online* (1998) 1:49–61.
77. Andreau N, Chalé JJ, Senard JM, Thalamas C, Montastruc JL, Rascol O. L-dopa induced sedation: a double-blind cross-over controlled study versus triazolam and placebo in healthy volunteers. *Clin Neuropharmacol.* (1999) 22:15–23. doi: 10.1097/00002826-199901000-00004
78. Ferreira JJ, Galitzky M, Thalamas C, Tiberge M, Montastruc JL, Sampaio C, Rascol O. Effect of ropinirole on sleep onset: a randomized placebo-controlled study in healthy volunteers. *Neurology* (2002) 58:460–2. doi: 10.1212/WNL.58.3.460
79. Cianchetti C. Dopamine agonists and sleep in man. In: Wauquier A, Gaillard JM, Monti JM, Radulovacki M, editors. *Sleep: Neurotransmitters and Neuromodulators.* New York, NY: Raven Press (1989). p. 121–34.
80. Trampus M, Ferri N, Adami M, Ongini E. The dopamine D1 receptor agonists, A68930 and SKF 38393, induce arousal and suppress REM sleep in the rat. *Eur J Pharmacol.* (1993) 235:83–7. doi: 10.1016/0014-2999(93)90823-Z
81. Ongini E, Bonizzoni E, Ferri N, Milani S, Trampus M. Differential effects of dopamine D1 and D2 receptor antagonist antipsychotics on sleep–wake patterns in the rat. *J Pharmacol Exp Ther.* (1993) 266:726–31.
82. Bamford NS, Robinson S, Palmiter RD, Joyce JA, Moore C, Meshul CK. Dopamine modulates release from corticostriatal terminals. *J Neurosci.* (2004) 24:9541. doi: 10.1523/JNEUROSCI.2891-04.2004
83. Gerfen CR. Molecular effects of dopamine on striatal-projection pathways. *Trends Neurosci.* (2000) 23:S64–70. doi: 10.1016/S1471-1931(00)00019-7
84. Ryoo HL, Pierrotti D, Joyce JN. Dopamine D3 receptor is decreased and D2 receptor is elevated in the striatum of Parkinson's disease. *Mov Disord.* (1998) 13:788. doi: 10.1002/mds.870130506
85. Song J, Kim J. Degeneration of dopaminergic neurons due to metabolic alterations and Parkinson's Disease. *Front Aging Neurosci.* (2016) 8:65. doi: 10.3389/fnagi.2016.00065
86. Garcia-Borreguero D, Cano-Pumarega I. New concepts in the management of restless legs Syndrome. *BMJ* (2017) 356:j104. doi: 10.1136/bmj.j104

87. Erikson KM, Jones BC, Hess EJ, Zhang Q, Beard JL. Iron deficiency decreases dopamine D1 and D2 receptors in rat brain. *Pharmacol Biochem Behav*. (2001) 69:409–18. doi: 10.1016/S0091-3057(01)00563-9
88. Wang X, Wiesinger J, Beard J, Felt B, Menzies S, Earley C, et al. Thy1 expression in the brain is affected by iron and is decreased in Restless Legs Syndrome. *J Neurol Sci.* (2004) 220:59–66. doi: 10.1016/j.jns.2004.02.004
89. Earley CJ, Hyland K, Allen RP. CSF dopamine, serotonin, and biopterin metabolites in patients with restless legs syndrome. *Mov Disord*. (2001) 16:144–9. doi: 10.1002/1531-8257(200101)16:1<144::AID-MDS1009>3.0.CO;2-F
90. Stiasny-Kolster K, Möller JC, Zschocke J, Bandmann O, Cassel W, Oertel WH, et al. Normal dopaminergic and serotonergic metabolites in cerebrospinal fluid and blood of restless legs syndrome patients. *Mov Disord*. (2004) 19:192–6. doi: 10.1002/mds.10631
91. Earley CJ, Hyland K, Allen RP. Circadian changes in CSF dopaminergic measures in restless legs syndrome. *Sleep Med*. (2006) 7:263–8. doi: 10.1016/j.sleep.2005.09.006
92. Connor JR, Wang XS, Allen RP, Beard JL, Wiesinger JA, Felt BT, Earley CJ. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. *Brain* (2009) 132(Pt 9):2403–12. doi: 10.1093/brain/awp125
93. Allen RP, Connor JR, Hyland K, Earley CJ. Abnormally increased CSF 3-ortho-methyldopa (3-OMD) in untreated restless legs syndrome (RLS) patients indicates more severe disease and possibly abnormally increased dopamine synthesis. *Sleep Med*. (2009) 10:123–8. doi: 10.1016/j.sleep.2007.11.012
94. Khan FH, Ahlberg CD, Chow CA, Shah DR, Koo BB. Iron, dopamine, genetics, and hormones in the pathophysiology of restless legs syndrome. *J Neurol.* (2017) 264:1634–41. doi: 10.1007/s00415-017-8431-1
95. Allen RP. Restless Leg Syndrome/willis-ekbom disease pathophysiology. *Sleep Med Clin*. (2015) 10:207–14. xi. doi: 10.1016/j.jsmc.2015.05.022
96. Earley CJ, Connor JR, Beard JL, Clardy SL, Allen RP. Ferritin levels in the cerebrospinal fluid and restless legs syndrome: effects of different clinical phenotypes. *Sleep* (2005) 28:1069–75. doi: 10.1093/sleep/28.9.1069
97. Mizuno S, Mihara T, Miyaoka T, Inagaki T, Horiguchi J. CSF iron, ferritin and transferrin levels in restless legs syndrome. *J Sleep Res*. (2005) 14:43–7. doi: 10.1111/j.1365-2869.2004.00403.x
98. Schmidauer C, Sojer M, Seppi K, Stockner H, Högl B, Biedermann B, et al. Transcranial ultrasound shows nigral hypoechogenicity in restless legs syndrome. *Ann Neurol*. (2005) 58:630–4. doi: 10.1002/ana.20572
99. Clardy SL, Earley CJ, Allen RP, Beard JL, Connor JR. Ferritin subunits in CSF are decreased in restless legs syndrome. *J Lab Clin Med.* (2006) 147:67–73. doi: 10.1016/j.lab.2005.06.011
100. Connor JR, Wang XS, Patton SM, Menzies SL, Troncoso JC, Earley CJ, et al. Decreased transferrin receptor expression by neuromelanin cells in restless legs syndrome. *Neurology* (2004) 62:1563–7. doi: 10.1212/01.WNL.0000123251.60485.AC
101. Rizzo G, Li X, Galantucci S, Filippi M, Cho YW. Brain imaging and networks in restless legs syndrome. *Sleep Med*. (2017) 31:39–48. doi: 10.1016/j.sleep.2016.07.018
102. Staedt J, Stoppe G, Kögler A, Riemann H, Hajak G, Munz DL, et al. Single photon emission tomography (SPET) imaging of dopamine D2-receptors in the course of dopamine replacement therapy in patients with nocturnal myoclonus syndrome (NMS). *J Neural Transm.* (1995) 99:187–93. doi: 10.1007/BF01271478
103. Ruottinen HM, Partinen M, Hublin C, Bergman J, Haaparanta M, Solin O, et al. An FDOPA PET study in patients with periodic limb movement disorder and restless legs syndrome. *Neurology* (2000) 54:502–4. doi: 10.1212/WNL.54.2.502
104. Michaud M, Soucy JP, Chabli A, Lavigne G, Montplaisir J. SPECT imaging of striatal pre and postsynaptic dopaminergic status in restless legs syndrome with periodic leg movements in sleep. *J Neurol*. (2002) 249:164–70. doi: 10.1007/PL00007859
105. Earley CJ, Kuwabara H, Wong DF, Gamaldo C, Salas R, Brašić JR, et al. The dopamine transporter is decreased in the striatum of subjects with restless legs syndrome. *Sleep* (2011) 34:341–7. doi: 10.1093/sleep/34.3.341
106. Kim KW, Jhoo JH, Lee SB, Lee SD, Kim TH, Kim SE, et al. Increased striatal dopamine transporter density in moderately severe old restless legs syndrome patients. *Eur J Neurol*. (2012) 19:1213–8. doi: 10.1111/j.1468-1331.2012.03705.x
107. Lin CC, Fan YM, Lin GY, Yang FC, Cheng CA, Lu KC, et al. 99mTc-TRODAT-1 SPECT as a potential neuroimaging biomarker in patients with restless legs syndrome. *Clin Nucl Med*. (2016) 41:e14–7. doi: 10.1097/RLU.0000000000000916
108. Oboshi Y, Ouchi Y, Yagi S, Kono S, Nakai N, Yoshikawa E, et al. In vivo mesolimbic D2/3 receptor binding predicts post therapeutic clinical responses in restless legs syndrome: a positron emission tomography study. *J Cereb Blood Flow Metab.* (2012) 32:654–62. doi: 10.1038/jcbfm.2011.201
109. Earley CJ, Kuwabara H, Wong DF, Gamaldo C, Salas RE, Brašić JR, et al. Increased synaptic dopamine in the putamen in restless legs syndrome. *Sleep* (2013) 36:51–7. doi: 10.5665/sleep.2300
110. Allen RP, Barker PB, Wehrl FW, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. *Neurology* (2001) 56:263–5. doi: 10.1212/WNL.56.2.263
111. Earley CJ, B Barker P, Horskà A, Allen RP. MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome. *Sleep Med*. (2006) 7:458–61. doi: 10.1016/j.sleep.2005.11.009
112. Margariti PN, Astrakas LG, Tsouli SG, Hadjigeorgiou GM, Konitsiotis S, Argyropoulou MI. Investigation of unmedicated early onset restless legs syndrome by voxel-based morphometry, T2 relaxometry, and functional MR imaging during the night-time hours. *AJNR Am J Neuroradiol*. (2012) 33:667–72. doi: 10.3174/ajnr.A2829
113. Moon HJ, Chang Y, Lee YS, Song HJ, Chang HW, Ku J, et al. T2 relaxometry using 3.0-tesla magnetic resonance imaging of the brain in early- and late-onset restless legs syndrome. *J Clin Neurol*. (2014) 10:197–202. doi: 10.3988/jcn.2014.10.3.197
114. Godau J, Klose U, Di Santo A, Schweitzer K, Berg D. Multiregional brain iron deficiency in restless legs syndrome. *Mov Disord.* (2008) 23:1184–7 doi: 10.1002/mds.22070
115. Rizzo G, Manners D, Testa C, Tonon C, Vetrugno R, Marconi S, et al. Low brain iron content in idiopathic Restless Legs Syndrome patients detected by phase imaging. *Mov Disord.* (2013) 28:1886–90. doi: 10.1002/mds.25576
116. Moon HJ, Chang Y, Lee YS, Song H, Chang HW, Ku J, et al. A comparison of MRI tissue relaxometry and ROI methods used to determine regional brain iron concentrations in restless legs syndrome. *Med Devices* (2015) 8:341–50. doi: 10.2147/MDER.S83629
117. Allen RP, Earley CJ. The role of iron in restless legs syndrome. *Mov Disord*. (2007) 22:S440–8. doi: 10.1002/mds.21607
118. Astrakas LG, Konitsiotis S, Margariti P, Tsouli S, Tzarouhi L, Argyropoulou MI. T2 relaxometry and fMRI of the brain in late-onset restless legs syndrome. *Neurology* (2008) 71:911–6. doi: 10.1212/01.wnl.0000325914.50764.a2
119. Spiegelhalder K, Feige B, Paul D, Riemann D, van Elst LT, Seifritz E, et al. Cerebral correlates of muscle tone fluctuations in restless legs syndrome: a pilot study with combined functional magnetic resonance imaging and anterior tibial muscle electromyography. *Sleep Med*. (2008) 9:177–83. doi: 10.1016/j.sleep.2007.03.021
120. Ku J, Cho YW, Lee YS, Moon HJ, Chang H, Earley CJ, Allen RP. Functional connectivity alternation of the thalamus in restless legs syndrome patients during the asymptomatic period: a resting-state connectivity study using functional magnetic resonance imaging. *Sleep Med*. (2014) 15:289–94. doi: 10.1016/j.sleep.2013.09.030
121. Liu C, Dai Z, Zhang R, Zhang M, Hou Y, Qi Z, et al. Mapping intrinsic functional brain changes and repetitive transcranial magnetic stimulation neuromodulation in idiopathic restless legs syndrome: a resting-state functional magnetic resonance imaging study. *Sleep Med*. (2015) 16:785–91. doi: 10.1016/j.sleep.2014.12.029
122. Gorges M, Rosskopf J, Müller HP, Lindemann K, Hornyak M, Kassubek J. Patterns of increased intrinsic functional connectivity in patients with restless legs syndrome are associated with attentional control of sensory inputs. *Neurosci Lett.* (2016) 617:264–9. doi: 10.1016/j.neulet.2016.02.043
123. Ku J, Lee YS, Chang HW, Earley CJ, Allen RP, Cho YW. Default mode network disturbances in restless legs syndrome/WilliseEkbom disease. *Sleep Med*. (2016) 23:6–11. doi: 10.1016/j.sleep.2016.05.007
124. Rizzo G, Tonon C, Testa C, Manners D, Vetrugno R, Pizza F, et al. Abnormal medial thalamic metabolism in patients with idiopathic

restless legs syndrome. *Brain* (2012) 135:3712–20. doi: 10.1093/brain/aws266
125. Winkelman JW, Schoerning L, Platt S, Jensen JE. Restless legs syndrome and central nervous system gamma-aminobutyric acid: preliminary associations with periodic limb movements in sleep and restless leg syndrome symptom severity. *Sleep Med*. (2014) 15:1225–30. doi: 10.1016/j.sleep.2014.05.019
126. Cervenka S, Pålhagen SE, Comley RA, Panagiotidis G, Cselényi Z, Matthews JC, et al. Support for dopaminergic hypoactivity in restless legs syndrome: a PET study on D2-receptor binding. *Brain* (2006) 129:2017–28. doi: 10.1093/brain/awl163
127. Bilgic B, Pfefferbaum A, Rohlfing T, Sullivan EV, Adalsteinsson E. MRI estimates of brain iron concentration in normal aging using quantitative susceptibility mapping. *Neuroimage* (2012) 59:2625–35. doi: 10.1016/j.neuroimage.2011.08.077
128. Benarroch EE. Brain iron homeostasis and neurodegenerative disease. *Neurology* (2009) 72:1436–40. doi: 10.1212/WNL.0b013e3181a26b30
129. Barbosa JH, Santos AC, Tumas V, Liu M, Zheng W, Haacke EM, et al. Quantifying brain iron deposition in patients with Parkinson's disease using quantitative susceptibility mapping, R2 and R2. *Magn Reson Imaging* (2015) 33:559–65. doi: 10.1016/j.mri.2015.02.021
130. Becker G, Seufert J, Bogdahn U, Reichmann H, Reiners K. Degeneration of substantia nigra in chronic Parkinson's disease visualized by transcranial color-coded real-time sonography. *Neurology* (1995) 45:182–4. doi: 10.1212/WNL.45.1.182
131. Zecca L, Berg D, Arzberger T, Ruprecht P, Rausch WD, Musicco M, et al. *In vivo* detection of iron and neuromelanin by transcranial sonography: a new approach for early detection of substantia nigra damage. *Mov Disord.* (2005) 20:1278–85. doi: 10.1002/mds.20550
132. Berg D. Transcranial ultrasound as a risk marker for Parkinson's disease. *Mov Disord.* (2009) 24 (Suppl. 2):S677–83. doi: 10.1002/mds.22540
133. Moos T, Rosengren Nielsen T. Ferroportin in the postnatal rat: implications for axonal transport and neuronal export of iron. *Semin Pediatr Neurol*. (2006) 13:149–57. doi: 10.1016/j.spen.2006.08.003
134. Ayton S, She P, Duce JA, Wong BXW, Sedjahtera A, Adlard PA, et al. Ceruloplasmin dysfunction and therapeutic potential for Parkinson disease. *Ann Neurol.* (2013) 73:554–9. doi: 10.1002/ana.23817
135. Dexter DT, Carayon A, Javoy-Agid F, Agid Y, Daniel SE, Lees AJ, et al. Alterations in the levels of iron, ferritin and other trace metals in Parkinson's disease and other neurodegenerative diseases affecting the basal ganglia. *Brain* (1991) 114:1953–75. doi: 10.1093/brain/114.4.1953
136. Hare DJ, Double KL. Iron and dopamine: a toxic couple. *Brain* (2016) 139(Pt 4):1026–35. doi: 10.1093/brain/aww022
137. Davies KM, Bohic S, Carmona A, Ortega R, Cottam V, Hare DJ, et al. Copper pathology in vulnerable brain regions in Parkinson's disease. *Neurobiol Aging* (2014) 35:858–66. doi: 10.1016/j.neurobiolaging.2013.09.034
138. Belaidi AA, Bush AI. Iron neurochemistry in Alzheimer's disease and Parkinson's disease: targets for therapeutics. *J Neurochem.* (2015) 469: 211–21. doi: 10.1111/jnc.13425
139. Zucca FA, Segura-Aguilar J, Ferrari E, Mu-oz P, Paris I, Sulzer D, et al. Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. *Prog Neurobiol*. (2015) 55:96–119. doi: 10.1016/j.pneurobio.2015.09.012
140. Napolitano A, Manini P, d'Ischia M. Oxidation chemistry of catecholamines and neuronal degeneration: an update. *Curr Med Chem.* (2011) 18:1832–45. doi: 10.2174/092986711795496863
141. Glinka Y, Gassen M, Youdim MB. Mechanism of 6-hydroxydopamine neurotoxicity. *J Neural Transm Suppl*. (1997) 50:55–66. doi: 10.1007/978-3-7091-6842-4_7
142. Monteiro HP, Winterbourn CC. 6-Hydroxydopamine releases iron from ferritin and promotes ferritin-dependent lipid peroxidation. *Biochem Pharmacol*. (1989) 38:4177–82. doi: 10.1016/0006-2952(89)90512-1
143. Hare DJ, Arora M, Jenkins NL, Finkelstein DI, Doble PA, Bush AI. Is early-life iron exposure critical in neurodegeneration? *Nat Rev Neurol*. (2015) 11:536–44. doi: 10.1038/nrneurol.2015.100
144. Oakley AE, Collingwood JF, Dobson J, Love G, Perrott HR, Edwardson JA, et al. Individual dopaminergic neurons show raised iron levels in Parkinson disease. *Neurology* (2007) 68:1820–5. doi: 10.1212/01.wnl.0000262033.01945.9a
145. Dusek P, Jankovic J, Le W. Iron dysregulation in movement disorders. *Neurobiol Dis*. (2012) 46:1–18. doi: 10.1016/j.nbd.2011.12.054
146. Liu Z, Shen HC, Lian TH, Mao L, Tang SX, Sun L, et al. Iron deposition in substantia nigra: abnormal iron metabolism, neuroinflammatory mechanism and clinical relevance. *Sci Rep*. (2017) 7:14973. doi: 10.1038/s41598-017-14721-1
147. Manconi M, Govoni V, De Vito A, Economou NT, Cesnik E, Casetta I, et al. Restless legs syndrome and pregnancy. *Neurology* (2004) 63:1065–9. doi: 10.1212/01.WNL.0000138427.83574.A6
148. Allen RP, Auerbach S, Bahrain H, Auerbach M, Earley CJ. The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. *Am J Hematol*. (2013) 88:261–4. doi: 10.1002/ajh.23397
149. Winkelman JW, Chertow GM, Lazarus JM. Restless legs syndrome in end-stage renal disease. *Am J Kidney Dis*. (1996) 28:372–8. doi: 10.1016/S0272-6386(96)90494-1
150. Connor JR, Boyer PJ, Menzies SL, Dellinger B, Allen RP, Ondo WG, Earley CJ. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndromev. *Neurology* (2003) 61:304–9. doi: 10.1212/01.WNL.0000078887.16593.12
151. Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndromev. *Neurology* (2000) 54:1698–700. doi: 10.1212/WNL.54.8.1698
152. Beard JL, Chen Q, Connor J, Jones BC. Altered monamine metabolism in caudate-putamen of iron-deficient ratsv. *Pharmacol Biochem Behav*. (1994) 48:621–4 doi: 10.1016/0091-3057(94)90323-9

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REVIEW
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Deep Brain Stimulation and Sleep-Wake Disturbances in Parkinson Disease: A Review

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Sleep-wake disturbances are common non-motor manifestations in Parkinson Disease (PD). Complex pathophysiological changes secondary to neurodegeneration in combination with motor symptoms and dopaminergic medications contribute to development of sleep-wake disturbances. The management of sleep complaints in PD is important as this symptom can affect daily activities and impair quality of life. Deep brain stimulation (DBS) is an effective adjunctive therapy for management of motor symptoms in PD. However, its effect on non-motor symptoms including sleep-wake disturbances is not widely understood. In this article, we reviewed studies assessing the effect of DBS at various therapeutic targets on sleep-wake disturbances. Of the studies examining the role of DBS in sleep-wake disturbances, the effect of subthalamic nucleus stimulation is most widely studied and has shown improvement in sleep quality, sleep efficiency, and sleep duration. Although, studies investigating changes in sleep with stimulation of thalamus, globus pallidus interna, and pedunculopontine nucleus are limited, they support the potential for modulation of sleep-wake centers with DBS at these sites. The mechanism by which DBS at different anatomical targets affects sleep-wake disturbances in PD is unclear and may involves multiple factors, including improved motor symptoms, medication adjustment, and direct modulation of sleep-wake centers.

Keywords: sleep-wake disturbances, deep brain stimulation, subthalamic nucleus, Parkinson disease, sleep-wake pathophysiology

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INTRODUCTION

Parkinson disease (PD) is a complex neurodegenerative disorder that leads to both motor and non-motor symptoms. The cardinal motor symptoms of PD include bradykinesia, rigidity, tremor, and gait difficulty. Non-motor manifestations include sleep disorders, neuropsychiatric symptoms, autonomic dysfunction, and cognitive decline (1). Conventionally, the management of PD was focused on motor symptoms and non-motor symptoms were often neglected. Over the last few decades, non-motor symptoms have gained more attention for their significant negative impact on quality of life in PD, leading to more exploration of how the neurodegenerative process influences these symptoms (2, 3).

Sleep-wake disturbances are a common non-motor symptom associated with PD and were first described by James Parkinson in his original article "Essay on shaking palsy" (4). Patients with PD can experience multiple sleep disorders, including sleep fragmentation, rapid eye movement (REM)

sleep behavior disorder (RBD), excessive daytime sleepiness (EDS), periodic limb movements of sleep (PLMS), and restless legs syndrome (RLS) (5). Sleep-wake disturbances in PD contribute to poor quality of life, impaired mood and behavior, and increased morbidity and mortality (3, 6, 7). Due to the limited treatment options for sleep disorders in PD, management of these symptoms can be challenging.

Deep brain stimulation (DBS) effectively treats the motor symptoms of PD, as well as improving motor fluctuations and quality of life (8–10). However, the effects of DBS therapy on non-motor symptoms, including sleep-wake disturbances, have received less attention. The available evidence suggests that DBS therapy can impact different aspects of sleep. We conducted a literature search on PubMed to identify studies evaluating the effects of DBS on either subjective or objective sleep parameters in PD. The following keywords were used in different combination for searching articles: "Deep brain stimulation," "Parkinson disease," "sleep disturbances," "sleep quality," "REM sleep behavior disorder," "restless legs syndrome," "excessive daytime sleepiness," subthalamic nucleus, "globus pallidus interna," "ventral intermediate nucleus," "pedunculopontine nucleus," "sleep pathophysiology." Both prospective and retrospective studies published in English language between 2000 and 2017 were reviewed. Also, relevant review articles on sleep disorders and Parkinson disease were reviewed. This article will briefly discuss pathophysiology of sleep-wake disturbances in PD; review existing literature exploring the effects of DBS at different therapeutic targets on sleep-wake disturbances, highlight the gaps in our understanding, and offer insight into potential future directions of investigating DBS as therapy for managing PD-related sleep disorders.

RESULTS

Pathophysiology of Sleep-Wake Disturbances in Parkinson Disease

The pathophysiological processes underlying sleep-wake disturbances in PD are complex, with influences from multiple factors such as neurochemical changes secondary to the neurodegenerative process, motor symptoms, autonomic dysfunction, and medication-induced alterations of sleep architecture and the circadian rhythm.

Dopaminergic neurons projecting to the striatum, cortex, and limbic structures play a significant role in regulation of the sleep-wake cycle (11). In PD, there is a gradual loss of dopaminergic neurons in the substantia nigra pars compacta and the ventral tegmental area (VTA) (12, 13). Loss of dopamine in mesocorticolimbic and mesostriatal pathways changes thalamocortical rhythms, resulting in impaired regulation of REM sleep, excessive daytime sleepiness, reduced deep sleep, and reduced sleep efficiency (11, 13, 14).

In addition, dysregulation of non-dopaminergic subcortical pathways from degenerative changes in the noradrenergic locus ceruleus, serotonergic raphe nucleus, and the cholinergic nucleus of Meynert and pedunculopontine nucleus (PPN) also play an important role in the development of sleep disorders (12, 15, 16). The PPN modulates wakefulness and REM sleep through its cholinergic inputs to the thalamic nuclei, particularly the relay nuclei and the reticular nucleus. Cholinergic inputs to these nuclei modulate firing patterns of thalamocortical and reticular thalamic neurons, thereby controlling transitions between wakefulness and sleep. PPN also provides input to orexin/hypocretin neurons located in hypothalamus and forebrain nucleus basalis, which regulate the sleep-wake cycle and promote arousal and attention (17). Some studies suggest that patients with PD may have loss of hypocretin in the brain and CSF, although other studies did not replicate this finding (18, 19). Loss of PPN neurons is implicated in sleep disorders as well as gait difficulty in PD (17).

Other factors contributing to sleep disturbances in PD patients can include nocturia, night-time cramps, motor symptoms including rigidity, tremor, dystonia, bradykinesia, and back pain (20–22). Nocturia is a common non-motor symptom in PD and is associated with increased nocturnal activity contributing to sleep maintenance insomnia (23). On polysomnography, PD patients with nocturia were shown to have reduced sleep efficiency and total sleep time (21). Motor symptoms such as bradykinesia, rigidity, and tremor occur frequently in PD patients with wearing off of dopaminergic medications at night. These symptoms impair bed mobility, interrupt sleep, and decrease sleep efficiency (24). Although dopaminergic medications can improve motor symptoms and therefore potentially improve sleep, they can also be associated with poor sleep quality, decreased REM sleep, and excessive daytime sleepiness, including unexpected sudden onset of sleep (sleep attacks) (25–27).

DBS in Parkinson Disease

DBS is an established therapy for motor complications in PD. The procedure involves surgical implantation of electrodes in specific brain regions. These electrodes are connected to a neurostimulator, which provides electrical impulses to the targeted areas and modulates brain circuits. The two commonly targeted sites for treating the cardinal motor symptoms of PD are subthalamic nucleus (STN) and globus pallidus interna (Gpi) (28). Other targets such as ventral intermediate nucleus (VIM) of thalamus are less often utilized. Multiple clinical trials have shown that high frequency DBS therapy can be superior to best medical therapy for motor complications in PD (8–10, 29). Despite clear efficacy of DBS in PD, its mechanism is not well understood and different hypotheses have been proposed (30, 31). Although, discussion of these hypotheses is beyond the scope of this article, it is suggested that DBS, through its excitatory and inhibitory effects on the targeted nucleus, disrupts abnormal information within cortico-basal ganglia-thalamic neural circuits, which results in improvement of motor symptoms (30, 31).

DBS and Sleep-Wake Disturbances in PD

The mechanism by which stimulation at different targets such as STN, GPi, and PPN regulates sleep architecture is not clearly understood. Effect of DBS on sleep disturbances may depend on the site of stimulation. STN has projections to sleep-regulatory centers including the thalamus, PPN, and cortex (32). Local

field potential recorded from STN during sleep have shown significant differences in band-power across different stages of sleep (33), suggesting a role in the sleep regulatory network. GPi is an important output nucleus of the basal ganglia which also has projections to sleep-wake modulating centers including the thalamus and PPN. Although the exact mechanism is unknown, it is possible that DBS at these sites modulates the sleep-wake network and directly affects sleep physiology. Both GPi and STN project to the globus pallidus externa (GPe), and it is suggested that improvement in sleep disturbances after DBS at these sites could be regulated through GPe (34).

The role of DBS in sleep-wake dysfunction in PD has been analyzed in multiple studies. These studies have utilized subjective and/or objective sleep measures (see below) to assess sleep outcomes after DBS surgery.

Measures of Sleep Parameters

Subjective sleep outcomes are measured with questionnaires, while objective sleep measures include polysomnography (PSG) and actigraphy. Commonly used scales for assessing subjective sleep include Parkinson Disease Sleep Scale (PDSS), PDSS-2, Pittsburgh Sleep Quality Index (PSQI), and Epworth Sleepiness Scale (ESS). PDSS is a validated self-rating scale consisting of 15 questions that quantify different aspects of sleep, including overall quality of nighttime sleep (item 1), sleep onset and sleep maintenance insomnia (items 2 and 3), nocturnal restlessness (items 4 and 5), distressing dreams (item 6), nocturnal psychosis (item 7), nocturia (items 8 and 9), nocturnal motor and sensory-motor symptoms (items 10–13), unsatisfactory sleep refreshment (item 14), and daytime dozing (item 15). Each question is rated on a visual analog scale from 0 (severe and always present) to 10 (not present) and scores are added. Higher scores indicate better sleep quality (35). PDSS-2 is a revised version of PDSS with more items on different aspects of sleep disturbances, such as restless legs syndrome and sleep apnea, and inclusion of a measure of frequency of symptoms (36). PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over a 1 month interval. Scores are generated based on seven components assessing subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Total scores range from 0 to 21 and a score >5 indicates impaired sleep quality (37). ESS is a self-rating scale with 8 questions (scored from 0 to 3) that assesses likelihood of falling asleep in different situations, such as reading or driving. The total scores range from 0 to 24 with a score >10 indicating excessive daytime sleepiness (38).

Subthalamic Nucleus (STN) DBS and Sleep-Wake Disturbances

The effect of STN DBS on sleep-wake disturbances has been examined in multiple studies (**Table 1**). Bauman-Vogel and colleagues studied 50 PD patients before and 6 months after bilateral STN DBS with Zurich sleep questionnaire, ESS, actigraphy, and PSG to assess both subjective and objective sleep parameters. They found that post STN DBS, self-reported mean sleep duration increased by around 40 mins ($p < 0.001$) and EDS reduced by 2.1 points ($p < 0.001$) on ESS. Improvement in total sleep time was also confirmed by actigraphy recording (improvement of ∼1 h, $p < 0.001$) and PSG (improvement by 21.2 min, $p = 0.016$). PSG results showed significant increase in sleep efficiency and deep sleep, and a reduction in wake after sleep onset (WASO) and REM latencies. PLMS indices doubled with stimulation, which was associated with reduction in dose of dopamine agonists. No significant change was seen in sleep fragmentation, occurrence of RBD and prevalence of RLS (39).

Multiple other studies have analyzed effect of STN DBS on sleep parameters. Nishida and colleagues evaluated 10 patients (bilateral STN 8, unilateral 2) with PDSS and PSG at 1 week prior to DBS surgery and 1 week post-DBS programming. They found significant improvement in subjective sleep quality and excessive sleepiness ($p = 0.01$) after DBS. PSG results showed a significant decrease in WASO and REM sleep without atonia and an increase in normal REM sleep duration after DBS ($p = 0.03$) (46). Another study evaluated 5 PD patients with bilateral STN using PSG and found significant reduction in WASO (−48%), latency to the first REM period (−58%), and significant increase in sleep efficiency (+60%) after 3 months of DBS. Total sleep time improved by 33% but this was not statistically significant. No changes in PLMS and RBD were observed (51). Iranzo and colleagues studied sleep outcomes in 11 PD patients with bilateral STN DBS. PSQI, ESS and PSG were done before and at 6 months post-DBS. They reported a significant improvement in PSQI scores (9.4 points) post-DBS. Improvement was seen in sleep quality, latency and sleep duration. PSG showed significant increase in continuous sleep, reduction in the arousal index and increase in nocturnal mobility. There was no change in RBD and PLMS index increased after surgery (54).

Few studies compared results of ON and OFF DBS stimulation on sleep-wake disturbances. Monaco and colleagues studied 10 patients with bilateral STN DBS and compared sleep parameters pre- and post-DBS (OFF and ON stimulation) at 3 months using PSQI questionnaire and PSG. The study found a significant improvement in subjective sleep quality (mean reduction of PSQI scores by 6.4 points) after surgery. There was a significant improvement in total sleep time (+ ∼80 mins), sleep efficiency, and duration of slow wave and REM sleep ($p < 0.01$) compared to pre-DBS evaluations. The difference was not seen when DBS was turned OFF. As none of the patients had PLMS and RBD pre- and post-DBS, these outcomes were not analyzed (52). In another study, Arnulf and colleagues evaluated 10 PD patients with PSG under OFF and ON stimulation conditions after 3–6 months of bilateral STN DBS. PSG was done during OFF and ON stimulation in two night sessions. A significant increase in sleep duration (47%), sleep efficiency (36%), stage 2 sleep (63%) and decrease in WASO (−51 mins) was seen ON stimulation compared to OFF stimulation. There were no significant differences in sleep fragmentation or RBD symptoms between ON and OFF stimulation. PLM indices were less frequent during OFF stimulation (55).

In another study, Amara and colleagues studied differential effects of alternate DBS frequencies on sleep measures in 20 patients with STN DBS (18 unilateral, 2 bilateral). Patients underwent PSG on 3 non-consecutive nights with DBS OFF, DBS at high frequency (≥130 Hz), and DBS at low frequency

TABLE 1 | Summary of studies examining the effects of STN DBS on sleep.

Study	*N*	Study type	Outcome measures	Outcome
Bauman-Vogel et al. (39)	50	Prospective, 6 mo	Zurich sleep questionnaire ESS Actigraphy recording PSG	Significant improvement in sleep duration & sleep efficiency Significant decrease in WASO, REM latency No change in sleep fragmentation, RBD and RLS
Amara et al. (40)	20	Cross sectional	PSG- DBS high freq vs. low freq	No significant difference in sleep parameters
Tolleson et al. (41)	5	Prospective, 6 mo	PSG	Reduced WASO, sleep latency and REM latency
Marques et al. (42)	31	Prospective, 6 mo	RLS	Emergence of RLS in 6 pts
Breen et al. (43)	11	Prospective, 6 mo	PDSS	Significant improvement in sleep quality
Deli et al. (44)	13	Prospective, 12 mo	PDSS-2	Significant improvement in sleep quality
Amara et al. (45)	53	Prospective, 6 mo	PSQI	Significant improvement in sleep quality
Nishida et al. (46)	10	Prospective, NR	PSG PDSS	Significant decrease in WASO Decrease in REM sleep without atonia and increase in normal REM sleep Improved subjective sleep quality
Chahine et al. (47)	17	Prospective, 6 mo	PDSS ESS IRLSSG scale	Significant improvement in sleep quality, ESS & RLS scores
Driver-dunckley et al. (48)	6	Retrospective	RLS	Significant improvement in RLS scores (improved by 84%) Mean LED reduction 56%
Lyons et al. (49)	43	Retrospective	Patient diaries ESS	Significant improvement in sleep quality, early morning dystonia No change in excessive daytime sleepiness
Hjort et al. (50)	10	Prospective, 3 mo	PDSS	Significant improvement in sleep quality No change in EDS and nocturia
Cicolin et al. (51)	5	Prospective, 3 mo	PSG	Significant reduction in WASO significant, increase in sleep efficiency, reduced REM latency No change in REM and PLMS
Monaco et al. (52)	10	Prospective, 3 mo	PSQI PSG—DBS ON vs. OFF	Significant improvement in subjective sleep quality ON DBS—Significant improvement in total sleep time, efficiency and duration of slow wave and REM sleep
Kedia et al. (53)	195	Retrospective	RLS	Emergence of RLS in 11 pts Mean LED reduction 74%
Iranzo et al. (54)	11	Prospective, 6 mo	PSQI PSG ESS	Significant improvement in subjective sleep quality Significant increase in continuous sleep, reduction in the arousal index and increase in nocturnal mobility There was no change in RBD and PLM increased after surgery
Arnulf et al. (55)	10	Prospective, 3 mo	PSG—DBS ON and OFF	ON DBS—Significant improvement in sleep duration, sleep efficiency, stage II sleep. Decrease in WASO No significant change in sleep fragmentation, RBD PLM worse with DBS ON

DBS, Deep Brain Stimulation; BL, bilateral; Uni, unilateral; PSG, Polysomnography; PSQI, Pittsburgh Sleep Quality Index; PDSS, Parkinson Disease Sleep Scale; WASO, wake time after sleep onset; ESS, Epworth Sleepiness scale; IRLSSG, International RLS Study Group; RBD, Rapid Eye Movement Sleep Behavior Disorder; LED, Levodopa equivalent dose.

(60 Hz). The authors did not see a significant difference in sleep efficiency or other sleep parameters between the two frequencies. A trend toward improvement was seen in total sleep time with stimulation at higher frequency and a shorter REM latency was seen with stimulation at lower frequency compared to OFF DBS (40). Surprisingly, sleep was not better with DBS ON compared to DBS OFF in many of the participants, suggesting that some patients may benefit from adaptive stimulation during which stimulation could be altered in different behavioral states (wake and sleep). Effects of microsubthalamotomy on sleep measures after bilateral STN DBS ($n = 15$) was evaluated in another study, which showed a significant improvement in sleep quality ($P < 0.001$) with participants reporting longer total sleep duration, decreased daytime sleepiness, and improvement in RLS symptoms in the immediate post-operative period prior to turning on DBS. PSG data showed an increase in total sleep time and sleep efficiency with a decrease in WASO and arousal index (56).

Additional studies utilized subjective sleep parameters as the primary outcome and showed significant improvement in sleep quality with STN DBS. Deli and colleagues measured PDSS-2 scores in 13 participants with PD related sleep complaints before and after STN DBS and found significant improvement in quality of sleep at 1 year ($p < 0.001$) (44). Hjort and colleagues assessed subjective sleep quality with PDSS questionnaire in 10 patients with bilateral STN DBS and compared results to controls who did not have DBS. They found a significant improvement in PDSS scores in the DBS group at 3 months compared to pre-DBS and controls. Significant improvement was seen in overall quality of sleep and nocturnal motor symptoms. There was no change in nocturia, sleep fragmentation, or daytime sleepiness (50). Another study assessing subjective sleep quality with PDSS also reported significant improvement in sleep parameters following STN DBS (43). In a study using the PSQI questionnaire, the effects of unilateral STN DBS on subjective sleep quality was examined in 53 consecutive PD patients before and after unilateral STN DBS. The study found that unilateral STN DBS significantly improved subjective sleep quality at 6 months compared to pre-DBS baseline ($p = 0.013$). PSQI sub-scores including sleep quality and sleep disturbances significantly improved ($p < 0.01$), while sleep latency, sleep duration, sleep efficiency, use of sleep medications, and daytime dysfunction showed a trend toward improvement (45). In a long-term study in 43 PD patients, bilateral STN DBS was shown to increase total sleep time and reduce patient reported sleep problems and early morning dystonia for up to 24 months. There was no change in excessive daytime sleepiness (49).

Studies on the effects of STN DBS on restless legs symptoms have conflicting results. Chahine and colleagues studied 17 PD patients with STN DBS and found significant improvement in International Restless Legs Syndrome Study Group (IRLSGG) rating scale scores at 6 months in six patients (-9.2, $p = 0.037$) as well as improvement in sleep quality and excessive sleepiness (47). A retrospective study also showed an improvement of 84% in IRLSGG scale scores after bilateral STN DBS. This improvement was despite a mean reduction in levodopa equivalent dose (LED) by 56% (48). On the contrary, a study by Kedia and colleagues reported emergence of RLS in 11 of 195 patients post-DBS surgery. The mean reduction in LED was 74% in patients who developed RLS compared to 40% reduction in those who did not develop RLS. This study did not use rigorous diagnostic criteria for RLS so some patients may have been misdiagnosed (53). Another study aimed to identify factors associated with development of RLS after STN DBS. The study found that, of 31 total participants, six patients who were originally free from RLS symptoms had emergence of RLS symptoms at 6 months after DBS. Interestingly, patients with emergence of RLS had a significantly higher dose of dopamine agonists post-DBS (mean 155 mg/day) compared to PD patients without emergence of RLS (mean 0.00 mg/day) ($p = 0.043$) and a lower percentage change in dopamine agonist treatment in RLS group compared to patients without RLS (0.00 vs. 66.67%, $p = 0.043$). The authors concluded that overstimulation resulting from cumulative effects of dopamine agonists and STN DBS may lead to emergence of RLS (42).

Globus Pallidus Internus (GPi) DBS and Sleep-Wake Disturbances

There is limited data on effect of GPi DBS on sleep-wake disturbances in PD. The only study analyzing effects of GPi DBS on objective sleep outcomes found improvement in sleep quality and efficiency, and decreased WASO, sleep latency and REM latency in 5 PD patients at 6 months. These improvements were not statistically significant (41). Other studies have reported improvement in subjective daytime sleepiness and sleep quality; however, in these studies, sleep-related parameters were not the primary outcome measures (57, 58).

In a randomized clinical trial comparing results GPi vs. STN DBS (NSTAPS) on clinical outcomes up to 3 years after surgery, subjective sleep quality was assessed with PDSS. The study reported that with bilateral GPi stimulation there was an improvement in PDSS scores at 12 months ($+7.2$, $n = 62$) and 36 months ($+ 12.1$, $n = 47$) compared to baseline. No significant difference was seen in PDSS scores between STN and GPi groups (59).

Role of Other DBS Targets in Sleep-Wake Disturbances

PPN is an important modulator of sleep-wake cycle. Few studies have investigated the effect of PPN stimulation on objective or subjective sleep parameters in PD. The influence of PPN stimulation on sleep was first reported in a single patient who underwent DBS placement in bilateral STN and PPN. PSG measures pre- and post-DBS with STN-ON and PPN-ON were compared. Both bilateral STN DBS and PPN DBS improved sleep efficiency and decreased WASO and nocturnal awakenings. Surprisingly, PPN DBS at 25 Hz significantly increased REM sleep duration, which was not seen with STN DBS (60). The same group assessed effect of PPN DBS on subjective sleep quality measures using ESS, PDSS and PSQI in six patients with bilateral STN and PPN DBS. Analysis was done under three circumstances during which STN DBS was kept ON: PPN-OFF, continuous PPN-ON, and cyclic PPN-ON. The duration of the study was not reported. Stimulation parameters were kept the same for 2 weeks prior to assessment. The authors found a significant improvement in daytime sleepiness with both continuous and cyclic PPN DBS and improvement in daytime sleepiness, nocturnal restlessness, and psychosis with cyclic PPN DBS. In this study another patient had PSG, which showed that PPN DBS (25 Hz) improved sleep efficiency, decreased awakenings, and significantly increased REM sleep (61). This group later evaluated long-term effects of PPN DBS on the subjective sleep quality in five patients using PDSS and ESS scales. Evaluations were done pre-DBS and post-DBS at 3 months and 12 months. During the study duration STN DBS was kept continuously ON, and PPN DBS was investigated under three conditions; STN-ON (185 Hz), PPN-ON (25 Hz), and PPN-cyclic (25 Hz) during which PPN was kept ON only at night for 12 h. Each stimulation parameter was kept for 2 weeks prior to assessment. All patients reported poor sleep quality prior to DBS. Post-DBS at 3 months there was a significant improvement in nocturnal sleep quality under all DBS conditions, with a mean improvement in PDSS global score by 41% in STN-ON ($P < 0.05$), 35% in PPN-ON

($P < 0.05$), and 57% in PPN-cyclic ($P < 0.05$). PPN DBS also improved sleep onset and maintenance insomnia compared to STN DBS, while PPN-cyclic improved nocturnal restlessness, psychosis and dozing compared to PPN-ON continuous and STN DBS. Sleep quality measures further improved at 12 months with PPN DBS. Excessive daytime sleepiness significantly improved at 3 months with only PPN-ON (46%; $P < 0.05$) and PPN-cyclic (60%; $P < 0.05$), and this improvement persisted at 12 months. STN DBS did not improve ESS score at 3 and 12 months (62).

Another study by Lim et al. studied effect of unilateral PPN DBS on PSG in five patients with Parkinsonism. The frequency of PPN DBS was 70 Hz in three patients with PD and between 5 and 30 Hz in two patients with Progressive supranuclear palsy (PSP). Assessments were done in both PPN-OFF and PPN-ON state up to 12 months after surgery. The study found a significant increase in REM sleep with PPN-ON as compared to PPN-OFF ($p = 0.03$) and WASO improved with PPN-ON ($p = 0.21$). Sleep duration and non-REM sleep remained unchanged. There was no change in RBD in two patients who had RBD (63).

PPN DBS was also found to have effect on alertness. A study involving two patients with STN DBS who subsequently underwent bilateral PPN DBS, showed that high-frequency PPN stimulation induces sleep. These findings were supported by results of daytime PSG study under different conditions including OFF stimulation, and left, right, and bilateral PPN stimulation at either low or higher frequencies. The authors found that high frequency stimulation (80 Hz) induced sleep and low frequency stimulation (10–25 Hz) enhanced alertness. In one patient sudden withdrawal of low-frequency stimulation consistently induced sleep within 0.6–1.7 min and REM sleep within 3–6 min (64).

The role of high frequency VIM DBS on sleep architecture was evaluated in one study. In this study six patients (4 PD and 2 ET) underwent PSG study during VIM OFF and ON DBS. No significant difference was noted in sleep spindle or architecture between OFF and ON DBS. Low frequency stimulation, either continuous or cyclic, in region of the reticular nuclei did not induce sleep in awake patients (65).

DISCUSSION

DBS therapy revolutionized the management of motor symptoms in PD and has become a widely accepted treatment option. However, its effect on non-dopaminergic symptoms such as neuropsychiatric issues, autonomic dysfunction, and sleep disturbances is not entirely clear and newer targets are being investigated (66). As non-motor symptoms have significant impact on quality of life in patients with PD, developing new treatments or understanding the impact of established treatments such as DBS on these symptoms is important. With the neuromodulatory potential of DBS on different neural circuits, its effect on non-dopaminergic symptoms including sleep-wake disturbances with stimulation at different targets have been studied.

The current evidence suggest that DBS therapy improves different aspects of sleep-wake disturbances in PD. Studies analyzing effects of STN DBS on both subjective and objective sleep parameters have shown a significant improvement in sleep quality, sleep efficiency and sleep duration (39, 46, 52, 54). The duration of WASO and REM latency is reduced after STN DBS, however, available data suggests that DBS therapy may not change sleep fragmentation or RBD (39, 50, 51, 54, 55). Conflicting outcomes were seen in studies investigating the influence of DBS on RLS, (42, 47, 53) with some studies showing significant improvement in RLS scores while other studies reported no change and re-emergence of RLS post-DBS. These conflicting results could be due to different study methodology and future studies with similar methodology may help us to delineate this further. The effects of STN DBS on sleep-wake disturbances in PD have been attributed to improvement in motor symptoms, reduction in dopaminergic medications, and neuromodulation of basal-ganglia circuits affecting sleep physiology (39, 55, 67). STN DBS effectively improves motor symptoms and improves nocturnal mobility, which contributes in improving sleep quality. STN DBS may also be potentially modulating sleep-wake centers. However the exact neuromodulatory effects of STN DBS on sleep physiology is unknown and is further complicated by the fact that the therapeutic mechanism of DBS is still debated (30). There is currently very limited literature on effects of other DBS targets. DBS of GPi has shown improvement in sleep quality and efficiency, as well as reduced time awake and shortened REM latency. These findings were similar to the effects of STN DBS on sleep. More studies evaluating the effects of GPi DBS on sleep disturbances in PD are needed. PPN is another important target, which is being explored for its effect on gait and posture (68). Available studies examining effects of PPN DBS on sleep have shown that low frequency stimulation of PPN improves excessive daytime sleepiness, increase REM sleep, and improves sleep quality. Although the thalamus is a common target for DBS in movement disorders, the role of thalamic stimulation on sleep is not known.

Despite limitations in the current understanding of the pathophysiological role of DBS in sleep, this therapy has provided a great opportunity to study the role of neuromodulation for different non-motor symptoms. As sleep disturbances contribute to impaired quality of life, the DBS-mediated improvement in sleep is encouraging, particularly in light of the limited treatment options for sleep disturbances. Studying the effects of DBS at different sites can also help in understanding sleep pathophysiology. Future studies with larger samples, examining and comparing effects of stimulation at different targets on various aspects of sleep are needed.

EXPERT STATEMENT

Sleep dysfunction is a disabling non-motor symptom experienced by the majority of patients with Parkinson disease (PD). Deep brain stimulation (DBS) is superior to best medical therapy (BMT) for improving the motor symptoms of PD. As the

impact of non-motor symptoms on quality of life in PD has been increasingly recognized, the research community has turned attention to investigating the influence of DBS on these symptoms.

Studies on the influence of subthalamic nucleus (STN) DBS on sleep have consistently shown that this therapy improves subjective sleep quality. Many studies also suggest improvement in objective sleep measures, although different aspects of sleep architecture are improved in different studies. This may depend on several factors, including baseline sleep function, types of sleep complaints (i.e., nocturnal sleep dysfunction vs. daytime sleepiness), age, PD disease duration, location of DBS electrode within the nucleus, DBS settings, PD motor phenotype, or other factors. The improvement in sleep due to STN DBS could be related to improved motor symptoms, changes in medications, or alteration of neural circuits responsible for sleep. Additional research is needed to better delineate who might benefit most from the effects of DBS on sleep. Some of the research suggests that different approaches may be needed for individual patients and closed loop stimulation methodologies may help meet this need. Additional study is also needed to better define the influence of DBS at other targets, such as globus pallidus interna (GPi) and pedunculopontine nucleus (PPN), on sleep. This is an exciting area with promise and much to still be learned.

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AUTHORS CONTRIBUTIONS

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REFERENCES

1. Kalia LV, Lang AE. Parkinson's disease. *Lancet* (2015) 386:896–912. doi: 10.1016/s0140-6736(14)61393-3
2. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. *Nature Rev Neurosci.* (2017) 18:435–50. doi: 10.1038/nrn.2017.62
3. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord.* (2009) 24:1641–9. doi: 10.1002/mds.22643
4. Parkinson J. An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci.* (2002) 14:223–36; discussion:2. doi: 10.1176/jnp.14.2.223
5. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. *Sleep Med Rev.* (2017) 35:33–50. doi: 10.1016/j.smrv.2016.08.001
6. Scaravilli T, Gasparoli E, Rinaldi F, Polesello G, Bracco F. Health-related quality of life and sleep disorders in Parkinson's disease. *Neurol Sci.* (2003) 24:209–10. doi: 10.1007/s10072-003-0134-y
7. Rolinski M, Szewczyk-Krolikowski K, Tomlinson PR, Nithi K, Talbot K, Ben-Shlomo Y, et al. REM sleep behaviour disorder is associated with worse quality of life and other non-motor features in early Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2014) 85:560–6. doi: 10.1136/jnnp-2013-306104
8. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schafer H, Botzel K, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med.* (2006) 355:896–908. doi: 10.1056/NEJMoa060281
9. Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ Jr, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* (2009) 301:63–73. doi: 10.1001/jama.2008.929
10. Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med.* (2013) 368:610–22. doi: 10.1056/NEJMoa1205158
11. Rye DB. The two faces of Eve: dopamine's modulation of wakefulness and sleep. *Neurology* (2004) 63(8 Suppl. 3):S2–7. doi: 10.1212/WNL.63.8_suppl_3.S2
12. Jellinger KA. Pathology of Parkinson's disease. changes other than the nigrostriatal pathway. *Mol Chem Neuropathol.* (1991) 14:153–97.
13. Eban-Rothschild A, Rothschild G, Giardino WJ, Jones JR, de Lecea L. VTA dopaminergic neurons regulate ethologically relevant sleep-wake behaviors. *Nat Neurosci.* (2016) 19:1356–66. doi: 10.1038/nn.4377
14. Fifel K, Vezoli J, Dzahini K, Claustrat B, Leviel V, Kennedy H, et al. Alteration of daily and circadian rhythms following dopamine depletion in MPTP treated non-human primates. *PLoS ONE* (2014) 9:e86240. doi: 10.1371/journal.pone.0086240
15. Pace-Schott EF, Hobson JA. The neurobiology of sleep: genetics, cellular physiology and subcortical networks. *Nat Rev Neurosci.* (2002) 3:591–605. doi: 10.1038/nrn895
16. Kalaitzakis ME, Gentleman SM, Pearce RK. Disturbed sleep in Parkinson's disease: anatomical and pathological correlates. *Neuropathol Appl Neurobiol.* (2013) 39:644–53. doi: 10.1111/nan.12024
17. Benarroch EE. Pedunculopontine nucleus: functional organization and clinical implications. *Neurology* (2013) 80:1148–55. doi: 10.1212/WNL.0b013e3182886a76
18. Thannickal TC, Lai YY, Siegel JM. Hypocretin (orexin) cell loss in Parkinson's disease. *Brain* (2007) 130(Pt. 6):1586–95. doi: 10.1093/brain/awm097
19. Fronczek R, Overeem S, Lee SY, Hegeman IM, van Pelt J, van Duinen SG, et al. Hypocretin (orexin) loss in Parkinson's disease. *Brain* (2007) 130(Pt. 6):1577–85. doi: 10.1093/brain/awm090
20. Dhawan V, Dhoat S, Williams AJ, Dimarco A, Pal S, Forbes A, et al. The range and nature of sleep dysfunction in untreated Parkinson's disease (PD). a comparative controlled clinical study using the Parkinson's disease sleep scale and selective polysomnography. *J Neurol Sci.* (2006) 248:158–62. doi: 10.1016/j.jns.2006.05.004
21. Vaughan CP, Juncos JL, Trotti LM, Johnson TM II, Bliwise DL. Nocturia and overnight polysomnography in Parkinson disease. *Neurourol Urodyn.* (2013) 32:1080–5. doi: 10.1002/nau.22365
22. Louter M, Munneke M, Bloem BR, Overeem S. Nocturnal hypokinesia and sleep quality in Parkinson's disease. *J Am Geriatrics Soc.* (2012) 60:1104–8. doi: 10.1111/j.1532-5415.2012.03966.x
23. Perez Lloret S, Rossi M, Merello M, Rascol O, Cardinali DP. Nonmotor symptoms groups in Parkinson's disease patients: results of a pilot, exploratory study. *Parkinson's Dis.* (2011) 2011:473579. doi: 10.4061/2011/473579
24. Louter M, van Sloun RJ, Pevernagie DA, Arends JB, Cluitmans PJ, Bloem BR, et al. Subjectively impaired bed mobility in Parkinson disease affects sleep efficiency. *Sleep Med.* (2013) 14:668–74. doi: 10.1016/j.sleep.2013.03.010
25. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* (1999) 52:1908–10.
26. Chahine LM, Daley J, Horn S, Duda JE, Colcher A, Hurtig H, et al. Association between dopaminergic medications and nocturnal sleep in early-stage Parkinson's disease. *Parkinsonism Relat Disord.* (2013) 19:859–63. doi: 10.1016/j.parkreldis.2013.05.009
27. Schafer D, Greulich W. Effects of parkinsonian medication on sleep. *J Neurol.* (2000) 247(Suppl. 4):IV/24-7. doi: 10.1007/pl00007770
28. Williams NR, Foote KD, Okun MS. STN vs. GPi deep brain stimulation: translating the rematch into clinical practice. *Mov Disord Clin Pract.* (2014) 1:24–35. doi: 10.1002/mdc3.12004
29. Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone

for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol.* (2010) 9:581–91. doi: 10.1016/s1474-4422(10)70093-4
30. Miocinovic S, Somayajula S, Chitnis S, Vitek JL. History, applications, and mechanisms of deep brain stimulation. *JAMA Neurol.* (2013) 70:163–71. doi: 10.1001/2013.jamaneurol.45
31. Chiken S, Nambu A. Mechanism of deep brain stimulation: inhibition, excitation, or disruption? *Neurosci.* (2016) 22:313–22. doi: 10.1177/1073858415581986
32. Benarroch EE. Subthalamic nucleus and its connections. *Anatom Subs Netw Effects Deep Brain Stimul.* (2008) 70:1991–5. doi: 10.1212/01.wnl.0000313022.39329.65
33. Thompson JA, Tekriwal A, Felsen G, Ozturk M, Telkes I, Wu J, et al. Sleep patterns in Parkinson's disease: direct recordings from the subthalamic nucleus. *J Neurol Neurosurg Psychiatry* (2018) 89:95–104. doi: 10.1136/jnnp-2017-316115
34. Qiu MH, Chen MC, Wu J, Nelson D, Lu J. Deep brain stimulation in the globus pallidus externa promotes sleep. *Neuroscience* (2016) 322:115–20. doi: 10.1016/j.neuroscience.2016.02.032
35. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2002) 73:629–35. doi: 10.1136/jnnp.73.6.629
36. Trenkwalder C, Kohnen R, Hogl B, Metta V, Sixel-Doring F, Frauscher B, et al. Parkinson's disease sleep scale–validation of the revised version PDSS-2. *Mov Disord.* (2011) 26:644–52. doi: 10.1002/mds.23476
37. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* (1989) 28:193–213.
38. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* (1991) 14:540–5.
39. Baumann-Vogel H, Imbach LL, Surucu O, Stieglitz L, Waldvogel D, Baumann CR, et al. The impact of subthalamic deep brain stimulation on sleep-wake behavior: a prospective electrophysiological study in 50 Parkinson patients. *Sleep* (2017) 40:zsx033. doi: 10.1093/sleep/zsx033
40. Amara AW, Walker HC, Joop A, Cutter G, DeWolfe JL, Harding SM, et al. Effects of subthalamic nucleus deep brain stimulation on objective sleep outcomes in Parkinson's disease. *Mov Disord Clin Pract.* (2017) 4:183–90. doi: 10.1002/mdc3.12375
41. Tolleson CM, Bagai K, Walters AS, Davis TL. A pilot study assessing the effects of pallidal deep brain stimulation on sleep quality and polysomnography in Parkinson's patients. *Neuromodulation* (2016) 19:724–30. doi: 10.1111/ner.12442
42. Marques A, Fantini ML, Morand D, Pereira B, Derost P, Ulla M, et al. Emergence of restless legs syndrome after subthalamic stimulation in Parkinson's disease: a dopaminergic overstimulation? *Sleep Med.* (2015) 16:583–8. doi: 10.1016/j.sleep.2014.11.020
43. Breen DP, Low HL, Misbahuddin A. The impact of deep brain stimulation on sleep and olfactory function in Parkinson's disease. *Open Neurol J* (2015) 9:70–2. doi: 10.2174/1874205x01509010070
44. Deli G, Aschermann Z, Acs P, Bosnyak E, Janszky J, Faludi B, et al. Bilateral subthalamic stimulation can improve sleep quality in Parkinson's disease. *J Parkinson's Dis.* (2015) 5:361–8. doi: 10.3233/jpd-150540
45. Amara AW, Standaert DG, Guthrie S, Cutter G, Watts RL, Walker HC. Unilateral subthalamic nucleus deep brain stimulation improves sleep quality in Parkinson's disease. *Parkinsonism Relat Disord.* (2012) 18:63–8. doi: 10.1016/j.parkreldis.2011.09.001
46. Nishida N, Murakami T, Kadoh K, Tohge R, Yamanegi M, Saiki H, et al. Subthalamic nucleus deep brain stimulation restores normal rapid eye movement sleep in Parkinson's disease. *Mov Disord.* (2011) 26:2418–22. doi: 10.1002/mds.23862
47. Chahine LM, Ahmed A, Sun Z. Effects of STN DBS for Parkinson's disease on restless legs syndrome and other sleep-related measures. *Parkinsonism Relat Disord.* (2011) 17:208–11. doi: 10.1016/j.parkreldis.2010.11.017
48. Driver-Dunckley E, Evidente VG, Adler CH, Hillman R, Hernandez J, Fletcher G, et al. Restless legs syndrome in Parkinson's disease patients may improve with subthalamic stimulation. *Mov Disord.* (2006) 21:1287–9. doi: 10.1002/mds.20911
49. Lyons KE, Pahwa R. Effects of bilateral subthalamic nucleus stimulation on sleep, daytime sleepiness, and early morning dystonia in patients with Parkinson disease. *J Neurosurg.* (2006) 104:502–5. doi: 10.3171/jns.2006.104.4.502
50. Hjort N, Ostergaard K, Dupont E. Improvement of sleep quality in patients with advanced Parkinson's disease treated with deep brain stimulation of the subthalamic nucleus. *Mov Disord.* (2004) 19:196–9. doi: 10.1002/mds.10639
51. Cicolin A, Lopiano L, Zibetti M, Torre E, Tavella A, Guastamacchia G, et al. Effects of deep brain stimulation of the subthalamic nucleus on sleep architecture in parkinsonian patients. *Sleep Med.* (2004) 5:207–10. doi: 10.1016/j.sleep.2003.10.010
52. Monaca C, Ozsancak C, Jacquesson JM, Poirot I, Blond S, Destee A, et al. Effects of bilateral subthalamic stimulation on sleep in Parkinson's disease. *J Neurol.* (2004) 251:214–8. doi: 10.1007/s00415-004-0305-7
53. Kedia S, Moro E, Tagliati M, Lang AE, Kumar R. Emergence of restless legs syndrome during subthalamic stimulation for Parkinson disease. *Neurology* (2004) 63:2410–2. doi: 10.1212/01.wnl.0000147288.26029.b8
54. Iranzo A, Valldeoriola F, Santamaria J, Tolosa E, Rumia J. Sleep symptoms and polysomnographic architecture in advanced Parkinson's disease after chronic bilateral subthalamic stimulation. *J Neurol Neurosurg Psychiatry* (2002) 72:661–4. doi: 10.1136/jnnp.72.5.661
55. Arnulf I, Bejjani BP, Garma L, Bonnet AM, Houeto JL, Damier P, et al. Improvement of sleep architecture in PD with subthalamic nucleus stimulation. *Neurology* (2000) 55:1732–4. doi: 10.1212/wnl.55.11.1732
56. Merlino G, Lettieri C, Mondani M, Belgrado E, Devigili G, Mucchiut M, et al. Microsubthalamotomy improves sleep in patients affected by advanced Parkinson's disease. *Sleep Med.* (2014) 15:637–41. doi: 10.1016/j.sleep.2013.12.016
57. Rodrigues JP, Walters SE, Watson P, Stell R, Mastaglia FL. Globus pallidus stimulation improves both motor and nonmotor aspects of quality of life in advanced Parkinson's disease. *Mov Disord.* (2007) 22:1866–70. doi: 10.1002/mds.21427
58. Volkmann J, Albanese A, Kulisevsky J, Tornqvist AL, Houeto JL, Pidoux B, et al. Long-term effects of pallidal or subthalamic deep brain stimulation on quality of life in Parkinson's disease. *Mov Disord.* (2009) 24:1154–61. doi: 10.1002/mds.22496
59. Odekerken VJ, Boel JA, Schmand BA, de Haan RJ, Figee M, van den Munckhof P, et al. GPi vs STN deep brain stimulation for Parkinson disease: three-year follow-up. *Neurology* (2016) 86:755–61. doi: 10.1212/wnl.0000000000002401
60. Romigi A, Placidi F, Peppe A, Pierantozzi M, Izzi F, Brusa L, et al. Pedunculopontine nucleus stimulation influences REM sleep in Parkinson's disease. *Eur J Neurol.* (2008) 15:e64-5. doi: 10.1111/j.1468-1331.2008.02167.x
61. Alessandro S, Ceravolo R, Brusa L, Pierantozzi M, Costa A, Galati S, et al. Non-motor functions in parkinsonian patients implanted in the pedunculopontine nucleus: focus on sleep and cognitive domains. *J Neurol Sci.* (2010) 289:44–8. doi: 10.1016/j.jns.2009.08.017
62. Peppe A, Pierantozzi M, Baiamonte V, Moschella V, Caltagirone C, Stanzione P, et al. Deep brain stimulation of pedunculopontine tegmental nucleus: role in sleep modulation in advanced Parkinson disease patients: one-year follow-up. *Sleep* (2012) 35:1637–42. doi: 10.5665/sleep.2234
63. Lim AS, Moro E, Lozano AM, Hamani C, Dostrovsky JO, Hutchison WD, et al. Selective enhancement of rapid eye movement sleep by deep brain stimulation of the human pons. *Ann Neurol.* (2009) 66:110–4. doi: 10.1002/ana.21631
64. Arnulf I, Ferraye M, Fraix V, Benabid AL, Chabardes S, Goetz L, et al. Sleep induced by stimulation in the human pedunculopontine nucleus area. *Ann Neurol.* (2010) 67:546–9. doi: 10.1002/ana.21912
65. Arnulf I, Bejjani BP, Garma L, Bonnet AM, Damier P, Pidoux B, et al. Effect of low and high frequency thalamic stimulation on sleep in patients with Parkinson's disease and essential tremor. *J Sleep Res.* (2000) 9:55–62. doi: 10.1046/j.1365-2869.2000.00171.x

66. Castrioto A, Moro E. New targets for deep brain stimulation treatment of Parkinson's disease. *Expert Rev Neurother.* (2013) 13:1319–28. doi: 10.1586/14737175.2013.859987
67. Amara AW, Watts RL, Walker HC. The effects of deep brain stimulation on sleep in Parkinson's disease. *Ther Adv Neurol Disord.* (2011) 4:15–24. doi: 10.1177/1756285610392446
68. Fournier-Gosselin MP, Lipsman N, Saint-Cyr JA, Hamani C, Lozano AM. Regional anatomy of the pedunculopontine nucleus: relevance for deep brain stimulation. *Mov Disord.* (2013) 28:1330–6. doi: 10.1002/mds.25620

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REVIEW
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Neuroimaging of Sleep Disturbances in Movement Disorders

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Sleep dysfunction is recognized as a distinct clinical manifestation in movement disorders, often reported early on in the disease course. Excessive daytime sleepiness, rapid eye movement sleep behavior disorder and restless leg syndrome, amidst several others, are common sleep disturbances that often result in significant morbidity. In this article, we review the spectrum of sleep abnormalities across atypical Parkinsonian disorders including multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS), as well as Parkinson's disease (PD) and Huntington's disease (HD). We also explore the current concepts on the neurobiological underpinnings of sleep disorders, including the role of dopaminergic and non-dopaminergic pathways, by evaluating the molecular, structural and functional neuroimaging evidence based on several novel techniques including magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Based on the current state of research, we suggest that neuroimaging is an invaluable tool for assessing structural and functional correlates of sleep disturbances, harboring the ability to shed light on the sleep problems attached to the limited treatment options available today. As our understanding of the pathophysiology of sleep and wake disruption heightens, novel therapeutic approaches are certain to transpire.

Keywords: neuroimaging, magnetic resonance imaging, positron emission tomography, sleep, Parkinson's disease, atypical Parkinsonism, REM behavior sleep disorder, excessive daytime sleepiness

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INTRODUCTION

Sleep-wake disturbances are increasingly being recognized as common symptoms in neurodegenerative diseases, particularly movement disorders. Given that the quality of sleep is intrinsically associated to the quality of life, sleep disturbances inevitably induce significant morbidity. Therefore, early identification and effective treatment of sleep abnormalities is of considerable therapeutic interest, particularly for improving quality of life, delaying institutionalization and potentially reducing healthcare costs (1). Furthermore, emerging evidence has demonstrated that disturbed sleep-wake cycles may precede, influence and/or facilitate disease progression, thus possessing the potential to serve as early indicators of ongoing neurodegeneration and providing a window of opportunity to administer disease-modifying interventions early in the course of neurodegeneration.

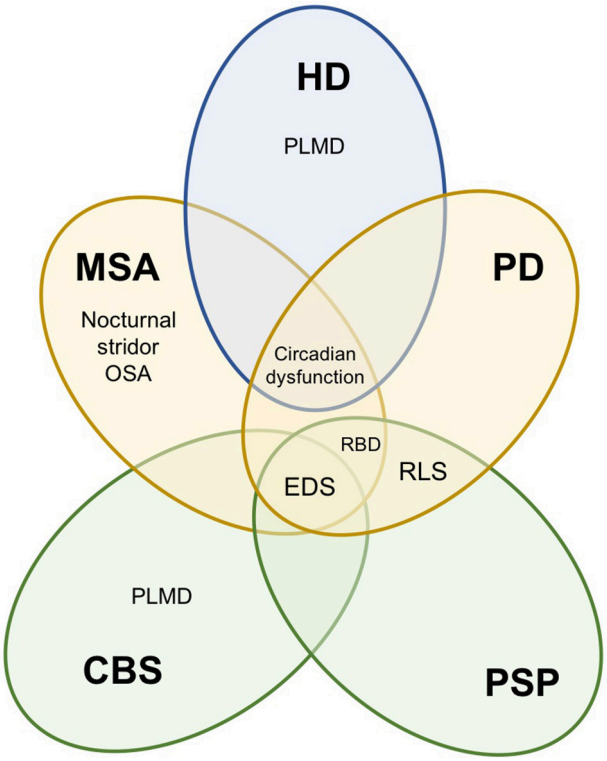

FIGURE 1 | Summary of sleep disturbances found in movement disorders. Movement disorders exhibit some overlap in sleep disturbances. PSP and CBS are tauopathies (green), PD and MSA are synucleinopathies (yellow) and HD is a hereditary disorder (blue). PSP, progressive supranuclear palsy; CBS, corticobasal syndrome; PD, Parkinson's disease; MSA, multiple system atrophy; HD, Huntington's disease; EDS, excessive daytime sleepiness; RBD, REM behavior sleep disorder, RLS, restless leg syndrome; PLMD, periodic limb movement disorder; OSA, obstructive sleep apnoea.

Sleep disturbances can manifest as insomnia, sleep-disordered breathing, sleep fragmentation, restless leg syndrome (RLS), periodic limb movement disorder (PLMD), excessive daytime sleepiness (EDS) and parasomnias associated with rapid eye movements (REM) sleep. Whilst there is considerable overlap in the types of sleep disturbances reported across movement disorders, some sleep problems are either unique to, or substantially more prevalent in certain movement disorders (**Figure 1**). The origin of these sleep disorders is multifactorial, including neurodegeneration of central sleep regulatory structures, circadian dysfunction, impact of motor and non-motor symptoms, and adverse effects of medications (2–5).

Neuroimaging techniques, such as magnetic resonance imaging (MRI) and functional MRI (fMRI) have played a fundamental role in characterizing the structural and functional changes in patients suffering from sleep disturbances. Positron emission tomography (PET) is a powerful technique for investigating *in vivo* abnormalities in brain metabolism and receptor distribution, by enabling the measurement of radioligand distribution, which is introduced into the body on a biologically active molecule (6). By revealing the regional patterns of activation associated with specific sleep disorders, data from imaging methods, including single photon emission computed tomography (SPECT) (7–10), have complemented and extended previous findings predominantly based on electroencephalography (EEG) studies, thus improving and better characterizing the pathogenic mechanisms of major sleep disturbances.

In this article, we review the major sleep disturbances commonly experienced by patients with movement disorders, including Parkinson's disease (PD), Huntington's disease (HD) and atypical Parkinsonism, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and corticobasal syndrome (CBS). We discuss the role of neuroimaging in identifying neural correlates of various sleep disorders, with the aim of assessing how these studies have improved our knowledge via the insight gained into the underlying mechanisms of major sleep disturbances (**Table 1**).

REGULATORY CIRCUITS INVOLVED IN SLEEP

Sleep is indispensable for promoting adequate health and bodily function, given that it is an active physiological process required for protection and normalization of all major organs and regulatory systems (11). Sleep is a global and dynamically regulated state, primarily by two intimately integrated internal biological mechanisms: circadian rhythm and homeostasis. These control mechanisms are expressed at all levels of biological organization, from genes and intracellular mechanisms to neural networks and central neuronal systems at the organismic level. Several brain structures, both subcortical and forebrain areas, have specific functions in sleep at different organizational levels, controlling sleep-wake transitions as well as alternating between rapid eye movement (REM) and non-REM sleep (**Figure 2**) (12).

The Circadian System

Circadian rhythms, which can be defined as physiological and behavioral cycles with a periodicity of approximately 24 h, are orchestrated by sophisticated molecular loops. Given that the circadian system dictates the 24-h rhythmicity in biological processes such as rest-activity behavior, hormonal level, feeding and body temperature, disruption of this system can ultimately lead to negative affects imposed on alertness, sleep quality, cognitive performance, mental health, motor control and metabolism (4). These functions are often impaired in neurodegenerative diseases, with multiple brain areas, including nuclei involved in circadian and sleep regulation, being affected by neurodegenerative processes. Therefore, it is not surprising that neurodegenerative disorders often illustrate a progressive breakdown of the normal cycles of sleep and wakefulness, which not only contribute to poor quality of life and morbidity; but could also influence the disease process itself.

Molecularly, an interlocking positive-negative feedback mechanism controlling gene transcription and their protein

TABLE 1 | Summary of functional and structural changes associated with common sleep disturbances in movement disorders.

Movement disorder	Sleep disturbance	Neuroimaging data	
		Functional changes	**Structural changes**
Parkinson's disease	REM behavior sleep disorder	Presynaptic dopaminergic system ↓ Postsynaptic dopaminergic system ↔ Cerebral perfusion and glucose metabolism ↑↓ Presynaptic serotonergic system ↔ Presynaptic cholinergic system ↓ Functional connectivity ↓	Gray matter volume ↓↑↔ White matter integrity ↓ Neuromelanin density ↓
	Excessive daytime sleepiness	Presynaptic dopaminergic system ↓ Cerebral perfusion ↑↓ Extrastriatal dopaminergic system ↓ Presynaptic serotonergic system ↓↔ Functional connectivity ↓	Gray matter volume ↓ White matter integrity ↓↔
	Restless leg syndrome	Presynaptic dopaminergic system ↓↑↔ Postsynaptic dopaminergic system ↓↑↔ Functional connectivity ↑	Gray matter volume ↓ White matter integrity ↓↑↔ Iron concentration ↓
Multiple System Atrophy	REM sleep behavior disorder	Presynaptic dopaminergic system ↓ Presynaptic cholinergic system ↓	–
	Excessive daytime sleepiness	–	Gray matter volume ↔
	Obstructive sleep apnea	Presynaptic cholinergic system ↓	
Progressive Supranuclear Palsy	REM behavior sleep disorder	–	Gray matter volume ↓ White matter integrity ↓
	Excessive daytime sleepiness	–	Gray matter volume ↓
	Restless leg syndrome	–	Gray matter volume ↔
Corticobasal Syndrome*	Excessive daytime sleepiness	–	–
	Periodic limb movement disorder	–	–
Huntington's disease*	Periodic limb movement disorder	–	–
	Circadian dysfunction	–	–

**No neuroimaging studies in sleep disorders specifically.*
REM, rapid eye movement.

products in individual cells of the suprachiasmatic nucleus (SCN) of the hypothalamus, which can be entrained to ambient conditions by light, is the foundation of circadian rhythmicity in mammals (12). Intrinsic circadian rhythmicity is outputted by action potentials generated by SCN cells, impinging on nuclei adjacent to the anterior hypothalamus, such as the subparaventricular nucleus (SPZ), paraventricular nucleus, dorsomedial nucleus (DMH) and the medial preoptic area, which, sequentially, convey circadian rhythmicity to structures involved in regulating physiological processes, such as the GABA-containing ventrolateral preoptic area (VPLO) and the locus coeruleus. The SCN circadian oscillator can receive feedback via melatonin, which is a sleep-related hormone secreted reliably from the pineal gland in response to polysynaptically conveyed signals from the SCN. Additionally, other neuromodulatory systems, such as acetylecholine, modulate the SCN's responsiveness to photic input from the retinohypothalamic tract (RHT). Temporal specificity is also demonstrated, given that the circadian pacemaker is responsive to specific modulatory signals exclusively at certain periods of the circadian day (12).

Anatomy of Sleep and Neuroendocrine Mediators

Neural circuits involved in sleep regulation can be broadly categorized under four subsystems: (1) wake-promoting; (2) non-REM sleep promoting; (3) REM sleep promoting; (4) non-REM-REM switch (13, 14). The neurodegenerative nature of movement disorders ultimately disrupts sleep regulation by interrupting the normal feedback between neuronal subsystems following accumulation of local neuropathology and concomitant changes in neurotransmitters.

The VLPO serves as a key hypothalamic structure, responsible for promoting non-REM sleep. The VLPO may initiate the onset of sleep via its reciprocal inhibition of brainstem-residing serotonergic, cholinergic and noradrenergic systems, alongside histaminergic arousal systems of the posterior hypothalamus and cholinergic systems of the basal forebrain, of which all are modulated by orexinergic arousal system of the lateral hypothalamus. Activated brain states of waking are promoted by these arousal systems, whereas the activated state of REM sleep is promoted by the cholinergic system alone (12).

Sleep-wake homeostatic information from endogenous chemical signals, such as the accumulation of adenosine during wake hours, and circadian input from the anterior hypothalamus both trigger the VLPO to initiate sleep onset. Once sleep has commenced, the alternation between non-REM and REM sleep is controlled by an ultradian oscillator in the mesopontine junction, which, in turn, is executively controlled by the interaction between aminergic REM-off and cholinergic REM-on cell groups (**Figure 2**). Interposed autoregulatory, inhibitory and excitatory circuits that involve serotonin, noradrenaline, acetylcholine, glutamate and GABA mediate the interaction between the two cell groups.

PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most common neurodegenerative disorder, pathologically characterized by dopaminergic neuronal atrophy in the substantia nigra and widespread intracellular inclusions containing aggregates of α-synuclein (15). PD may be perceived as an admirable illustration of where efforts to comprehend impaired sleep-wake homeostasis precipitated significant advances in understanding the disease biology and progression. Conversely, sleep disorders in HD and atypical Parkinsonism, including PSP, MSA and CBS, have not been systematically studied.

REM Sleep Behavior Disorder

Idiopathic REM sleep behavior disorder (iRBD) is a parasomnia characterized by the lack of normal skeletal muscle atonia during REM sleep, resulting in dream-enacting behaviors often associated with violent or aggressive dreams (16). Over recent years, it is now increasingly recognized that RBD is associated with neurodegenerative disease, particularly α-synucleinopathies such as PD, MSA and dementia with Lewy Bodies (DLB) (17–19). Presumed to be a preliminary symptom of progressive neurodegeneration, RBD can precede the clinical manifestation of these α-synucleinopathies by several years, with risk estimates of up to 33% at 5 years RBD diagnosis, 76% at 10 years and 91% at 14 years (20, 21), making RBD one of the strongest clinical predictors of synucleinopathy onset (22).

Diurnal and nocturnal sleep problems are highly prevalent in PD, affecting up to 88% of the PD population, with RBD, specifically, affecting up to 50% (23, 24). Studies have demonstrated that sleep difficulties are essential predictors of poor quality of life, with most reports proposing that disturbance of sleep, lack of independence and depression are the fundamental determinants of poor quality of life (25).

Though PD is currently diagnosed when patients present with key motor symptoms including bradykinesia, rigidity, tremor or postural instability (26), the term *prodromal* has surfaced to describe the period between the onset of motor symptoms and striatal neurodegeneration, with basal ganglia degeneration suggested to commence up to 7 years prior to diagnosis (27, 28). However, prodromal symptoms such as hyposmia and RBD can emerge decades earlier in some cases, with approximately 20% of PD patients reporting RBD onset prior to motor symptomology (29). This highlights that RBD has the potential to serve as the most promising prodromal marker (30, 31). Prominently, long-term cohort studies insinuate that up to 90% of individuals who suffer from isolated RBD will go onto develop PD or atypical Parkinsonism (21, 32). However, the pathophysiology of RBD in prodromal and established PD remains unclear.

Molecular Imaging

Early imaging studies using SPECT and PET to image presynaptic dopamine transporter (DAT) and presynaptic vesicular dopamine transporters in RBD confirmed that these patients exhibit subclinical striatal dopaminergic deficit (33, 34). Consequent larger cohorts comparing RBD patients with healthy controls illustrated that 20–40% of RBD subjects exhibit

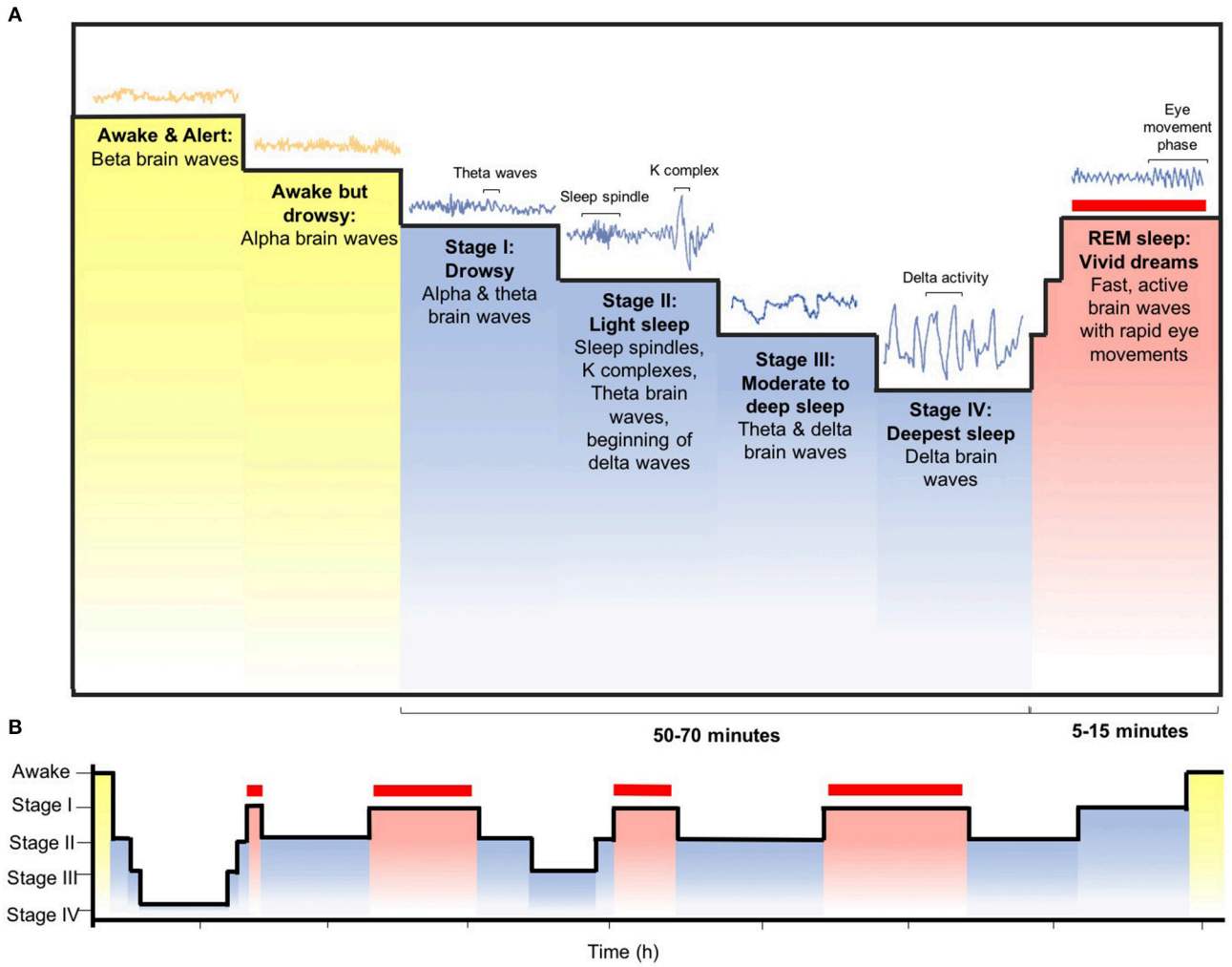

FIGURE 2 | Sleep patterns and stages. **(A)** A complete sleep cycle typically takes, on average, between 90 and 110 min. There are two fundamental types of sleep: rapid eye movement (REM) sleep and non-REM sleep, which can be divided into stages I–IV. These non-REM stages correspond to the accumulating depth of sleep, as reflected by the progressive emergence of high-voltage, low-frequency brain wave activity, which dominate the deepest stages of non-REM sleep (stage III and IV, also identified as slow-wave sleep). Cardinal wave activity of stage II are sleep spindle and K-complex waveforms, who's timings are influenced by a slow oscillation (<1 Hz). REM sleep, also identified as active or paradoxical sleep, is characterized by wake-like, high-frequency, low-amplitude activity and atonia (i.e., low muscle tone). **(B)** During each of the four to five cycles that transpire each night of adult human sleep, non-REM (blue bars) and REM sleep (red bars) alternate. During the earlier proportion of the night, non-REM sleep is deeper, occupying a disproportionately large amount of time, particularly within the first cycle where the REM stage may be brief or terminated. As the night progresses, non-REM sleep becomes shallow, with more of each cycle being allocated to REM. A reliable oscillator times the sustained period of length of the non-REM and REM cycle, of which the amplitude varies according to extrinsic factors.

abnormal nigro-striatal functioning, particularly at the putamen level (35–37).

One of the earliest studies, however, was carried out by Eisensehret and colleagues who employed SPECT tracers [^{123}I]IBZM and [^{123}I]IPT-SPECT, as markers of post-synaptic dopamine type-2 receptors (D_2R) density and presynaptic DAT, respectively, to gain an insight into striatal dopaminergic integrity in five patients with iRBD compared to 14 PD patients and seven controls (34). They found a reduction in striatal [^{123}I]IPT uptake in iRBD compared to controls, though no differences were found in striatal [^{123}I]IBZM. Despite the small sample sizes, this study was one of the first to report a reduction in striatal dopamine transporters in idiopathic clinically manifest RBD. Further, iRBD patients exhibit a decline in striatal [^{123}I]FP-CIT uptake that reflects progressive nigrostriatal dopamine depletion (38). Whilst iRBD was reported to be associated with a loss of DAT within the entire basal ganglia compared to controls at baseline, the mean reduction in striatal [^{123}I]FP-CIT uptake from baseline to 3 years was 19.36% in the right putamen, 15.57% in the left putamen, 7.14% in the right caudate and 10.81% in the left caudate (38). Given the extent of caudate denervation at baseline, these findings suggest that nigro-caudate deafferentation may reflect RBD pathophysiology and putaminal deafferentation may serve as a marker of increasing severity of

PD. In this direction, caudate [^{123}I]FP-CIT-SPECT uptake may serve as a marker of RBD specifically and putaminal [^{123}I]FP-CIT-SPECT uptake may serve as a more sensitive marker of the progression of dopaminergic dysfunction, thus both useful for studying the potential disease-modifying compounds in iRBD.

Studies have also demonstrated that nigro-putaminal functionality is impaired to a mild extent in patients with subclinical RBD (REM sleep without muscle atonia, but not RBD on polysomography), with clinically manifest idiopathic RBD patients exhibiting moderate impairment and PD patients demonstrating the most severe dopaminergic impairment (39, 40). A [^{18}F]DOPA PET study scanned PD patients twice with a 5-year interval to assess the rate of disease progression and found that the disease process initially affects the posterior putamen, followed by the anterior putamen and caudate nucleus (41), whereas PD patients with iRBD displayed a more sever nigro-caudate deafferentation compared to the PD patients without RBD, whilst preserving the nigro-putaminal functionality (40), which is in line with Eisensehr and colleagues (39). These findings corroborate with the notion that nigro-caudate deafferentation may be a hallmark of RBD itself, independent of PD diagnosis. Dopaminergic imaging may, therefore, hold the potential to monitor progression throughout the prodromal phase.

Although, taken together, these results implicate the nigrostriatal dopaminergic system in the pathophysiology of RBD, it remains unclear as to what extent this system is directly involved with the increase in motor activity during REM sleep. A [^{123}I]FP-CIT-SPECT study by Eisensehr observed that muscle activity during REM sleep lasting persistently longer than 0.5 s was independently associated with reduced striatal [^{123}I]IPT uptake in iRBD patients (39). Although these results were not reproduced by Kim and colleagues, who found that electromyography (EMG) activities during REM sleep were not associated with striatal DAT density (36), they were partially replicated by Zoetmulder and colleagues who illustrated that EMG-activity in the mentalis muscle correlated with putaminal [^{123}I]FP-CIT uptake in iRBD patients, (42). Although these findings suggest that amplified muscle activity during REM sleep is associated to nigrostriatal dopaminergic system in RBD and dopaminergic function in PD, it may not be essential for the development of RBD, thus not directly associated with the severity of RBD symptomology in PD.

An interesting study applying [^{99m}Tc]-EDC SPECT with simultaneous polysomnographic (PSG) recordings demonstrated increased perfusion in the supplementary motor area during a REM sleep behavior episode (43), which was subsequently confirmed by Mayer and colleagues who reported bilateral activation of the premotor (supplementary motor) areas, the periaqueductal area, the interhemispheric cleft, the anterior lobe of the cerebellum and the dorsal and ventral pons (44). These studies implicate a common motor pathway in RBD, localizing the motor generators responsible for dream enactment behavior to include the supplementary motor area, bypassing the basal ganglia. These results corroborate with a previous study in PD patients with RBD, illustrating the "normalization" of movement during REM sleep, indicating that the motor cortex may generate movements during RBD, following the pyramidal tract bypassing the extrapyramidal system (45).

Prior observations of dopaminergic deficits in RBD have been extended by an imaging study with [^{18}F]FDG PET and [^{99m}Tc]-EDC SPECT, which aimed to determine whether Parkinson disease-related covariance pattern (PDRP) of cerebral glucose metabolism and perfusion, respectively, is analogous in iRBD (46). PDRP topography is characterized by elevated activity in pontine, pallidothalamic and cerebellar metabolic activity and reduced activity in parietal and premotor association regions. iRBD patients exhibited increased expression of the PDRP, with long-term clinical follow-up data highlighting that iRBD patients with network-level functional abnormalities at baseline were more likely to phenoconvert to PD/DLB (46). These results indicate network abnormalities in iRBD patients, which hold the potential to predict those who are likely to develop PD.

How does dopaminergic denervation contribute to RBD? Rye hypothesized that GABAergic output from the basal ganglia targets the glutamatergic retrorubral field and/or midbrain extrapyramidal area, which subsequently activate the ventromedial medullary zone, promoting REM atonia (47). Nigral dopamine depletion occurs transiently or persistently in pathological states such as PD. Therefore, following dopaminergic neuronal loss in the substantia nigra, we can expect heightened phasic discharge of the internal segment of the globus pallidus to excessively inhibit neurons of the midbrain extrapyramidal area, thereby permitting the expression of movements that overcome REM atonia. This is supported by the reversal of excessive nocturnal movements following excessive inhibition of the midbrain extramyramidal area by pallidotomy (48).

The variability in RBD progression to Parkinsonism may be mediated by the spread of damage in the ventral mesopontine junction to the substantia nigra. In PD, neuronal degeneration has been suggested to originate at either the dorsal or ventral portion of the brainstem, extending rostrally or caudally (49). Therefore, PD would manifest first if the lesions originate in the rostroventral midbrain, nearby the caudoventral part of the substantia nigra *pars compacta*, where the putamen-labeled afferents reside (50). RBD, on the other hand, would manifest first if the lesions begin in the caudoventral mesopontine junction (49). The variability in paths of neurodegeneration could justify why RBD either precedes PD or develops at different stages of PD.

Whilst SPECT and PET imaging studies have demonstrated a contributory role for dopaminergic dysfunction in RBD pathophysiology, pharmacological evidence has indicated that serotonergic dysfunction may also play a fundamental role in RBD development and severity. Treatment with D_2/D_3 receptor agonists, including pramipexole, have proven to provide little benefit in alleviating RBD-specific symptomology, possibly because post-synaptic dopaminergic integrity remains in-tact, as demonstrated by Eisensehr and colleagues, who found no difference in striatal D_2 receptor density between iRBD and controls (34). Nevertheless, therapies predominantly targeting serotonergic functionality, such as melatonin and clonazepam, effectively treat RBD symptomology, whilst serotonin reuptake

inhibitors (SSRI) are typical causative agents of medication-induced RBD (51). Furthermore, nigrostriatal dopaminergic denervation is a primary feature of PD; whereas RBD manifests in a proportion of PD patients, indicating that additional factors are likely to contribute to the underlying pathogenesis of RBD.

To investigate this notion, a combined PET study enabled authors Kotagal et al. (52) to gain an insight into the role of the cholinergic, serotoninergic and dopaminergic systems in RBD pathophysiology. In this study, 80 non-demented PD patients were enrolled and divided into two groups: PD patients positive for RBD and PD patients negative for RBD, after being assessed by Mayo Sleep Questionnaire. All subjects were scanned with three selective radioligands: [^{11}C]PMP, [^{11}C]DASB and [^{11}C]DTBZ, which served as markers for presynaptic acetylcholinersterase (AChE), presynaptic serotonin transporter (SERT) and presynaptic vesicular monoamine transporter type 2 (VMAT2), respectively. PD patients with RBD exhibited a reduction in AChE levels within the neocortex, limbic cortex and thalamus in comparison with PD patients without RBD (52). No differences were found in striatal VMAT2 levels or SERT availability within the striatum or raphe nucleus between the two groups. Furthermore, SERT availability within the brainstem and thalamus, as measured by [^{123}I]FP-CIT-SPECT, was found to not significantly differ between iRBD patients and controls (53, 54). These results, taken together, indicate that serotonergic integrity does not have an impact on RBD pathogenesis, though cholinergic dysfunction appears to play a prominent role in the development of RBD symptoms in PD.

Molecular imaging has provided us with an insight into the mechanisms underlying RBD in PD, with most studies assessing dopaminergic function and highlighting that presynaptic dopaminergic deficit is strongly associated with RBD, thus likely to play a role in its pathogenesis. Molecular imaging investigating non-dopaminergic systems in RBD is incredibly limited, thus more studies are required to assess their roles in RBD pathophysiology, particularly the cholinergic and noradrenergic systems.

MR Imaging

Multi-modal MR imaging techniques have been utilized to investigate the mechanisms underlying RBD in patients with PD, often complimenting the findings reported from molecular imaging studies. A cross-sectional resting-state fMRI study investigating functional connectivity in nigrostriatal and nigrocortical pathways reported altered connectivity in both pathways (substantia nigra, putamen and occipital regions) in RBD patients compared to PD patients and controls (55), consistent with hypotheses of dopamimergic degeneration. This was further inenforced by a combined fMRI and [^{123}I]FP-CIT-SPECT study, which aimed to explore whether connectivity dysfunction within basal ganglia networks is reflected in iRBD (56). Rolinski et al. (56) revealed that iRBD patients exhibit significant connectivity dysfunction of basal ganglia network, as well as frontal lobe regions, compared to healthy controls. No significant differences in basal ganglia connectivity was identified between iRBD and PD patients, suggesting that RBD and PD patients exhibit an analogous level of decline in basal ganglia functional connectivity. However, large scale longitudinal studies are compulsory to track the progression of functional connectivity in iRBD patients who convert to PD, in order to corroborate if basal ganglia connectivity could serve as a potential marker for identifying iRBD patients at risk of converting to PD.

As well as functional alterations, RBD-specific patterns of atrophy have also been explored, in order to better understand the contribution of subcortical and cortical atrophy to alterations in the sleep-wake cycle. Voxel-based morphometry (VBM) revealed early RBD-positive PD patients, with an average disease duration of 6.5 months, had reduced cortical gray matter volume in the parietal operculum, middle occipital gyrus, insular cortex, superior temporal gyrus and hippocampus compared to RBD-negative PD patients (57). Further, RBD-positive PD patients have been reported to exhibit prominent volume loss in the anterior cingulate cortex, pontomesencephalic tegmentum, thalamus, hypothalamus, amygdala, putamen and medullary reticular formation compared to those without RBD and controls (58). There has been a relative lack of consistency in the results dictated from structural imaging studies in iRBD, with only one demonstrating a smaller volume in the pontine tegmentum (59), two others revealing a subtle structural change in this region using MRI diffusion sequences (60, 61), and one repoting no volume change in this area (62). Furthermore, previous neuroimaging studies in PD-RBD reported no significant volume changes in the pontomesencephalic tegmentum (57, 63, 64). However, it is important to note that cholinergic, glutamatergic and GABAergic neurons reside in the pontomesencephalic tegmentum, thus postulating that dysregulation of non-dopaminergic systems may contribute to RBD, whilst the volume loss in the medullary reticular formation may be implicated in the loss of muscle atonia during REM sleep. A preclinical study using transgenic mice models with impaired glycine and GABA receptor function presented with an RBD phenotype, which was rescuable using melatonin and clonazepam (65). In this direction, dysfunctional neurotransmission of glycine and GABA could play a key role in the pathogenesis of RBD, though *in vivo* studies are required to confirm this in humans.

Diffusion tensor imaging, together with T1-weighted MR imaging has enabled Ford et al. (57) to study microstructural white matter changes and atrophy, simultaneously. PD patients with RBD exhibited reduced fractional anisotropy (FA) within the inferior and superior longitudinal fasciculus, inferior fronto-occipital, longitudinal fasciculi and corticospinal tract, as well as increased mean diffusivity (MD) within the inferior longitudinal fasciculi. These results highlight widespread pathological changes in white matter microstructure, as well as reduced gray matter volume constrained to parietal and temporal lobes (57). These findings are in line with previous DTI studies in subjects with iRBD (60, 61), suggesting that microstructural impairment may contribute to RBD symptomology.

Neuromelanin-sensitive MR imaging has demonstrated that PD patients with RBD exhibit a greater loss of neuromelanin within the locus coeruleus compared to PD patients without RBD (63). Specifically, loss of neuromelanin within the locus coeruleus was linked with abnormal muscle tone during REM

sleep (63). This is particularly interesting as the locus coeruleus is acknowledged to play a critical role in regulating the sleep-wake cycle via its projections to the ventral tegmental area, hypothalamus, thalamus, hippocampus and amygdala, thus substantiating the contribution of the noradrenergic system in the pathophysiology of RBD.

Evidence from SPECT and PET studies have suggested a role for dopaminergic dysfunction in RBD pathogenesis, though dysfunction of non-dopaminergic systems, including the noradrenergic and cholinergic systems, are likely to also play a role in the development of RBD in PD. Additionally, MR imaging modalities have suggested that functional connectivity and microstructural changes contribute to the development of RBD in PD, giving an insight into the neural structures which may play a key role in RBD. However, largescale longitudinal studies are indispensable to fully comprehend the mechanisms underlying RBD, thus propelling the development of targeted therapies.

Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) is one of the most common and burdensome non-motor symptoms in both early and advanced PD, substantively impacting on the patient's quality of life (66). EDS is described as an inappropriate and undesirable sleepiness during waking hours (67), which has been found to cause mild to severe cognitive impairment, with particular deficits in attention, memory and judgment (68). The prevalence of EDS has been reported to be higher in PD than in the general population, ranging from 16 to 74% (69, 70). This heterogeneity may reflect the fact that EDS has been found to rise with disease severity (71–73), as well as correlate with disease duration (74, 75), Hoehn and Yahr stage (76) and MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (76, 77). However, the lack of correlation found between Hoehn and Yahr stage and EDS has led to the notion that sleepiness severity is not dependent on nocturnal sleep disruption, cognitive and motor impairment or anti-Parkinsonian therapy, but is actually associated with PD-specific pathology (75, 78–85).

Molecular Imaging

The pathophysiology of EDS may be a result of substantial degeneration of both the nigrostriatal dopaminergic system and extrastriatal neurons within the lower brainstem and midbrain, which pose as key regulators of the sleep-wake cycle (86). PET and SPECT molecular imaging studies have implicated both serotonergic and dopaminergic nigrostriatal dysfunction in EDS pathophysiology.

We recently carried out a [^{123}I]FP-CIT SPECT study to investigate the potential implication of the presynaptic dopaminergic system in EDS. We found that PD patients with EDS generally had a worse clinical picture compared to PD without EDS, presenting with worse autonomic and cognitive function, depression and overall burden of non-motor symptom burden (87–90). Further, PD patients with EDS exhibited reduced DAT uptake within the caudate, with lower caudate DAT uptake correlating with worse EDS severity. More interestingly, abnormal caudate uptake and disease duration were found to predict the development of EDS, indicating that dopaminergic deficits in the caudate may contribute to EDS etiology (90). This is in corroboration with a study carried out by Happe and colleagues who reported a loss of [^{123}I]FP-CIT uptake within the caudate, putamen and striatum, which inversely correlated with the severity of daytime sleepiness in moderate PD (H&Y stage 2) but not in early PD (H&Y stage 1), as measured by the Epworth sleepiness scale (91). Additionally, by investigating cerebral blood flow patterns in PD patients with EDS by employing [^{123}I]iodoamphetamine SPECT, Matsui and colleagues reported hypoperfusion within the right caudate and the left parietal and temporal association cortex, as well as hyperperfusion within the right thalamus (92). These results suggest that cortical hypoperfusion relative to hyperperfusion within the brainstem may be related to EDS pathogenesis in PD. Interestingly, caudate functionality has been consistently demonstrated in these studies to be associated with EDS, with a reduction of caudate metabolism potentially reflecting dopamine depletion.

The caudate nucleus has recently surfaced as a common node in the regulator systems affiliated with sleep problems, given its complex role in modulating the impact of impulses between the thalamus and cortex. Neurotoxic lesion studies have revealed that bilateral striatal lesions cause a reduction in wakefulness, which is attenuated when the caudoputamen lesions include the nucleus accumbens (93). These findings emphasize that the caudate is implicated in promoting wakefulness, whereas the nucleus accumbens predominately enhances sleepiness. Therefore, hypometabolism and dopamine depletion within the caudate may cause sleepiness.

The extrastriatal dopaminergic system has also been explored *in vivo* (94, 95). A recent preliminary PET study employing [^{11}C]PHNO, a radioligand selective for dopamine type-3 (D_3) receptors, reported lower D_3 receptor availability in the hypothalamus of 12 PD patients with EDS, which also correlated with daytime sleepiness severity (95). Although this study suggests that D_3 receptor availability may be associated with EDS, it does not provide a principal cause for this decline. This led the authors to suggest that reduced monoamine transmission within important nuclei implicated in sleep control are accountable for adaptive changes in D_3 receptor availability. A possible alternative explanation is that there is direct neuronal degeneration of dopamine receptor-expressing neurons within the hypothalamic dopaminergic networks (95).

Given that preclinical data implicates the brainstem raphe nuclei in the ascending arousal system, which promotes wakefulness and prevents EDS (96), the serotonergic system has also been investigated *in vivo*. A combined PET study utilizing [^{11}C]DASB and [^{18}F]DOPA, as markers of SERT and monoaminergic terminals function, respectively, revealed that PD subjects with EDS exhibited a reduction in SERT availability within the rostral raphe, locus coeruleus, thalamus and hypothalamus, as well as reduced [^{18}F]DOPA uptake within the locus coeruleus, rostral raphe and ventral tegmental area (97). Since the authors controlled for depression and fatigue, it can be suggested that monoaminergic dysfunction may contribute to the

mechanisms underlying EDS. However, these findings have not been replicated (54).

Molecular imaging has consistently demonstrated the caudate to be associated with EDS, as shown by a negative correlation between its metabolic activity and dopaminergic function and the severity of EDS. However, there is a real lack of non-dopaminergic exploration using molecular imaging techniques, which is critical to further expand our understading of daytime sleepiness, especially because wake-promoting neurotransmitters include norepinephrine, acetylcholine, hypocrein, histamine and hypocretin, which may be dysregulated in PD.

MR Imaging

At the structural level, whole-brain studies revealed widespread reductions of gray matter volume in the frontal, occipital, temporal and limbic lobes, as well as the right parahippocampus and nucleus basalis of Meynert in PD with EDS compared to PD without EDS (98, 99). Whole-brain white matter analysis of DTI data have revealed that PD patients with EDS exhibit elevated levels of white matter axonal damage, indexed by reduced fractional anisotropy within the fornix compared to those without EDS, which also correlated inversely with daytime sleepiness severity (100). Furthermore, Chondrogiorgi and colleagues revealed that PD patients with EDS exhibited a reduction of white matter integrity [as demonstrated by an increase in axial diffusivity (AD)] within the projection, association and brainstem fibers compared to PD patients without EDS (99), which corroborated with reports made by Gama et al. (101) and Kato et al. (98), who found widespread cortical and subcortical atrophy within frontal, temporal, limbic and insular regions, as well as the middle cerebellar preduncles. Although a larger cohort study is required to confirm these findings, these findings are suggestive of fornix fibers degeneration, which connects the hypothalamus and hippocampus, playing a potential role in EDS development. Hypothalamic dysfunction could lead to microstructural changes in the fornix, thus together contributing to the development of sleepiness in PD. Additionally, longitudinal studies are a necessity to gain an insight into the long-term role of structural and functional alterations in EDS pathophysiology in PD.

At the functional level, increased EDS was inversely associated with decreased functional connectivity within the thalamocortical and default mode networks, potentially reflecting the disengagement of sensory and motor processing from the stream of consciousness (102, 103). Additional rs-fMRI studies using whole-brain analysis identified regional homogeneity within the inferior gyrus and cerebellum, which inversely correlated with ESS score, and increased regional homogeneity in the paracentral lobule, which positively correlated with ESS scores (104). Subsequent functional connectivity analysis of these regions demonstrated a reduction in functional connectivity in the frontal, temporal, insula and limbic lobes, as well as the cerebellum, in EDS-positive PD patients compared to EDS-negative patients (104). The frontal, temporal and insula regions have been reported to play a role in the development of EDS, given the marked atrophy within the gray matter of these regions (92, 98).

Despite some negative findings, such as no significant EDS-related changes in FA (99), most studies observed a reduction in structural and/or functional features, including white matter integrity, white matter axonal damage, brain volume and functional connectivity in key neural structures involved in regulating alertness and sleepiness. However, further multimodal studies are required to gain a deeper understanding of the way in which structural changes are associated with EDS, particularly by carrying out longitudinal studies.

RESTLESS LEG SYNDROME

Idiopathic restless leg syndrome (iRLS), also known as Willis-Ekbom disease (WED), is a common neurological disorder characterized by strong feelings of restlessness and troublesome paraesthesia-like sensations in the lower legs, particularly at rest. Contrariwise, symptomology usually improves or disappears once the subject starts physical activity. This condition affects sleep and health (105–107), as well as quality of life, which has been reported to be analogous or worse than those suffering from congestive heart failure, osteoarthritis, stroke or depression (106, 108–116).

Most iRLS patients display some initial clinical benefit when administered dopaminergic drugs, including dopamine agonists and levodopa. Large-scale clinical trials encompassing diverse patient populations reported good clinical response to dopamine agonist in approximately 60–75% of participants (117). Therefore, in general clinical practice, a failure to respond to dopaminergic treatment should flag concern regarding the accuracy of diagnosis, but does not automatically exclude a diagnosis of iRLS.

Molecular Imaging

SPECT and PET molecular imaging techniques have been employed to investigate the role of dopaminergic dysfunction in the pathophysiology of iRLS, by imaging post-synaptic D_2 receptor binding, and presynaptic DAT (118). However, few studies have aimed to characterize the underlying mechanisms of RLS in PD cohorts specifically. Generally, brain imaging studies evaluating dopaminergic function in iRLS patients have yielded inconclusive results though some have provided evidence for the pathogenic role of the dopaminergic dysfunction, which is in line with the effectiveness of dopaminergic therapies (119).

Striatal DAT density has been found to be compromised in iRLS patients, as demonstrated by two molecular studies employing [^{99M}Tc]TRODAT-1 SPECT (120) and [^{11}C]methylphenidate PET (121). This presynaptic dopaminergic deficit is in line with studies employing [^{18}F]DOPA, where iRLS patients exhibited reduced [^{18}F]DOPA uptake in the putamen and caudate compared to controls, highlighting the potential role that dopaminergic dysfunction plays in RLS pathophysiology (122). However, a 4-year longitudinal [^{123}I]-FP-CIT SPECT study in 88 *de novo* PD patients revealed that elevated DAT availability within the caudate and putamen was associated with the presence of RLS at baseline and follow-up, compared to those without RLS (123), suggesting that PD patients with RLS

may have a comparatively preserved presynaptic dopaminergic pathways.

Striatal and extrastriatal D_2 receptor availability in *de novo* RLS patients has been investigated using [^{11}C]raclopride and [^{11}C]FLB-457, respectively, with RLS participants illustrating increased availability of D_2 receptor within the thalamus and cingulate cortex (124), but a reduction of D_2 receptor binding within the caudate and putamen (125). The elevation of D_2 receptor availability in RLS could be a result of the upregulation of D_2 receptor in response to low levels of endogenous dopamine. Striatal and extrastriatal dopaminergic dysfunction and alterations in somatosensory processing may contribute to the mechanisms underlying RLS. Michaud et al. (126) employed [^{123}I]-β-CIT and [^{123}]IBZM to assess pre- and post-synaptic dopaminergic impairment, respectively. Reduced striatal D_2 receptor binding was observed in RLS patients compared to healthy controls, though no differences were identified in presynaptic DAT binding (126). Given that presynaptic DAT uptake was within the normal range, reduced D_2 receptor availability is likely to reflect downregulation of D_2 receptor due to elevated synaptic dopamine levels, supporting the role of post-synaptic dopaminergic dysfunction in the pathophysiology of RLS.

Although there is good evidence supporting the notion that dopaminergic dysfunction contributes to RLS manifestation, some molecular imaging studies have revealed conflicting results. A [^{123}I]-β-CIT and [^{123}]IBZM SPECT study reported a reduction in putaminal and caudate DAT uptake, and no difference in striatal D_2 receptor density, in *de novo* iRLS patients ($n = 13$) compared to controls ($n = 12$) (127). Conversely, other studies have demonstrated that no difference resides in dopaminergic activity between RLS patients and controls, with no striatal or frontal D_2 receptor differences between RLS patients, early PD and healthy controls (128). These results, taken together, suggest that the underlying mechanisms of RLS are likely to involve non-dopaminergic systems, with the underlying mechanisms likely to be divergent from PD where presynaptic dopaminergic neuronal integrity is largely affected. In a study that examined real-time DAT binding potentials, RLS patients exhibited a reduction of striatal DAT binding in both day and night scans, suggesting that membrane-bound striatal DAT, but not total cellular DAT is depleted in RLS (121).

There are no studies, to date, exploring the non-dopaminergic basis of RLS in PD, which is required to enhance our understanding of this disorder, especially given the conflicting results in dopaminergic integrity between studies.

MR Imaging

Studies exploring structural changes in RLS are very limited. The first study to report morphologic changes in RLS was published earlier this year, who found that RLS patients had a 7.5% decrease in cortical thickness in the bilateral post-central gyrus. Further, there was a decline in the corpus callosum posterior midbody, suggesting an alteration in white matter properties in the somatosensory pathway (129). Other studies exploring white matter microstructural changes have revealed altered fractional anisotropy in temporal regions, internal capsule cerebellum and pons in iRLS patients compared to controls, with no changes in gray matter (130). These results indicate that microstructural alterations in white matter, but not gray matter atrophy, may contribute to the development of iRLS. Nevertheless, Rizzo and colleagues reported no microstructural changes in iRLS subjects (131), thus arguing against structural or microstructural abnormalities having an association with iRLS. A functional neuroimaging study by Bucher and colleagues reported that iRLS patients exhibit activation in the cerebellum and thalamus (132), which is supported by structural cerebral and thalamic findings reported by Etgen et al. (133).

Iron deficiency has also been repeatedly shown to be associated with RLS, especially given that CSF ferritin levels are low and CSF transferrin levels are high in RLS patients (134). However, total iron and ferritin levels in the substantia nigra region are elevated in PD, resulting in oxidative stress and potentially leading to dopamine depletion (135). In idiopathic RLS, central nervous system iron storage may be impaired, though systemic iron may be normal (136). Utilizing MRI techniques, regional brain iron concentration has been assessed in iRLS patients, which reported decreased iron in the midbrain, which has been found to correlate with the severity of RLS (137). In a recent study with a 7-T MRI scanner, iRLS patients exhibited a reduction in iron levels, as measured by quantitative magnetic susceptibility mapping (SWI), within the thalamus and dentate nucleus, but not in the substantia nigra, when compared to controls (138). The mechanism by which iron deficiency leads to dopaminergic dysfunction remains uncertain. Iron has a complex effect on dopaminergic function, serving as a cofactor for tyrosine hydroxylase and is integral to D_2 receptor function (139, 140).

Although PD and RLS are both related to central dopaminergic dysfunction, the evidence of an association between these disorders is limited to a few studies that report inconsistent results. Long-term prosective controlled studies are warranted to not only assess the pathophysiology of RLS in PD, but also the link between PD and RLS as clinical association studies differ widely. Currently, there are not functional MRI studies rhat have focused on patients with PD-RLS/Functional and molecular imaging studies of PD vs. PD-RLS are necessary to better understand the mechanisms involved in these disorders.

MULTIPLE SYSTEM ATROPHY

MSA is an adult-onset, fatal neurodegenerative disorder characterized by a combination of autonomic dysfunction, Parkinsonian features and cerebellar and pyramidal features (141). The neuropathological hallmark of MSA is α-synuclein-immunoreactive inclusions that predominantly affect oligodendrocytes (142). The underlying neuropathology may contribute to the sleep disorders observed in this disease, with sleep dysfunction acknowledged to be an associated comorbidity. Some sleep disorders such as RBD and vocalization appear to have a higher prevalence in MSA than in PD, despite the same disease duration, and are typically associated with more severe motor symptoms, depression, longer disease duration and longer duration of levodopa treatment (143).

REM Sleep Behavior Disorder

MSA patients have reduced REM and slow-wave sleep, with a recent multicenter study revealing that polysomnography-confirmed RBD is present in up to 88% of patients with MSA. RBD has also been shown to precede the onset of MSA by more than 1 year in 44% of patients (144).

Given that both acetylcholine- and monoamine- containing neurons of the brainstem have been implicated in REM sleep (47), Gilman and colleagues employed [^{11}C]DTBZ PET and [^{123}I]IBVM SPECT, markers of striatal monoaminergic presynaptic terminals and cholinergic presynaptic terminals, respectively, to explore the neurochemical basis of RBD in 13 subjects with probable MSA (145). The MSA subjects exhibited a reduction in mean striatal [^{11}C]DTBZ uptake, as well as a reduction in [^{123}I]IBVM uptake within the thalamus (145). These results reflect the degeneration of dopaminergic neurons in the substantia nigra, as well as degeneration of cholinergic neurons in the pedunculopontine tegmental and laterodorsal tegmental nuclei. However, given the lack of correlation found between thalamic [^{123}I]IBVM uptake and severity of REM atonia loss, it can be assumed that degenerative changes in the pedunculopontine tengmental and laterodorsal tegmental nuclei do not contribute to RBD. Striatal [^{11}C]DTBZ binding, however, was inversely correlated with severity of REM atonia loss, which led the authors to conclude that loss of nigrostriatal dopaminergic projections may contribute to RBD in MSA.

Excessive Daytime Sleepiness

The prevalence and nature of EDS in MSA has not been systematically investigated. However, the few studies which have evaluated sleepiness have reported that 50% of MSA patients suffer from EDS (143), though Multiple Sleep Latency Tests in this subset of patients have revealed normal or mildly reduced sleep latencies (70, 146). In a multicenter survey, Epworth sleepiness scale scores from patients with MSA were comparable to PD, though higher compared to controls, with EDS present in 28% of MSA subjects (147). In contrast to PD, EDS did not correlate with dopaminergic treatment, and disease severity weakly correlated. However, sleep-disordered breathing and sleep efficiency predicted EDS in MSA (147).

One of the potential neuroanatomic substrates for EDS in MSA includes the hypocretin neuronal network within the lateral hypothalamus, which is acknowledged to play a fundamental role in promoting alertness. In an autopsy study of 7 MSA patients, the number of hypocretin neurons were significantly reduced compared to controls (148), though other studies have demonstrated that MSA patients have normal hypocretin levels in the cerebrospinal fluid (CSF) (146, 149). These findings suggest that substantial neurodegeneration is required in order for a measurable difference in CSF hypocretin levels to be detectable. Alternatively, EDS observed in MSA may be related to a loss of cholinergic alerting neurons from the brainstem, as Schmeichel and colleagues have reported that MSA subjects have a significant loss of cholinergic neurons within the laterodorsal tegmental and pedunculopontine tegmental nuclei within the pons (150). However, *in vivo* molecular imaging studies are required to confirm this notion in MSA subjects.

In an interesting cross-sectional MRI study including 16 PD cases, 13 MSA and 14 PSP, alongside 12 healthy controls, Gama and colleagues sought to evaluate and compare the three groups regarding EDS and its association to brain MRI morphometry. MSA subjects with EDS did not exhibit any EDS-specific brain atrophy, though PD subjects with EDS presented with more atrophy of the medial cerebellar peduncle compared to PD patients without EDS and PSP subjects exhibited atrophy within the midbrain compared to controls (101). The authors concluded that widespread neurodegeneration of brainstem sleep structures were related to sleep abnormalities in these subjects.

Sleep Disordered Breathing

Various types of sleep disordered breathing can arise in MSA. Nocturnal stridor and obstructive sleep apnea (OSA) occur more frequently than central sleep apnea, ranging from 40 to 42% for nocturnal stridor in MSA cases (151, 152) and 15–37% for OSA, with both carrying the risk off sudden death (144, 152). Laryngeal dysfunction and narrowing of the upper airway at the level of the vocal cords, laryngeal inlet, base of the tongue and soft palate has been reported in early descriptions of MSA (153, 154). Other factors, including rigidity, hypokinesia, dystonia, rigidity and paralysis of the upper airway muscles may predispose to OSA or nocturnal stridor in MSA (155).

Gilman and colleagues used [^{123}I]IBVM SPECT to measure thalamic cholinergic terminal density and [^{11}C]DTBZ to measure striatal monoaminergic terminal density to investigate the neuropshyiologic basis of OSA in MSA (156). The authors reported that thalamic [^{123}I]IBVM uptake inversely correlated with OSA severity, with no correlations found between [^{11}C]DTBZ and OSA severity. Given the limited number of cholinergic neuronal cell bodies in the thalamus (157), thalamic [^{123}I]IBVM binding may serve as a surrogate marker for the density of cholinergic neurons in the pontine pedunculopontine tegmental and laterodorsal tegmental nuclei. Therefore, projections from pedunculopontine tegmental and laterodorsal tegmental nuclei to the medulla and pons may be more applicable in the pathophysiology of OSA, especially given that OSA mirrors collapse of the upper airway musculature, which receives cholinergic innervation from motor neurons of the lower brainstem.

To the best of our knowledge, there are no other PET or MR studies exploring the neurochemical or neuroanatomical correlates of sleep disorders in MSA. Further studies, both structural and functional neuroimaging, are required to enhance our understanding of these sleep disturbances in MSA.

PROGRESSIVE SUPRANUCLEAR PALSY

PSP belongs to the family of tauopathies, characterized by abnormalities in the hyperphosphorylation and aggregation of the microtubule-associated protein, tau, resulting in degeneration of cortical and subcortical brain structures, particularly within the midbrain (158). A PSP patient typically presents with postural instability, supranuclear ophthalmoplegia, Parkinsonism and pseudobulbar palsy (159).

Although more commonly reported in synucleinopathies, RBD has also been observed in PSP. In a relatively small study of 15 PSP patients, 15 PD patients and 15 age-matched controls, REM sleep without atonia and RBD were similarly present amongst the two cohorts (33 vs. 28%) (160), which was confirmed by Diederich et al. (161). In fact, a polysomnographically recorded study demonstrated that RBD and REM sleep without atonia are common also in PSP, and that sleep was more severely impaired in PSP than in PD (162).

Given the lack of neuroimaging studies assessing sleep disturbances in PSP, in this section, we discuss the findings from neuroimaging studies which may have relevance to sleep regulation.

PSP is pathologically characterized by abnormal accumulation of tau protein, with prominent atrophy in the midbrain (163). Most PSP patients also exhibit neurodegeneration of cholinergic neurons at the level of the pedunculopontine tegmentum, which is acknowledged to play a fundamental role in the regulation of REM sleep (164). Atrophy of the brainstem have been reflected in MR morphometry studies, which have described a reduction in the antero-posterior diameter of the midbrain and smaller ratio between midbrain area and pons (165–167).

Several subcortical structures degenerate over the course of PSP, as demonstrated by Saini et al. (168) and Whitwell et al. (169), who reported non-specific atrophy of the thalamus. However, after attempting to delineate the thalamus, Padovani and colleagues revealed that the pulvinar, dorsomedial and anterior nuclei of the thalamus was atrophic in PSP (170, 171). This was in corroboration with a previous study carried out by Price and colleagues who reported reduced gray matter in the thalamus and hypothalamus in PSP compared to controls (172). Studies have also reported prominent white matter atrophy within the midbrain and pons (169, 173, 174), with a loss of white matter volumes in the brainstem and subcortical structures of PSP patients. Whitwell and colleagues reported reduced fractional anisotropy within the pons and increased mean diffusivity within the thalamus of PSP patients ($n = 18$), with the midbrain exhibiting a decrease in fractional anisotropy and increase in mean diffusivity (175).

In an MRI study carried out by Lehericy et al. (176), 10 PSP subjects had marked gray matter atrophy in the medial thalamus and anterodorsal midbrain/hypothalamic area compared to controls. Reduced white matter volumes were evident in the basal forebrain/inferior globus pallidus/subthalamic area, midbrain and pons, amongst other cortical and subcortical regions. Further, DTI analysis revealed that PSP subjects exhibited lower fractional anisotropy in the white matter of the thalamus, midbrain, cerebellum and cortical regions (176).

The brainstem, thalamus and hypothalamus play essential roles in regulating sleep, with the brainstem and the hypothalamus centrally regulating the pace for sleep-related activity throughout the brain and the thalamus being targeted by both central and decentral regulators to induce global sleep-related oscillatory activity (177). The pons, in particular, is important for REM sleep, with several pontine structures contributing to the generation of each specific polygraphic event that characterizes REM sleep. The pontine tegmentum also encompasses the region where cholinergic activation can trigger behavioral and bioelectric signs of REM sleep (178), with the pedunculopontine tegmental nuclei, in particular, thought to be critical for generating REM sleep, and its connections to the reticular nuclei of the thalamus thought to be important for generating spindles (179). In this direction, degeneration and pathological changes within these regions could underlie RBD within PSP subjects, though neuroimaging studies are required to confirm whether an association is present in PSP.

CORTICOBASAL SYNDROME

CBS also belongs to the family of taupathies, though much less common than other atypical Parkinsonian disorders. CBS patients characteristically present with myoclonus, dystonia, progressive asymmetric levodopa-resistant Parkinsonism, and further cortical signs, such as alien limb phenomena, apraxia and cortical sensory loss (180). The neuropathological hallmark of CBS is unusual accumulation of hyperphosphorylated 4-repeat (4R) tau in the form of neurofibrillary tangles, coiled bodies and neuropil threads together with astrocytic plaques.

The literature on CBS is primarily limited to case reports, likely due to the rarity of CBS. Two case reports of RBD have been reported (181, 182), though in a larger case series of CBS patients, only 1 out of 11 patients had RBD (183). A descriptive study including five CBS patients reported that none had RBD, two had sleep disordered breathing, four had periodic limb movements during sleep and all five patients had insomnia (184).

CSF hypocretin levels have been evaluated in CBS and found to be significantly lower than in patients with PD. The sample size was quite small ($n = 7$) and the majority of the effect may have been primarily due to one outlier (185). Further, pathological studies have demonstrated that CBS patients have a significant loss of choline acetyltransferase (ChAT)-positive neurons within the nucleus basalis of Meynert compared to PSP (186).

There have been no studies, to-date, exploring the neuropathological basis of sleep disturbances in CBS using neuroimaging techniques. A data-driven meta-analysis identifying and comparing the neural correlates of CBS for atrophy measurements included 200 CBS patients and 318 controls (187). This study identified four brain regions with significant atrophy: (1) the bilateral anterior thalamus; (2) the posterior midcingulate cortex, bilateral posterior frontomedian cortex and the premotor area/supplementary motor area; (3) the posterior superior frontal sulcus and precentral gyrus/middle frontal gyrus; (4) the left posterior superior frontal sulcus and middle frontal gyrus. This is particularly interesting as thalamic neurons provide state-dependent gating of sensory information through their ability to create differential patterns of electrogenic activity during wakefulness and sleep. It has been argued that both central and decentral regulators target the thalamus, inducing global sleep-related oscillatory activity (177).

Striatal DAT uptake in patients with CBS is characterized by large variability, with [^{123}I]FP-CIT found to be normal bilaterally in four CBS patients and only unilaterally reduced in the other four cases (188). These results highlight the hemispheric asymmetry in the putamen and caudate [^{123}I]FP-CIT uptake, thus reflects the highly asymmetrical involvement and substantia nigra *pars compacta* neuronal loss implicating both ventral and dorsal tiers in CBS (189, 190), as opposed to PD, where cell loss is typically confined to the substantia *nigra pars compacta* ventral tiers. Given the association found between striatal dopamine depletion and sleep disturbances in PD, it could be assumed that a similar mechanism underlies sleep disorders in CBS. However, this needs to be investigated in MSA exhibiting specific sleep disorders in well-designed, controlled studies.

HUNTINGTON'S DISEASE

Huntington's disease (HD) is a hereditary and fatal neurodegenerative disease, characterized by chorea, psychiatric symptoms and cognitive dysfunction, which manifest as a result of an expanded trinucleotide CAG sequence in the huntingtin gene (HTT) on chromosome 4 (191, 192). HD-specific pathology is defined by aggregations of intranuclear inclusions of mutated huntingtin in the brain. These aggregates have been reported to interact and impair the function of several transcription factors, ultimately inducing a loss of striatal GABAergic medium spiny neurons (MSNs), as well as cortical MSNs (193, 194). There is growing awareness that, alongside the psychiatric and cognitive syptoms, sleep and circadian abnormalities are also present. However, it remains unclear if they are directly caused by HD gene-related pathology or are merely a consequence of having a neurodegenerative disease.

The changes seen in HD appear to have very little in common with sleep disturbances in the neurological disorders mentioned above. For example, the incidence of RBD in the early stages of HD are reported to be fairly low, which is consistent with the fact that although dopaminergic pathology is evident in HD, it does not dominate at early stages (195). At subsequent stages of HD when dopamine-mediated function has deteriorated, the degeneration of this pathway is only part of a much wider picture. Other parasomnias that are associated with neurodegenerative disease, such as RLS, is not significantly increased in the HD population, though periodic limb movement disorder (PLMD) appears to be more frequent in this population compared to controls. It is important to note, however, that it is difficult to distinguish between PLMD and chorea—which is part of their movement disorder. Although sleep disorder studies in HD are rare or non-existent, we could gain critical insight into the potential sleep comorbidity in HD by investigating the molecular, structural and functional basis of sleep-related circuitry in HD. Here, we discuss the neuronal circuitry known to be implicated in sleep and affected in HD, as demonstrated by neuroimaging techniques.

HD pathology is characterized by atrophy and degeneration of the neostriatum and cortex that eventually comprises of the whole brain including subcortical structures (85, 196). Although sleep disturbances were originally reported to be associated with the degree of atrophy within the caudate (197), more recent findings revealed this correlation to be weak (198).

Molecular Imaging

The hypothalamus is critical for the regulation of sleep and metabolism, as well as playing a key role in the regulation of automatic functions such as heartbeat and breathing. A [^{11}C]PK11195 and [^{11}C]raclopride PET study with the aim of assessing *in vivo* D_2 receptor integrity and microglial activation in premanifest ($n = 10$) and manifest ($n = 9$) HD gene carriers reported a significant decrease in hypothalamic [^{11}C]raclopride uptake in both premanifest and manifest HD gene carriers, as well as a significant increases in mean hypothalamic [^{11}C]PK11195 uptake (199). This study was the first to demonstrate a significant loss of D_2 receptors, as well as increased microglial activation within the hypothalamus of HD (199). This is in corroboration with a multimodal imaging study which used MRI, [^{11}C]PK11195 and [^{11}C]raclopride PET to investigate volumetric differences, as well as microglial activation and D_2/D_3 receptor binding in premanifest and symptomatic HD gene carriers (200). The authors found increased microglial activation within the hypothalamus, amongst other regions, as well as a reduction in hypothalamic D_2/D_3 receptor binding in premanifest HD gene carriers. This is particularly interesting as, even though sleep was not specifically investigated in this cohort, the hypothalamus is known to play a critical role in regulation sleep, emotion and appetite (201–203).

MR Imaging

Studies employing voxel-based morphometry analyses have reported a reduction in voxel signal intensity within the hypothalamus in early symptomatic stages of the disease (204, 205). Soneson and colleagues have revealed, using both VBM and logistic regression analyses, that hypothalamic changes are visible from up to 15 years before the predicted onset of motor symptoms (206). Hypothalamic dysfunction in HD patients would not only have an impact on circadian rhythm and daytime sleepiness, but would affect additional relevant functions that have an influence on sleep. Although evidence from MRI studies have suggested that neurodegeneration in the hypothalamus presents very early in HD, the function or structure of the suprachiasmatic nuclei, which resides in the anterior, ventral region of the hypothalamus, has not been rigorously examined in post-mortem brain. However, significant loss and atrophy of orexin/hypocrein neurons have been identified in HD (207), alongside the degeneration of the thalamus (208–210), which is crucial for the generation of sleep and wakefulness. However, it has been poorly studied, with little known about if or how thalamic pathology impacts on sleep in HD.

Given the lack of neuroimaging studies specifically exploring the pathology underlying changes in sleep and circadian activity in HD, the pathophysiology of sleep comorbidities in HD remains unclear. There is, therefore a dire need for studies investigating HD-specific sleep issues to enhance our understanding the cause of these symptoms in HD, thus help us understand how they can be treated.

CONCLUSION AND FUTURE DIRECTIONS

Sleep is a multifaceted phenomenon, regulated by an intricate interplay between several neurotransmitter systems. Although efforts have been made to delineate structural and functional correlates of sleep disturbances, there is a need for standardization across studies, especially given the discord between various studies. Furthermore, multimodal neuroimaging studies hold the key to further understand the simultaneous disruption of various systems, which may all, in some way, play a role in sleep disturbances.

Overall, neuroimaging techniques are unparalleled tools for investigating the mechanisms underlying sleep impairments in movement disorders. These invaluable techniques have provided some insights into the pathophysiology of sleep disorders, unraveling the involvement of both dopaminergic and non-dopaminergic systems. Nonetheless, the visualization of functional and neuroanatomical hallmarks of these sleep disorders remains an active and challenging area. There is a great need of imaging studies specifically seeking to understand neuropathological substrates of sleep disorders in atypical Parkinsonism and HD, which could potentially serve as novel targets for pharmacotherapy.

AUTHOR CONTRIBUTIONS

TY gave input into the article design; wrote the first draft; prepared and revised the manuscript and generated the figures. GP, HW revised the manuscript for intellectual content. MP revised the manuscript for intellectual content and gave final approval of the manuscript.

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REFERENCES

1. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord*. (2002) 8:193–7. doi: 10.1016/S1353-8020(01)00015-3
2. Kaynak D, Kiziltan G, Kaynak H, Benbir G, Uysal O. Sleep and sleepiness in patients with Parkinson's disease before and after dopaminergic treatment. *Eur J Neurol*. (2005) 12:199–207. doi: 10.1111/j.1468-1331.2004.00971.x
3. Fronczek R, Overeem S, Lee SY, Hegeman IM, Van Pelt J, Van Duinen SG, et al. Hypocretin (orexin) loss in Parkinson's disease. *Brain* (2007) 130:1577–85. doi: 10.1093/brain/awm090
4. Videnovic A, Lazar AS, Barker RA, Overeem S. 'The clocks that time us'–circadian rhythms in neurodegenerative disorders. *Nat Rev Neurol*. (2014) 10:683–93. doi: 10.1038/nrneurol.2014.206
5. Wilson H, Giordano B, Turkheimer FE, Chaudhuri KR, Politis M. Serotonergic dysregulation is linked to sleep problems in Parkinson's disease. *Neuroimage Clin*. (2018) 18:630–7. doi: 10.1016/j.nicl.2018.03.001
6. Politis M, Piccini P. Positron emission tomography imaging in neurological disorders. *J Neurol*. (2012) 259:1769–80. doi: 10.1007/s00415-012-6428-3
7. Pagano G, Ferrara N, Brooks DJ, Pavese N. Age at onset and Parkinson disease phenotype. *Neurology* (2016) 86:1400–7. doi: 10.1212/WNL.0000000000002461
8. Pagano G, Niccolini F, Politis M. The serotonergic system in Parkinson's patients with dyskinesia: evidence from imaging studies. *J Neural Transm*. (2017) 125:1217–23. doi: 10.1007/s00702-017-1823-7
9. Pagano G, Yousaf T, Politis M. PET molecular imaging research of levodopa-induced dyskinesias in Parkinson's disease. *Curr Neurol Neurosci Rep*. (2017) 17:90. doi: 10.1007/s11910-017-0794-2
10. Pagano G, Polychronis S, Wilson H, Giordano B, Ferrara N, Niccolini F, et al. Diabetes mellitus and Parkinson disease. *Neurology* (2018) 90:e1654–62. doi: 10.1212/WNL.0000000000005475
11. Colten HR, Altevogt BM. In: Colten HR, Altevogt BM, editors. Sleep disorders and sleep deprivation: An unmet public health problem. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*. Washington DC: National Academy of Sciences (2006).
12. Pace-Schott EF, Hobson JA. The neurobiology of sleep: genetics, cellular physiology and subcortical networks. *Nat Rev Neurosci*. (2002) 3:591–605. doi: 10.1038/nrn895
13. Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. *Neuron* (2010) 68:1023–42. doi: 10.1016/j.neuron.2010.11.032
14. Brown RE, Basheer R, Mckenna JT, Strecker RE, Mccarley RW. Control of sleep and wakefulness. *Physiol Rev*. (2012) 92:1087–187. doi: 10.1152/physrev.00032.2011
15. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. *Nat Rev Dis Primers* (2017) 3:17013. doi: 10.1038/nrdp.2017.13
16. Iranzo A, Santamaria J, Tolosa E. Idiopathic rapid eye movement sleep behaviour disorder: diagnosis, management, and the need for neuroprotective interventions. *Lancet Neurol*. (2016) 15:405–19. doi: 10.1016/S1474-4422(16)00057-0
17. Iranzo A, Molinuevo JL, Santamaria J, Serradell M, Marti MJ, Valldeoriola F, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. *Lancet Neurol*. (2006) 5:572–7. doi: 10.1016/S1474-4422(06)70476-8
18. Boeve BF. REM sleep behavior disorder: updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. *Ann N Y Acad Sci*. (2010) 1184:15–54. doi: 10.1111/j.1749-6632.2009.05115.x
19. Oertel WH, Depboylu C, Krenzer M, Vadasz D, Ries V, Sixel-Doring F, et al. REM sleep behavior disorder as a prodromal stage of alpha-synucleinopathies: symptoms, epidemiology, pathophysiology, diagnosis and therapy. *Nervenarzt* (2014) 85:19–25. doi: 10.1007/s00115-013-3891-8
20. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology* (2009) 72:1296–300. doi: 10.1212/01.wnl.0000340980.19702.6e
21. Iranzo A, Fernandez-Arcos A, Tolosa E, Serradell M, Molinuevo JL, Valldeoriola F, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. *PLoS ONE* (2014) 9:e89741. doi: 10.1371/journal.pone.0089741
22. Pagano G, De Micco R, Yousaf T, Wilson H, Chandra A, Politis M. REM behaviour disorder predicts motor progression and cognitive decline in Parkinson's disease. *Neurology* (2018). doi: 10.1212/WNL.0000000000006134
23. Factor SA, Mcalarney T, Sanchez-Ramos JR, Weiner WJ. Sleep disorders and sleep effect in Parkinson's disease. *Mov Disord*. (1990) 5:280–5. doi: 10.1002/mds.870050404
24. Rolinski M, Szewczyk-Krolikowski K, Tomlinson PR, Nithi K, Talbot K, Ben-Shlomo Y, et al. REM sleep behaviour disorder is associated

with worse quality of life and other non-motor features in early Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2014) 85:560–6. doi: 10.1136/jnnp-2013-306104
25. Karlsen KH, Tandberg E, Arsland D, Larsen JP. Health related quality of life in Parkinson's disease: a prospective longitudinal study. *J Neurol Neurosurg Psychiatry* (2000) 69:584–9. doi: 10.1136/jnnp.69.5.584
26. Reichmann H. Clinical criteria for the diagnosis of Parkinson's disease. *Neurodegener Dis*. (2010) 7:284–90. doi: 10.1159/000314478
27. Hawkes CH. The prodromal phase of sporadic Parkinson's disease: does it exist and if so how long is it? *Mov Disord*. (2008) 23:1799–807. doi: 10.1002/mds.22242
28. Stern MB, Lang A, Poewe W. Toward a redefinition of Parkinson's disease. *Mov Disord*. (2012) 27:54–60. doi: 10.1002/mds.24051
29. Postuma RB, Berg D. Advances in markers of prodromal Parkinson disease. *Nat Rev Neurol*. (2016) 12:622–34. doi: 10.1038/nrneurol.2016.152
30. Iranzo A, Tolosa E, Gelpi E, Molinuevo JL, Valldeoriola F, Serradell M, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol*. (2013) 12:443–53. doi: 10.1016/S1474-4422(13)70056-5
31. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a Parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med*. (2013) 14:744–8. doi: 10.1016/j.sleep.2012.10.009
32. Howell MJ, Schenck CH. Rapid eye movement sleep behavior disorder and neurodegenerative disease. *JAMA Neurol*. (2015) 72:707–12. doi: 10.1001/jamaneurol.2014.4563
33. Albin RL, Koeppe RA, Chervin RD, Consens FB, Wernette K, Frey KA, et al. Decreased striatal dopaminergic innervation in REM sleep behavior disorder. *Neurology* (2000) 55:1410–2. doi: 10.1212/WNL.55.9.1410
34. Eisensehr I, Linke R, Noachtar S, Schwarz J, Gildehaus FJ, Tatsch K. Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder. Comparison with Parkinson's disease and controls. *Brain* (2000) 123:1155–60. doi: 10.1093/brain/123.6.1155
35. Iranzo A, Lomena F, Stockner H, Valldeoriola F, Vilaseca I, Salamero M, et al. Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study [corrected]. *Lancet Neurol*. (2010) 9:1070–7. doi: 10.1016/S1474-4422(10)70216-7
36. Kim YK, Yoon IY, Kim JM, Jeong SH, Kim KW, Shin YK, et al. The implication of nigrostriatal dopaminergic degeneration in the pathogenesis of REM sleep behavior disorder. *Eur J Neurol*. (2010) 17:487–92. doi: 10.1111/j.1468-1331.2009.02854.x
37. Heller J, Brcina N, Dogan I, Holtbernd F, Romanzetti S, Schulz JB, et al. Brain imaging findings in idiopathic REM sleep behavior disorder (RBD)–a systematic review on potential biomarkers for neurodegeneration. *Sleep Med Rev*. (2017) 34:23–33. doi: 10.1016/j.smrv.2016.06.006
38. Iranzo A, Valldeoriola F, Lomena F, Molinuevo JL, Serradell M, Salamero M, et al. Serial dopamine transporter imaging of nigrostriatal function in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. *Lancet Neurol*. (2011) 10:797–805. doi: 10.1016/S1474-4422(11)70152-1
39. Eisensehr I, Linke R, Tatsch K, Kharraz B, Gildehaus JF, Wetter CT, et al. Increased muscle activity during rapid eye movement sleep correlates with decrease of striatal presynaptic dopamine transporters. IPT and IBZM SPECT imaging in subclinical and clinically manifest idiopathic REM sleep behavior disorder, Parkinson's disease, and controls. *Sleep* (2003) 26:507–12. doi: 10.1093/sleep/26.5.507
40. Arnaldi D, De Carli F, Picco A, Ferrara M, Accardo J, Bossert I, et al. Nigro-caudate dopaminergic deafferentation: a marker of REM sleep behavior disorder? *Neurobiol Aging* (2015) 36:3300–5. doi: 10.1016/j.neurobiolaging.2015.08.025
41. Nurmi E, Ruottinen HM, Bergman J, Haaparanta M, Solin O, Sonninen P, et al. Rate of progression in Parkinson's disease: a 6-[18F]fluoro-L-dopa PET study. *Mov Disord*. (2001) 16:608–15. doi: 10.1002/mds.1139
42. Zoetmulder M, Nikolic M, Biernat H, Korbo L, Friberg L, Jennum P. Increased motor activity during REM sleep is linked with dopamine function in idiopathic REM sleep behavior disorder and Parkinson disease. *J Clin Sleep Med*. (2016) 12:895–903. doi: 10.5664/jcsm.5896
43. Dauvilliers Y, Boudousq V, Lopez R, Gabelle A, De Cock VC, Bayard S, et al. Increased perfusion in supplementary motor area during a REM sleep behaviour episode. *Sleep Med*. (2011) 12:531–2. doi: 10.1016/j.sleep.2011.10.001
44. Mayer G, Bitterlich M, Kuwert T, Ritt P, Stefan H. Ictal SPECT in patients with rapid eye movement sleep behaviour disorder. *Brain* (2015) 138:1263–70. doi: 10.1093/brain/awv042
45. De Cock VC, Vidailhet M, Leu S, Texeira A, Apartis E, Elbaz A, et al. Restoration of normal motor control in Parkinson's disease during REM sleep. *Brain* (2007) 130:450–6. doi: 10.1093/brain/awl363
46. Holtbernd F, Gagnon JF, Postuma RB, Ma Y, Tang CC, Feigin A, et al. Abnormal metabolic network activity in REM sleep behavior disorder. *Neurology* (2014) 82:620–7. doi: 10.1212/WNL.0000000000000130
47. Rye DB. Contributions of the pedunculopontine region to normal and altered REM sleep. *Sleep* (1997) 20:757–88. doi: 10.1093/sleep/20.9.757
48. Vitek J, Kaneoke Y, Turner R, Baron M, Bakay R, De Long M. Neuronal activity in the internal (GPi) and external (GPe) segments of the globus pallidus (GP) of Parkinsonian patients is similar to that in the MPTP-treated primate model of Parkinsonism [abstract]. *Soc Neurosci Abstr*. (1993) 19:1584.
49. Lai YY, Hsieh KC, Nguyen D, Peever J, Siegel JM. Neurotoxic lesions at the ventral mesopontine junction change sleep time and muscle activity during sleep: an animal model of motor disorders in sleep. *Neuroscience* (2008) 154:431–43. doi: 10.1016/j.neuroscience.2008.03.085
50. Parent A, Mackey A, De Bellefeuille L. The subcortical afferents to caudate nucleus and putamen in primate: a fluorescence retrograde double labeling study. *Neuroscience* (1983) 10:1137–50. doi: 10.1016/0306-4522(83)90104-5
51. Mccarter SJ, Boswell CL, St Louis EK, Dueffert LG, Slocumb N, Boeve BF, et al. Treatment outcomes in REM sleep behavior disorder. *Sleep Med*. (2013) 14:237–42. doi: 10.1016/j.sleep.2012.09.018
52. Kotagal V, Albin RL, Muller ML, Koeppe RA, Chervin RD, Frey KA, et al. Symptoms of rapid eye movement sleep behavior disorder are associated with cholinergic denervation in Parkinson disease. *Ann Neurol*. (2012) 71:560–8. doi: 10.1002/ana.22691
53. Arnaldi D, Fama F, De Carli F, Morbelli S, Ferrara M, Picco A, et al. The role of the serotonergic system in REM sleep behavior disorder. *Sleep* (2015) 38:1505–9. doi: 10.5665/sleep.5000
54. Qamhawi Z, Towey D, Shah B, Pagano G, Seibyl J, Marek K, et al. Clinical correlates of raphe serotonergic dysfunction in early Parkinson's disease. *Brain* (2015) 138:2964–73. doi: 10.1093/brain/awv215
55. Ellmore TM, Castriotta RJ, Hendley KL, Aalbers BM, Furr-Stimming E, Hood AJ, et al. Altered nigrostriatal and nigrocortical functional connectivity in rapid eye movement sleep behavior disorder. *Sleep* (2013) 36:1885–92. doi: 10.5665/sleep.3222
56. Rolinski M, Griffanti L, Piccini P, Roussakis AA, Szewczyk-Krolikowski K, Menke RA, et al. Basal ganglia dysfunction in idiopathic REM sleep behaviour disorder parallels that in early Parkinson's disease. *Brain* (2016) 139:2224–34. doi: 10.1093/brain/aww124
57. Ford AH, Duncan GW, Firbank MJ, Yarnall AJ, Khoo TK, Burn DJ, et al. Rapid eye movement sleep behavior disorder in Parkinson's disease: magnetic resonance imaging study. *Mov Disord*. (2013) 28:832–6. doi: 10.1002/mds.25367
58. Boucetta S, Salimi A, Dadar M, Jones BE, Collins DL, Dang-Vu TT. Structural brain alterations associated with rapid eye movement sleep behavior disorder in Parkinson's disease. *Sci Rep*. (2016) 6:26782. doi: 10.1038/srep26782
59. Hanyu H, Inoue Y, Sakurai H, Kanetaka H, Nakamura M, Miyamoto T, et al. Voxel-based magnetic resonance imaging study of structural brain changes in patients with idiopathic REM sleep behavior disorder. *Parkinsonism Relat Disord*. (2012) 18:136–9. doi: 10.1016/j.parkreldis.2011.08.023
60. Unger MM, Belke M, Menzler K, Heverhagen JT, Keil B, Stiasny-Kolster K, et al. Diffusion tensor imaging in idiopathic REM sleep behavior disorder reveals microstructural changes in the brainstem, substantia

nigra, olfactory region, and other brain regions. *Sleep* (2010) 33:767–73. doi: 10.1093/sleep/33.6.767
61. Scherfler C, Frauscher B, Schocke M, Iranzo A, Gschliesser V, Seppi K, et al. White and gray matter abnormalities in idiopathic rapid eye movement sleep behavior disorder: a diffusion-tensor imaging and voxel-based morphometry study. *Ann Neurol.* (2011) 69:400–7. doi: 10.1002/ana.22245
62. Rahayel S, Montplaisir J, Monchi O, Bedetti C, Postuma RB, Brambati S, et al. Patterns of cortical thinning in idiopathic rapid eye movement sleep behavior disorder. *Mov Disord.* (2015) 30:680–7. doi: 10.1002/mds.25820
63. Garcia-Lorenzo D, Longo-Dos Santos C, Ewenczyk C, Leu-Semenescu S, Gallea C, Quattrocchi G, et al. The coeruleus/subcoeruleus complex in rapid eye movement sleep behaviour disorders in Parkinson's disease. *Brain* (2013) 136:2120–9. doi: 10.1093/brain/awt152
64. Salsone M, Cerasa A, Arabia G, Morelli M, Gambardella A, Mumoli L, et al. Reduced thalamic volume in Parkinson disease with REM sleep behavior disorder: volumetric study. *Parkinsonism Relat Disord.* (2014) 20:1004–8. doi: 10.1016/j.parkreldis.2014.06.012
65. Brooks PL, Peever JH. Impaired GABA and glycine transmission triggers cardinal features of rapid eye movement sleep behavior disorder in mice. *J Neurosci.* (2011) 31:7111–21. doi: 10.1523/JNEUROSCI.0347-11.2011
66. Politis M, Wu K, Molloy S, G Bain P, Chaudhuri KR, Piccini P. Parkinson's disease symptoms: the patient's perspective. *Mov Disord.* (2010) 25:1646–51. doi: 10.1002/mds.23135
67. Verbaan D, Van Rooden SM, Visser M, Marinus J, Van Hilten JJ. Nighttime sleep problems and daytime sleepiness in Parkinson's disease. *Mov Disord.* (2008) 23:35–41. doi: 10.1002/mds.21727
68. Adler CH, Thorpy MJ. Sleep issues in Parkinson's disease. *Neurology* (2005) 64:S12–20. doi: 10.1212/WNL.64.12_suppl_3.S12
69. Hobson DE, Lang AE, Martin WR, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. *JAMA* (2002) 287:455–63. doi: 10.1001/jama.287.4.455
70. Arnulf I. Excessive daytime sleepiness in Parkinsonism. *Sleep Med Rev.* (2005) 9:185–200. doi: 10.1016/j.smrv.2005.01.001
71. O'suilleabhain PE, Dewey RB Jr. Contributions of dopaminergic drugs and disease severity to daytime sleepiness in Parkinson disease. *Arch Neurol.* (2002) 59:986–9. doi: 10.1001/archneur.59.6.986
72. Diederich NJ, Vaillant M, Mancuso G, Lyen P, Tiete J. Progressive sleep 'destructuring' in Parkinson's disease. A polysomnographic study in 46 patients. *Sleep Med.* (2005) 6:313–8. doi: 10.1016/j.sleep.2005.03.011
73. Thannickal TC, Lai YY, Siegel JM. Hypocretin (orexin) cell loss in Parkinson's disease. *Brain* (2007) 130:1586–95. doi: 10.1093/brain/awm097
74. Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J. Daytime sleepiness and other sleep disorders in Parkinson's disease. *Neurology* (2001) 57:1392–6. doi: 10.1212/WNL.57.8.1392
75. Tan EK, Lum SY, Fook-Chong SM, Teoh ML, Yih Y, Tan L, et al. Evaluation of somnolence in Parkinson's disease: comparison with age- and sex-matched controls. *Neurology* (2002) 58:465–8. doi: 10.1212/WNL.58.3.465
76. Kumar S, Bhatia M, Behari M. Excessive daytime sleepiness in Parkinson's disease as assessed by Epworth Sleepiness Scale (ESS). *Sleep Med.* (2003) 4:339–42. doi: 10.1016/S1389-9457(03)00105-9
77. Pal S, Bhattacharya KF, Agapito C, Chaudhuri KR. A study of excessive daytime sleepiness and its clinical significance in three groups of Parkinson's disease patients taking pramipexole, cabergoline and levodopa mono and combination therapy. *J Neural Transm.* (2001) 108:71–7. doi: 10.1007/s007020170098
78. Rye DB, Bliwise DL, Dihenia B, Gurecki P. FAST TRACK: daytime sleepiness in Parkinson's disease. *J Sleep Res.* (2000) 9:63–9. doi: 10.1046/j.1365-2869.2000.00201.x
79. Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter ML, et al. Parkinson's disease and sleepiness: an integral part of PD. *Neurology* (2002) 58:1019–24. doi: 10.1212/WNL.58.7.1019
80. Brodsky MA, Godbold J, Roth T, Olanow CW. Sleepiness in Parkinson's disease: a controlled study. *Mov Disord.* (2003) 18:668–72. doi: 10.1002/mds.10429
81. Pagano G, Rengo G, Pasqualetti G, Femminella GD, Monzani F, Ferrara N, et al. Cholinesterase inhibitors for Parkinson's disease: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* (2015) 86:767–73. doi: 10.1136/jnnp-2014-308764
82. Pagano G, Niccolini F, Politis M. Imaging in Parkinson's disease. *Clin Med.* (2016) 16:371–5. doi: 10.7861/clinmedicine.16-4-371
83. Roy R, Niccolini F, Pagano G, Politis M. Cholinergic imaging in dementia spectrum disorders. *Eur J Nucl Med Mol Imaging* (2016) 43:1376–86. doi: 10.1007/s00259-016-3349-x
84. Schulz J, Pagano G, Fernandez Bonfante JA, Wilson H, Politis M. Nucleus basalis of Meynert degeneration precedes and predicts cognitive impairment in Parkinson's disease. *Brain* (2018) 141:1501–16. doi: 10.1093/brain/awy072
85. Pagano G, Niccolini F, Politis M. Current status of PET imaging in Huntington's disease. *Eur J Nucl Med Mol Imaging* (2016) 43:1171–82. doi: 10.1007/s00259-016-3324-6
86. Poryazova R, Benninger D, Waldvogel D, Bassetti CL. Excessive daytime sleepiness in Parkinson's disease: characteristics and determinants. *Eur Neurol.* (2010) 63:129–35. doi: 10.1159/000276402
87. Pagano G, Tan EE, Haider JM, Bautista A, Tagliati M. Constipation is reduced by beta-blockers and increased by dopaminergic medications in Parkinson's disease. *Parkinsonism Relat Disord.* (2015) 21:120–5. doi: 10.1016/j.parkreldis.2014.11.015
88. Pagano G, Niccolini F, Yousaf T, Wilson H, Polychronis S, Chaudhuri KR, et al. Urinary dysfunction in early de novo patients with Parkinson's disease. *Mov Disord.* (2017) 32:939–40. doi: 10.1002/mds.26967
89. Pagano G, Yousaf T, Wilson H, Niccolini F, Polychronis S, Chaudhuri KR, et al. Constipation is not associated with dopamine transporter pathology in early drug-naive patients with Parkinson's disease. *Eur J Neurol.* (2018) 25:307–12. doi: 10.1111/ene.13503
90. Yousaf T, Pagano G, Niccolini F, Politis M. Excessive daytime sleepiness may be associated with caudate denervation in Parkinson disease. *J Neurol Sci.* (2018) 387:220–7. doi: 10.1016/j.jns.2018.02.032
91. Happe S, Baier PC, Helmschmied K, Meller J, Tatsch K, Paulus W. Association of daytime sleepiness with nigrostriatal dopaminergic degeneration in early Parkinson's disease. *J Neurol.* (2007) 254:1037–43. doi: 10.1007/s00415-006-0483-6
92. Matsui H, Nishinaka K, Oda M, Hara N, Komatsu K, Kubori T, et al. Excessive daytime sleepiness in Parkinson disease: a SPECT study. *Sleep* (2006) 29:917–20. doi: 10.1093/sleep/29.7.917
93. Qiu MH, Vetrivelan R, Fuller PM, Lu J. Basal ganglia control of sleep-wake behavior and cortical activation. *Eur J Neurosci.* (2010) 31:499–507. doi: 10.1111/j.1460-9568.2009.07062.x
94. Politis M, Piccini P, Pavese N, Koh SB, Brooks DJ. Evidence of dopamine dysfunction in the hypothalamus of patients with Parkinson's disease: an *in vivo* 11C-raclopride PET study. *Exp Neurol.* (2008) 214:112–6. doi: 10.1016/j.expneurol.2008.07.021
95. Pagano G, Molloy S, Bain PG, Rabiner EA, Chaudhuri KR, Brooks DJ, et al. Sleep problems and hypothalamic dopamine D3 receptor availability in Parkinson disease. *Neurology* (2016) 87:2451–6. doi: 10.1212/WNL.0000000000003396
96. Schwartz JR, Roth T. Neurophysiology of sleep and wakefulness: basic science and clinical implications. *Curr Neuropharmacol.* (2008) 6:367–78. doi: 10.2174/157015908787386050
97. Pavese N, Metta V, Simpson BS, Marohy TA, Ramlackhansingh A, Chaudhuri KR, et al. Sleep regulatory centres dysfunction in Parkinson's disease patients with excessive daytime sleepiness. An *in vivo* pet study.*Parkinsonism Relat Disord.* (2012) 18:S24–5. doi: 10.1016/S1353-8020(11)70174-2
98. Kato S, Watanabe H, Senda J, Hirayama M, Ito M, Atsuta N, et al. Widespread cortical and subcortical brain atrophy in Parkinson's disease with excessive daytime sleepiness. *J Neurol.* (2012) 259:318–26. doi: 10.1007/s00415-011-6187-6
99. Chondrogiorgi M, Tzarouchi LC, Zikou AK, Astrakas LG, Kosta P, Argyropoulou MI, et al. Multimodal imaging evaluation of excessive daytime sleepiness in Parkinson's disease. *Int J Neurosci.* (2016) 126:422–8. doi: 10.3109/00207454.2015.1023437
100. Matsui H, Nishinaka K, Oda M, Niikawa H, Komatsu K, Kubori T, et al. Disruptions of the fornix fiber in Parkinsonian patients with excessive daytime sleepiness. *Parkinsonism Relat Disord.* (2006) 12:319–22. doi: 10.1016/j.parkreldis.2006.01.007

101. Gama RL, Tavora DG, Bomfim RC, Silva CE, De Bruin VM, De Bruin PF. Sleep disturbances and brain MRI morphometry in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy–a comparative study. *Parkinsonism Relat Disord*. (2010) 16:275–9. doi: 10.1016/j.parkreldis.2010.01.002
102. Ward AM, Mclaren DG, Schultz AP, Chhatwal J, Boot BP, Hedden T, et al. Daytime sleepiness is associated with decreased default mode network connectivity in both young and cognitively intact elderly subjects. *Sleep* (2013) 36:1609–15. doi: 10.5665/sleep.3108
103. Killgore WD, Vanuk JR, Knight SA, Markowski SM, Pisner D, Shane B, et al. Daytime sleepiness is associated with altered resting thalamocortical connectivity. *Neuroreport* (2015) 26:779–84. doi: 10.1097/WNR.0000000000000418
104. Wen MC, Ng SY, Heng HS, Chao YX, Chan LL, Tan EK, et al. Neural substrates of excessive daytime sleepiness in early drug naive Parkinson's disease: a resting state functional MRI study. *Parkinsonism Relat Disord*. (2016) 24:63–8. doi: 10.1016/j.parkreldis.2016.01.012
105. Earley CJ, Heckler D, Allen RP. Repeated IV doses of iron provides effective supplemental treatment of restless legs syndrome. *Sleep Med*. (2005) 6:301–5. doi: 10.1016/j.sleep.2005.01.008
106. Winkelman JW, Redline S, Baldwin CM, Resnick HE, Newman AB, Gottlieb DJ. Polysomnographic and health-related quality of life correlates of restless legs syndrome in the Sleep Heart Health Study. *Sleep* (2009) 32:772–8. doi: 10.1093/sleep/32.6.772
107. Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. *Sleep Med*. (2010) 11:807–15. doi: 10.1016/j.sleep.2010.07.007
108. Abetz L, Allen R, Follet A, Washburn T, Earley C, Kirsch J, et al. Evaluating the quality of life of patients with restless legs syndrome. *Clin Ther*. (2004) 26:925–35. doi: 10.1016/S0149-2918(04)90136-1
109. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, et al. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med*. (2005) 165:1286–92. doi: 10.1001/archinte.165.11.1286
110. Kushida C, Martin M, Nikam P, Blaisdell B, Wallenstein G, Ferini-Strambi L, et al. Burden of restless legs syndrome on health-related quality of life. *Qual Life Res*. (2007) 16:617–24. doi: 10.1007/s11136-006-9142-8
111. Happe S, Reese JP, Stiasny-Kolster K, Peglau I, Mayer G, Klotsche J, et al. Assessing health-related quality of life in patients with restless legs syndrome. *Sleep Med*. (2009) 10:295–305. doi: 10.1016/j.sleep.2008.01.002
112. Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States. *Mov Disord*. (2011) 26:114–20. doi: 10.1002/mds.23430
113. Salas RE, Kwan AB. The real burden of restless legs syndrome: clinical and economic outcomes. *Am J Manag Care* (2012) 18:S207–212.
114. Innes KE, Flack KL, Selfe TK, Kandati S, Agarwal P. Restless legs syndrome in an appalachian primary care population: prevalence, demographic and lifestyle correlates, and burden. *J Clin Sleep Med*. (2013) 9:1065–75. doi: 10.5664/jcsm.3084
115. Durgin T, Witt EA, Fishman J. The humanistic and economic burden of restless legs syndrome. *PLoS ONE* (2015) 10:e0140632. doi: 10.1371/journal.pone.0140632
116. Stevens MS. Restless legs syndrome/willis-ekbom disease morbidity: burden, quality of life, cardiovascular aspects, and sleep. *Sleep Med Clin*. (2015) 10:369–73, xv–xvi. doi: 10.1016/j.jsmc.2015.05.017
117. Fulda S, Wetter TC. Where dopamine meets opioids: a meta-analysis of the placebo effect in restless legs syndrome treatment studies. *Brain* (2008) 131:902–17. doi: 10.1093/brain/awm244
118. Taylor S, Gafton J, Shah B, Pagano G, Chaudhuri KR, Brooks DJ, et al. Progression of nonmotor symptoms in subgroups of patients with non-dopamine-deficient Parkinsonism. *Mov Disord*. (2016) 31:344–51. doi: 10.1002/mds.26456
119. Ferini-Strambi L, Marelli S, Galbiati A. Clinical pharmacology and efficacy of rotigotine (Neupro(R) patch) in the treatment of restless leg syndrome. *Expert Opin Drug Metab Toxicol*. (2016) 12:967–75. doi: 10.1080/17425255.2016.1194393
120. Lin CC, Fan YM, Lin GY, Yang FC, Cheng CA, Lu KC, et al. 99mTc-TRODAT-1 SPECT as a potential neuroimaging biomarker in patients with restless legs syndrome. *Clin Nucl Med*. (2016) 41:e14–17. doi: 10.1097/RLU.0000000000000916
121. Earley CJ, Kuwabara H, Wong DF, Gamaldo C, Salas R, Brasic J, et al. The dopamine transporter is decreased in the striatum of subjects with restless legs syndrome. *Sleep* (2011) 34:341–7. doi: 10.1093/sleep/34.3.341
122. Ruottinen HM, Partinen M, Hublin C, Bergman J, Haaparanta M, Solin O, et al. An FDOPA PET study in patients with periodic limb movement disorder and restless legs syndrome. *Neurology* (2000) 54:502–4. doi: 10.1212/WNL.54.2.502
123. Moccia M, Erro R, Picillo M, Santangelo G, Spina E, Allocca R, et al. A four-year longitudinal study on restless legs syndrome in Parkinson disease. *Sleep* (2016) 39:405–12. doi: 10.5665/sleep.5452
124. Cervenka S, Palhagen SE, Comley RA, Panagiotidis G, Cselenyi Z, Matthews JC, et al. Support for dopaminergic hypoactivity in restless legs syndrome: a PET study on D2-receptor binding. *Brain* (2006) 129:2017–28. doi: 10.1093/brain/awl163
125. Turjanski N, Lees AJ, Brooks DJ. Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies. *Neurology* (1999) 52:932–7. doi: 10.1212/WNL.52.5.932
126. Michaud M, Soucy JP, Chabli A, Lavigne G, Montplaisir J. SPECT imaging of striatal pre- and postsynaptic dopaminergic status in restless legs syndrome with periodic leg movements in sleep. *J Neurol*. (2002) 249:164–70. doi: 10.1007/PL00007859
127. Kim KW, Jhoo JH, Lee SB, Lee SD, Kim TH, Kim SE, et al. Increased striatal dopamine transporter density in moderately severe old restless legs syndrome patients. *Eur J Neurol*. (2012) 19:1213–8. doi: 10.1111/j.1468-1331.2012.03705.x
128. Tribl GG, Asenbaum S, Happe S, Bonelli RM, Zeitlhofer J, Auff E. Normal striatal D2 receptor binding in idiopathic restless legs syndrome with periodic leg movements in sleep. *Nucl Med Commun*. (2004) 25:55–60. doi: 10.1097/00006231-200401000-00008
129. Lee BY, Kim J, Connor JR, Podskalny GD, Ryu Y, Yang QX. Involvement of the central somatosensory system in restless legs syndrome: a neuroimaging study. *Neurology* (2018) 90:e1834–41. doi: 10.1212/WNL.0000000000005562
130. Belke M, Heverhagen JT, Keil B, Rosenow F, Oertel WH, Stiasny-Kolster K, et al. DTI and VBM reveal white matter changes without associated gray matter changes in patients with idiopathic restless legs syndrome. *Brain Behav*. (2015) 5:e00327. doi: 10.1002/brb3.327
131. Rizzo G, Manners D, Vetrugno R, Tonon C, Malucelli E, Plazzi G, et al. Combined brain voxel-based morphometry and diffusion tensor imaging study in idiopathic restless legs syndrome patients. *Eur J Neurol*. (2012) 19:1045–9. doi: 10.1111/j.1468-1331.2011.03604.x
132. Bucher SF, Seelos KC, Oertel WH, Reiser M, Trenkwalder C. Cerebral generators involved in the pathogenesis of the restless legs syndrome. *Ann Neurol*. (1997) 41:639–45. doi: 10.1002/ana.410410513
133. Etgen T, Draganski B, Ilg C, Schroder M, Geisler P, Hajak G, et al. Bilateral thalamic gray matter changes in patients with restless legs syndrome. *Neuroimage* (2005) 24:1242–7. doi: 10.1016/j.neuroimage.2004.10.021
134. Earley CJ, Allen RP, Beard JL, Connor JR. Insight into the pathophysiology of restless legs syndrome. *J Neurosci Res*. (2015) 62:623–8. doi: 10.1002/1097-4547(20001201)62:5<623::AID-JNR1>3.0.CO;2-H
135. Oshiro S, Morioka MS, Kikuchi M. Dysregulation of iron metabolism in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. *Adv Pharmacol Sci*. (2011) 2011:378278. doi: 10.1155/2011/378278
136. Allen RP, Earley CJ. The role of iron in restless legs syndrome. *Mov Disord*. (2007) 22:S440–8. doi: 10.1002/mds.21607
137. Allen RP, Barker PB, Wehrl FW, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. *Neurology* (2001) 56:263–5. doi: 10.1212/WNL.56.2.263
138. Li X, Allen RP, Earley CJ, Liu H, Cruz TE, Edden R, et al. Brain iron deficiency in idiopathic restless legs syndrome measured by quantitative magnetic susceptibility at 7 tesla. *Sleep Med*. (2016) 22:75–82. doi: 10.1016/j.sleep.2016.05.001
139. Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. *J Clin Neurophysiol*. (2001) 18:128–47. doi: 10.1097/00004691-200103000-00004

140. Connor JR, Boyer PJ, Menzies SL, Dellinger B, Allen RP, Ondo WG, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. *Neurology* (2003) 61:304–9. doi: 10.1212/01.WNL.0000078887.16593.12
141. Abbott SM, Videnovic A. sleep disorders in atypical Parkinsonism. *Mov Disord Clin Pract*. (2014) 1:89–96. doi: 10.1002/mdc3.12025
142. Trojanowski JQ, Revesz T, Neuropathology Working Group On MSA. Proposed neuropathological criteria for the post mortem diagnosis of multiple system atrophy. *Neuropathol Appl Neurobiol*. (2007) 33:615–20. doi: 10.1111/j.1365-2990.2007.00907.x
143. Ghorayeb I, Yekhlef F, Chrysostome V, Balestre E, Bioulac B, Tison F. Sleep disorders and their determinants in multiple system atrophy. *J Neurol Neurosurg Psychiatry* (2002) 72:798–800. doi: 10.1136/jnnp.72.6.798
144. Plazzi G, Corsini R, Provini F, Pierangeli G, Martinelli P, Montagna P, et al. REM sleep behavior disorders in multiple system atrophy. *Neurology* (1997) 48:1094–7. doi: 10.1212/WNL.48.4.1094
145. Gilman S, Koeppe RA, Chervin RD, Consens FB, Little R, An H, et al. REM sleep behavior disorder is related to striatal monoaminergic deficit in MSA. *Neurology* (2003) 61:29–34. doi: 10.1212/01.WNL.0000073745.68744.94
146. Martinez-Rodriguez JE, Seppi K, Cardozo A, Iranzo A, Stampfer-Kountchev M, Wenning G, et al. Cerebrospinal fluid hypocretin-1 levels in multiple system atrophy. *Mov Disord*. (2007) 22:1822–4. doi: 10.1002/mds.21668
147. Moreno-Lopez C, Santamaria J, Salamero M, Del Sorbo F, Albanese A, Pellecchia MT, et al. Excessive daytime sleepiness in multiple system atrophy (SLEEMSA study). *Arch Neurol*. (2011) 68:223–30. doi: 10.1001/archneurol.2010.359
148. Benarroch EE, Schmeichel AM, Low PA, Parisi JE. Depletion of putative chemosensitive respiratory neurons in the ventral medullary surface in multiple system atrophy. *Brain* (2007) 130:469–75. doi: 10.1093/brain/awl357
149. Abdo WF, Bloem BR, Kremer HP, Lammers GJ, Verbeek MM, Overeem S. CSF hypocretin-1 levels are normal in multiple-system atrophy. *Parkinsonism Relat Disord*. (2008) 14:342–4. doi: 10.1016/j.parkreldis.2007.08.012
150. Schmeichel AM, Buchhalter LC, Low PA, Parisi JE, Boeve BW, Sandroni P, et al. Mesopontine cholinergic neuron involvement in Lewy body dementia and multiple system atrophy. *Neurology* (2008) 70:368–73. doi: 10.1212/01.wnl.0000298691.71637.96
151. Silber MH, Levine S. Stridor and death in multiple system atrophy. *Mov Disord*. (2000) 15:699–704.
152. Vetrugno R, Provini F, Cortelli P, Plazzi G, Lotti EM, Pierangeli G, et al. Sleep disorders in multiple system atrophy: a correlative video-polysomnographic study. *Sleep Med*. (2004) 5:21–30. doi: 10.1016/j.sleep.2003.07.002
153. Shy GM, Drager GA. A neurological syndrome associated with orthostatic hypotension: a clinical-pathologic study. *Arch Neurol*. (1960) 2:511–27. doi: 10.1001/archneur.1960.03840110025004
154. Shimohata T, Shinoda H, Nakayama H, Ozawa T, Terajima K, Yoshizawa H, et al. Daytime hypoxemia, sleep-disordered breathing, and laryngopharyngeal findings in multiple system atrophy. *Arch Neurol*. (2007) 64:856–61. doi: 10.1001/archneur.64.6.856
155. Vincken WG, Gauthier SG, Dollfuss RE, Hanson RE, Darauay CM, Cosio MG. Involvement of upper-airway muscles in extrapyramidal disorders. A cause of airflow limitation. *N Engl J Med*. (1984) 311:438–42. doi: 10.1056/NEJM198408163110704
156. Gilman S, Chervin RD, Koeppe RA, Consens FB, Little R, An H, et al. Obstructive sleep apnea is related to a thalamic cholinergic deficit in MSA. *Neurology* (2003) 61:35–9. doi: 10.1212/01.WNL.0000073624.13436.32
157. Rico B, Cavada C. A population of cholinergic neurons is present in the macaque monkey thalamus. *Eur J Neurosci*. (1998) 10:2346–52. doi: 10.1046/j.1460-9568.1998.00246.x
158. Rampello L, Butta V, Raffaele R, Vecchio I, Battaglia G, Cormaci G, et al. Progressive supranuclear palsy: a systematic review. *Neurobiol Dis*. (2005) 20:179–86. doi: 10.1016/j.nbd.2005.03.013
159. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia *Arch Neurol*. (1964) 10:333–59. doi: 10.1001/archneur.1964.00460160003001
160. Arnulf I, Merino-Andreu M, Bloch F, Konofal E, Vidailhet M, Cochen V, et al. REM sleep behavior disorder and REM sleep without atonia in patients with progressive supranuclear palsy. *Sleep* (2005) 28:349–54. doi: 10.1093/sleep/28.3.349
161. Diederich NJ, Leurgans S, Fan W, Chmura TA, Goetz CG. Visual hallucinations and symptoms of REM sleep behavior disorder in Parkinsonian tauopathies. *Int J Geriatr Psychiatry* (2008) 23:598–603. doi: 10.1002/gps.1945
162. Sixel-Doring F, Schweitzer M, Mollenhauer B, Trenkwalder C. Polysomnographic findings, video-based sleep analysis and sleep perception in progressive supranuclear palsy. *Sleep Med*. (2009) 10:407–15. doi: 10.1016/j.sleep.2008.05.004
163. Dickson DW, Ahmed Z, Algom AA, Tsuboi Y, Josephs KA. Neuropathology of variants of progressive supranuclear palsy. *Curr Opin Neurol*. (2010) 23:394–400. doi: 10.1097/WCO.0b013e32833be924
164. Warren NM, Piggott MA, Perry EK, Burn DJ. Cholinergic systems in progressive supranuclear palsy. *Brain* (2005) 128:239–49. doi: 10.1093/brain/awh391
165. Oba H, Yagishita A, Terada H, Barkovich AJ, Kutomi K, Yamauchi T, et al. New and reliable MRI diagnosis for progressive supranuclear palsy. *Neurology* (2005) 64:2050–5. doi: 10.1212/01.WNL.0000165960.04422.D0
166. Longoni G, Agosta F, Kostic VS, Stojkovic T, Pagani E, Stosic-Opincal T, et al. MRI measurements of brainstem structures in patients with Richardson's syndrome, progressive supranuclear Palsy-Parkinsonism, and Parkinson's disease. *Mov Disord*. (2011) 26:247–55. doi: 10.1002/mds.23293
167. Massey LA, Jager HR, Paviour DC, O'sullivan SS, Ling H, Williams DR, et al. The midbrain to pons ratio: a simple and specific MRI sign of progressive supranuclear palsy. *Neurology* (2013) 80:1856–861. doi: 10.1212/WNL.0b013e318292a2d2
168. Saini J, Bagepally BS, Sandhya M, Pasha SA, Yadav R, Thennarasu K, et al. Subcortical structures in progressive supranuclear palsy: vertex-based analysis. *Eur J Neurol*. (2013) 20:493–501. doi: 10.1111/j.1468-1331.2012.03884.x
169. Whitwell JL, Duffy JR, Strand EA, Machulda MM, Senjem ML, Gunter JL, et al. Neuroimaging comparison of primary progressive apraxia of speech and progressive supranuclear palsy. *Eur J Neurol*. (2013) 20:629–37. doi: 10.1111/ene.12004
170. Padovani A, Borroni B, Brambati SM, Agosti C, Broli M, Alonso R, et al. Diffusion tensor imaging and voxel based morphometry study in early progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry* (2006) 77:457–63. doi: 10.1136/jnnp.2005.075713
171. Cordato NJ, Duggins AJ, Halliday GM, Morris JG, Pantelis C. Clinical deficits correlate with regional cerebral atrophy in progressive supranuclear palsy. *Brain* (2005) 128:1259–66. doi: 10.1093/brain/awh508
172. Price S, Paviour D, Scahill R, Stevens J, Rossor M, Lees A, et al. Voxel-based morphometry detects patterns of atrophy that help differentiate progressive supranuclear palsy and Parkinson's disease. *Neuroimage* (2004) 23:663–9. doi: 10.1016/j.neuroimage.2004.06.013
173. Canu E, Agosta F, Baglio F, Galantucci S, Nemni R, Filippi M. Diffusion tensor magnetic resonance imaging tractography in progressive supranuclear palsy. *Mov Disord*. (2011) 26:1752–5. doi: 10.1002/mds.23739
174. Saini J, Bagepally BS, Sandhya M, Pasha SA, Yadav R, Pal PK. *In vivo* evaluation of white matter pathology in patients of progressive supranuclear palsy using TBSS. *Neuroradiology* (2012) 54:771–80. doi: 10.1007/s00234-011-0983-7
175. Whitwell JL, Schwarz CG, Reid RI, Kantarci K, Jack CRJr, Josephs KA. Diffusion tensor imaging comparison of progressive supranuclear palsy and corticobasal syndromes. *Parkinsonism Relat Disord*. (2014) 20:493–8. doi: 10.1016/j.parkreldis.2014.01.023
176. Lehericy S, Hartmann A, Lannuzel A, Galanaud D, Delmaire C, Bienaimee MJ, et al. Magnetic resonance imaging lesion pattern in Guadeloupean Parkinsonism is distinct from progressive supranuclear palsy. *Brain* (2010) 133:2410–25. doi: 10.1093/brain/awq162

177. Coulon P, Budde T, Pape HC. The sleep relay–the role of the thalamus in central and decentral sleep regulation. *Pflugers Arch*. (2012) 463:53–71. doi: 10.1007/s00424-011-1014-6
178. Reinoso-Suarez F, De Andres I, Rodrigo-Angulo ML, Garzon M. Brain structures and mechanisms involved in the generation of REM sleep. *Sleep Med Rev*. (2001) 5:63–77. doi: 10.1053/smrv.2000.0136
179. Benarroch EE. Pedunculopontine nucleus: functional organization and clinical implications. *Neurology* (2013) 80:1148–55. doi: 10.1212/WNL.0b013e3182886a76
180. Gibb WR, Luthert PJ, Marsden CD. Corticobasal degeneration. *Brain* (1989) 112:1171–92. doi: 10.1093/brain/112.5.1171
181. Kimura K, Tachibana N, Aso T, Kimura J, Shibasaki H. Subclinical REM sleep behavior disorder in a patient with corticobasal degeneration. *Sleep* (1997) 20:891–4. doi: 10.1093/sleep/20.10.891
182. Wetter TC, Brunner H, Collado-Seidel V, Trenkwalder C, Winkelmann J. Sleep and periodic limb movements in corticobasal degeneration. *Sleep Med*. (2002) 3:33–6. doi: 10.1016/S1389-9457(01)00097-1
183. Cooper AD, Josephs KA. Photophobia, visual hallucinations, and REM sleep behavior disorder in progressive supranuclear palsy and corticobasal degeneration: a prospective study. *Parkinsonism Relat Disord*. (2009) 15:59–61. doi: 10.1016/j.parkreldis.2008.01.011
184. Roche S, Jacquesson JM, Destee A, Defebvre L, Derambure P, Monaca C. Sleep and vigilance in corticobasal degeneration: a descriptive study. *Neurophysiol Clin*. (2007) 37:261–4. doi: 10.1016/j.neucli.2007.05.002
185. Yasui K, Inoue Y, Kanbayashi T, Nomura T, Kusumi M, Nakashima K. CSF orexin levels of Parkinson's disease, dementia with Lewy bodies, progressive supranuclear palsy and corticobasal degeneration. *J Neurol Sci*. (2006) 250:120–3. doi: 10.1016/j.jns.2006.08.004
186. Kasashima S, Oda Y. Cholinergic neuronal loss in the basal forebrain and mesopontine tegmentum of progressive supranuclear palsy and corticobasal degeneration. *Acta Neuropathol*. (2003) 105:117–24. doi: 10.1007/s00401-002-0621-x
187. Albrecht F, Bisenius S, Morales Schaack R, Neumann J, Schroeter ML. Disentangling the neural correlates of corticobasal syndrome and corticobasal degeneration with systematic and quantitative ALE meta-analyses. *NPJ Parkinsons Dis*. (2017) 3:12. doi: 10.1038/s41531-017-0012-6
188. Cilia R, Rossi C, Frosini D, Volterrani D, Siri C, Pagni C, et al. Dopamine transporter SPECT imaging in corticobasal syndrome. *PLoS ONE* (2011) 6:e18301. doi: 10.1371/journal.pone.0018301
189. Oyanagi K, Tsuchiya K, Yamazaki M, Ikeda K. Substantia nigra in progressive supranuclear palsy, corticobasal degeneration, and Parkinsonism-dementia complex of Guam: specific pathological features. *J Neuropathol Exp Neurol*. (2001) 60:393–402. doi: 10.1093/jnen/60.4.393
190. Dickson DW, Bergeron C, Chin SS, Duyckaerts C, Horoupian D, Ikeda K, et al. Office of Rare Diseases neuropathologic criteria for corticobasal degeneration. *J Neuropathol Exp Neurol*. (2002) 61:935–46. doi: 10.1093/jnen/61.11.935
191. Niccolini F, Haider S, Reis Marques T, Muhlert N, Tziortzi AC, Searle GE, et al. Altered PDE10A expression detectable early before symptomatic onset in Huntington's disease. *Brain* (2015) 138:3016–29. doi: 10.1093/brain/awv214
192. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. *Cell* (1993) 72:971–83.
193. Davies SW, Turmaine M, Cozens BA, Difiglia M, Sharp AH, Ross CA, et al. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. *Cell* (1997) 90:537–48. doi: 10.1016/S0092-8674(00)80513-9
194. Li SH, Cheng AL, Zhou H, Lam S, Rao M, Li H, et al. Interaction of Huntington disease protein with transcriptional activator Sp1. *Mol Cell Biol*. (2002) 22:1277–87. doi: 10.1128/MCB.22.5.1277-1287.2002
195. Andre VM, Cepeda C, Levine MS. Dopamine and glutamate in Huntington's disease: a balancing act. *CNS Neurosci Ther*. (2010) 16:163–78. doi: 10.1111/j.1755-5949.2010.00134.x
196. Niccolini F, Politis M. Neuroimaging in Huntington's disease. *World J Radiol*. (2014) 6:301–12. doi: 10.4329/wjr.v6.i6.301
197. Hansotia P, Wall R, Berendes J. Sleep disturbances and severity of Huntington's disease. *Neurology* (1985) 35:1672–4. doi: 10.1212/WNL.35.11.1672
198. Arnulf I, Nielsen J, Lohmann E, Schiefer J, Wild E, Jennum P, et al. Rapid eye movement sleep disturbances in Huntington disease. *Arch Neurol*. (2008) 65:482–8. doi: 10.1001/archneur.65.4.482
199. Politis M, Pavese N, Tai YF, Tabrizi SJ, Barker RA, Piccini P. Hypothalamic involvement in Huntington's disease: an *in vivo* PET study. *Brain* (2008) 131:2860–9. doi: 10.1093/brain/awn244
200. Politis M, Pavese N, Tai YF, Kiferle L, Mason SL, Brooks DJ, et al. Microglial activation in regions related to cognitive function predicts disease onset in Huntington's disease: a multimodal imaging study. *Hum Brain Mapp*. (2011) 32:258–70. doi: 10.1002/hbm.21008
201. Swaab DF. Neuropeptides in hypothalamic neuronal disorders. *Int Rev Cytol*. (2004) 240:305–75. doi: 10.1016/S0074-7696(04)40003-5
202. Petersen A, Bjorkqvist M. Hypothalamic-endocrine aspects in Huntington's disease. *Eur J Neurosci*. (2006) 24:961–7. doi: 10.1111/j.1460-9568.2006.04985.x
203. Petersen A, Gabery S. Hypothalamic and limbic system changes in Huntington's Disease. *J Huntingtons Dis*. (2012) 1:5–16. doi: 10.3233/JHD-2012-120006
204. Kassubek J, Juengling FD, Kioschies T, Henkel K, Karitzky J, Kramer B, et al. Topography of cerebral atrophy in early Huntington's disease: a voxel based morphometric MRI study. *J Neurol Neurosurg Psychiatry* (2004) 75:213–20.
205. Douaud G, Gaura V, Ribeiro MJ, Lethimonnier F, Maroy R, Verny C, et al. Distribution of grey matter atrophy in Huntington's disease patients: a combined ROI-based and voxel-based morphometric study. *Neuroimage* (2006) 32:1562–75. doi: 10.1016/j.neuroimage.2006.05.057
206. Soneson C, Fontes M, Zhou Y, Denisov V, Paulsen JS, Kirik D, et al. Early changes in the hypothalamic region in prodromal Huntington disease revealed by MRI analysis. *Neurobiol Dis*. (2010) 40:531–43. doi: 10.1016/j.nbd.2010.07.013
207. Roos RA, Aziz NA. Hypocretin-1 and secondary signs in Huntington's disease. *Parkinsonism Relat Disord*. (2007) 13:S387–390. doi: 10.1016/S1353-8020(08)70035-X
208. Aron AR, Schlaghecken F, Fletcher PC, Bullmore ET, Eimer M, Barker R, et al. Inhibition of subliminally primed responses is mediated by the caudate and thalamus: evidence from functional MRI and Huntington's disease. *Brain* (2003) 126:713–23. doi: 10.1093/brain/awg067
209. Kassubek J, Juengling FD, Ecker D, Landwehrmeyer GB. Thalamic atrophy in Huntington's disease co-varies with cognitive performance: a morphometric MRI analysis. *Cereb Cortex* (2005) 15:846–53. doi: 10.1093/cercor/bhh185
210. Hobbs NZ, Henley SM, Ridgway GR, Wild EJ, Barker RA, Scahill RI, et al. The progression of regional atrophy in premanifest and early Huntington's disease: a longitudinal voxel-based morphometry study. *J Neurol Neurosurg Psychiatry* (2010) 81:756–63. doi: 10.1136/jnnp.2009.190702

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Excessive Daytime Sleepiness and REM Sleep Behavior Disorders in Parkinson's Disease: A Narrative Review on Early Intervention With Implications to Neuroprotection

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Sleep contributes to the consolidation of our memory and facilitates learning. Short term sleep deprivation temporarily reduces mnestic capacity, whereas long lasting sleep deprivation is associated with structural changes in the hippocampus and cortical areas. However, it is unknown whether early intervention and treatment of sleep disorders could have a neuroprotective effect. In neurodegenerative diseases sleep disorders can occur at preclinical stages and are frequently observed in patients with established Parkinson's disease (PD) and other α-synucleinopathies. REM sleep behavior disorder (RBD) is recognized as a hallmark for the development of α-synucleinopathies and may predict early cognitive decline, while excessive daytime sleepiness (EDS) is present in 12% of patients with PD before treatment initiation and increases continuously over time, causing substantial restrictions for the patients' social life. In more advanced disease, EDS is associated with dementia. Even though well recognized, limited attention has been given to genetics or the treatment of RBD and EDS in early PD. Systematic screening and early intervention can be expected to increase the patients' quality of life, but it remains unclear if this will also impact disease progression. Intervention studies in preclinical and early stages of α-synucleinopathies are needed to increase our understanding of the underlying pathomechanisms and may also provide important inroads to help clarify whether sleep disturbances are secondary to the neurodegenerative process or also contribute to disease exacerbation.

Keywords: early Parkinson's disease, sleep, genetics, EDS, RBD

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INTRODUCTION

The wish for restorative sleep is equal for any human. Close to one third of the human life is spent asleep and perfect sleep means awakening refreshed and oblivious to the hours spent at rest. A number of conditions have to be satisfied in order to sleep well. These include the duration, continuity, rhythmicity, quality, and amount of time spent in different sleep stages. Short term sleep disruption can temporarily impede most behavioral processes (1) and lead to deficits in attention, executive function, non-declarative and declarative

memory, and emotional reactivity and sensory perception (2, 3). Conversely, a good night's sleep or daytime napping has significant beneficial effects on human alertness and experienced well-being (4, 5), and the synaptic homeostasis hypothesis indicates sleep as the essential phase to facilitate plasticity of the brain and memory consolidation, by reducing the burden of plasticity on neurons while restoring neuronal selectivity and the ability to learn (6). The complexity of our sleep/wake system makes sleep vulnerable to disturbances, which then can lead to adverse health outcomes.

Sleep quality and duration change with aging (7). The increasingly disturbed sleep in the elderly is caused by a weakening of the circadian system with a blunted diurnal melatonin level (8), as well as, changes in the sleep and wake regulating systems (9). Reciprocally, weakened sleep structures render the patient prone to the development of sleep disturbances and subsequently reduced daytime function. Other reasons for sleep disorders in the elderly may be the occurrence of diseases causing sleep disruption or medication.

It remains unclear to what extent disturbances of sleep caused by aging or disease contribute to the development of neurodegenerative diseases or whether they are only a byproduct of other conditions. Further, it is unknown if early intervention to treat sleep disturbances may delay the neurodegenerative processes. This viewpoint will address these matters, focusing on two major sleep disorders: Excessive daytime sleepiness (EDS) and REM sleep behavior disorder (RBD). EDS and RBD occur frequently in early α-synucleinopathies and have possible implications for further disease development. Early detection and intervention may clarify parts of the riddle as to what extent sleep disturbances contribute to the cause or the consequence of PD. Finally, sleep deprivation will be shortly discussed as increasing evidence indicates that this may also be a key player in these neurodegenerative diseases.

EARLY PARKINSON'S DISEASE AND SLEEP DISORDERS

Disturbed or impaired sleep is very common in PD. The most frequent sleep disturbances recorded in PD are EDS, RBD and insomnia. The pathogenesis of these sleep disturbances may be attributed to the underlying disease pathologies involving the brainstem and the hypothalamus, or be the consequence of indirect mechanisms, for example dopaminergic medication or PD-related motor and non-motor symptoms (10–12). EDS is typically more prevalent in later stages of the disease, whilst RBD may be present years before the classic clinical features of PD and other α-synucleinopathies such as dementia with Lewy bodies occur (13).

Several subtypes of PD exist: While age of onset (14) and motor-subtype (15) have long been recognized as important prognostic factors for the course of PD, certain non-motor patterns are now also considered to indicate different neuropathological pathways and progression rates (16). Sleep phenotypes observed in PD are proposed to be associated with specific patterns of pathological progression, which can have subsequent impact on clinical presentations. For example, the brainstem-dominant phenotype is reported to relate to non-motor symptoms, such as olfactory disturbances and psychiatric symptoms (17). These findings remain debated but may be useful to indicate prognosis or treatment response, and more studies of the natural history of sleep disturbances and disease progression from premotor- and early motor-stages of disease will help to clarify if sleep symptoms help to define specific PD subtypes.

RBD IN EARLY PD

RBD is a parasomnia triggered by lower brainstem dysfunction, resulting in lack of physiological atonia during REM sleep (18). Consequently, patients may enact their dreams physically or vocally during REM sleep (19). RBD is a major risk factor for the development of α-synucleinopathies, occurring in 20–75% of patients (20, 21). It has been associated with more severe motor symptoms and signs, and more depression/anxiety (16), and was found to be one of the strongest clinical predictors of cognitive impairment after older age (22).

RBD is accepted as a risk marker and in the context of research is increasingly used to estimate likelihood ratios of developing PD. Patients with incident RBD without Parkinsonism will on average be diagnosed with an α-synucleinopathy within a decade of the onset of the sleep disorder (23). The emergence of RBD can be attributed to the initial α-synuclein pathology associated dysfunction in the brainstem, which later ascends to more rostral structures. The motor symptoms only manifest after the loss of about 80% of the substantia nigra cells (24, 25). Furthermore, a PET study detected microglial activation in the substantia nigra of patients with idiopathic RBD (26), implicating neuroinflammation in the early stages of α-synucleinopathies.

Not all patients with PD will display clinically relevant RBD, indicating that additional factors are involved in the co-occurrence of RBD and PD. Several genetic variants have been identified, which in addition to influencing susceptibility for PD, may also affect the risk of developing RBD. Among these are pathogenic variants in *GBA*, the gene encoding for the enzyme Glucocerebrosidase, which are associated with idiopathic RBD and worsening of the frequency of symptoms of RBD over time in both the non-PD population (27, 28) and in PD patients (27, 29–31). RBD also preceded the onset of the cardinal motor symptoms of PD SNCA p.A53T carriers (32), although the association of RBD with more common PD-risk *SNCA* variants is inconclusive (33–35). In contrast, polymorphism in *SCARB2* and *MAPT* have been associated with a reduced risk of developing PD or RBD in the non-PD population (33, 36). Combining genetic and clinical sleep data may assist in identifying individuals susceptible to PD in the prodromal phase, and in doing so offer an important window of time for neuroprotective treatment or lifestyle interventions.

EDS IN EARLY PD

EDS in PD is defined as an inappropriate increased sleep propensity or increased need of time spent asleep, and is most

frequently measured with the Epworth Sleepiness Scale (positive if score >10) (37). EDS causes frequent, major social problems and may interfere with the patients' driving abilities. The increase in frequency of EDS with disease duration and severity may be explained by an advancing neurodegenerative process. Other causes for EDS in PD are the potential sedating effect of dopaminergic medication, as well as secondary increased sleep propensity during daytime due to dysregulated and insufficient night time sleep (38).

Occurrence of EDS in the general population has been associated with the development of dementia and especially AD (39, 40). It remains uncertain to what extent EDS may precede the development of Parkinsonism and whether the occurrence of EDS in early PD foretells a certain disease progression. The only two studies to examine EDS longitudinally in the general population report a higher risk for the subsequent development of PD (41, 42). In our population based incident cohort study, drug naïve patients with PD reported more frequent EDS compared to age and sex matched controls, and an increased Epworth Sleepiness Scale score at baseline was found to be the main risk for the subsequent development of EDS (43). Nevertheless, results remain contrary, with findings of both increased and equivalent prevalence of EDS compared to matched healthy control subjects (44, 45). To avoid the confounding influence of dopaminergic treatment on sleepiness more longitudinal population studies are needed, examining drug naive patients and the role of EDS as a prodromal or associated feature in early PD.

There are no proven genetic risk factors for EDS in PD. Several studies have investigated a link between EDS and the Catechol O-methyltransferase (COMT) val158met polymorphism, which affects synaptic dopamine levels following neurotransmitter release, but the results are inconsistent (46, 47). Interestingly, in the Sleep Heart Health Study, daytime sleepiness was found to be associated with an intronic variant in the gene encoding phosphodiesterase 4D (PDE4D) (48). PDE4D is implicated in memory consolidation, one of the functions of sleep, and might represent a therapeutic target for cognition enhancement. Furthermore, in PD, *PDE4D* is significantly hypermethylated compared to controls (49), and PDE4 inhibitors have been shown to have a neuroprotective effect in mice treated with MPTP (50), whilst broad spectrum PDE inhibitors protect cultured neurons against amyloid-beta (Aβ) and α- synuclein-induced synapse damage (51).

LESSONS FROM OTHER FIELDS: THE ROLE OF SLEEP DEPRIVATION

Mounting evidence points to short- or long-term sleep deprivation as a cause to structural and pathological changes in the brain. A number of animal studies document the sensitivity of the hippocampus to chronic sleep deprivation (52) and an imaging study reported increased neuronal loss in the hippocampus of patients with chronic insomnia (53). In mice, sleep deprivation promotes astrocytic phagocytosis and microglial activation (54), likely leading to exacerbated phagocytosis of synaptic elements.

Several studies also show that sleep is the most important diurnal phase for clearance of neuronal metabolites such as Aβ42 (55–57). In addition, the reduction of slow wave sleep increase the level of brain Aβ prior to amyloid deposition, the hallmark of Alzheimer's disease (AD), which is also observed in patients with dementia with Lewy bodies (DLB) and PD (58), indicating that interventions targeting sleep that reduce amyloid burden could be of significance in the prevention or treatment of both AD and α-synucleinopathies.

GENETIC INFLUENCES ON SLEEP: CLUES FOR INTERVENTION STRATEGIES

Healthy people vary in their preferences for sleep timing and length, and response to sleep deprivation and susceptibility to sleep disorders varies from person to person. Although environmental factors can account for much of this variability, an individual's underlying genetic architecture (including genetic mutations and polymorphisms, and epigenetic changes) undoubtedly influences sleep. As discussed, relatively little is known about the role of genetic variants in sleep-related disorders in α-synucleinopathies, but recent advances in the study of circadian genes and epigenetics in other fields suggests possible targets for intervention therapies.

Sleeping and waking outside of the times set by the internal circadian clock can cause negative health outcomes, including neurological issues. In the general population, mistimed sleep, like that associated with jet lag or shift work, disrupts the rhythms of hundreds of genes, including key regulators of gene expression and core clock genes, notably *CLOCK* and *ARNTL* (*BMAL1*) (59). Interestingly, the phase and amplitude of the clock genes may also be altered in PD (60–62), proposing that sleep dysfunction seen in early PD may reflect an underlying pathology in the molecular clock. The molecular mechanisms that disrupt circadian regulation in PD are not clear, however patients with α-synucleinopathies exhibit DNA methylation changes associated with clock genes, for example decreased methylation of the *NPAS2* gene promoter from PD patients (63) and of *PER1* and *CRY1* from DLB patients (64) leukocytes have been reported. Although effects on the central circadian clock have not been shown, aberrant DNA methylation of key clock genes in the PD brain may potentiate widespread circadian deregulation and the development of sleep disorders and/or PD. Alternative theories point to the role of progressive dopaminergic loss within the nigrostriatal system, since dopamine both regulates and is regulated by the clock genes in the hypothalamic suprachiasmatic nucleus and peripheral brain areas (65, 66).

The association between dopaminergic therapies and circadian genetic markers in PD has not been investigated, but animal models have demonstrated increased mRNA levels of selected clock genes after application of D_1 and D_2 dopamine receptor agonists (67), while D_2 dopamine antagonists blunted the rhythm of striatal *PER2* (68). These observations have

implications for circadian abnormalities seen in PD, especially in medicated patients or in advanced disease.

DISCUSSION

Sleep problems are among the earliest symptoms of PD and increase with disease progression. RBD and EDS are the most common documented disorders affecting the patient, whereas research on disruption of the circadian system is just at the beginnings. It is not yet known if early treatment of sleep disorders could reduce the risk of developing α-synucleinopathies or slow disease progression, but as our understanding of the restorative role that sleep plays increases (6), the suggestion that interventions targeting sleep disorders will have positive implications for α-synucleinopathy disease susceptibility and progression gains credence.

To date there is limited evidence that behavioral or pharmaceutical interventions to regularize sleep/wake activity might be therapeutically useful in neurodegenerative disease. As in humans, sleep deprivation in mice can cause degeneration of neurons. Mouse models of Huntington's disease (HD) display degeneration of sleep rhythms, and early pharmacological intervention to restore sleep by treatment with the sedative clonazepam at the onset of the light phase, normalizes clock gene oscillation in these mice and significantly improves cognitive performance in this model (69). More recently, the motor symptoms of the HD mice were also alleviated following early time-restricted feeding intervention that improved circadian rhythmicity (70). These observations give hope that treatments or lifestyle interventions aimed at restoring circadian rhythms are promising targets to slow the neurodegenerative processes and could also improve other circadian gene-regulated functions that are impaired in PD.

Sleep disturbances, especially insomnia, in young adults seem to have the potential to cause structural changes of the brain. To what extent this may have health consequences decades later one can only speculate. A recent published Nordic study reports a 1.24 and 1.94 hazards ratio for the risk of developing dementia 3–10 years following midlife and late-life insomnia, respectively (71). However, it remains uncertain whether insomnia is one of the causes or a consequence of neurodegenerative processes or a combination of both. Effects of sleep deprivation have mainly been shown to be associated to amyloid deposition, and there are an increasing number of reports referring to co-existing amyloidopathy in PD patients with dementia (72, 73). Whether these patients experienced more or serious insomnia is to our knowledge not yet shown, though investigating a possible association is of interest. In AD, how the amount and quality of sleep affects Aβ aggregation is not fully understood, but animal studies indicate the importance of delaying the onset of this pathology in impacting the time of onset of disease, and such manipulation may be a powerful way to modulate amyloid pathology in the preclinical stages of disease.

Sleep disturbances in young and middle-aged adults may herald the pathological processes leading to α-synucleinopathies. Considering the negative health implications of long-term sleep disruption, they may even potentiate the development of neurodegenerative disease. This might be augmented in some individuals with a genetic predisposition to circadian dysfunction or neurodegeneration, for example genetic variants in circadian clock genes are associated with susceptibility to PD and other neurodegenerative disorders (74–76), and to cognitive impairment in the general elderly population (77). Further genetic and epigenetic factors influencing the aging process, response to treatment, or susceptibility to sleep disorders directly, can also be expected to play a role in modulating sleep disorders and the underlying neurodegenerative processes, and will provide useful insights into the biological basis of these disorders, and potential targets for future intervention therapies.

To establish if and when early treatment of sleep disturbances changes the course of neurodegenerative disease, there is a need for longitudinal population studies of the natural history of the development of sleep disorders and the conversion to α-synucleinopathies. The focus should be on early changes in circadian rhythms, sleep deprivation, EDS and RBD several decades before the manifest occurrence of motor symptoms in PD. Such work will bring us closer to the goal of intervention studies, by revealing the severity and timing of the onset of circadian disturbances in sufferers of PD compared to the occurrence in the otherwise healthy aging population. The enrollment of patients with idiopathic RBD or carriers of mutations in *GBA* are promising strategies to enrich studies for individuals at risk of converting to PD. Collaborative efforts between cohorts will also hasten progress to understand the implications of maximizing sleep health on the prevalence of PD and α-synucleinopathies in the future generations.

AUTHOR CONTRIBUTIONS

MG contributed conception of the review. MG and JM-G wrote the first draft of the manuscript. GA wrote sections, and critically reviewed the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

REFERENCES

1. Balkin TJ, Rupp T, Picchioni D, Wesensten NJ. Sleep loss and sleepiness: current issues. *Chest* (2008) 134:653–60. doi: 10.1378/chest.08-1064
2. Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Semin Neurol.* (2005) 25:117–29. doi: 10.1055/s-2005-867080
3. Jones K, Harrison Y. Frontal lobe function, sleep loss and fragmented sleep. *Sleep Med Rev.* (2001) 5:463–75. doi: 10.1053/smrv.2001.0203
4. Ellenbogen JM. Cognitive benefits of sleep and their loss due to sleep deprivation. *Neurology* (2005) 64:E25–7. doi: 10.1212/01.wnl.0000164850.68115.81
5. Stickgold R, Walker MP. Sleep-dependent memory consolidation and reconsolidation. *Sleep Med.* (2007) 8:331–43. doi: 10.1016/j.sleep.2007.03.011
6. Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron* (2014) 81:12–34. doi: 10.1016/j.neuron.2013.12.025

7. Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep* (1995) 18:425–32. doi: 10.1093/sleep/18.6.425
8. Munch M, Knoblauch V, Blatter K, Schroder C, Schnitzler C, Krauchi K, et al. Age-related attenuation of the evening circadian arousal signal in humans. *Neurobiol Aging* (2005) 26:1307–19. doi: 10.1016/j.neurobiolaging.2005.03.004
9. Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. *Neuron* (2010) 68:1023–42. doi: 10.1016/j.neuron.2010.11.032
10. Yousaf T, Pagano G, Niccolini F, Politis M. Increased dopaminergic function in the thalamus is associated with excessive daytime sleepiness. *Sleep Med.* (2018) 43:25–30. doi: 10.1016/j.sleep.2017.11.1137
11. Yousaf T, Pagano G, Niccolini F, Politis M. Excessive daytime sleepiness may be associated with caudate denervation in Parkinson disease. *J Neurol Sci.* (2018) 387:220–27. doi: 10.1016/j.jns.2018.02.032
12. Pagano G, Molloy S, Bain PG, Rabiner EA, Chaudhuri KR, Brooks DJ, et al. Sleep problems and hypothalamic dopamine D3 receptor availability in Parkinson disease. *Neurology* (2016) 87:2451–6. doi: 10.1212/WNL.0000000000003396
13. Claassen DO, Josephs KA, Ahlskog JE, Silber MH, Tippmann-Peikert M, Boeve BF. REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. *Neurology* (2010) 75:494–9. doi: 10.1212/WNL.0b013e3181ec7fac
14. Pagano G, Ferrara N, Brooks DJ, Pavese N. Age at onset and Parkinson disease phenotype. *Neurology* (2016) 86:1400–7. doi: 10.1212/WNL.0000000000002461
15. Rajput AH, Voll A, Rajput ML, Robinson CA, Rajput A. Course in Parkinson disease subtypes: a 39-year clinicopathologic study. *Neurology* (2009) 73:206–12. doi: 10.1212/WNL.0b013e3181ae7af1
16. Fereshtehnejad SM, Romenets SR, Anang JB, Latreille V, Gagnon JF, Postuma RB. New clinical subtypes of Parkinson disease and their longitudinal progression: a prospective cohort comparison with other phenotypes. *JAMA Neurol.* (2015) 72:863–73. doi: 10.1001/jamaneurol.2015.0703
17. Marras C, Chaudhuri KR. Nonmotor features of Parkinson's disease subtypes. *Mov Disord.* (2016) 31:1095–102. doi: 10.1002/mds.26510
18. Iranzo A, Santamaria J, Tolosa E. Idiopathic rapid eye movement sleep behaviour disorder: diagnosis, management, and the need for neuroprotective interventions. *Lancet Neurol.* (2016) 15:405–19. doi: 10.1016/S1474-4422(16)00057-0
19. *American Academy of Sleep Medicine Board of, International Classification of Sleep Disorders*. Darien, IL: American Academy of Sleep Medicine (2014).
20. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med.* (2013) 14:744–8. doi: 10.1016/j.sleep.2012.10.009
21. Postuma RB, Pelletier A, Berg D, Gagnon JF, Escudier F, Montplaisir J. Screening for prodromal Parkinson's disease in the general community: a sleep-based approach. *Sleep Med.* (2016) 21:101–5. doi: 10.1016/j.sleep.2015.12.016
22. Schrag A, Siddiqui UF, Anastasiou Z, Weintraub D, Schott JM. Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study. *Lancet Neurol.* (2017) 16:66–75. doi: 10.1016/S1474-4422(16)30328-3
23. Iranzo A, Tolosa E, Gelpi E, Molinuevo JL, Valldeoriola F, Serradell M, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol.* (2013) 12:443–53. doi: 10.1016/S1474-4422(13)70056-5
24. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* (2003) 24:197–211. doi: 10.1016/S0197-4580(02)00065-9
25. Boucetta S, Salimi A, Dadar M, Jones BE, Collins DL, Dang-Vu TT. Structural brain alterations associated with rapid eye movement sleep behavior disorder in Parkinson's disease. *Sci Rep.* (2016) 6:26782. doi: 10.1038/srep26782
26. Stokholm MG, Iranzo A, Ostergaard K, Serradell M, Otto M, Svendsen KB, et al. Assessment of neuroinflammation in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a case-control study. *Lancet Neurol.* (2017) 16:789–96. doi: 10.1016/S1474-4422(17)30173-4
27. Gan-Or Z, Mirelman A, Postuma RB, Arnulf I, Bar-Shira A, Dauvilliers Y, et al. GBA mutations are associated with Rapid Eye Movement Sleep Behavior Disorder. *Ann Clin Transl Neurol.* (2015) 2:941–5. doi: 10.1002/acn3.228
28. Beavan M, McNeill A, Proukakis C, Hughes DA, Mehta A, Schapira AH. Evolution of prodromal clinical markers of Parkinson disease in a GBA mutation-positive cohort. *JAMA Neurol.* (2015) 72:201–8. doi: 10.1001/jamaneurol.2014.2950
29. McNeill A, Duran R, Hughes DA, Mehta A, Schapira AH. A clinical and family history study of Parkinson's disease in heterozygous glucocerebrosidase mutation carriers. *J Neurol Neurosurg Psychiatry* (2012) 83:853–4. doi: 10.1136/jnnp-2012-302402
30. Thaler A, Gurevich T, Bar Shira A, Gana Weisz M, Ash E, Shiner T, et al. A "dose" effect of mutations in the GBA gene on Parkinson's disease phenotype. *Parkinsonism Relat Disord.* (2017) 36:47–51. doi: 10.1016/j.parkreldis.2016.12.014
31. Jesus S, Huertas I, Bernal-Bernal I, Bonilla-Toribio M, Caceres-Redondo MT, Vargas-Gonzalez L, et al. GBA variants influence motor and non-motor features of Parkinson's disease. *PLoS ONE* (2016) 11:e0167749. doi: 10.1371/journal.pone.0167749
32. Papadimitriou D, Antonelou R, Miligkos M, Maniati M, Papagiannakis N, Bostantjopoulou S, et al. Motor and nonmotor features of carriers of the p.A53T alpha-synuclein mutation: a Longitudinal Study. *Mov Disord.* (2016) 31:1226–30. doi: 10.1002/mds.26615
33. Fernandez-Santiago R, Iranzo A, Gaig C, Serradell M, Fernandez M, Pastor P, et al. MAPT association with REM sleep behavior disorder. *Neurol Genet.* (2017) 3:e131. doi: 10.1212/NXG.0000000000000131
34. Toffoli M, Dreussi E, Cecchin E, Valente M, Sanvilli N, Montico M, et al. SNCA 3'UTR genetic variants in patients with Parkinson's disease and REM sleep behavior disorder. *Neurol Sci.* (2017) 38:1233–40. doi: 10.1007/s10072-017-2945-2
35. Li Y, Kang W, Zhang L, Zhou L, Niu M, Liu J. Hyposmia is associated with RBD for PD patients with variants of SNCA. *Front Aging Neurosci.* (2017) 9:303. doi: 10.3389/fnagi.2017.00303
36. Gan-Or Z, Girard SL, Noreau A, Leblond CS, Gagnon JF, Arnulf I, et al. Parkinson's disease genetic loci in rapid eye movement sleep behavior disorder. *J Mol Neurosci.* (2015) 56:617–22. doi: 10.1007/s12031-015-0569-7
37. Trenkwalder C, Kohnen R, Hogl B, Metta V, Sixel-Doring F, Frauscher B, et al. Parkinson's disease sleep scale–validation of the revised version PDSS-2. *Mov Disord.* (2011) 26:644–52. doi: 10.1002/mds.23476
38. Gjerstad MD, Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? *Neurology* (2006) 67:853–8. doi: 10.1212/01.wnl.0000233980.25978.9d
39. Jaussent I, Bouyer J, Ancelin ML, Berr C, Foubert-Samier A, Ritchie K, et al. Excessive sleepiness is predictive of cognitive decline in the elderly. *Sleep* (2012) 35:1201–7. doi: 10.5665/sleep.2070
40. Foley D, Monjan A, Masaki K, Ross W, Havlik R, White L, et al. Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older Japanese-American men. *J Am Geriatr Soc.* (2001):49:1628–32. doi: 10.1111/j.1532-5415.2001.49271.x
41. Abbott RD, Ross GW, White LR, Tanner CM, Masaki KH, Nelson JS, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. *Neurology* (2005) 65:1442–6. doi: 10.1212/01.wnl.0000183056.89590.0d
42. Gao J, Huang X, Park Y, Hollenbeck A, Blair A, Schatzkin A, et al. Daytime napping, nighttime sleeping, and Parkinson disease. *Am J Epidemiol.* (2011) 173:1032–8. doi: 10.1093/aje/kwq478
43. Tholfsen LK, Larsen JP, Schulz J, Tysnes OB, Gjerstad MD. Development of excessive daytime sleepiness in early Parkinson disease. *Neurology* (2015) 85:162–8. doi: 10.1212/WNL.0000000000001737
44. Duncan GW, Khoo TK, Yarnall AJ, O'Brien JT, Coleman SY, Brooks DJ, et al. Health-related quality of life in early Parkinson's disease: the impact of nonmotor symptoms. *Mov Disord.* (2014) 29:195–202. doi: 10.1002/mds.25664
45. Giganti F, Ramat S, Zilli I, Guidi S, Raglione LM, Sorbi S et al. Daytime course of sleepiness in de novo Parkinson's disease patients. *J Sleep Res.* (2013) 22:197–200. doi: 10.1111/jsr.12000

46. Breen DP, Williams-Gray CH, Mason SL, Foltynie T, Barker RA. Excessive daytime sleepiness and its risk factors in incident Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2013) 84:233–4. doi: 10.1136/jnnp-2012-304097
47. Mylius V, Moller JC, Strauch K, Oertel WH, Stiasny-Kolster K. No significance of the COMT val158met polymorphism in restless legs syndrome. *Neurosci Lett.* (2010) 473:151–4. doi: 10.1016/j.neulet.2010.02.042
48. Gottlieb DJ, O'Connor GT, Wilk JB. Genome-wide association of sleep and circadian phenotypes. *BMC Med Genet.* (2007) 8(Suppl 1):S9. doi: 10.1186/1471-2350-8-S1-S9
49. Kaut O, Schmitt I, Tost J, Busato F, Liu Y, Hofmann P, et al. Epigenome-wide DNA methylation analysis in siblings and monozygotic twins discordant for sporadic Parkinson's disease revealed different epigenetic patterns in peripheral blood mononuclear cells. *Neurogenetics* (2017) 18:7–22. doi: 10.1007/s10048-016-0497-x
50. Yang L, Calingasan NY, Lorenzo BJ, Beal MF. Attenuation of MPTP neurotoxicity by rolipram, a specific inhibitor of phosphodiesterase IV. *Exp Neurol.* (2008) 211:311–4. doi: 10.1016/j.expneurol.2007.02.010
51. Bate C, Williams A. cAMP-Inhibits Cytoplasmic Phospholipase A(2) and protects neurons against amyloid-beta-induced synapse damage. *Biology* (2015) 4:591–606. doi: 10.3390/biology4030591
52. Kreutzmann JC, Havekes R, Abel T, Meerlo P. Sleep deprivation and hippocampal vulnerability: changes in neuronal plasticity, neurogenesis and cognitive function. *Neuroscience* (2015) 309:173–90. doi: 10.1016/j.neuroscience.2015.04.053
53. Joo EY, Kim H, Suh S, Hong SB. Hippocampal substructural vulnerability to sleep disturbance and cognitive impairment in patients with chronic primary insomnia: magnetic resonance imaging morphometry. *Sleep* (2014) 37:1189–98. doi: 10.5665/sleep.3836
54. Bellesi M, de Vivo L, Chini M, Gilli F, Tononi G, Cirelli C. Sleep loss promotes astrocytic phagocytosis and microglial activation in mouse cerebral cortex. *J Neurosci.* (2017) 37:5263–73. doi: 10.1523/JNEUROSCI.3981-16.2017
55. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. *Science* (2013) 342:373–7. doi: 10.1126/science.1241224
56. Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science* (2009) 326:1005–7. doi: 10.1126/science.1180962
57. Ju YS, Ooms SJ, Sutphen C, Macauley SL, Zangrilli MA, Jerome G, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid-beta levels. *Brain* (2017) 140:2104–11. doi: 10.1093/brain/awx148
58. Gomperts SN, Rentz DM, Moran E, Becker JA, Locascio JJ, Klunk WE, et al. Imaging amyloid deposition in Lewy body diseases. *Neurology* (2008) 71:903–10. doi: 10.1212/01.wnl.0000326146.60732.d6
59. Archer SN, Laing EE, Moller-Levet CS, van der Veen DR, Bucca G, Lazar AS, et al. Mistimed sleep disrupts circadian regulation of the human transcriptome. *Proc Natl Acad Sci USA.* (2014) 111:E682–91. doi: 10.1073/pnas.1316335111
60. Cai Y, Liu S, Sothern RB, Xu S, Chan P. Expression of clock genes Per1 and Bmal1 in total leukocytes in health and Parkinson's disease. *Eur J Neurol.* (2010) 17:550–4. doi: 10.1111/j.1468-1331.2009.02848.x
61. Breen DP, Vuono R, Nawarathna U, Fisher K, Shneerson JM, Reddy AB, et al. Sleep and circadian rhythm regulation in early Parkinson disease. *JAMA Neurol.* (2014) 71:589–95. doi: 10.1001/jamaneurol.2014.65
62. Ding H, Liu S, Yuan Y, Lin Q, Chan P, Cai Y. Decreased expression of Bmal2 in patients with Parkinson's disease. *Neurosci Lett.* (2011) 499:186–8. doi: 10.1016/j.neulet.2011.05.058
63. Lin Q, Ding H, Zheng Z, Gu Z, Ma J, Chen L, et al. Promoter methylation analysis of seven clock genes in Parkinson's disease. *Neurosci Lett.* (2012) 507:147–50. doi: 10.1016/j.neulet.2011.12.007
64. Liu HC, Hu CJ, Tang YC, Chang JG. A pilot study for circadian gene disturbance in dementia patients. *Neurosci Lett.* (2008) 435:229–33. doi: 10.1016/j.neulet.2008.02.041
65. Mendoza J, Challet E. Circadian insights into dopamine mechanisms. *Neuroscience* (2014) 282:230–42. doi: 10.1016/j.neuroscience.2014.07.081
66. Sleipness EP, Sorg BA, Jansen HT. Diurnal differences in dopamine transporter and tyrosine hydroxylase levels in rat brain: dependence on the suprachiasmatic nucleus. *Brain Res.* (2007) 1129:34–42. doi: 10.1016/j.brainres.2006.10.063
67. Imbesi M, Yildiz S, Dirim Arslan A, Sharma R, Manev H, Uz T. Dopamine receptor-mediated regulation of neuronal "clock" gene expression. *Neuroscience* (2009) 158:537–44. doi: 10.1016/j.neuroscience.2008.10.044
68. Hood S, Cassidy P, Cossette MP, Weigl Y, Verwey M, Robinson B, et al. Endogenous dopamine regulates the rhythm of expression of the clock protein PER2 in the rat dorsal striatum via daily activation of D2 dopamine receptors. *J Neurosci.* (2010) 30:14046–58. doi: 10.1523/JNEUROSCI.2128-10.2010
69. Pallier PN, Maywood ES, Zheng Z, Chesham JE, Inyushkin AN, Dyball R, et al. Pharmacological imposition of sleep slows cognitive decline and reverses dysregulation of circadian gene expression in a transgenic mouse model of Huntington's disease. *J Neurosci.* (2007) 27:7869–78. doi: 10.1523/JNEUROSCI.0649-07.2007
70. Wang HB, Loh DH, Whittaker DS, Cutler T, Howland D, Colwell CS. Time-restricted feeding improves circadian dysfunction as well as motor symptoms in the Q175 mouse model of Huntington's disease. *eNeuro* (2018) 5:ENEURO.0431-17.2017. doi: 10.1523/ENEURO.0431-17.2017
71. Sindi S, Johansson L, Skoog J, Mattsson AD, Sjoberg L, Wang HX, et al. Sleep disturbances and later cognitive status: a multi-centre study. *Sleep Med.* (2018) 52:26–33. doi: 10.1016/j.sleep.2017.11.1149
72. Irwin DJ, White MT, Toledo JB, Xie SX, Robinson JL, Van Deerlin V, et al. Neuropathologic substrates of Parkinson disease dementia. *Ann Neurol.* (2012) 72:587–98. doi: 10.1002/ana.23659
73. Petrou M, Dwamena BA, Foerster BR, MacEachern MP, Bohnen NI, Muller ML, et al. Amyloid deposition in Parkinson's disease and cognitive impairment: a systematic review. *Mov Disord.* (2015) 30:928–35. doi: 10.1002/mds.26191
74. Gu Z, Wang B, Zhang YB, Ding H, Zhang Y, Yu J, et al. Association of ARNTL and PER1 genes with Parkinson's disease: a case-control study of Han Chinese. *Sci Rep.* (2015) 5:15891. doi: 10.1038/srep15891
75. Chen Q, Huang CQ, Hu XY, Li SB, Zhang XM. Functional CLOCK gene rs1554483 G/C polymorphism is associated with susceptibility to Alzheimer's disease in the Chinese population. *J Int Med Res.* (2013) 41:340–6. doi: 10.1177/0300060513476430
76. Lou F, Li M, Ren Y, Luo XG, Liu N, Li X. CLOCK rs1801260 polymorphism is associated with susceptibility to Parkinson's disease in a Chinese population. *Neurosci Bull.* (2017) 33:734–6. doi: 10.1007/s12264-017-0167-5
77. Lin E, Kuo PH, Liu YL, Yang AC, Kao CF, Tsai SJ. Effects of circadian clock genes and environmental factors on cognitive aging in old adults in a Taiwanese population. *Oncotarget* (2017) 8:24088–98. doi: 10.18632/oncotarget.15493

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White Matter Tract Alterations in Drug-Naïve Parkinson's Disease Patients With Excessive Daytime Sleepiness

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Excessive daytime sleepiness (EDS) is relatively frequent in patients with Parkinson's disease (PD), having a prominent burden on patients' quality of life and causing dangerous events such as motor-vehicle accidents. Previous studies have indicated the role of certain neural tracts in the pathophysiology of sleep disturbances, especially in PD patients. We hypothesized that white matter integrity and connectivity might be altered in patients with PD and EDS. Therefore, this study investigated brain white matter microstructure alterations in patients with Parkinson's disease with EDS (PD-EDS) compared to healthy controls and PD patients without EDS (PD-nEDS). Diffusion MRI connectometry was used to carry out group analysis between PD patients with and without EDS and healthy individuals. EDS in PD patients is associated with decreased connectivity in the left and right fornix, left and right inferior longitudinal fasciculus (ILF), left inferior and middle cerebellar peduncles in comparison to PD-nEDS group. These differences between PD-EDS and PD-nEDS patients reflects microstructural changes with respect to sleep-related circuits, which can pave the way for future investigations considering EDS pathogenesis in Parkinson's disease.

Keywords: excessive daytime sleepiness, Parkinson's disease, diffusion MRI, connectometry, PPMI

INTRODUCTION

Non-motor symptoms in Parkinson's disease (PD) have been given more attention during recent years, mainly due to their massive burden on patients' quality of life (1, 2). Affecting up to 60% of PD patients, excessive daytime sleepiness (EDS) is characterized by inappropriate sleepiness during the waking time. It could be present anytime in the course of PD, even before the appearance of the motor symptoms (3–5) and be regarded as a risk factor for the development of neurodegenerative diseases in future (6). Moreover, a longitudinal study revealed that the presentation of EDS progresses throughout the course of the disease from 4 to 41% in 8 years (7). Multiple factors are supposed to be associated with the prevalence of EDS including age, sex, presence of rapid eye movement (REM) sleep behavior disorder (RBD), mood disorders and cognitive impairment (5, 8–10).

However, the underlying pathophysiology of EDS in PD is not understood completely. Based on the animal studies, there is growing evidence noticing dopamine as a significant contributor in the wake and sleep cycles (11). Moreover, since sudden sleep periods might lead to tragic events such as motor-vehicle accidents, elucidating the neuropathological mechanisms of EDS would be of great value, especially in PD patients.

Several studies have investigated cerebral structural changes in PD with EDS (PD-EDS) patients, using different imaging modalities. Single photon emission computed tomography (SPECT) imaging showed significant hypoperfusion in left temporal and parietal cortices in patients with EDS (PD-EDS) compared to patients without EDS (PD-nEDS) (7). Another SPECT study showed more severe nigrostriatal dysfunction in PD-EDS in comparison to PD-nEDS group (8). Yousaf et al. used Dopamine transporter SPECT imaging and revealed that increased DAT binding ratio in thalamus, proposing probable dopamine transporter upregulation in response to dopamine deprivation in PD-EDS patients compared to PD-nEDS patients (10). In another study, Yousaf et al. found the loss of dopaminergic activity in caudate nucleus as an indicator of EDS severity along with being a predictor of developing EDS over a period of 3 years (11).

Considering gray matter (GM), studies have shown that EDS is associated with regional brain atrophy in the middle medial cerebellar peduncle (12) as well as frontal, temporal, occipital, and limbic lobes in PD patients (13). However, a multimodal imaging study showed increased volume in the gray matter of the bilateral hippocampus and parahippocampal gyri. Furthermore, using diffusion tensor imaging (DTI), increased axial diffusivity (AD) was observed in certain white matter tracts including the left anterior thalamic radiation, corticospinal tract and superior longitudinal fasciculus (SLF) in PD-EDS patients (14). Another DTI study indicated that patients with EDS have reduced connectivity only in the fornix (15). Recently, resting-state functional MRI (rs-fMRI) revealed decreased regional homogeneity (ReHo) in the inferior frontal gyrus and left cerebellum, besides decreased functional connectivity (FC) of these regions in frontal and temporal lobes and cerebellum in PD patients suffering from EDS compared to PD-nEDS group (16). Moreover, in another rs-fMRI study, it was indicated that reduced functional connectivity is observed in the thalamostriatal network among PD-EDS patients (17). Although, all of the studies above provide evidence regarding brain alternations in PD-EDS patients, however, further studies are required to reveal new aspects of EDS development in PD patients.

DTI has been used widely by neuroscientists in the past decade for evaluating the white matter microstructure, especially in neurodegenerative disorders such as PD (18). However, due to certain limitations of end-to-end fiber tracking, connectometry was introduced as a novel approach to investigate white matter changes, using the concept of local connectome (19). Therefore, study variables can be tested for possible associations with local connectomes, which is defined by the degree of connectivity between adjacent voxels within a fascicle. In addition, Connectometry relies on the Spin Distribution Function (SDF) that measures the density of water diffusion in any direction, then reporting the peak SDF for each direction as quantitative anisotropy (QA). Consequently, we hypothesize structural networks may be responsible for exhibiting Parkinson related EDS and could be revealed using connectometry. This study aimed to investigate white matter microstructure alterations by using connectometry in patients with PD-EDS, in comparison to PD-nEDS and healthy individuals.

MATERIALS AND METHODS

Participants

Participants involved in this research were recruited from Parkinson's Progression Markers Initiative (PPMI, http://www.ppmi-info.org/). The study was approved by the institutional review board of all participating sites in Europe, including Attikon University Hospital (Greece), Hospital Clinic de Barcelona and Hospital Universitario Donostia (Spain), Innsbruck University (Austria), Paracelsus-Elena Clinic Kassel/University of Marburg (Germany), Imperial College London (UK), Pitié-Salpêtrière Hospital (France), University of Salerno (Italy), and in the USA, including Emory University, Johns Hopkins University, University of Alabama at Birmingham, PD and Movement Disorders Center of Boca Raton, Boston University, Northwestern University, University of Cincinnati, Cleveland Clinic Foundation, Baylor College of Medicine, Institute for Neurodegenerative Disorders, Columbia University Medical Center, Beth Israel Medical Center, University of Pennsylvania, Oregon Health & Science University, University of Rochester, University of California at San Diego, University of California, San Francisco. Written informed consent was obtained from all participants before study enrolment. To be enrolled into the PPMI study, all patients were required to fulfill the following criteria: (1) met the standard diagnostic criteria for PD, (2) diagnosed within 2 years before the initial visit, (3) Hoehn & Yahr (H&Y) stage ≤ 2 at baseline, (4) demonstrated deficits on DaTscan imaging, and (5) not on any PD medication. Diffusion MRI images were obtained for 16 with EDS (9 females and 7 males), as indicated by the Epworth Sleepiness Scale scores $> = 10$, 45 PD patients without EDS (29 females and 16 males), and 17 healthy controls (10 females and 7 males). **Table 1** shows the demographic and baseline level characteristics of participants in different groups.

Neuropsychiatric Measurement

The neuropsychiatric assessment was performed using the 15-item Geriatric Depression Scale (GDS). For sleep disturbance, RBD and EDS were measured with the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), and ESS, respectively.

Data Acquisition

Data used in the preparation of this paper was obtained from Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data/). This dataset was acquired on a 3 Tesla Siemens scanner, producing 64 DWI (repetition time = 7,748 ms, echo time = 86 ms; voxel size: $2.0 \times 2.0 \times 2.0$ mm^3; field of view = 224×224 mm) at b = 1,000 s/mm^2 and one

TABLE 1 | Demographic and baseline clinical information of patients with Parkinson disease.

Feature	PD-EDS ($n = 16$)	PD-nEDS ($n = 45$)	HC ($n = 17$)	*P*-value*
Age at diagnosis in years (mean ± SD)	62.31 ± 8.8	58.44 ± 9.3	61.36 ± 11.25	0.308
Male/Female no.	7/9	16/29	7/10	0.449
Handedness (L/R)	1/15	6/39	3/14	0.766
Education years (mean ± SD)	16.18 ± 2.4	14. 6 ± 3.03	16 ± 2.89	0.086
Duration of disease in months (mean ± SD)	8.2 ± 7.03	7.92 ± 8.29	–	0.937
ESS (mean ± SD)	11.5 ± 1.75	5.62 ± 2.34	4 ± 2.54	0.000
University of Pennsylvania Smell Identification Test (UPSIT) (mean ± SD)	20.18 ± 7.75	23.37 ± 8.29	32.7 ± 5.16	0.000
H & Y stage (mean ± SD)	1.81 ± 0.4	1.71 ± 0.45	–	0.523
UPDRS III (mean ± SD)	28.18 ± 8.32	24.31 ± 6.88	–	0.072
GDS score (mean ± SD)	3.8 ± 1.72	4.2 ± 1.17	4.1 ± 1.21	0.749
MOCA score (mean ± SD)	28.31 ± 1.25	27.31 ± 2.28	28 ± 1.06	0.294
RBDSQ (mean ± SD)	5.06 ± 3.04	3.66 ± 2.54	3 ± 2.03	0.130

H & Y stage, Hoen and Yahr stage; ESS, Epworth Sleepiness Scale; UPDRS III, Unified Parkinson's Disease Rating Scale part III; GDS, Geriatric Depression Scale; MoCA, Montreal Cognitive Assessment; RBD, REM Behavior Disorder Screening Questionnaire.

**P-value of one-way ANOVA for age at diagnosis, education years and disease duration, Pearson Chi-square for gender, handedness and H&Y stage and Kruskal–Wallis test for ESS, UPSIT, UPRDS part III, GDS scale, MoCA score, and RBDSQ.*

b0 image along with a 3D T1-weighted structural scan (repetition time = 8.2 ms, echo time = 3.7 ms; flip angle = 8°, voxel size: 1.0 × 1.0 × 1.0 mm^3; field of view = 240 mm, acquisition matrix = 240 × 240).

Diffusion MRI Data Processing

Diffusion MRI data were corrected for subject motion, eddy current distortions, and susceptibility artifacts due to the magnetic field inhomogeneity using ExploreDTI toolbox (20).

Connectometry Analysis

Diffusion data were reconstructed in the MNI space using q-space diffeomorphic reconstruction to obtain the spin distribution function (SDF). A diffusion sampling length ratio of 1.25 was used, and the output resolution was 1 mm.

Diffusion MRI connectometry (19) was performed to compare group differences in a total of 57 subjects. The group difference was quantified utilizing groupwise *t*-test. The SDF was normalized. A t threshold of 2.5 was assigned to select local connectomes, and the local connectomes were tracked using a deterministic fiber tracking algorithm. All tracks generated from bootstrap resampling were included. A length threshold of 40 mm was used to select tracks. The seeding density was 50 seeds per mm^3. To estimate the false discovery rate, a total of 1,000 randomized permutations were applied to the group label to obtain the null distribution of the track length. The analysis was conducted using DSI Studio (http://dsi-studio.labsolver.org).

Statistical Analysis

All statistical analyses were performed in the R statistical package (v3.4.3). To compare between group differences, normality of data was assessed by Shapiro–Wilk test. In case of normal distribution and meeting parametric assumptions, demographic and tests were compared using independent sample *t*-test, two-way ANOVA and chi-square tests, unless Kruskal–Wallis and fisher exact tests were used. *P* values < 0.05 were considered as significant.

RESULTS

Demographic Data

In total, 16 PD-EDS (56.2% female) and 45 PD-nEDS propensity score matched subjects (64.4% female), were included in the study. As shown in **Table 1**, except for UPSIT and ESS score, no significant difference was found between any of demographic variables and motor or neuropsychiatric tests between groups. Mean Age of PD-EDS patients was 62.3 ± 8.8 years, they all had disease duration less than a year and average disease duration was 8.2 ± 7.0 months and H&Y score of 1 or 2. PD-nEDS patients had a mean age of 58.4 ± 9.3 years, with a mean disease duration of 7.9 ± 8.3 months and H&Y score of 1 or 2.

Connectometry Results

PD-EDS Patients vs. PD-nEDS Patients

Compared with PD-nEDS patients, PD-EDS patients showed decreased connectivity in left and right fornix, left, and right inferior longitudinal fasciculus (ILF), middle cerebellar peduncle and left inferior cerebellar peduncle (FDR = 0.021978) (**Figure 1**).

PD-nEDS Patients vs. HC

As shown in **Figure 2**, the PD-nEDS group demonstrated decreased connectivity in the left inferior fronto-occipital fasciculus, the splenium, the left corticospinal

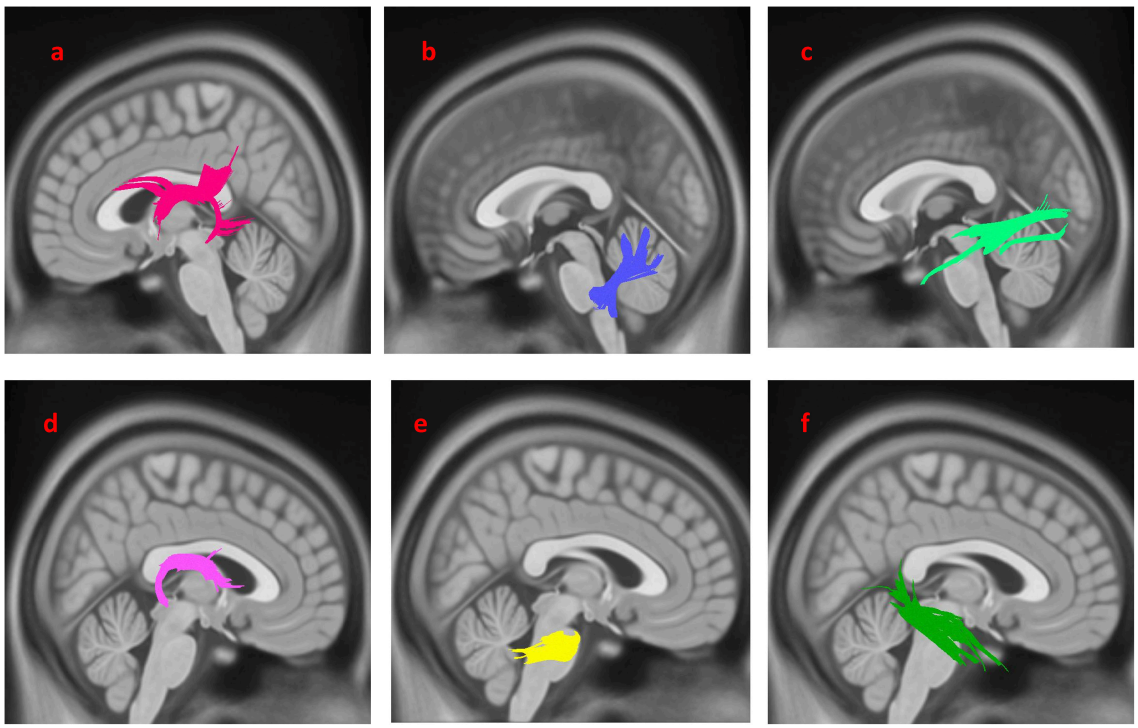

FIGURE 1 | White matter pathways with significantly reduced anisotropy in PD-EDS patients compared to patients without EDS (FDR = 0.021978). **(a)** Left fornix, **(b)** left inferior cerebellar peduncle, **(c)** left inferior longitudinal fasciculus, **(d)** right fornix, **(e)** bilateral middle cerebellar peduncle, **(f)** right inferior longitudinal fasciculus. The results are overlaid on ICBM152 (mni_icbm152_t1) from the McConnell Brain Imaging Center using DSI-STUDIO software.

tract (CST) and the left cingulum contrast to HC (FDR = 0.0277136).

PD-EDS Patients vs. HC

The group differences between PD-EDS patients and HC are shown in **Figure 3**. The differences were that connectivity in HC was higher than that in PD-EDS patients in the left inferior fronto-occipital fasciculus, the left ILF, the body of the corpus callosum, the splenium, the left CST and the right cingulum (FDR = 0.0383761).

DISCUSSION

In this study, we have compared brain white matter microstructure alterations in PD-EDS, PD-nEDS patients, and the control group. Using connectometry, the connectivity (regarding the QA) in the left and right fornix, left and right ILF, middle cerebellar peduncle and left inferior cerebellar peduncle decreased in PD-EDS patients more than it did in PD-nEDS patients. These changes might be concerning the cerebral pathogenesis of EDS in PD patients. It was also demonstrated that connectivity in both PD-EDS and PD-nEDS groups is lower than HC in the left inferior fronto-occipital fasciculus, parts of the corpus callosum, the left CST and cingulum, which are suggested to be involved in PD pathogenesis by previous studies (21–24).

Various mechanisms have been proposed for the etiology of sleep disturbances in PD (25, 26). PD is a subtype of synucleinopathy characterized by alpha-synuclein deposit in neurons and its following induction of neuron degeneration. This course can involve any part of brain including sleep regulating circuits (27). As it is proposed, orexin is one of the most critical neurotransmitters participating in the wakefulness physiology. There are several studies indicating orexin neuron loss in PD patients suffering from sleep disorders. Besides, current evidence supports that the orexin secretion could be partially regulated by dopamine and serotonin (28–30). Studies have indicated that D1 agonists stimulate orexin neurons in animal models while D2 and D3 agonists have a sedative action by blocking the arousal system (31). Consistently, it is revealed that while higher extracellular levels of dopamine promote wakefulness (32), a longtime high-dose use of levodopa disrupts circadian sleep pattern in PD patients due to its inhibitory effect via D2 and D3 receptors (25, 33). However, since we have studied PD patients who were drug-naïve, we can propose that EDS and its correlated changes in tracts such as fornix (and with direct interaction with orexin neurons) are not secondary phenomena and could happen independently from PD treatment.

A DTI study in 2006 indicated reduced fractional anisotropy in the fornix in PD-EDS group, being correlated with ESS score as well (15). The results of our study also show decreased connectivity in the left and right fornix in PD-EDS, compared to healthy controls and patients without EDS. As it was mentioned before, the role of fornix could be explained by the tracts passing through it. Fornix is mainly constructed by fibers connecting hypothalamus to hippocampus. Hypothalamus

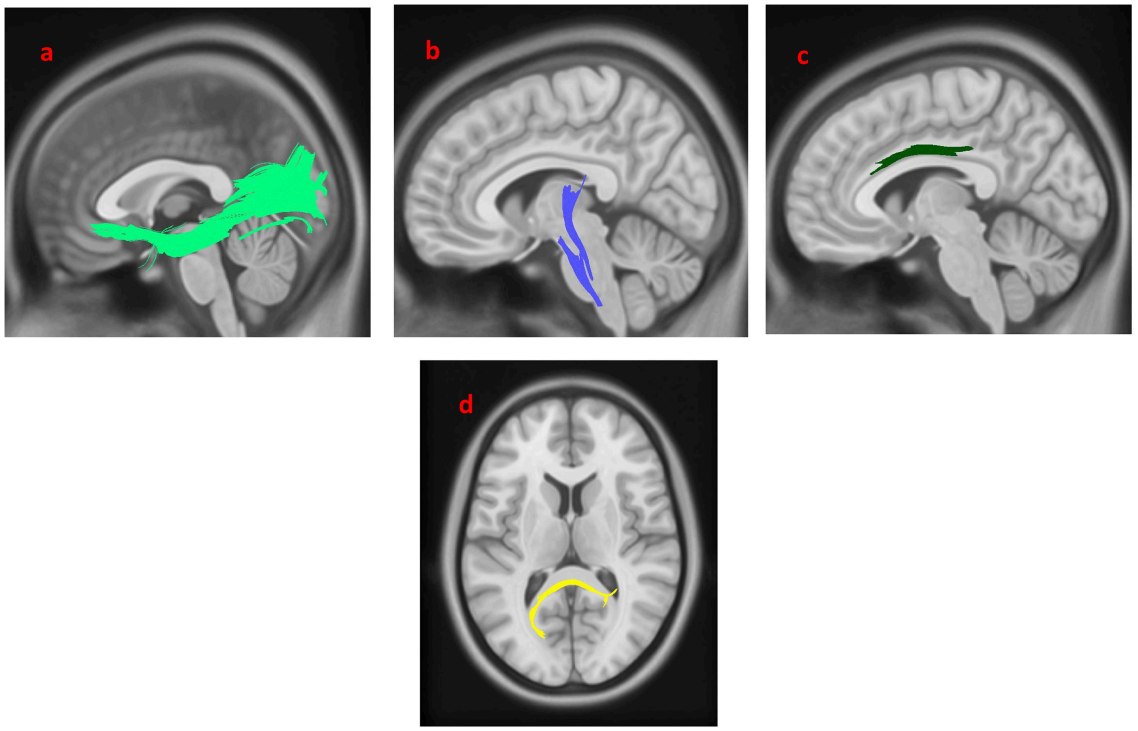

FIGURE 2 | White matter pathways with significantly reduced anisotropy in PD-nEDS patients compared to healthy control (FDR = 0.0277136). **(a)** Left inferior fronto-occipital fasciculus, **(b)** left corticospinal tract, **(c)** left cingulum, **(d)** splenium. The results are overlaid on ICBM152 (mni_icbm152_t1) from the McConnell Brain Imaging Center using DSI-STUDIO software.

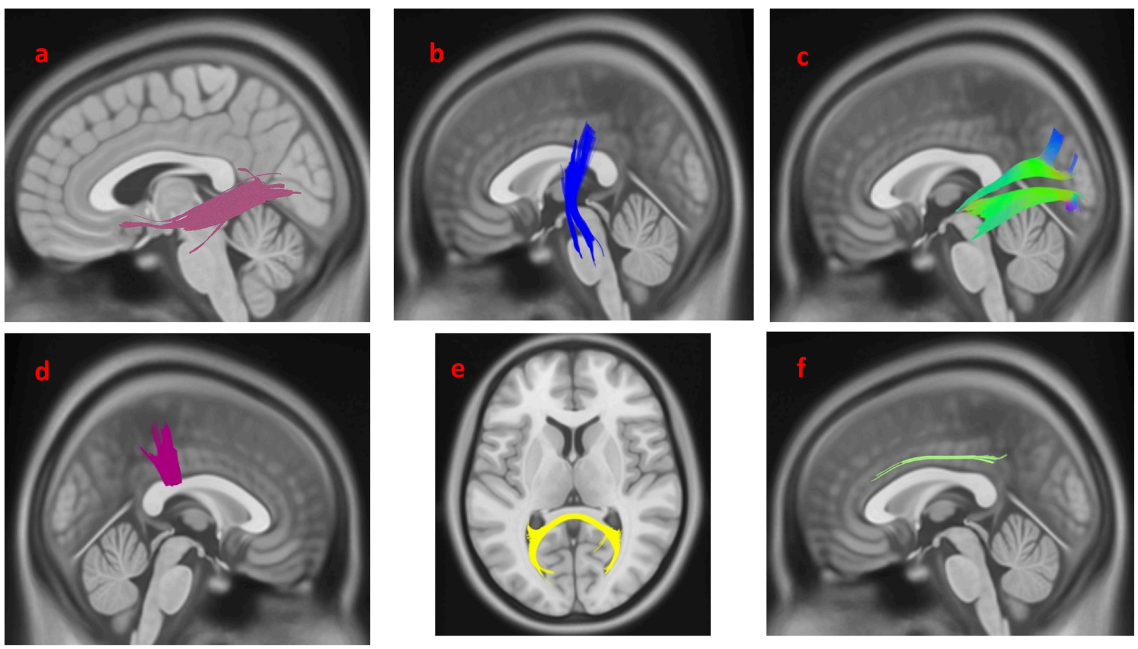

FIGURE 3 | White matter pathways with significantly reduced anisotropy in PD-EDS patients compared to healthy control (FDR = 0.0383761). **(a)** Left inferior fronto-occipital fasciculus, **(b)** left corticospinal tract, **(c)** left inferior longitudinal fasciculus, **(d)** body of the corpus callosum, **(e)** splenium, **(f)** left cingulum. The results are overlaid on ICBM152 (mni_icbm152_t1) from the McConnell Brain Imaging Centre using DSI-STUDIO software.

serves as a fountain for orexin secreting neurons and have global connections with many areas. Studies have shown that the disruption of these tracts and also hypothalamic neuron degeneration (that is also associated with a lower level of orexin) could influence the sleep cycle (15, 34, 35).

DTI analysis by Chondrogiorgi et al. indicated that AD values are increased in the SLF in PD patients with EDS, similar to our study suggesting FA reduction in SLF being related to the development of EDS (14). Besides, our analysis showed that ILF connectivity is decreased in patients with EDS. While involvement of SLF was suggested in patients with impaired alertness in patients having ischemic brain injury, ILF involvement was shown in a group of PD patients with RBD and depressive symptoms (36, 37). These results suggest that mentioned tracts might contribute to EDS neuropathogenesis in PD patients.

Using rs-fMRI research, it was shown that EDS is closely related to the thalamocortical connectivity alternation (38). In another rs-fMRI study using PPMI dataset, Wen et al. indicated that although PD patients with EDS have decreased ReHo in the inferior frontal gyrus and left cerebellum, they have increased ReHo in the left paracentral lobule (16). FC analysis regarding these three regions in PD-EDS group revealed decreased FC of the left cerebellum posterior lobe with the right insula (16). In the past, it was believed that the cerebellum is only involved in motor functions (16). However, recent studies have suggested a role for the cerebellum in sleep-related disorders such as EDS (39, 40). In fact, it is suggested that cerebellum is involved in adjusting various nerve functions such as cognition, emotion, and movement in association with the frontal lobe. It has been indicated by DelRosso and Hoque that this association is weaker in individuals with sleep deprivation compared to individuals with normal sleep (39). Results from our study also show decreased connectivity in middle and left inferior cerebellar peduncle in PD patients with EDS.

Moreover, Gama et al. indicated that patients with EDS suffer from more severe atrophy of medial cerebellar peduncle in comparison with patients without EDS in their gray matter imaging work (12). Another study evaluating GM by Kato et al. demonstrated that PD-EDS patients have significant widespread gray matter atrophy compared to PD-nEDS and controls. Involvement of gray matter in PD-EDS patients was similar to PD patients with dementia (13). This result suggested that EDS could be one of the first presentations of dementia in PD. This study also showed that the basal forebrain atrophy occurs in PD patients, especially PD-EDS patients, and in the substantia innominata, which may be related to the cholinergic neurons loss and corresponds to the regional atrophy of cortical gray matter (13). Moreover, a recent study has revealed that the EDS score was lower in controls than both PD without dementia and PD with dementia (41).

Several limitations should be considered interpreting the results of this study. First, there was a limited number of cases with EDS, having diffusion MRI imaging in PPMI database. Second, longitudinal assessment of white matter changes regarding EDS would help to interpret the results in a better way. Finally, the recognition of EDS in PD patients seems to be difficult. Although, using a questionnaire such as the ESS is relatively simple, the use of ESS has been shown to be subjective (42). Using neuroimaging data for recognition of EDS in PD might lead to earlier and more accurate diagnosis, improving patients' quality of life and guiding clinicians to reach better therapeutic options.

In summary, in the early stages of PD, patients with EDS have decreased connectivity in certain tracts such as fornix and cerebellar peduncles compared to patients without EDS and HC group. However, as there has been limited knowledge about the pathophysiology of EDS in PD, future studies using longitudinal approach, are required to clarify the association between EDS and brain structure alternation in PD and might help to explain some of the contradictory findings.

ETHICS STATEMENT

All procedures performed here, including human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethical Committee of Zahedan University of Medical Sciences (license # Ir.zaums.rec.1397.314).

INFORMED CONSENT

Written Informed consent was obtained from all individual participants included in the study.

AUTHOR CONTRIBUTIONS

AA-G, MS, and MA contributed to the conception and design of the study. BM, MMZ, GK, MM, PS, and MA contributed to data collection and analysis. AA-G, MM, GK, and MA contributed to writing and revising the manuscript.

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REFERENCES

1. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol.* (2006) 5:235–45. doi: 10.1016/S1474-4422(06)70373-8
2. Liu JB, Leng JL. Investigation of nonmotor symptoms in first-degree relatives of patients with different clinical types of parkinson's Disease. *Parkinson Dis.* (2019) 2019:1654161. doi: 10.1155/2019/1654161
3. Knie B, Mitra MT, Logishetty K, Chaudhuri KR. Excessive daytime sleepiness in patients with Parkinson's disease. *CNS Drugs.* (2011) 25:203–12. doi: 10.2165/11539720-000000000-00000
4. Simuni T, Caspell-Garcia C, Coffey C, Chahine LM, Lasch S, Oertel WH, et al. Correlates of excessive daytime sleepiness in *de novo* Parkinson's disease: a case control study. *Mov Disord.* (2015) 30:1371–81. doi: 10.1002/mds.26248
5. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. *Sleep Med Rev.* (2017) 35:33–50. doi: 10.1016/j.smrv.2016.08.001
6. Zhou J, Zhang J, Lam SP, Chan JW, Mok V, Chan A, et al. Excessive daytime sleepiness predicts neurodegeneration in idiopathic REM sleep behavior disorder. *Sleep.* (2017) 40:zsx041. doi: 10.1093/sleep/zsx041
7. Matsui H, Nishinaka K, Oda M, Hara N, Komatsu K, Kubori T, et al. Excessive daytime sleepiness in Parkinson disease: a SPECT study. *Sleep.* (2006) 29:917–20. doi: 10.1093/sleep/29.7.917
8. Happe S, Baier PC, Helmschmied K, Meller J, Tatsch K, Paulus W. Association of daytime sleepiness with nigrostriatal dopaminergic degeneration in early Parkinson's disease. *J Neurol.* (2007) 254:1037–43. doi: 10.1007/s00415-006-0483-6
9. Gjerstad MD, Alves G, Maple-Grodem J. Excessive daytime sleepiness and REM sleep behavior disorders in parkinson's disease: a narrative review on early intervention with implications to neuroprotection. *Front Neurol.* (2018) 9:961. doi: 10.3389/fneur.2018.00961
10. Yousaf T, Pagano G, Niccolini F, Politis M. Increased dopaminergic function in the thalamus is associated with excessive daytime sleepiness. *Sleep Med.* (2018) 43:25–30. doi: 10.1016/j.sleep.2017.11.1137
11. Yousaf T, Pagano G, Niccolini F, Politis M. Excessive daytime sleepiness may be associated with caudate denervation in Parkinson disease. *J Neurol Sci.* (2018) 387:220–7. doi: 10.1016/j.jns.2018.02.032
12. Gama RL, Tavora DG, Bomfim RC, Silva CE, de Bruin VM, de Bruin PF. Sleep disturbances and brain MRI morphometry in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy - a comparative study. *Parkin Relat Disord.* (2010) 16:275–9. doi: 10.1016/j.parkreldis.2010.01.002
13. Kato S, Watanabe H, Senda J, Hirayama M, Ito M, Atsuta N, et al. Widespread cortical and subcortical brain atrophy in Parkinson's disease with excessive daytime sleepiness. *J Neurol.* (2012) 259:318–26. doi: 10.1007/s00415-011-6187-6
14. Chondrogiorgi M, Tzarouchi LC, Zikou AK, Astrakas LG, Kosta P, Argyropoulou MI, et al. Multimodal imaging evaluation of excessive daytime sleepiness in Parkinson's disease. *Int J Neurosci.* (2016) 126:422–8. doi: 10.3109/00207454.2015.1023437
15. Matsui H, Nishinaka K, Oda M, Niikawa H, Komatsu K, Kubori T, et al. Disruptions of the fornix fiber in Parkinsonian patients with excessive daytime sleepiness. *Parkinson Relat Disord.* (2006) 12:319–22. doi: 10.1016/j.parkreldis.2006.01.007
16. Wen MC, Ng SY, Heng HS, Chao YX, Chan LL, Tan EK, et al. Neural substrates of excessive daytime sleepiness in early drug naive Parkinson's disease: a resting state functional MRI study. *Parkinson Relat Disord.* (2016) 24:63–8. doi: 10.1016/j.parkreldis.2016.01.012
17. Plante DT, Birn RM, Walsh EC, Hoks RM, Cornejo MD, Abercrombie HC. Reduced resting-state thalamostriatal functional connectivity is associated with excessive daytime sleepiness in persons with and without depressive disorders. *J Affect Disord.* (2018) 227:517–20. doi: 10.1016/j.jad.2017.11.054
18. Jones DK, Knosche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. *Neuroimage.* (2013) 73:239–54. doi: 10.1016/j.neuroimage.2012.06.081
19. Yeh FC, Badre D, Verstynen T. Connectometry: a statistical approach harnessing the analytical potential of the local connectome. *Neuroimage.* (2016) 125:162–71. doi: 10.1016/j.neuroimage.2015.10.053
20. Leemans A, Jeurissen B, Sijbers J, Jones D. ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. In: *17th Annual Meeting of International Society of Magnetic Resonance in Medicine*. Honolulu, HI. (2009). p. 3537.
21. Braak H, Sandmann-Keil D, Gai W, Braak E. Extensive axonal Lewy neurites in Parkinson's disease: a novel pathological feature revealed by alpha-synuclein immunocytochemistry. *Neurosci Lett.* (1999) 265:67–9. doi: 10.1016/S0304-3940(99)00208-6
22. Gallagher C, Bell B, Bendlin B, Palotti M, Okonkwo O, Sodhi A, et al. White matter microstructural integrity and executive function in Parkinson's disease. *J Int Neuropsychol Soc.* (2013) 19:349–54. doi: 10.1017/S1355617712001373
23. Hall JM, Ehgoetz Martens KA, Walton CC, O'Callaghan C, Keller PE, Lewis SJ, et al. Diffusion alterations associated with Parkinson's disease symptomatology: a review of the literature. *Parkinson Relat Disord.* (2016) 33:12–26. doi: 10.1016/j.parkreldis.2016.09.026
24. Zhang Y, Wu IW, Tosun D, Foster E, Schuff N. Progression of regional microstructural degeneration in parkinson's disease: a multicenter diffusion tensor imaging study. *PLoS ONE.* (2016) 11:e0165540. doi: 10.1371/journal.pone.0165540
25. French IT, Muthusamy KA. A review of sleep and its disorders in patients with parkinson's disease in relation to various brain structures. *Front Aging Neurosci.* (2016) 8:114. doi: 10.3389/fnagi.2016.00114
26. Yousaf T, Pagano G, Wilson H, Politis M. Neuroimaging of sleep disturbances in movement disorders. *Front Neurol.* (2018) 9:767. doi: 10.3389/fneur.2018.00767
27. Claassen DO, Kutscher SJ. Sleep disturbances in Parkinson's disease patients and management options. *Nat Sci Sleep.* (2011) 3:125–33. doi: 10.2147/NSS.S18897
28. Thannickal TC, Lai YY, Siegel JM. Hypocretin (orexin) cell loss in Parkinson's disease. *Brain.* (2007) 130(Pt 6):1586–95. doi: 10.1093/brain/awm097
29. Monti JM, Jantos H. The roles of dopamine and serotonin, and of their receptors, in regulating sleep and waking. *Prog Brain Res.* (2008) 172:625–46. doi: 10.1016/S0079-6123(08)00929-1
30. Wienecke M, Werth E, Poryazova R, Baumann-Vogel H, Bassetti CL, Weller M, et al. Progressive dopamine and hypocretin deficiencies in Parkinson's disease: is there an impact on sleep and wakefulness? *J Sleep Res.* (2012) 21:710–7. doi: 10.1111/j.1365-2869.2012.01027.x
31. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* (1991) 14:540–5. doi: 10.1093/sleep/14.6.540
32. Espana RA, Scammell TE. Sleep neurobiology from a clinical perspective. *Sleep.* (2011) 34:845–58. doi: 10.5665/SLEEP.1112
33. Nausieda PA, Weiner WJ, Kaplan LR, Weber S, Klawans HL. Sleep disruption in the course of chronic levodopa therapy: an early feature of the levodopa psychosis. *Clin Neuropharmacol.* (1982) 5:183–94. doi: 10.1097/00002826-198205020-00003
34. Yoshida K, McCormack S, Espana RA, Crocker A, Scammell TE. Afferents to the orexin neurons of the rat brain. *J Comp Neurol.* (2006) 494:845–61. doi: 10.1002/cne.20859
35. Kessler BA, Stanley EM, Frederick-Duus D, Fadel J. Age-related loss of orexin/hypocretin neurons. *Neuroscience.* (2011) 178:82–8. doi: 10.1016/j.neuroscience.2011.01.031
36. Lee AY, Shin DG, Park JS, Hong GR, Chang PH, Seo JP, et al. Neural tracts injuries in patients with hypoxic ischemic brain injury: diffusion tensor imaging study. *Neurosci Lett.* (2012) 528:16–21. doi: 10.1016/j.neulet.2012.08.053
37. Ghazi Sherbaf F, Rahmani F, Jooyandeh SM, Aarabi MH. Microstructural changes in patients with parkinson disease and rem sleep behavior disorder: depressive symptoms versus non-depressed. *Acta Neurol Belg.* (2018) 118:415–21. doi: 10.1007/s13760-018-0896-x
38. Killgore WD, Vanuk JR, Knight SA, Markowski SM, Pisner D, Shane B, et al. Daytime sleepiness is associated with altered resting thalamocortical connectivity. *Neuroreport.* (2015) 26:779–84. doi: 10.1097/WNR.0000000000000418
39. DelRosso LM, Hoque R. The cerebellum and sleep. *Neurol Clin.* (2014) 32:893–900. doi: 10.1016/j.ncl.2014.07.003
40. Liu X, Yan Z, Wang T, Yang X, Feng F, Fan L, et al. Connectivity pattern differences bilaterally in the cerebellum posterior lobe in healthy subjects

after normal sleep and sleep deprivation: a resting-state functional MRI study. *Neuropsychiatr Dis Treat.* (2015) 11:1279–89. doi: 10.2147/NDT.S84204

41. Compta Y, Santamaria J, Ratti L, Tolosa E, Iranzo A, Muñoz E, et al. Cerebrospinal hypocretin, daytime sleepiness and sleep architecture in Parkinson's disease dementia. *Brain.* (2009) 132:3308–17. doi: 10.1093/brain/awp263
42. Benbadis SR, Mascha E, Perry MC, Wolgamuth BR, Smolley LA, Dinner DS. Association between the Epworth sleepiness scale and the multiple sleep latency test in a clinical population. *Ann Intern Med.* (1999) 130(4 Pt 1):289–92. doi: 10.7326/0003-4819-130-4-199902160-00014

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