


RESEARCH ARTICLE

Tossing and Turning in Bed: Nocturnal Movements in Parkinson's Disease

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ABSTRACT: Background: Sleep disturbances and nocturnal hypokinesia are common in Parkinson's disease (PD). Recent work using wearable technologies showed fewer nocturnal movements in PD when compared with controls. However, it is unclear how these manifest across the disease spectrum.

Objectives: We assessed the prevalence of sleep disturbances and nocturnal hypokinesia in early and advanced PD and their relation to nonmotor symptoms and dopaminergic medication.

Methods: A total of 305 patients with PD with diverse disease severity (Hoehn and Yahr [H&Y] stage 1 = 47, H&Y stage 2 = 181, H&Y stage 3 = 77) and 205 healthy controls

continuously wore a tri-axial accelerometer on the lower back for at least 2 days. Lying, turning, and upright -time at night were extracted from the acceleration signals. Percent upright time and nighttime walking were classified as sleep interruptions. The number, velocity, time, side, and degree of rotations in bed were used to evaluate nocturnal movements.

Results: Nocturnal lying time was similar among all groups (healthy controls, 7.5 ± 1.2 hours; H&Y stage 1, 7.3 ± 0.9 hours; H&Y stage 2, 7.2 ± 1.3 hours; H&Y stage 3, 7.4 ± 1.6 hours; $P = 0.501$). However, patients with advanced PD had more upright periods, whereas the number and velocity of their turns were reduced

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wearable sensors in Parkinson's disease. The intellectual property rights are held by the Tel Aviv Medical Center. A.M. and J.H. also serve as consultants for the Michael J. Fox Foundation, Biogen, Sanofi (J.H.), and Neuroderm (A.M.) in areas relating to the use of wearable sensors to assess mobility in Parkinson's disease. The other authors have nothing to report.

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($P \leq 0.021$). Recently diagnosed patients (<1 year from diagnosis) were similar to controls in the number of nocturnal turns ($P = 0.148$), but showed longer turning time ($P = 0.001$) and reduced turn magnitude ($P = 0.002$). Reduced nocturnal movements were associated with increased PD motor severity and worse dysautonomia and cognition and with dopaminergic medication.

Conclusions: Using wearable sensors for continuous monitoring of movement at night may offer an unbiased

measure of disease severity that could enhance optimal nighttime dopaminergic treatment and utilization of turning strategies. © 2020 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; sleep; nocturnal movements; wearable sensors; accelerometers

Sleep disturbances occur in 60% to 98% of patients with Parkinson's disease (PD).¹ Rapid eye movement (REM) sleep behavior disorder (RBD) has been extensively studied and is considered an early marker of PD.^{2,3} However, RBD is not the only sleep-related symptom associated with PD (and other synucleinopathies).² Excessive daytime sleepiness, insomnia, sleep fragmentation, and night akinesia^{1,2} have also been described and acknowledged as significant predictors of morbidity. A recent population-based study showed that poor sleep quality and short sleep duration as assessed using self-report questionnaires increased the risk of parkinsonism and PD in the 2 years after baseline measurement.³ In addition, sleep-related symptoms are increasingly recognized as a major contributor to disease burden and reduced quality of life.^{1,2,4,5}

Self-report questionnaires can provide subjective assessment of sleep quality⁶; however, they introduce bias, underreporting or overreporting of sleep problems,³ are more prone to measurement error, and do not provide insight on the underlying biological processes as objective measures. The "gold standard" for the evaluation of nocturnal sleep is polysomnographic monitoring (PSG).⁷ PSG consists of measuring neural function, eye movements, muscle activity, respiratory status, and electrocardiography activity^{1,2} while the person sleeps overnight in a laboratory setting. This assessment allows for quantification and classification of disturbances during the different sleep stages (ie, non-REM and REM) and their distribution throughout the night.⁷ However, PSG is time, cost, and labor intensive, may not reflect the typical behavior because of the unfamiliar environment, and cannot be routinely conducted. As such, simpler and less expensive methods have been suggested to help with the assessment of sleep quality.^{6,8,9}

Wearable sensors and portable monitoring devices include inertial measurement units such as accelerometers and gyroscopes that enable the assessment of movement. Although such sensors cannot provide information on sleep stages, these types of devices (eg, actigraph) have been used in several disciplines for measuring rest/activity.^{10,11} The American Academy of Sleep Medicine stated that actigraphy is not indicated for routine diagnosis or management of sleep disorders, nonetheless, it may be useful as an aid in the evaluation of sleep-wake

activity, particularly in typical sleep/activity cycles as in insomnia, circadian-rhythm disorders, or medical and psychiatric conditions where it is difficult to obtain an accurate sleep diary.¹² Moreover, quantification of movement during the night could provide important insights into the frequency and severity of sleep impairments and has the possibility to inform care.¹³

Recent pilot studies using wearable technologies reported that patients with PD have more sleep interruptions, with more awake time during the night than their bed partners¹⁴ and fewer nighttime movements, reflecting nocturnal hypokinesia.¹⁴ Nocturnal sleep disturbances have been associated with advanced motor disease, non-motor symptoms, and quality of life.¹⁴ However, less is known about the frequency and pattern of nocturnal movements in early-stage disease. Our aim was to test the hypothesis that reduced nocturnal movements as measured by a wearable sensor in the patients' homes and can already be observed in early-stage PD are related to cardinal symptoms such as bradykinesia and rigidity, nonmotor symptoms, and dopaminergic medication.

Methods

Participants

We evaluated cross-sectional wearable sensor data collected from 304 patients with PD who participated in 3 studies (V-TIME,¹⁵ $n = 125$; PIGD,¹⁶ $n = 37$; BEAT-PD, $n = 142$). Participants were included if they were diagnosed with PD by a movement disorders specialist based on the UK brain bank criteria, in stages 1 to 3 on the Hoehn and Yahr scale (H&Y),¹⁷ and were able to provide informed written consent attesting to their willingness to wear a wearable sensor for at least 2 consecutive days. Patients were excluded if they had any other neurological, orthopedic, or psychiatric disorders or had significant cognitive impairment (Montreal Cognitive Assessment¹⁸ cutoff score of <21). A group of healthy, age-matched healthy controls (HC; $n = 205$) was also included (similar exclusion criteria) for the comparison of nocturnal movements. The studies were approved by local ethical committees and performed according to the principles of the Declaration of

Helsinki. All participants gave their informed written consent prior to participation.

Procedures

Participants underwent a clinical evaluation. Information on medical history and medication regime was obtained. Disease severity was evaluated using the Movement Disorders Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS)¹⁹ during *on* medication. Rigidity, bradykinesia, and the Postural Instability Gait Difficulty (PIGD) scores were calculated from the MDS-UPDRS.²⁰ The Montreal Cognitive Assessment¹⁸ assessed global cognitive function, whereas the Trail Making Test (TMT)²¹ evaluated executive function. Mood was assessed using Beck Depression Inventory.²² The Non-Motor Symptoms Scale evaluated non-motor symptoms,²³ whereas the presence of RBD was evaluated using the REM Sleep Behavior Disorder Questionnaire.²⁴ Each participant was asked to wear a triaxial accelerometer-based device; the Axivity AX3 (Axivity Ltd, Newcastle, UK) is a body-fixed sensor, which is attached to the body with medical tape,^{25,26} or the DynaPort MiniMod Module (McRoberts BV, The Hague, Netherlands), which is worn on the body using a Velcro belt.^{16,27} Both devices were placed on the lower back (area L4-5) of the participants for continuous monitoring for at least 48 hours (including 2 nights). The devices similarly measure vertical, anteroposterior, and mediolateral accelerations, capturing data at 100 Hz (16-bit resolution). At the end of the collection period, the participants returned the devices to the medical center (via mail or courier) for processing.

Nocturnal Movement Analysis

Nocturnal movement outcomes included nocturnal rest interruptions defined as percent upright position and percent walking duration from the total nocturnal

rest time. Nocturnal movements were defined as the number of position changes and included turning duration, velocity, degree, and side of turn in bed.

Nocturnal rest was defined based on orientation differentiating between lying and upright positions.²⁸ Raw acceleration signals were extracted from the devices and the same algorithm was used for analysis of all signals.²⁹ High-frequency noise was removed using a moving average with a fixed 10-second window. When the sensor is placed in orthogonal orientations, the accelerations recorded are between +1 g to −1 g. Because the sensor is located on the lower back, the vertical acceleration was chosen to represent lying. The vertical acceleration axis signal was divided into personalized sliding windows of 1 second with an overlap of 0.5 seconds from which the mean magnitude values were extracted. Mean values below 0.4 g (approximately 33° from ground) were considered the threshold for lying. Bouts of lying longer than 5 minutes, between 21:00 PM to 08:00 AM were considered in the analysis of nocturnal rest. This time window was chosen to maximize the ability to detect nocturnal rest but was personalized based on data inspection. The beginning of night rest was defined as the first index in the first long lying bout (>60 minutes) and the end night as the last index of the last long lying bout based on the first upright position for more than 15 minutes (Fig. 1). Nocturnal rest interruptions were defined as events upright position such as sitting or getting out of bed and walking during the night. Nocturnal rest was considered resumed after a “rest interruption” if it lasted more than 15 minutes.

Body position while lying was approximated from the mediolateral and anteroposterior acceleration axes by transforming from Cartesian coordinates to polar coordinates to create Θ angles.³⁰ We defined the following 4 positions in bed using defined thresholds on Θ : (1) back, $\Theta \leq 45^\circ$; (2) belly, $\Theta \geq 135^\circ$; (3) right side, $\Theta > 45^\circ$ & $\Theta < 135^\circ$; (4) left side, $\Theta < -45^\circ$ & $\Theta > -135^\circ$. Turning

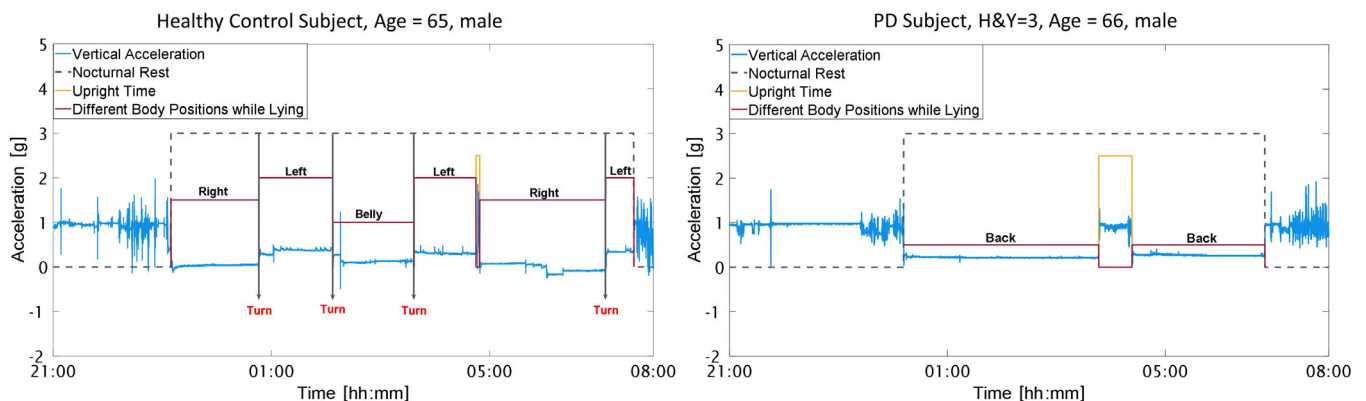


FIG. 1. An example of the acceleration signal during night time assessment. Positions and turns are displayed for a healthy control participant and a patient with PD. Note the reduced number of turns and the prolonged supine position during the night shown by the patient when compared with the age-matched control. In addition, note the segment of walking in the early hours of the morning. Hoehn and Yahr, H&Y; PD, Parkinson's disease. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1. Participant characteristics

Measures	Healthy Controls, n = 205	H&Y 1, n = 47	H&Y 2, n = 181	H&Y 3, n = 77	P Value Between Healthy and PD Participants*	P Value Between PD Stages**
Age, y	66.3 ± 13.3 (41–89)	62.8 ± 10.3 (36–80)	68.3 ± 8.5 (43–87)	72.2 ± 7.1 (54–85)	0.049	<0.0001
Sex, % males	34	68	66	61	<0.0001	0.732
Disease duration, y	–	2.3 ± 1.9 (0.5–9)	5.6 ± 4.4 (0.5–23)	9.7 ± 6.9 (2–37)	–	<0.0001
LEDD, mg/d	–	274.7 ± 270.8 (75–1358)	616.5 ± 469.8 (40–2250)	979.4 ± 613.9 (75–2580)	–	<0.0001
MDS-UPDRS part I	4.3 ± 4.0 (1–20)	5.0 ± 4.5 (1–22)	8.1 ± 5.9 (2–22)	13.7 ± 6.2 (2–26)	<0.0001	<0.0001
MDS-UPDRS part II	3.2 ± 5.2 (0–22)	3.6 ± 5.9 (0–29)	8.7 ± 7.4 (0–37)	19.1 ± 7.2 (2–39)	<0.0001	<0.0001
MDS-UPDRS part III	0.8 ± 1.2 (0–5)	10.4 ± 5.1 (6–17)	25.6 ± 10.5 (8–51)	37.5 ± 13.8 (15–80)	<0.0001	<0.0001
Montreal Cognitive Assessment	26.1 ± 2.7 (23–30)	24.9 ± 2.7 (21–30)	24.6 ± 3.8 (21–30)	23.3 ± 4.5 (21–30)	<0.0001	0.001
Bradykinesia score	2.8 ± 5.1 (0–15)	7.1 ± 7.8 (0–35)	8.9 ± 7.2 (0–28)	12.0 ± 4.1 (8–35)	<0.0001	<0.0001
Rigidity score	1.5 ± 2.3 (0–8)	2.4 ± 3.1 (0–14)	3.6 ± 3.5 (0–16)	6.2 ± 3.7 (0–18)	<0.0001	<0.0001
PIGD score	0	0.9 ± 1.1 (0–6)	2.2 ± 1.7 (0–8)	9.0 ± 2.6 (1–11)	<0.0001	<0.0001
Trail Making Test A	60.9 ± 30.1 (20.4–205.0)	57.7 ± 23.4 (23.2–119)	86.7 ± 47.8 (23.0–316.0)	122.2 ± 68.9 (32.0–345.0)	<0.0001	<0.0001
Trail Making Test B	107.8 ± 62.9 (86–360)	107.2 ± 52.8 (83–360)	146.6 ± 77.1 (93–360)	206.5 ± 97.9 (91–360)	<0.0001	<0.0001
Non Motor Symptoms Scale	3.4 ± 3.2 (0–13)	5.4 ± 3.5 (0–13)	8.3 ± 4.7 (2–21)	12.1 ± 3.4 (7–17)	<0.0001	<0.0001
Rapid Eye Movement Sleep Behavior Disorder Questionnaire	1.9 ± 1.6 (0–6)	2.5 ± 2.7 (0–10)	2.9 ± 2.7 (0–10)	2.8 ± 2.2 (0–10)	<0.0001	0.413
Beck Depression Inventory	4.4 ± 5.7 (0–23)	5.8 ± 5.2 (0–25)	8.8 ± 6.3 (2–32)	16.7 ± 4.2 (12–22)	<0.0001	0.001
Nocturnal movements	7.5 ± 1.2 (2.8–11.0)	7.3 ± 0.99 (4.7–9.0)	7.2 ± 1.28 (3.7–10.9)	7.4 ± 1.6 (3.9–11.2)	0.431	0.501
Nocturnal rest duration, hour	0.8 ± 0.8 (0.0–5.2)	1.6 ± 2.9 (0.0–16.5)	1.5 ± 1.9 (0.0–14.0)	3.4 ± 3.8 (0.0–20.3)	<0.0001 ^a	0.072
Percent upright, %	0.1 ± 0.1 (0.0–0.5)	0.1 ± 0.5 (0.0–3.9)	0.1 ± 0.1 (0.0–0.6)	0.1 ± 0.2 (0.0–1.0)	0.677	0.363
Number of turns	5.9 ± 3.2 (1.0–17.0)	5.5 ± 2.4 (1.0–11.0)	3.8 ± 2.9 (0.0–16.0)	1.9 ± 2.2 (0.0–10.0)	<0.0001 ^a	0.001 ^a
Turn duration, s	1.9 ± 2.2 (0.2–19.9)	2.7 ± 4.4 (0.8–29.9)	6.7 ± 8.4 (0.58–66.9)	10.7 ± 13.8 (0.93–73.5)	<0.0001 ^a	0.002 ^a
Turn degree (magnitude), degree	41.1 ± 16.9 (9.7–156.0)	36.4 ± 13.2 (13.2–94.5)	35.4 ± 15.2 (4.58–101.4)	37.6 ± 17.2 (10.9–87.2)	0.023	0.182
Turn velocity, deg/sec	24.0 ± 11.6 (1.4–59.2)	17.6 ± 8.1 (5.7–45.6)	11.2 ± 7.2 (1.21–33.2)	9.4 ± 7.1 (0.5–25.1)	<0.0001 ^a	0.001 ^a

Data are mean ± standard deviation and range or percentage as indicated.

*P value adjusted for age and gender.

**P value adjusted for age, gender, and disease duration.

^aSignificant P values after adjusting for multiple comparisons using Bonferroni correction.

Hoehn and Yahr stage 1, H&Y 1; Hoehn and Yahr stage 2, H&Y 2; Hoehn and Yahr stage 3, H&Y 3; PD, Parkinson's disease; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; PIGD, postural instability gait difficulty.

was defined as a change from 1 static position (eg, back, belly, right, or left) to another (based on a minimum of 10°). If a short (<30 seconds) interruption to an upright position occurred, it was considered part of turning, whereas a longer upright bout was analyzed separately as wake time at night. For each change in position (turn) we calculated the duration, degrees, and velocity. Data extracted for each feature for each participant was aggregated across the duration of collection. Median values were calculated for each participant and averaged within group.

Statistical Analysis

Descriptive statistics are reported as means \pm standard deviations. Differences between groups were explored using analysis of variance based on H&Y scale (0–3) or Kruskal-Wallis for measures with abnormal distribution. The majority of HC were women (66%), whereas the majority of PD patients were men (65.5%; $P < 0.0001$). Thus, all analyses that compared the controls and patients were adjusted to sex. To explore the impact of the disease on nocturnal movement, the analysis was adjusted to age and gender. Differences between recently diagnosed patients (<1 year from diagnosis) and an age-matched HC group ($n = 144$) were evaluated using t tests. To explore

changes throughout the night, the data for each night were divided into quartiles (personalized for each participant) and averaged across collection. A repeated-measure analysis of variance was used to evaluate the differences between the beginning of the night (1st quartile) and end of night (4th quartile) for early-stage and advanced-stage PD (HY1 vs. HY2 and HY3), that is, group \times time. The associations between nocturnal movements, motor and nonmotor symptoms, and medications were evaluated using Spearman correlation coefficients. Analysis was corrected for multiple comparisons using Bonferroni corrections. Statistical significance after correction was set to $P = 0.006$, and the analysis was performed using SPSS for Windows version 22 (IBM Corp., Armonk, NY). Anonymized data will be shared by request from any qualified investigator.

Results

Data on nocturnal function were analyzed from a total of 3037 nights obtained from 510 participants: HC = 205, H&Y1 = 47, H&Y2 = 181, H&Y3 = 77. Participant characteristics are presented in Table 1. Patients in the H&Y3 group were older than the 3 other

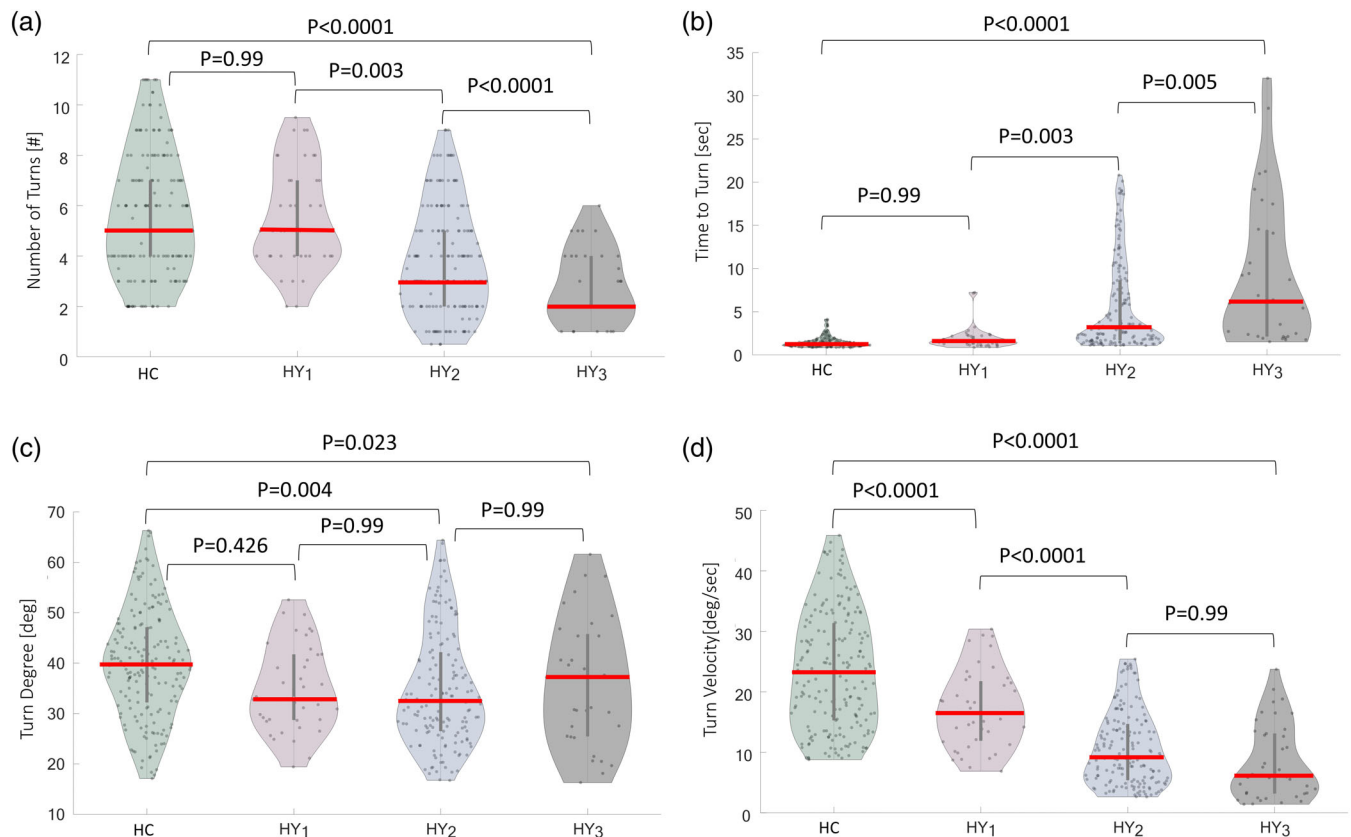


FIG. 2. Differences in nocturnal movements across disease severity as measured by H&Y staging. (a) Number of turns during the night. (b) Average turn duration. (c) Average magnitude of turns (degree). (d) Angular velocity of turns. The violin plots present the measures as scatter plots (for all participants) with the median of the group represented by the widest section. P values represent post hoc analysis between each H&Y stage. HC, healthy controls; Hoehn and Yahr stage 1, HY1; Hoehn and Yahr stage 2, HY2; Hoehn and Yahr stage 3, HY3. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2. Sleep parameters of recently diagnosed patients (<1 year from diagnosis) and healthy age-matched controls

Measures	Healthy Controls, n = 144	Recently Diagnosed Patients, n = 48	P Value
Age, y	62.5 ± 13.7 (41–88)	66.1 ± 10.6 (36–87)	0.101
Sex, % male	39	73	<0.0001
Hoehn and Yahr stage	0	1.6 ± 0.6 (1–2)	<0.0001
MDS–UPDRS part 1	4.5 ± 4.1 (0–20)	6.4 ± 5.1 (1–18)	0.023
MDS–UPDRS part 2	3.4 ± 5.3 (0–22)	6.2 ± 6.9 (0–29)	0.008
MDS–UPDRS part 3	0.8 ± 1.3 (0–5)	16.6 ± 8.9 (6–87)	<0.0001
Bradykinesia score	2.2 ± 3.8 (0–15)	7.4 ± 7.8 (0–35)	0.001
Rigidity score	1.4 ± 2.3 (0–8)	2.1 ± 2.5 (0–14)	0.109
PIGD score	0	0.9 ± 1.0 (0–6)	<0.0001
LEDD, mg/d	–	286.5 ± 378.4 (50–1025)	<0.0001
Montreal Cognitive Assessment	26.1 ± 2.8 (22–30)	23.8 ± 4.06 (21–30)	<0.0001
Rapid Eye Movement Sleep Behavior Disorder Questionnaire	1.9 ± 1.6 (0–6)	2.8 ± 2.6 (0–9)	0.021
Non Motor Symptoms Scale	3.6 ± 3.3 (0–13)	5.6 ± 3.4 (0–15)	0.003
Nocturnal measures			
Nocturnal rest duration, hour	7.3 ± 1.1 (2.8–11)	7.4 ± 1.0 (4.7–9.5)	0.755
Percent upright, %	0.7 ± 0.8 (0–9.5)	1.6 ± 3.8 (0–16.4)	0.001 ^a
Percent walk, %	0.05 ± 0.08 (0–0.4)	0.2 ± 0.6 (0–3.9)	0.038
Number of turns	6.1 ± 3.1 (0–17)	5.3 ± 2.9 (0–11)	0.148
Turn duration, s	1.9 ± 2.1 (0.6–15.8)	3.2 ± 4.0 (0.8–22.5)	0.001 ^a
Turn degree (magnitude), degree	40.8 ± 16.9 (5–163.2)	34.7 ± 13.7 (13.2–87.2)	0.002 ^a
Turn velocity, deg/sec	23.4 ± 11.4 (3.7–59.2)	16.2 ± 8.8 (2.6–41.2)	<0.0001 ^a

Data are mean ± standard deviation and range or percentage as indicated.

^aSignificant *P* values after adjusting for multiple comparisons using Bonferroni correction.

LEDD, levodopa equivalent daily dose; MDS–UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; PIGD, postural instability gait difficulty.

groups ($P < 0.001$). Within each of the PD groups, the men and women were similar in measures of nocturnal movement. Based on self-report, none of the participants used a continuous positive airway pressure device during the study.

Nocturnal Movements and Disease Severity

Differences in nocturnal movements are presented in Table 1. Nocturnal rest duration did not differ with disease severity. However, the number of turns during the night and their velocity declined with disease progression while turning duration increased, but not the magnitude of the turn (see Fig. 2).

A total of 48 patients (16%) were less than 1 year from diagnosis at the time of assessment. These recently diagnosed patients showed greater percent of upright time at night when compared with the age-matched HC ($P = 0.001$). The number of turns at night was similar to controls, but recently diagnosed patients showed longer turn duration ($P = 0.001$) with reduced magnitude ($P = 0.002$; Table 2).

Position assessment showed that 32% of the patients spent more than 50% of night rest in the supine position when compared with only 6% of the HC. Of the patients, 90% were right-hand dominant. A total of 37% of the patients reported the right side of the body as the most affected, 46% reported the left as more affected, and

17% manifested with symmetrical involvement. Patients avoided lying on the most-affected side, spending only 4% and 6% of the night on the affected side (left and right, respectively; $P = 0.002$). This was only significant for patients in H&Y1.

Assessment of changes throughout the night showed that patients with advanced PD had a greater percent of upright bouts during the later stages of the night as compared to the beginning of the night ($1.6\% \pm 2.1\%$ vs. $6.3\% \pm 3.1\%$; time effect $P < 0.001$), and this was significantly more (group effect $P < 0.0001$) than in patients in early-stage PD ($1.3\% \pm 1.2\%$ vs. $1.9\% \pm 1.7\%$; time effect $P = 0.615$). Differences were not observed in the number of rotations or their velocity between the beginning of the night to later stages in the night. Nonetheless, among patients with advanced PD, the magnitude of the turn rotations was significantly lower ($P < 0.0001$) during the later stages of the night ($27.3^\circ \pm 21.3^\circ$) as compared to the beginning of the night ($36.4^\circ \pm 16.2^\circ$). This reduction was not observed in early-stage PD ($35.7^\circ \pm 11.4^\circ$ vs. $36.3^\circ \pm 9.2^\circ$; $P = 0.73$).

Nocturnal Movements, Motor and Nonmotor Symptoms, and Relation to Medications

The associations between nocturnal movements and motor and nonmotor symptoms of PD are presented in Figure 3. Specifically of note are the inverse correlations

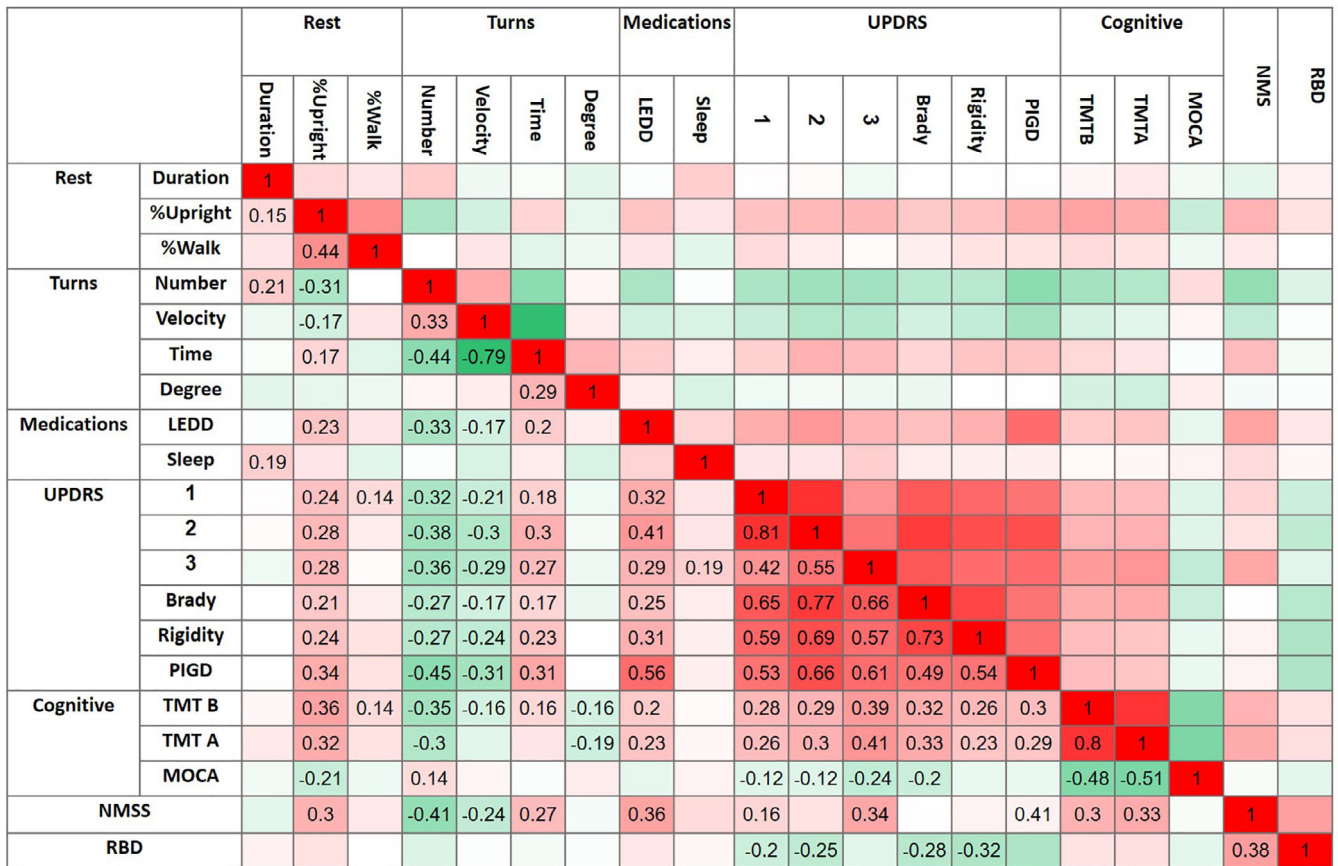


FIG. 3. Heat map showing correlation coefficients between measures of nocturnal rest and motor and nonmotor symptoms in the patients with Parkinson's disease. Darker pixels reflect higher correlation values (red positive, green negative). The *r* value is indicated only in the pixels when the correlation was significant at *P* < 0.001. LEDDD, levodopa equivalent daily dose; MOCA, Montreal Cognitive Assessment; NMSS, Non-Motor Symptoms Scale for Parkinson's Disease; PIGD, postural instability gait difficulty; RBD, rapid eye movement sleep behavior disorder; TMT A, Trail Making Test A; TMT B, Trail Making Test B; UPDRS, Unified Parkinson's Disease Rating Scale. [Color figure can be viewed at wileyonlinelibrary.com]

between cognitive function (as measured by the TMT). These were observed in Trail Making Test-A, Trail Making Test-B, and Trail Making Test B-A, a measure of executive function, and the number of rotations during the night (*r* = [-0.16]–[-0.35]; *P* < 0.0001). The Non-Motor Symptoms Scale scores were inversely associated with turning at night (*r* = -0.41; *P* < 0.0001), whereas the higher Non-Motor Symptoms Scale scores were also associated with more upright time (*r* = 0.30; *P* = 0.001) and more specifically with nocturnal urination (question 9: *r* = -0.42; *P* < 0.0001). Nocturnal movements were all significantly associated with levodopa equivalent daily dose and motor severity, rigidity, bradykinesia, and the PIGD score (Fig. 3).

Discussion

In this study, we used a single wearable sensor, placed on the lower back, to assess nocturnal movement in a large cohort of patients with PD with varying disease severity and healthy adults. Our results reveal

the following: (1) patients with PD show more fragmentation of nocturnal rest, with greater percentage of upright time during the night when compared with controls, and this increases with disease severity; (2) nocturnal movements are reduced even in early-stage PD and are associated with bradykinesia and rigidity; (3) reduced nocturnal movements were associated with motor severity, dysautonomia, cognitive function, and dose of dopaminergic medication (recall Fig. 3).

Previous work showed that patients with moderate to severe PD have more nocturnal rest interruptions and greater hypokinesia than their matched controls.¹⁴ Our analysis extends earlier findings by also showing that reduced nocturnal movements are apparent across the disease spectrum even in early stages (<1 year from diagnosis). Reduced nocturnal movements, specifically turning duration, velocity, and magnitude were associated with greater bradykinesia, rigidity, and PIGD scores. An investigation of the rigidity scores of these recently diagnosed patients revealed no clinically detectable axial rigidity (item 3.3a on the MDS-UPDRS) in any of the patients, yet turning duration, degree, and velocity

differed from the HC. Interestingly, a recent longitudinal study tracking individuals with confirmed RBD until the point of PD diagnosis showed that, in retrospect, altered turning in bed was one of the earlier motor signs appearing 7 to 11 years before diagnosis.³¹ These findings suggest that turning in bed may provide additional information on classical disease symptoms that are not necessarily observed or may even be missed using the conventional clinical assessment in early-stage PD.

Deficits in nocturnal movements deteriorated with disease severity, specifically the timing and magnitude of turning in bed. Interestingly, there is a large body of literature on deficits in upright turns during gait in patients with PD.^{27,32,33} Turning during upright ambulation is a complex movement that requires force, balance, and coordination, which has been associated with an increased risk of falls.^{27,33} Patients with PD commonly take several short, rigid steps with reduced magnitude to turn instead of the fluid turning motion that is typical in healthy individuals.^{32,34} Remarkably, the pattern of movement during upright turning seems similar to that during turning while supine in bed at night. Moreover, turning in bed was associated with the postural and gait score as calculated from the MDS-UPDRS, potentially reflecting similar underlying deficits such as axial rigidity and reduced angular velocity. These findings suggest that turning in bed may be a sensitive measure of disease progression and potentially even an early marker of disease. In the future, it may be interesting to combine nocturnal movement measures with other markers of PD progression.

Similar to previous reports,^{9,14} the patients in our study also tended to spend a greater part of their night in the supine position when compared with the HC. We further found that the side of onset influenced the turning position. Even in early-stage disease, most of the participants preferred the supine position, limiting rotation onto the affected side (either left or right). From a biomechanical standpoint, turning toward the less-affected side provides more flexibility of movement as the affected shoulder is not constrained under the body in a protracted position.³⁵ Patients with PD also show axial kinesthetic deficits that have been associated with abnormalities in automatic postural reactions³⁶ and may contribute to nocturnal positioning. An alternative explanation for this avoidance could be related to sensory input from the affected side, shoulder pain, or positional discomfort, which are highly common in PD.³⁷ In this sense, avoiding weight bearing on the more-affected side could be a form of functional compensation and should be further explored. Turning in bed is a physiological necessity aimed to preserve perfusion and health.³⁸ Besides the discomfort of positional immobility, prolonged supine sleep has been associated with complications such as pressure sores, aspiration pneumonia, sleep-breathing disorders (eg, obstructive sleep apnea), reduced daytime vigilance, and supine

hypertension.³⁸ Therefore, providing treatment to improve sleep quality and nocturnal movements is a highly important goal not only as a symptomatic effect but also for better disease management.

Nocturnal rest interruptions were associated with self-report of other nonmotor symptoms and specifically with nocturnal urination. Although this association may seem trivial, it is actually bidirectional with each symptom affecting the other. The added benefit of using technology to assess these symptoms lies in the objective quantification of “bathroom night-time trips,” which in turn can assist in directing care. Reduced nocturnal movements were also associated with impaired executive function. Here too, a bidirectional, reciprocal interaction between cognitive decline and sleep alterations is possible. Cognitive decline can impact sleep quality as observed in older adults and patients with Alzheimer’s disease and dementia,³⁹ whereas sleep fragmentation in older adults has been associated with decreased cortical volume, brain atrophy, and cognitive decline.^{40,41} In fact, poor sleep has been suggested to exacerbate the neurodegenerative process and cognitive decline.⁴² These interactive processes may accelerate the clinical deterioration and the reduced quality of life of patients,⁴³ suggesting the intriguing possibility that improving sleep quality may slow down disease progression, delay dementia, and impede other PD complications. This question needs further research.

Interestingly, we found that patients with advanced PD had more sleep interruptions (greater percent of upright position) later during the night as compared to during the beginning of the night. Normal sleep architecture changes throughout the night with more deep sleep early in the night and more REM sleep and short awakenings in early hours of the morning.⁷ In the present study, the increase in the percent time in the upright position (which could reflect awakenings) was not observed in the HC or the patients with early-stage PD, but could only be observed in patients with advanced PD. This suggests that the upright time does not simply relate to the normal change in sleep architecture during the night. It should be noted, however, that percent walking time was not increased despite the increase in upright time in the advanced PD patients. Within this group, only a small proportion of patients reported RBD (17%). However, the possibility that RBD is a contributor to this finding cannot be ruled out, as PSG was not collected. Our findings also show that the patients with advanced disease had reduced magnitude of turns during the later stages of the night (that was not observed in patients with milder disease) and greater association with rigidity. Thus alternatively, it is possible that the increase in time spend in the upright position is a compensation for difficulty in turning and increased discomfort.

This finding is consistent with previous studies showing more sleep interruptions later during the night¹⁴

and with the moderate negative correlation we found between nocturnal movement measures and levodopa equivalent daily dose. Nocturnal hypokinesia in PD has been considered the result of the neurodegenerative process, dopaminergic levels, and a disorder of circadian rhythm.⁴⁴ Clearly, this association could be more complex, reflecting disease severity as well as reduced effectiveness of medication as the night progresses. Recent trials evaluating the effect of a rotigotine transdermal patch or subcutaneous apomorphine infusion and levodopa-carbidopa intestinal gel infusion on nocturnal immobility showed significant improvements in the number and degree of axial turns during the night.^{44,45} These findings support the use of continuous therapies in the management of nocturnal hypokinesia and the utility of using wearable sensors for monitoring therapeutic effects.

To our knowledge, this is the largest study to date that quantitatively examined nocturnal movements in patients with PD collected in the home over several nights. Nonetheless, our study has several limitations. Data from our wearable sensors cannot provide information on sleep stages or sleep disorders such as RBD, thus we opted not to discuss sleep but, rather, nocturnal rest to avoid confusion, although previous studies using actigraphy have shown high correlations between nocturnal movements and sleep stages as classified by PSG.^{10,11} Data were not accompanied by diaries, video recording, or self-report, limiting the ability to attest to sleep versus a just lying-down condition. Similarly, if lying down was not detected (eg, people who rest in a sofa chair and do not meet the threshold for lying down) were not included in the analysis, this will be reported in the future. Data were collected during only 2 nights. This may have affected the participants' sleeping behavior. Information on sleeping arrangements (eg, the existence of a bed partner) was not collected and should be considered in the future as a potential confounder. Concomitant non-PD medications (eg, diuretics, antihypertensive, benzodiazepines, and other sleep medication) were not available for many of the participants. In addition, accurate timing of dopaminergic medication was not available. This information could be helpful to assess the dopaminergic effect on hypokinesia and specifically morning *off*. We are currently in the process of obtaining this information for future analysis. Lastly, we used only one sensor placed on the lower back to minimize patient burden. This location provides valuable information on axial mobility but is not useful for the assessment of peripheral limb movements (eg, Restless Leg Syndrome, periodic leg movements syndrome).

Our findings show that reduced nocturnal movements were associated with increased PD motor severity and worse dysautonomia. From a clinical perspective, using wearable sensors for continuous monitoring at night can augment clinical assessment by obtaining precise,

objective, accurate, and valuable information on disease symptoms at night without having to rely on expensive PSG or subjective self-report questionnaires. Because sleep quality contributes to quality of life,^{1,2,4,5} objective assessment using wearable sensors could help direct optimal nighttime dopaminergic treatment and utilization of turning strategies to ultimately improve sleep and as a byproduct, the quality of life of patients. ■

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