Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Circadian Rest-Activity Rhythms Predict Cognitive Function in Early Parkinson's Disease Independently of Sleep

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Abstract: Background: Cognitive impairment is a common and debilitating symptom of Parkinson's disease (PD), and its etiology is likely multifactorial. One candidate mechanism is circadian disruption. Although there is evidence of circadian abnormalities in PD, no studies have directly assessed their association with cognitive impairment.
Objectives: Investigate whether circadian rest-activity rhythm is associated with cognitive function in PD independently of sleep.
Methods: Thirty-five participants with PD wore wrist actigraph monitors and completed sleep diaries for 7 to 10 days, then underwent neuropsychological testing. Rest-activity rhythm was characterized using nonparametric circadian rhythm analysis of actigraphy data. Objective sleep parameters were also estimated using actigraphy data. Hierarchical regression models assessed the independent contributions of sleep and rest-activity rhythm to cognitive performance.
Results: Less stable day-to-day rest-activity rhythm was associated with poorer executive, visuospatial, and psychomotor functioning, but not with memory. Hierarchical regressions showed that interdaily stability's contribution to cognitive performance was independent of sleep's contributions. Whereas sleep contributed to executive function, but not psychomotor or visuospatial performance, rest-activity rhythm stability significantly contributed to variance in all three of these domains, uniquely accounting for 14.4% to 17.6% of their performance variance.
Conclusions: Our findings indicate that circadian rest-activity rhythm is associated with cognitive impairment independently of sleep. This suggests the possible utility of rest-activity rhythm as a biomarker for circadian function in PD. Future research should explore interventions to stabilize behavioral rhythms in order to strengthen circadian function, which, in turn, may reduce cognitive impairment in PD.

Parkinson's disease (PD) is characterized by motor disturbance as well as by a range of nonmotor symptoms.[1] One of the most common and debilitating is cognitive impairment, which is present in approximately one third of individuals with PD at time of diagnosis, increasing in prevalence and severity with disease duration and progressing to dementia for many of these individuals.[2] Even subtle cognitive impairment can have a significant impact on quality of life for persons with early PD and caregivers. Commonly affected cognitive domains in PD without dementia include executive function, attention, visuospatial function, and memory, with attention and executive function being prevalent at earlier stages of the disease.[3] The etiology of cognitive impairment in PD is likely multifactorial, and identifying mechanisms may be important for clinical management.

A candidate mechanism of cognitive impairment in PD is circadian dysfunction. In humans, the circadian system is a network of oscillators with approximately 24-hour cycles that regulate biological functions at every level throughout the brain and body.

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Disruption to this system can broadly impact physical, emotional, and cognitive health either directly or through its influence on sleep.[4] Although it is well established that sleep affects cognitive performance,[5] circadian function likely also affects it independently. For example, rodent studies have demonstrated that disrupted rest-activity rhythm contributes to executive dysfunction and memory deficits above and beyond the effects of the previous night's sleep.[6] In humans, multiple studies document the negative cognitive effects of shift work[7] and jet lag,[8] both of which feature disrupted circadian rest-activity rhythms.

Although there is mounting evidence that circadian function is impaired in PD,[9] there has been no direct assessment of associations between circadian and cognitive impairment in this population. A study by Whitehead et al.[10] found preliminary evidence for this association with a correlation between rest-activity amplitude and Mini-Mental State Examination (MMSE) score. The MMSE is a brief dementia screen that does not capture many cognitive impairments common in PD (e.g., executive dysfunction), so comprehensive and domain-specific cognitive assessment is needed. Moreover, it is difficult to conclude a specifically *circadian* role in cognition based only on actigraphic rest-activity data, which reflect not only circadian function, but also sleep and sleep-wake timing. Given the known relation between sleep and cognitive impairment in PD,[11,12] Whitehead et al.'s[10] finding may not, in fact, indicate an independent circadian association with cognition.

Despite the possible confluence of circadian and sleep contributions to actigraphy data, there are advantages to using actigraphy to characterize behavioral rhythms (e.g., noninvasive, inexpensive), and many investigators are using this method to estimate possible circadian dysfunction in PD. For example, studies have found that individuals with PD consistently demonstrate lower rest-activity amplitude than their age-matched peers (i.e., increased motor activity at night and decreased activity during the day),[10,13,14] as well as rest-activity patterns that are more fragmented and less stable.[10,14,15] These rest-activity patterns co-occur with dysregulated melatonin, cortisol, and peripheral clock gene expression,[14] which suggests that they include a possible circadian component. Actigraphy's potential for capturing circadian dysfunction suggests that it should not be dismissed as a tool for exploring circadian function in PD. Rather, analytical techniques should be applied to assess the unique association of circadian with cognitive function independently of sleep.

In the present study, we assessed associations between circadian rest-activity rhythms and multidomain cognitive function in PD, using analytical techniques to reveal the unique association of rest-activity rhythms with cognition independent of sleep.

Participants and Methods

Thirty-five individuals with idiopathic PD (mean age = 66.2; standard deviation [SD] = 7.9; 13 women) were recruited from the outpatient Movement Disorders Clinic of the Boston Medical Center. They had been assessed as part of a study to test the feasibility of using actigraphy to measure sleep quality in PD[15] and the relation of nighttime sleep to cognition.[16] Study procedures were approved by the Boston University Institutional Review Board, and participants provided informed consent. All participants were right-handed, except for 2 left-handed individuals, and were highly educated (mean years of education = 16.8; SD = 2.4). None of the participants was demented as indexed by MMSE scores >25 and performance on multiple neuropsychological tests. They had no history of substance abuse, head injury, or neurological disorders besides PD. Participants had mild-moderate PD severity per scores on the UPDRS (mean score = 25.1; SD = 9.4). Median H&Y stage was 2 (range = 1–3). Mean disease duration was 8.8 years (SD = 5.1). All participants were taking medication; we calculated levodopa equivalent dosages (LEDs) based on convention.[17] LED was not significantly correlated with sleep, rest-activity, or cognitive variables ($rs < 0.39$, $Ps > 0.54$).

Participants' overall sleep characteristics were assessed with the Parkinson's Disease Sleep Scale (PDSS), a 15-item self-report questionnaire measuring overall quality of sleep, sleep onset and maintenance, insomnia, nocturnal restlessness, nocturnal hallucinations, distressing/vivid dreams, nocturia, nocturnal motor symptoms, sleep refreshment, and daytime dozing.[18] Participants' mean score of 105.8 (SD = 20.6) of a possible 150, where lower scores reflect worse symptoms, represents moderate sleep disturbance that is consistent with early/moderate PD.[18] PDSS score was not correlated with any rest-activity or cognitive variables ($rs < 0.32$, $Ps > 0.64$). Nine of the 35 participants endorsed "acting out dreams," one of whom had a formal diagnosis of REM sleep behavioral disorder (RBD). Although the sample size was too small to detect differences between suspected RBD versus non-RBD participants, visual inspection of data suggested that there was no difference in the pattern of association between circadian and cognitive variables between these two subgroups.

Measures

Sleep Diaries

Participants completed daily sleep diaries during a 7- to 10-day period that documented bed and rise times.

Actigraphy: Sleep and Circadian Rest-Activity Rhythm

Participants wore actigraphs (Actiwatch AW-64; Mini Mitter, Sunriver, OR) continuously over the same 7- to 10-day period on the nondominant wrist. These accelerometers recorded raw activity counts in 30-second epochs at the rate of 30 Hz. Using a threshold of 40 activity counts within an epoch for "wake" and sleep diaries to corroborate bed and rise times, we calculated total sleep time, sleep onset latency, wake after sleep onset (i.e., duration of wakefulness during the sleep period), and sleep efficiency (i.e., percentage of time in bed spent asleep). We calculated circadian rest-activity variables using nonparametric circadian rhythm analyses[19,20]:

Relative amplitude (RA): ratio of average activity level during the least active 5 hours to the most active 10 hours of each day.

TABLE 1 *Correlations between circadian and cognitive variables*

	Memory Composite		Executive Function Composite		Psychomotor Speed Composite		Visuospatial Function Composite	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Circadian: interdaily stability	0.176	0.311	0.401[1]	0.017	0.424[1]	0.011	0.396[1]	0.018
Circadian: fragmentation	−0.215	0.214	−0.190	0.275	−0.239	0.167	−0.112	0.522
Circadian: relative amplitude	0.160	0.360	0.206	0.235	0.147	0.401	0.154	0.376

[1] Correlation is significant at $P < 0.05$ level (two-tailed).

Interdaily stability (IS): ratio of activity level variance within each 24-hour pattern to the overall variance, essentially a signal-to-noise measure indicating the degree of consistency from day to day. A higher value indicated a more stable rhythm.

Intradaily variability (IV): ratio of the mean squares of the difference between consecutive hours and the mean squares around the overall mean, a measure of fragmentation. A lower value indicated less fragmented rhythm.

Neuropsychological Tests: Cognitive Performance

Cognition was assessed using standardized neuropsychological tests of executive function and attention, memory, psychomotor speed, and visuospatial function, as described in Stavitsky et al.[16] Tests of executive function and attention included Verbal Fluency (FAS and Category-Animals), Ruff Figural Fluency, Digit Span Backward, Spatial Span Backward, Trail-Making Test B, and the Stroop Color-Word Test. Tests of memory included the California Verbal Learning Test-II (CVLT-II), including List A total, Short Delay Free Recall, Long Delay Free Recall, and Yes/No Recognition, and the Brief Visual Memory Test, including Learning, Delayed Recall, and Yes/No Recognition (BVMT). Tests of psychomotor speed included Trail Making Test A and the Purdue Pegboard Test. Tests of visuospatial function included Benton Judgment of Line Orientation, Clock Drawing, and the Money Road-Map Test.

Procedures

Detailed procedures for recruitment and enrollment are described in Stavitsky et al.'s 2010 study.[15] Briefly, after participants were screened for eligibility, they began wearing wrist actigraphs for the following 7 to 10 days. They were instructed to wear their actigraphs continuously and to not change their daily routines or their medication regimens. After actigraphic monitoring, participants underwent neuropsychological testing in the laboratory.

Statistical Analyses

Participants' scores on neuropsychological tests were converted to z-scores based on a matched normal control sample assessed in a previous study.[16] Z-scores were averaged for executive function, psychomotor speed, visuospatial function, and memory to create composite scores of each domain.

To test the hypothesis that rest-activity rhythm contributes to variance in cognitive performance independently of sleep, we performed hierarchical regressions with sleep and rest-activity rhythmicity measures as predictors. To preserve statistical power and to avoid multicollinearity, we decided a priori that only variables significantly correlating with cognitive performance would be used in the hierarchical regression analysis.

Sleep Variables

Both sleep onset latency (SOL) and sleep efficiency (SE) were significantly correlated with executive function ($rs > 0.427$, $Ps < 0.01$). We decided to use only SE because SOL and SE are highly correlated with each other, and SE is the sleep variable conventionally considered to reflect overall sleep quality.[21] Wake after sleep onset and sleep duration did not correlate with cognitive variables and therefore were not included in hierarchical regression analyses.

Rest-Activity Rhythm Variables

Among the rest-activity rhythm variables, only IS was significantly correlated with cognitive variables ($rs > 0.396$, $Ps < 0.05$; Table 1). Because both endogenous circadian rhythms and environmentally imposed behavioral schedules (i.e., sleep-wake timing) contribute to IS, we sought to dissociate these two elements by calculating both the interdaily stability of rest-activity rhythms (IS) and the interdaily stability of sleep-wake schedules based on sleep diary data (IS_{SW}). Of these, IS was significantly correlated with cognitive variables, and IS_{SW} was not ($rs < 0.251$, $Ps > 0.146$). Therefore, we used only IS, and not IS_{SW}, in the hierarchical regression analyses.

These hierarchical regression analyses were performed separately with executive function, psychomotor speed, and visuospatial function as the model outcomes. Because no sleep or rest-activity variables correlated with memory composite scores, we did not perform the regressions with memory as the outcome. For each hierarchical regression, the first model (model 1) included only SE, and the second model (model 2) included SE and IS.

Results

With executive function as the outcome (Table 2), model 1 (SE only) was significant ($F[1,33] = 7.059$; $R^2 = 0.181$; $P = 0.012$), with SE explaining 18.1% of the variance in

TABLE 2 *Summary of hierarchical regression analysis for sleep and circadian contributions to executive function*

	F	R^2	R^2 Change	*P*	Beta	*t*	*P*	Collinearity (VIF)
Model 1	7.059	0.181	0.181	0.012				
Sleep efficiency					0.425	2.657	0.012	1.000
Model 2	7.460	0.325	0.144	0.002				
Sleep efficiency					0.405	2.742	0.010	1.003
Interdaily stability					0.380	2.573	0.015	1.003

TABLE 3 *Summary of hierarchical regression analysis for sleep and circadian contributions to visuospatial function*

	F	R^2	R^2 Change	*P*	Beta	*t*	*P*	Collinearity (VIF)
Model 1	0.301	0.009	0.009	0.591				
Sleep efficiency					0.096	0.544	0.591	1.000
Model 2	3.109	0.163	0.154	0.046				
Sleep efficiency					0.075	0.457	0.651	1.003
Interdaily stability					0.393	2.385	0.023	1.003

performance. The addition of IS in model 2 (SE + IS) contributed an additional 14.4% of the variance in executive performance, which was significant ($F[1,32] = 7.460$; $R^2 = 0.325$; $\Delta R^2 = 0.144$; $P = 0.002$). Multicollinearity was not a concern, indicated by variance inflation factors (VIFs) substantially lower than the acceptable threshold of 10 (SE, Tolerance = 0.997, $VIF = 1.003$; IS, Tolerance = 0.997, $VIF = 1.003$).

With visuospatial function as the outcome (Table 3), model 1 was not significant ($F[1,33] = 0.301$; $R^2 = 0.009$; $P = 0.591$), but model 2 was ($F[1,32] = 3.109$; $R^2 = 0.163$; $\Delta R^2 = 0.154$; $P = 0.046$), with IS contributing a significant portion of the variance (15.4%) to the model. SE did not predict visuospatial function ($\beta = 0.075$; $t(34) = 0.457$; $P = 0.651$), but IS did ($\beta = 0.393$; $t(34) = 2.385$; $P = 0.023$).

Similarly, model 1 failed to predict psychomotor speed ($F[1,33] = 0.603$; $P = .443$; $R^2 = 0.019$; Table 4), but model 2 was significant ($F[1,32] = 3.741$; $R^2 = 0.194$; $\Delta R^2 = 0.176$; $P = 0.035$), with IS uniquely explaining 17.6% of the variance in psychomotor speed. SE did not predict psychomotor speed ($\beta = 0.114$; $t(34) = 0.707$; $P = 0.485$), but IS did ($\beta = 0.420$; $t(34) = 2.602$; $P = 0.014$).

Discussion

Among individuals with PD, a more stable circadian rest-activity rhythm was associated with better performance on executive, psychomotor, and visuospatial tasks, and sleep did not account for these associations. In fact, only rest-activity stability, and not sleep efficiency, was significantly associated with psychomotor speed and visuospatial function. We further ruled out daily sleep scheduling's contribution by showing that the interdaily stability of sleep-wake timing could not fully explain the association between rest-activity rhythm and cognition. Together, these findings suggest that endogenous circadian function is likely to be the major factor in the observed relation between rest-activity rhythm and cognition.

One possible mechanism by which circadian function contributes to cognition in PD is through its regulation of arousal. Through clock gene expression and suprachiasmatic nucleus (i.e., "master clock") projections to wake-promoting brain regions, the circadian system directly regulates brain arousal, which is required for vigilance, working memory, learning, and other cognitive functions.[6] Furthermore, because cognitive function itself follows diurnal rhythms of behaviors that are also modulated by the circadian system, a disrupted circadian system may compound the effects of blunted arousal and sleep disturbance through less robust time-of-day signaling.

Our findings add to the accumulating evidence for the interaction between cognitive function and the circadian system. It is possible that cognitive impairment may affect daily activities and lifestyle, leading to altered daily activity rhythms and circadian regulation. Alternatively, altered circadian rhythms can also contribute to cognitive decline in aging and neurodegenerative disease. For example, less robust and delayed rest-activity rhythms in older women predicted the development of dementia or mild cognitive impairment 5 years later.[22] In those at risk for Alzheimer's disease (AD) by virtue of having an affected parent, there is already a detectable phase delay in circadian body temperature rhythm more than 10 years preceding expected cognitive symptom onset.[23] These prospective findings suggest that circadian dysregulation is not merely a symptom of cognitive decline, but

TABLE 4 *Summary of hierarchical regression analysis for sleep and circadian contributions to psychomotor speed*

	F	R^2	R^2 Change	*P*	Beta	*t*	*P*	Collinearity (VIF)
Model 1	0.603	0.019	0.019	0.443				
Sleep efficiency					0.136	0.777	0.443	1.000
Model 2	3.741	0.194	0.176	0.035				
Sleep efficiency					0.114	0.707	0.485	1.003
Interdaily stability					0.420	2.602	0.014	1.003

rather a driver of pathogenesis.[24] In fact, bright light therapy, a circadian intervention, was able to attenuate cognitive decline in elderly group care residents over the course of 1 year,[25] and a 4-week dose of bright light therapy was able to improve MMSE scores in individuals with AD dementia.[26]

There has been less evidence for circadian associations with cognitive function in PD and, until the present study, none that demonstrated separate contributions from circadian rest-activity rhythm and sleep. Our findings indicate that actigraphy-derived rest-activity rhythm is not merely a proxy for sleep in its association with cognition in PD, but can serve as an independent predictor. This finding suggests that in addition to addressing nighttime sleep, there may be benefit to directly targeting behavioral rhythms. For example, a behavioral rhythm intervention that includes timed BLT, consistent sleep-wake timing (i.e., creating the opposite effect induced by shift-work, jet lag, and napping), meal timing, and other activity scheduling may help to strengthen circadian entrainment in order to improve rhythm stability. Because the circadian system interacts intimately with multiple motor and nonmotor systems affected in PD, improving rhythm stability may not only improve cognition, but "raise the water for all boats," such as for mood, autonomic function, and sleep. These behavioral interventions would be low risk, easily disseminated, and present no issues of drug interaction or side effects—welcome news to individuals with PD given their medication burdens.

Limitations of the present study include small sample size and limited range of disease stage (mild to moderate). A larger sample would allow greater statistical power to control for age and for disease duration and severity in our assessment of circadian and sleep contributions to cognitive performance in PD. Without a reference group of non-PD participants, we were also unable to discern any PD-specific associations between rest-activity rhythm, sleep, and cognition. In addition, the potential effects of daily scheduled behaviors and environmental conditions (e.g., work, exercise, food intake, and light exposure), as well as participants' chronotype, should be controlled or accounted for.

Future research should measure circadian function in PD using multiple biomarkers (e.g., melatonin secretion, blood pressure), as well as measure sleep architecture (i.e., using polysomnography), in order to more fully characterize circadian and sleep associations with nonmotor symptoms of PD. Investigators should also prospectively assess changes in rest-activity rhythms and cognition in PD, and test the efficacy of circadian intervention for improving cognitive impairment and other nonmotor symptoms, with the ultimate goal of improving quality of life for those with PD.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. Study procedures were approved by the Boston University Institutional Review Board, and participants provided informed consent.

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