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Hallucinations, dreaming and frequent dozing in Parkinson's disease: Impact of right-hemisphere neural networks

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Abstract

Objective—To relate sleep disturbances in Parkinson's disease (PD) to hemispheric asymmetry of initial presentation.

Background—Sleep disturbances are common in PD arising from the neurodegenerative process underlying the disease, which is usually lateralized at onset. Patients with left-side onset (LPD: right hemisphere dysfunction) exhibit reduced vigilance relative to those with right-side onset (RPD: left hemisphere dysfunction), leading us to hypothesize that sleep-related disturbances, particularly excessive daytime sleepiness, would be more severe for LPD than for RPD.

Methods—Thirty-one non-demented participants with PD (17 RPD and 14 LPD) and 17 age-matched control participants with chronic health conditions (CO) were administered the Parkinson's Disease Sleep Scale and polysomnography was performed on a subset of the PD participants.

Results—Both PD subgroups exhibited more nighttime motor symptoms than the CO group, but only LPD endorsed more nocturnal hallucinations and daytime dozing. Controlling for mood additionally revealed more vivid dreaming in LPD than RPD. There were no significant differences between LPD and RPD on measures of sleep architecture.

Conclusions—Increased dreaming, hallucinations, and daytime somnolence in LPD may be related to changes in right-hemisphere neural networks implicated in the generation and control of visual images, arousal and vigilance. Our results underscore the need to consider side of onset in regard to sleep disturbances in PD.

Keywords

Parkinson's disease; hemiparkinsonism; sleep disturbances; hypersomnia

INTRODUCTION

PD is a neurodegenerative disorder that is characterized by the disruption of dopaminergic projections from the substantia nigra to the basal ganglia. Besides being a motor disorder, it leads to impairments in cognition (1), perception (2) and sleep (3), as well as to neuropsychiatric symptoms (4). Underlying these non-motor deficits are disruptions of the fronto-thalamo-striatal circuit (5) and the cholinergic, noradrenergic and serotonergic systems (6).

Sleep problems are estimated to occur in over 75% of patients with PD over the course of the disease (7–9). The most common are sleep fragmentation, sleep-related breathing disorders, restless legs-periodic leg movements, REM behavior sleep disorder, and sleep-related psychosis (i.e., nocturnal hallucinations). Patients also experience disturbances of arousal, namely sleep attacks and excessive daytime sleepiness (10,11).

Motor signs of PD typically begin on one side of the body. Side of onset is a significant but often overlooked clinical and neuropathological factor in the study of PD. Those patients whose symptoms begin on the left side of the body (LPD) have greater right hemisphere pathology and those with symptoms starting on the right (RPD) have greater left hemisphere pathology (12). Motor-symptom asymmetry in PD predicts visuospatial and vigilance deficits as well as fatigue in LPD (13–18) and poorer verbal memory performance in RPD (16,19). The side of initial onset tends to remain more affected as the disease progresses (20) and the basal ganglia and substantia nigra show considerable neuropathological asymmetry (21).

In the present study, we aimed to relate sleep disturbances in PD to the hemispheric side of onset. As some sleep-related disturbances, such as excessive daytime sleepiness, may precede the manifestation of motor symptoms by several years (22), identifying and treating these sleep problems early may enhance functioning and protect quality of life for patients ultimately diagnosed with PD.

The link between left-onset symptoms and reductions in vigilance led us to hypothesize that sleep disturbances, particularly excessive daytime sleepiness, would be more severe in LPD than RPD. Group differences were examined on a variety of sleep disturbances using the Parkinson's Disease Sleep Scale (PDSS) (23) and sleep architecture using overnight polysomnography (PSG).

METHODS

Participants

Thirty-one patients with PD (30 men, 1 woman) were recruited from the outpatient Movement Disorders Clinic at the Veterans Administration Boston Healthcare System. Seventeen age-matched control subjects (CO) (10 men, 7 women) were recruited from the VA community. The study was approved by the Boston University Medical Center and Veterans Administration Institutional Review Boards and all participants provided informed consent. Individuals meeting DSM-IV (24) or Emre and colleagues' (2007) criteria (25) for dementia or those who scored 23 or below on the Mini-Mental State Examination (MMSE) (26) were excluded, as were those with a history of substance abuse, head injury or Post-traumatic Stress Disorder. None of the patients met criteria for Dementia with Lewy Bodies as per McKeith and colleagues (2006). All control participants presented with a chronic debilitating condition including chronic back pain, diabetes, or cancer but not any neurological disorders.

PD medication information was obtained by the neurologist (R.D.) and levodopa equivalent dosages were calculated based on previous reports with 100 mg levodopa=83 mg levodopa with a COMT inhibitor=1 mg pramipexole=1 mg pergolide (27). All PD patients were taking levodopa and 22 were on dopamine agonists (10 RPD, 12 LPD). In addition, two RPD and one LPD were taking selegiline, one RPD and two LPD were taking amantadine. No participant was taking anticholinergic medication. Side of motor symptom onset was obtained by patient report and motor examination by the neurologist. Motor symptom severity was quantified using the Unified Parkinson's Disease Rating Scale (UPDRS) (28) and Hoehn and Yahr stage (29). Asymmetry was calculated as the sum of scores of right and left-sided UPDRS items measuring tremor, rigidity, finger taps, alternating hand movements, leg agility and arm swing (30,31).

Measures

PD and Control groups—Mood was assessed using the Depression Anxiety and Stress Scale (DASS) (32,33). The measure consists of 21 questions in three subscales of depression, anxiety and stress, and a total mood score, with higher scores indicating greater impairment.

Subjective sleep complaints were assessed using the Parkinson's Disease Sleep Scale (PDSS) (23), a simple screening measure of sleep disturbances. To date, the PDSS is the only formal, validated instrument designed to quantify various aspects of sleep problems in PD. It has been used in identifying sleep disturbances such as sleep maintenance insomnia and excessive daytime sleepiness (34). The scale consists of 15 common symptoms. A score of 0 indicates worse symptoms/poorer quality of sleep and 10 indicates no symptoms/better quality of sleep. In the current study, the 15 items were examined as nine factors comprising composite scores of the individual items, as described elsewhere (23). The factors were overall quality of sleep, sleep onset and maintenance insomnia, nocturnal restlessness, nocturnal hallucinations, distressing/vivid dreams, nocturia, nocturnal motor symptoms (including sensory complaints, early morning dystonia and cramps during the night), sleep refreshment, and daytime dozing.

PD group—Standard overnight polysomnography was performed on 11 RPD and 7 LPD who agreed to participate, at the General Clinical Research Center of the Boston University Medical Center. The electroencephalogram (EEG) was recorded from the C3 and C4 electrodes and was referenced to an average of A1 and A2. The polysomnography monitored body functions including brain electrical activity (EEG), eye movements (electro-oculogram), muscle activity (electromyogram), and respiratory effort. Number of awakenings, sleep latency and total sleep time (minutes), Stages REM, 1, 2, 3, 4, sleep efficiency, wake-time after sleep onset (minutes) were calculated with *Compumedics ProFusion PSG2 Software*.

Statistical Analyses

Analyses of variance (ANOVA) were performed to examine differences between the RPD, LPD and CO groups followed by post-hoc analyses when indicated. For variables relevant only to the PD groups (e.g., motor symptom asymmetry, medication dosages, polysomnographic measures), Bonferroni-corrected independent-sample t-tests were performed. These analyses were followed by analyses of covariance (ANCOVA) controlling for total mood score (DASS-total). Multiple regression analyses were conducted using PDSS-derived sleep factors as criterion variables and group and DASS-total as predictor variables. Finally, all analyses were repeated excluding women because of their low representation in the sample.

RESULTS

Clinical and demographic characteristics of the groups are presented in Table 1. There were no significant differences between groups in age, education, or MMSE. RPD presented with significantly higher DASS-stress, DASS-anxiety and DASS-depression scores than the CO group, but no differences were found between the LPD and CO or between the two PD groups. There were no significant differences between RPD and LPD in disease severity as indexed by Hoehn and Yahr stage ($\chi^2=4.32$, $p=.12$) or duration ($t[28]=.75$, $p=.46$). As expected, on the UPDRS, RPD presented with greater motor symptom severity on the right side and LPD on the left side. RPD group had a higher total UPDRS score than LPD ($t[13]=-2.5$, $p=.03$). The PD groups did not differ in levodopa dosage equivalents of dopaminergic medication ($t[27]=.22$, $p=.83$).

The results of the sleep questionnaire are reported in Table 2. There were overall group differences in the PDSS total score ($F[.45]=5.03$, $p=.01$), nocturnal hallucinations ($F[2,45]=5.87$, $p=.005$), nocturia ($F[2,45]=3.2$, $p=.048$), nocturnal motor symptoms ($F[2,45]=5.91$, $p=.$

005) and daytime dozing ($F[2,45]=9.19$, $p<.0001$). RPD and LPD both endorsed more symptoms than CO on the PDSS total ($p=.04$ and $p=.02$, respectively). LPD reported significantly greater frequency of nocturnal hallucinations than CO ($p=.004$), whereas RPD did not differ from CO ($p=.13$). There was a trend toward LPD endorsing more symptoms of nocturia than CO ($p=.06$), but no differences were apparent between the PD groups ($p=1.0$) or between RPD and CO ($p=.21$). Both PD groups reported significantly more frequent nocturnal motor symptoms than CO (RPD $p=.01$; LPD $p=.02$) but did not differ from each other ($p=1.0$). Relative to CO, LPD showed more frequent daytime dozing ($p<.0001$), with RPD showing a similar trend ($p=.06$).

Because RPD presented with higher stress, anxiety and depression scores than LPD or CO, and all three mood scores were negatively associated with items on the PDSS, analyses were repeated with overall mood score (DASS-total) as a covariate. The three groups were significantly different on nocturnal hallucinations ($F[1,44]=4.86$, $p=.01$), daytime dozing ($F[1,44]=7.01$, $p=.002$) with a trend for frequency of vivid dreams ($F[1,44]=2.89$, $p=.07$) (Figure 1). The groups no longer differed on the PDSS total ($F[2,44]=2.04$, $p=.14$) and nocturia ($F[2,44]=2.12$, $p=.13$). Post-hoc analyses revealed significant differences between LPD and CO ($p=.007$) but not between RPD and CO ($p=.65$) on nocturnal hallucinations. LPD reported more hallucinations than RPD ($p=.02$). LPD reported significantly more distressing dreams than RPD ($p=.02$) with no differences between either PD group and CO (RPD $p=.32$; LPD $p=.20$). Similarly for daytime dozing, no differences were found between RPD and CO ($p=.16$), but LPD reported more frequent daytime dozing than CO ($p=.001$) and RPD ($p=.01$).

To investigate whether the higher frequency of vivid dreaming, hallucinations and daytime dozing in LPD was associated with disease severity, Spearman rank-order correlations were performed for LPD and RPD separately. No significant correlations were found between Hoehn & Yahr stage and any of these symptoms for either group ($p > 0.1$ in each case). For the UPDRS total score, Pearson correlation was significant with vivid dreaming for LPD ($p=.02$) but not RPD ($p=0.5$). Hallucinations and daytime dozing were not correlated with UPDRS total for either PD group ($p > 0.2$ in each case). No association was found between the UPDRS asymmetry score for right and left side and hallucinations, vivid dreams or daytime dozing ($p>0.1$).

All of the above analyses were repeated excluding women because of their low representation in the sample. All significant differences between the three groups remained for all of the above analyses. Further, frequency of vivid dreams became significantly different ($F[2,37]=3.97$, $p=.03$) across groups, with LPD reporting more vivid dreams than CO ($p=.02$) but no differences between CO and RPD ($p=.49$) nor between the PD groups ($p=.21$).

Polysomnographic findings are reported in Table 3. Two RPD presented with a respiratory distress index (RDI) above 30, indicating the presence of severe obstructive sleep apnea. Two additional RPD presented with an RDI of 12.2 and 15.8, indicating mild obstructive sleep apnea. No other patient showed respiratory distress indicative of sleep apnea. Analysis of sleep EEG findings demonstrated a virtual absence of slow-wave sleep (Stages III and IV), normal amounts of REM, and 'light' Stage II sleep. Bonferroni-corrected t-tests revealed no significant group differences for any of the measures of sleep architecture. No differences in demographic, clinical variables or PDSS sleep measures were found between the subset of the PD patients who participated in the overnight study and the entire sample of participants.

DISCUSSION

To our knowledge, this is the first report that significant sleep disturbances in PD are related to the side of motor symptom onset. After controlling for mood scores, we found that both

RPD and LPD reported more frequent sleep disturbances than did the control group. LPD experienced more nocturnal hallucinations, disturbing dreams, and excessive daytime sleepiness than RPD. The differences between LPD and RPD were not accounted for by differences in age, disease severity, medication type or dosage, as the groups did not differ on any of these factors, nor in mood, as all analyses were performed after adjusting for differences in mood scores. The differences between LPD and RPD in self-reported sleep disturbances were not accounted for by differences in EEG-measured sleep architecture as no such differences emerged when overnight polysomnography was performed. In addition, the greater frequency of reported daytime dozing in LPD than RPD cannot be accounted for by obstructive sleep apnea, as polysomnographic findings revealed the presence of sleep apnea in four patients with RPD and none with LPD.

Though the physiological substrates of hallucinations and dreaming are yet to be completely understood, there is some evidence that in PD, vivid dreaming and sleep disruptions may serve as precursors to hallucinations (35,36). Dreaming and visual hallucinations are related to REM sleep and may be mediated by the ponto-geniculo-occipital (PGO) waves (37,38) that have been detected in animals during REM sleep and implicated in dream-related internal stimulus generation and visual perceptions (39,40). Because the PGO generator (nucleus pedunculopontinus) and other brainstem regions directly involved in the control of sleep/wake cycles are linked to the neurodegenerative process of PD (41), it has been suggested that abnormal PGO activity could be responsible for generation of vivid dreaming as well as hallucinations during wakefulness in these patients (38).

The basal ganglia may play an important role in regulating sleep/wake activity. Neuroimaging studies in healthy adults have demonstrated particularly robust increases in activation of the basal ganglia during transition from wakefulness to slow wave and to REM sleep (42). The basal ganglia are involved in the mediating network that connects the brainstem to the cortex and this network contains multiple back-projections to the pedunculopontine tegmentum. The role of the basal ganglia in sleep/wake activity may therefore be the regulation of ascending thalamocortical activation and rostral transmission of PGO waves from the brainstem through the thalamus to the forebrain (42,43).

Alterations in right-hemispheric cortical activation via asymmetrical basal ganglia functioning may explain disturbed visual processing and more frequent dreaming in patients with LPD. The basal ganglia neural networks are part of the thalamocortical circuit projecting to cortical areas involved in higher-order visual processing (44). Imaging studies of patients with Dementia with Lewy Bodies and of patients with PD have demonstrated selective activation of right-hemisphere brain regions (i.e., right parietal and temporal areas) (45,46) in patients with visual hallucinations. In normal adults, despite the general deactivation of the parietal and frontal cortices during REM sleep dreaming, there is selective activation of the right parietal operculum (47). In LPD, abnormal functioning of the basal ganglia-thalamocortical circuitry may increase the thalamic input to right temporo-parietal areas (48) and lead to abnormal PGO activity (38). Consequently, these alterations in right-hemispheric cortical activation may result in disturbed visual processing and more frequent dreaming in patients with LPD.

Right-hemisphere dysfunction may also account for more frequent daytime dozing in LPD. Excessive daytime sleepiness is a common non-motor symptom that occurs in approximately 30% of non-demented patients with PD (49). Right-hemisphere neural networks have been implicated in arousal and vigilance levels in healthy adults (50–52), and these right-hemisphere vigilance functions are particularly sensitive to sleep deprivation (53). There is also evidence for a functional deterioration of the fronto-temporo-parietal network in the right hemisphere of patients with narcolepsy, a disorder characterized by the loss of hypocretin-secreting neurons (54). Although no studies have examined laterality in the loss of hypocretin neurons of the

hypothalamus, in patients with PD there is significant loss of these neurons (55), increasing with disease severity and progression (56). Impairment in right-hemisphere functions consequently could account for more frequently reported excessive daytime sleepiness in LPD.

Hallucinations and excessive daytime sleepiness in PD are considered by some to be a side effect of dopaminergic medication rather than a part of the disease process. Several studies have demonstrated, however, that hallucinations are not related to dose or duration of medication (57–60) and high-dose levodopa infusions do not induce hallucinations in PD (61). With respect to daytime sleepiness, though, there is compelling evidence for dopaminergic medication as a direct cause of drowsiness (62,63); it is clear that other disease-related factors may also contribute to the development of daytime somnolence (22,64–67). In our sample, daytime sleepiness and hallucinations in LPD alone could not be attributed solely to the use of dopaminergic medications, as there were no LPD-RPD differences in dose of either levodopa or dopamine agonists.

An important limitation of our study is the low representation of women, especially in the PD groups. Gender differences have been reported for non-motor symptoms of PD, with women presenting more often with depression and men presenting more often with behavioral disturbances (68). Likewise, gender differences appear to exist for sleep disorders, with women reporting a higher prevalence of insomnia and restless legs syndrome, whereas REM behavior sleep disorder, characterized by loss of normal muscle atonia and acting-out of dreams, is more common in men (69). Underlying the gender differences in both sleep and non-motor symptoms of PD may be distinct pathophysiological mechanisms, which underscores the importance of including both men and women in future studies of the etiology and symptomatology of PD.

In our sample, RPD presented with higher scores on a measure of stress, anxiety and depression than did the LPD and control group. In all three groups, these symptoms were related to the subjective sleep disturbances, with those endorsing more mood symptoms also reporting higher frequency of sleep-related problems. There is evidence that mood symptoms impact sleep complaints in both younger and older adults, with those expressing a greater degree of sleep problems also reporting more mood symptoms such as depression and anxiety (70). In the current study, adjusting for mood symptoms highlighted significant differences between patients with LPD and RPD on the dreams, hallucinations and daytime dozing items of the sleep questionnaire, thereby emphasizing the group differences in sleep disturbances that are intrinsic to the disease rather than secondary to other disease-related symptoms such as depression and anxiety (71).

The current study did not find any hemispheric differences in sleep architecture between LPD and RPD. Polysomnography limited to 24 hours, however, may have missed important sleep disorders that are common in PD, namely REM behavior sleep disorder and restless legs syndrome. In light of the current finding of side-of-onset differences in sleep-related disturbances, it is important for future studies examining a wider range of objective sleep measures in PD to consider side of symptom onset.

In summary, we found an effect of side of motor symptom onset on sleep disturbances in PD. In particular, there were differences in the frequency of reported distressing/vivid dreams, hallucinations and daytime dozing. Research is needed to understand how the side of symptom onset is related to specific sleep disorders such as REM behavior sleep disorder and restless legs syndrome, which are common in PD and are likely related to the neuropathologic process of the disease. Elucidating the etiology of sleep disturbances in PD is important as identification and early treatment of these disturbances may substantially enhance the quality of life in patients with this disease.

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Figure 1.

Mean frequency of nocturnal hallucinations, vivid dreaming and daytime dozing in CO, RPD and LPD groups. * Indicates differences between LPD and CO groups after controlling for mood; ** indicates differences between LPD and RPD after controlling for mood. No differences were found between RPD and CO on these variables. *In the standard version of the questionnaire, higher numbers indicate lower frequency of symptoms. For greater clarity of interpretation, we modified the scale so that higher numbers indicate higher frequency of symptoms.*

Table 1

Demographic and clinical characteristics of control subjects (CO), patients with right-side onset PD (RPD) and patients with left-side onset PD (LPD). Means (SD) are reported.

	CO (n=17)	RPD (n=17)	LPD (n=14)
Age (in years)	65.6 (7.5)	71.5 (12.1)	67.6 (10.6)
Education (in years)	15.2 (2.0)	13.3 (2.7)	13.8 (2.7)
MMSE	27.9 (1.6)	26.4 (2.2)	26.5 (2.5)
DASS total mood score	5.76 (4.5)	17.1 (11.4) ^a	12.4 (9.2)
Hoehn & Yahr stage [^]	n/a	2.00 (2.0–4.0)	3.00 (1.0–3.0)
UPDRS right total	n/a	7.35 (2.4)	3.43 (3.1) ^b
UPDRS left total	n/a	3.18 (1.6)	5.86 (3.0) ^b
UPDRS total	n/a	19.7 (5.0)	13.3 (4.5) ^b
Disease duration	n/a	6.76 (4.2)	8.15 (5.9)
Levodopa equivalent dose (mg/day)	n/a	477.4 (219.4)	499.7 (328.3)

^aSignificant difference from CO at p<.01 level

^bSignificant difference from RPD at p<.01 level

[^]Median (range) is reported

MMSE - Mini-Mental Status Examination; DASS - Depression, Anxiety and Stress Scale.

Table 2
A comparison of sleep factors in patients with right and left side of onset PD as assessed with the Parkinson's Disease Sleep Scale (PDSS). Data is reported from the entire sample and only patients who completed overnight PSG. A higher score indicates less frequent symptoms, whereas a lower score indicates more frequent symptoms. Means (SD) are reported.

	CO (n=17)	RPD (n=17)	LPD (n=14)	RPD (PSG) (n=9)	LPD (PSG) (n=10)
Quality	5.71 (2.0)	5.35 (3.1)	5.21 (2.7)	6.00 (3.00)	5.00 (2.8)
Insomnia	12.2 (4.5)	12.4 (4.9)	12.6 (4.6)	13.3 (4.7)	13.2 (4.9)
Restlessness	16.4 (4.0)	13.6 (5.5)	15.5 (3.6)	15.2 (3.8)	16.5 (3.5)
Dreams	8.29 (1.9)	8.35 (1.3)	6.93 (2.7) ^d	8.33 (1.4)	7.30 (3.0)
Night hallucinations	9.94 (.24)	9.18 (1.3)	8.00 (2.5) ^{bcd}	9.11 (1.7)	7.70 (2.83)
Nocturia	14.8 (3.7)	12.2 (3.7)	11.2 (5.1)	11.9 (4.5)	10.8 (5.9)
Motor symptoms	36.0 (5.0)	27.8 (8.1) ^a	27.8 (10.3) ^b	27.3 (8.5)	26.9 (12.1)
Refreshment	7.12 (2.2)	5.29 (3.1)	5.79 (2.7)	6.22 (4.49)	6.10 (2.73)
Daytime dozing	7.82 (2.1)	5.59 (3.0)	3.71 (2.9) ^{bcd}	5.67 (2.78)	3.10 (3.0)
PDSS total	118.2 (16.6)	99.6 (24.1) ^d	95.8 (21.6) ^b	102.9 (24.3)	96.6 (24.4)

^a Significant difference from CO at p <.05 level

^b Significant difference from CO at p <.01 level

^c Significant difference from CO when controlling for DASS total at p <.05 level

^d Significant difference from RPD when controlling for DASS total at p <.05 level

DASS - Depression, Anxiety and Stress Scale; PSG - polysomnography

Table 3

A comparison of sleep architecture in patients with RPD and LPD. Means (SD) are reported.

	RPD (n=11)	LPD (n=7)
RDI	16.6 (21.7)	2.8 (3.4)
Number Awakenings	27.8 (13.4)	28.4 (10.6)
WASO (in mins)	108.2 (49.3)	128.9 (48.6)
Sleep Latency (in mins)	29.5 (32.0)	19.1 (19.2)
Total Sleep time (in mins)	278.6 (59.9)	310.3 (67.6)
Sleep Efficiency	.623 (.14)	.662 (.13)
Stage REM	.124 (.10)	.106 (.04)
Stage 1	.151 (.16)	.219 (.12)
Stage 2	.645 (.17)	.626 (.12)
Stage 3	.054 (.04)	.038 (.05)
Stage 4	.026 (.05)	.011 (.02)

WASO - Wake Onset Sleep Latency; REM - Rapid Eye Movement; RDI –Respiratory Distress Index