Psychosis in Parkinson's Disease Without Dementia: Common and Comorbid With Other Non-Motor Symptoms

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Abstract

Psychosis in Parkinson's disease (PD) is common and associated with a range of negative outcomes. Dementia and psychosis are highly correlated in PD, but the frequency and correlates of psychosis in patients without cognitive impairment are not well understood. One hundred and ninety-one non-demented PD patients at two movement disorders centers participated in a study of neuropsychiatric complications in PD and completed a detailed neurological and neuropsychiatric assessment, including the rater-administered Parkinson Psychosis Rating Scale for hallucinations, delusions, and minor symptoms of psychosis (illusions and misidentification of persons). Psychotic symptoms were present in 21.5% of the sample. Visual hallucinations were most common (13.6%), followed by auditory hallucinations (6.8%), illusions or misidentification of people (7.3%), and paranoid ideation (4.7%). Visual hallucinations and illusions or misidentification of people were the most common comorbid symptoms (3.1%). Depression ($P = 0.01$) and rapid eye movement behavior disorder symptoms ($P = 0.03$) were associated with psychosis in a multivariable model. The odds of experiencing psychotic symptoms were approximately five times higher in patients with comorbid disorders of depression and sleep-wakefulness. Even in patients without global cognitive impairment, psychosis in PD is common and most highly correlated with other non-motor symptoms. Screening for psychosis should occur at all stages of PD as part of a broad non-motor assessment. In addition, these findings suggest a common neural substrate for disturbances of perception, mood, sleep-wakefulness, and incipient cognitive decline in PD.

Keywords

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Numerous psychiatric and other non-motor complications are common in Parkinson's disease (PD). In cross-sectional studies, the most prevalent and well-studied disorders in specialty care settings are depression (20%–40%), dementia (20%–30%), and psychosis (15%–30%),[1–3] but the cumulative prevalence of these disorders is much higher.[4] In a recent study, up to 60% of community-based PD patients experienced delusions or hallucinations over the course of approximately a decade.[5]

In addition to being highly prevalent, psychosis in PD (PD-P; i.e., hallucinations, delusions, or minor symptoms [e.g., sense of presence, visual illusions, or passage hallucinations][6]) is a challenging clinical problem because it has been found to increase caregiver stress and is the main risk factor for nursing home placement.[7] Regarding risk factors, PD-P has generally been linked to PD medications since the introduction of levodopa in the mid-1960s.[8] However, recent research has suggested that the etiology of PD-P is complex. Though many studies have examined the effect of dopamine replacement therapy on PD-P, a small number have examined other potential correlates of psychosis, such as dementia, comorbid psychiatric illness, and sleep disorders.[7]

More specifically, there are limited studies examining the frequency and correlates of PD-P in non-demented patients. A recent study[9] did examine "thought disorders," defined by vivid dreams, hallucinations, delusions, and/or psychosis based on a single Unified Parkinson's Disease Rating Scale (UPDRS) item, in non-demented patients. The study found that thought disorders were associated with increasing PD duration, depressive and dysautonomic symptoms, and lower Mini–Mental State Examination[10] (MMSE) scores. However, psychosis was not evaluated using a specific psychosis instrument, and the cut-off score used to characterize patients as non-demented was low, likely leading to inclusion of patients with significant cognitive impairment in the study sample. In another recent study[11] of hallucinations in non-demented patients, in a multivariate model, neuropsychiatric symptoms were associated with the presence of psychosis, but this study examined only hallucinations and used a global measure (i.e., the Neuropsychiatric Inventory[12]) to assess neuropsychiatric symptoms.

Because psychosis is a risk factor for the development of PD dementia[13] and mortality,[14] recognition of psychosis before the onset of significant cognitive impairment would help identify patients at increased risk of subsequent cognitive decline. In addition, identification of other clinical and demographic factors associated with PD-P might allow for the development of a patient risk profile for psychosis, facilitating the identification of psychosis at an early stage and identifying patients who may have a supra-additive risk for subsequent cognitive decline.

The main aims of this study were (1) to examine the frequency of PD-P in patients without dementia and (2) to determine the clinical and demographic factors independently associated with psychosis in this PD subgroup.

Patients and Methods

Subjects

The study population was drawn from a larger group of 242 subjects with complete data who were established patients with a diagnosis of PD[15] at the Parkinson's Disease Centers at the University of Pennsylvania (Philadelphia, Pennsylvania, USA) or the Philadelphia Veterans Affairs Medical Center (VAMC; Philadelphia, Pennsylvania, USA). Participants were evaluated as part of a study of the frequency and correlates of psychiatric and cognitive disorders in PD. A non-demented group of 191 subjects was defined by having an MMSE score 28, including 5 (2.6%) who were taking an antipsychotic. An MMSE cut-off score

<28 has been shown to have 100% sensitivity and 100% negative predictive value for a diagnosis of PD dementia,[16] so a study population only including an MMSE score 28 should not include any patients with dementia. For consistency and to avoid underestimates, the 5 patients taking an antipsychotic were included in the psychosis cohort, although 1 of the 5 patients did not endorse current psychosis at the time of evaluation. The final non-demented study population consisted of 191 outpatients (N = 155 at the University of Pennsylvania; N = 36 at the Philadelphia VAMC). The typical study participant was an older white male (Table 1).

Procedures

The institutional review boards at the University of Pennsylvania and the Philadelphia VAMC approved the study, and written informed consent was obtained before study participation. A trained research assistant administered the psychiatric and neuropsychological instruments and conducted a chart review. When available, collateral information about the presence of psychotic symptoms was obtained from an informed other(s). Neurological assessments were completed by movement disorder neurologists, nurses with expertise in PD, or a geriatric psychiatrist (D.W.) with training in the administration of neurological assessments.

Measures

Demographic and Clinical Characteristics—As part of the screening process, patients provided the following information: age, sex, race, marital status, years of formal education, duration of PD, and current PD medications. Levodopa dosage was recorded as levodopa equivalent daily dosages (LEDDs).[17]

Neurological—Severity of PD was assessed with the UPDRS[18] motor section (UPDRS part III; range = 0–108, with higher scores indicating greater motor impairment). Severity of disease was also measured based on the duration of illness and the Hoehn and Yahr (H & Y) scale (range = 0–5, with higher range indicating more severe disease).[19] For between-group comparisons, the median Hoehn and Yahr score was used instead of mean because of non-normality of the data.

Psychiatric—Current (i.e., past week) psychosis was assessed with a modified[20] Parkinson's Psychosis Rating Scale (PPRS),[21] originally a six-item clinician-administered questionnaire (range = 6–24, with higher scores indicating greater severity of psychosis) that fulfills criteria as a suggested scale for rating PD psychosis.[22] Only the three PPRS items covering "visual hallucinations," "illusions and misidentification of persons," and "paranoid ideation" (i.e., persecutory and/or jealous type of delusional thinking) were considered as symptoms of psychosis, because the items for "sleep disturbance," "confusion," and "sexual preoccupation" are not clearly symptoms of psychosis and are more likely the result of comorbid dementia, delirium, or impulse control disorder. In addition, an item for auditory hallucinations was added, creating a modified four-item instrument with a range from 4 to 16 (with higher scores indicating greater severity of psychosis).[20] For the aims of this study, a subject was considered to be experiencing psychosis if any of these four items was endorsed. Therefore, we included symptoms typically considered to be "minor" symptoms of psychosis, consistent with recent research.[6]

Depression was assessed with the 30-item Inventory for Depressive Symptomatology (IDS),[23] a rater-administered depression rating scale (range = 0–84, with higher scores indicating greater severity of depression). An IDS cutoff of 14, which has demonstrated good sensitivity and specificity for a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*[24] diagnosis of depression,[25] was used to indicate the presence

of clinically significant depression. Anxiety was measured using the Spielberger State Anxiety Inventory[26] (SAI; range = 20–80, with higher scores indicating greater anxiety severity).

Sleep disorder symptoms were assessed with a modified Parkinson's Disease Sleep Scale (PDSS),[27] with the visual analog scale converted to a 4-point Likert scale (a range from 0 to 3 for each item, with higher score representing increasing severity of symptom). The two items for rapid eye movement sleep behavior disorder (RBD) and distressing dreams or nightmares were summed to calculate the severity of RBD symptoms (range, 0–6, with higher scores indicating greater severity of sleep symptoms). Excessive daytime sleepiness (EDS) was assessed with the Epworth Sleepiness Scale (ESS)[28] (range = 0–24, with higher scores indicating greater daytime sleepiness). Apathy was measured with the Apathy Scale[29] (AS; scores, 0–42, with higher scores indicating greater apathy severity).

Cognitive Assessment—Global cognitive abilities were assessed with the MMSE (scores, 0–30, with lower scores indicating increasing severity of cognitive impairment).[10]

Statistical Analysis

All analyses were conducted using the PASW Statistics (*version 20.0*) software.[30] Bivariate comparisons between psychotic and nonpsychotic subjects were made using a two-sample *t* test (for continuous variables), the chi-square test (for categorical variables), or a nonparametric test. Variables associated with psychosis at *P* value <0.10 on bivariate analysis were included in multivariate analyses using logistic regression models, with only a single variable entered at a time for variables demonstrating multicollinearity (i.e., correlation >0.6). Given that Hoehn and Yahr stage and UPDRS motor score are both measures of disease severity, only one was entered into a given model. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported for logistic regression models. A *P* value 0.05 was considered to be significant for all analyses.

Results

Subject Characteristics

A total of 191 non-demented subjects were included in the sample. Mean participant age was 63.1 years, and 71.7% were male (Table 1). Average duration of PD was 6.4 years, with a median Hoehn and Yahr stage of 2.0.

Psychotic symptoms were present in 21.5% of the sample. Specifically, visual hallucinations were most common (13.6%), followed by auditory hallucinations (6.8%) and illusions or misidentification of people (7.3%). Paranoid ideation was the least common symptom (4.7%). Of those with two psychotic symptoms, visual hallucinations and illusions or misidentification of people co-occurred most commonly (3.1%). Visual and auditory hallucinations occurred together in 1.6% of the subjects. Of those experiencing three psychotic symptoms, visual hallucinations, auditory hallucinations, and illusions or misidentification of people co-occurred most commonly (1.1%).

Mean IDS score was 18.5 and mean SAI score was 39.2, suggesting mild depressive and anxiety symptoms, on average. Mean RBD score was only 1.0, but RBD symptoms of some intensity were present in approximately 50.0% of patients. Mean ESS score was 9.9, which is at the cutoff for clinically significant EDS symptoms. Mean apathy score was 11.7, indicating mild severity of apathy overall. Correlations were high between depression and anxiety (Pearson's r = 0.79), anxiety and apathy (Pearson's r = 0.62), and depression and apathy (Pearson's r = 0.61).

Mean (standard deviation [SD]; range) MMSE score was 29.2 (0.8; 28–30), suggesting intact global cognitive abilities on average, to be expected given that we restricted the sample to patients with MMSE scores ≥ 28.

Variables Associated With Psychosis on Bivariate Analysis

Increasing Hoehn and Yahr score ($P = 0.05$), duration of disease ($P = 0.005$), and UPDRS motor score ($P = 0.03$) were all associated with occurrence of psychosis (Table 2). For PD medications, there was a trend effect for levodopa LEDD ($P = 0.06$), but no association with dopamine agonist treatment.

Regarding non-motor symptoms, increasing severity of depression ($P < 0.001$), anxiety ($P < 0.001$), RBD symptoms ($P = 0.002$), daytime sleepiness ($P = 0.001$), and apathy ($P = 0.008$) were all correlated with psychosis. Lower MMSE score had a trend effect with psychosis, but was not statistically significant ($P = 0.09$).

Independent Predictors of Psychosis

Based on the variables found to be associated with psychosis on bivariate analysis and entering single variables when a pair of variables demonstrated multicollinearity (i.e., depression overlapped with anxiety and apathy), we performed multivariable logistic regression analyses (with presence of psychosis as the dependent variable) that included duration of disease, Hoehn and Yahr stage, levodopa LEDD, IDS score, RBD score, ESS score, and MMSE score as independent variables.

In the multivariable model (Wald's chi-square = 49.23; df = 1; $P < 0.001$), IDS score ($P = 0.01$), and RBD score ($P = 0.03$) were associated with psychosis (Table 3). Higher Hoehn and Yahr stage ($P = 0.06$) and ESS score ($P = 0.07$) demonstrated a trend association with psychosis. SAI score was also found to be associated with psychosis (OR, 1.04; 95% CI: 1.01–1.07; $P = 0.02$) when substituted for IDS in the model.

Effect of Comorbid Affective and Sleep-Wakefulness Disorders

Given the significant findings and reported overlap between depression and disorders of sleep-wakefulness in PD, we created a new variable for patients with both a depressive disorder and a disorder of sleep-wakefulness (i.e., for the latter, either any positive RBD score or an ESS score ≥ 10). Entering this variable into a logistic regression model with the same covariates demonstrated that patients with this combination of neuropsychiatric symptoms had nearly five times greater odds of experiencing psychosis (OR = 4.6; 95% CI: 2.05–10.30; $P < 0.001$).

Discussion

Although there is extensive literature on the frequency and correlates of psychosis in PD, the unique aspects of this study were a relatively large sample size, the focus on non-demented patients defined by a high cut-off score on the MMSE, the use of a psychosis rating scale, and the inclusion of detailed assessments for a range of other non-motor symptoms. Because cognitive impairment and dementia is a strong correlate of psychosis in PD,[5] our aim was to better determine the frequency and predictors of psychosis in patients without significant impairment, a subgroup of PD patients in whom psychosis might be both over-looked and have a different etiology.

The etiology of psychosis in PD appears to be complex. Models for the pathogenesis of psychosis in PD include both cortical and subcortical involvement and roles for multiple neurotransmitters (e.g., dopamine, serotonin, and acetylcholine), genetics, visual-processing

abnormalities, PD medications, sleep-wake cycle dysregulation, and cognitive impairment.[5,31–33] Not surprisingly, given our high MMSE cut-off score, global cognition was not associated with psychosis in our sample. Instead, we found that four common non-motor symptoms (i.e., depression, anxiety, RBD symptoms, and apathy, with a trend for daytime sleepiness) were associated with psychosis, even in multivariable models. One recent study in early PD patients[34] reported mixed findings for the association between psychosis and depression, psychosis, and RBD symptoms, and neuropsychiatric symptoms in multivariable analyses were not associated with the development of psychosis.

Our research suggests that hallucinations are common in non-demented PD patients, affecting approximately 20%–25% of patients, which is different than recent research that utilized less sensitive and specific psychosis measures[9] or only studied early-stage patients.[34] In addition, we found that age and PD medications were not associated with psychosis in non-demented patients, which suggest different risk factors for psychosis when patients with dementia are excluded. Rather, a range of non-motor symptoms seem to be the most significant correlate of psychosis in this group. By combining these variables, we found that those patients with both depression and a disorder of sleep-wakefulness had a significantly higher chance of being diagnosed with comorbid psychosis (OR = 4.6).

These findings in non-demented patients suggest a common neural substrate for psychosis, affective symptoms, and sleep-wakefulness disorders in PD at a stage of the illness where the pathology is predominantly in the brainstem, midbrain, basal forebrain, and dorsal striatum.[35] Overlapping with the purported neural substrate of psychosis, mild cognitive deficits are relatively common in early PD and such cognitive deficits are associated with striatal dysfunction, midbrain cholinergic deficits, and, possibly, brainstem noradrenergic deficits.[36] Depression and anxiety symptoms in PD are common early in the course of PD, at times occurring even before the onset of motor symptoms, and are associated with midbrain monoaminergic changes.[37,38] Finally, disorders of sleep-wakefulness are associated with psychosis[39] and are linked with brainstem deficit in neurodegenerative diseases.[40,41]

Several limitations are worth noting. First, our findings are not applicable to the more general PD population, because the sample was predominantly elderly white males receiving specialized care. Second, our study was not a longitudinal study, so we cannot determine true risk factors for the development of psychosis. Third, the use of the MMSE as the global cognitive measure means that some patients likely had mild cognitive deficits in spite of normal MMSE scores. Finally, we did not have data available for all variables reported to be associated with psychosis in PD (e.g., measures of visual processing).

Conclusion

In summary, we found that psychosis is still relatively common in non-demented PD patients, with a range of non-motor symptoms most strongly associated with its occurrence. Comorbid psychiatric and other non-motor symptoms may herald the earliest stage of more serious psychiatric symptoms and cognitive decline in PD,[42] and future longitudinal studies examining predictors of long-term cognitive decline in this population should include a detailed assessment of a range of psychiatric and other non-motor symptoms.

Acknowledgments

References

1. Lauterbach EC. The neuropsychiatry of Parkinson's disease and related disorders. Psychiatr Clin North Am. 2004; 27:801–825. [PubMed: 15550293]

2. Aarsland D, Larsen JP, Lim NG, et al. Range of neuropsychiatric disturbances in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1999; 67:492–496. [PubMed: 10486397]

3. Schrag A. Psychiatric aspects of Parkinson's disease: an update. J Neurol. 2004; 251:795–804. [PubMed: 15258780]

4. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sørensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol. 2003; 60:387–392. [PubMed: 12633150]

5. Forsaa EB, Larsen JP, Wentzel-Larsen T, et al. A 12-year population-based study of psychosis in Parkinson disease. Arch Neurol. 2010; 67:996–1001. [PubMed: 20697051]

6. Fenelon G, Soulas T, Zenasni F, de Langavant LC. The changing face of Parkinson's disease-associated psychosis: a cross-sectional study based on the new NINDS-NIMH criteria. Mov Disord. 2010; 25:763–766. [PubMed: 20437542]

7. Friedman JH. Parkinson's disease psychosis 2010: a review article. Parkinsonism Relat Disord. 2011; 16:553–560. [PubMed: 20538500]

8. Fénelon G, Goetz CG, Karenberg A. Hallucinations in Parkinson disease in the prelevodopa era. Neurology. 2006; 66:93–98. [PubMed: 16401853]

9. Debs R, Cochen De Cock V, Negre-Pages L, Aristin M, Senard A, Rascol O. Thought disorders among non-demented outpatients with Parkinson's disease: prevalence and associated factors. J Neural Transm. 2010; 117:1183–1188. [PubMed: 20803301]

10. 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; 12:189–198. [PubMed: 1202204]

11. Svetel M, Smiljkovi T, Pekmezovi T, Kosti V. Hallucinations in Parkinson's disease: cross-sectional study. Acta Neurol Belg. 2012; 112:33–37. [PubMed: 22427287]

12. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994; 44:2308–2314. [PubMed: 7991117]

13. Factor SA, Feustel PJ, Freidman JH, et al. Longitudinal outcome of Parkinson's disease patients with psychosis. Neurology. 2003; 60:1756–1761. [PubMed: 12796526]

14. Forsaa EB, Larsen JP, Wentzel-Larsen T, Alves G. What predicts mortality in Parkinson disease? A prospective population-based long-term study. Neurology. 2010; 75:1270–1276. [PubMed: 20921512]

15. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson's disease. Arch Neurol. 1999; 56:33–39. [PubMed: 9923759]

16. Dalrymple-Alford JC, MacAskill MR, Nakas CT, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. Neurology. 2010; 75:1717–1725. [PubMed: 21060094]

17. 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. 2005; 287:455–463. [PubMed: 11798367]

18. Fahn, S.; Elton, RL. the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn, S.; Marsden, CD.; Calne, D.; Goldstein, M., editors. Recent Developments in Parkinson's Disease. Florham Park, New Jersey, USA: Macmillan Health Care Information; 1987. p. 153-163.

19. Hoehn MH, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology. 1967; 17:427–442. [PubMed: 6067254]

20. Mavandadi S, Nazem S, Ten Have TR, et al. Use of latent variable modeling to delineate psychiatric and cognitive profiles in Parkinson's disease. Am J Geriatr Psychiatry. 2009; 17:986–995. [PubMed: 19855199]

21. Friedberg G, Zoldan J, Weizman A, Melamed E. Parkinson Psychosis Rating Scale: a practical instrument for grading psychosis in Parkinson's disease. Clin Neuropharmacol. 1998; 21:280–284. [PubMed: 9789707]

22. Fernandez HH, Aarsland D, Fénelon G, et al. Scales to assess psychosis in Parkinson's disease: critique and recommendations. Mov Disord. 2008; 23:484–500. [PubMed: 18175343]

23. Rush AJ, Giles DE, Schlesser MA, Fulton SL, Weissenburger J, Burns C. The Inventory for Depressive Symptomatology (IDS): preliminary findings. Psychiatry Res. 1985; 18:65–87. [PubMed: 3737788]

24. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Washington, DC: American Psychiatric Association; 2000. Text Revision.

25. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med. 1996; 26:477–486. [PubMed: 8733206]

26. Spielberger, CD.; Gorsuch, RL.; Lushene, R.; Vagg, PR.; Jacobs, GA. Manual for the State-Trait Anxiety Inventory (Form Y). Palo Alto, California, USA: Consulting Psychologists Press; 1983.

27. Chaudhuri KR, Pal S, DiMarco A, 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; 73:629–635. [PubMed: 12438461]

28. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep. 1991; 14:540–545. [PubMed: 1798888]

29. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 1992; 4:134–139. [PubMed: 1627973]

30. Version 20.0. Chicago, Illinois, USA: IBM; 2011. PASW for Windows [computer program].

31. Gallagher DA, Parkkinen L, O'sullivan SS, et al. Testing an aetiological model of visual hallucinations in Parkinson's disease. Brain. 2011; 134:3299–3309. [PubMed: 21921019]

32. Fenelon G. Psychosis in Parkinson's disease: phenomenology, frequency, risk factors, and current understanding of pathophysiologic mechanisms. CNS Spectr. 2008; 13(Suppl 4):18–25. [PubMed: 18323763]

33. Shine JM, Halliday GM, Naismith SL, Lewis SJG. Visual misperceptions and hallucinations in Parkinson's disease: dysfunction of attentional control networks? Mov Disord. 2011; 26:2154–2159. [PubMed: 21953814]

34. Morgante L, Colosimo C, Antonini A, et al. Psychosis associated to Parkinson's disease in early stages: relevance of cognitive decline and depression. J Neurol Neurosurg Psychiatry. 2011; 83:76–82. [PubMed: 21836035]

35. Braak H, Rub U, Del Tredici K. Cognitive decline correlates with neuropathological stage in Parkinson's disease. J Neurol Sci. 2006; 248:255–258. [PubMed: 16814807]

36. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in Parkinson's disease. Lancet Neurol. 2010; 9:1200–1213. [PubMed: 20880750]

37. Politis M, Wu K, Loane C, et al. Depressive symptoms in PD correlate with higher 5-HTT binding in raphe and limbic structures. Neurology. 2010; 75:1920–1927. [PubMed: 21098407]

38. Hesse S, Meyer PM, Strecker K, et al. Monoamine transporter availability in Parkinson's disease patients with or without depression. Eur J Nucl Med Mol Imaging. 2009; 36:428–435. [PubMed: 19037640]

39. Pacchetti C, Manni R, Zangaglia R, et al. Relationship between hallucinatons, delusions, and rapid eye movement sleep behavior disorder in Parkinson's disease. Mov Disord. 2005; 20:1439–1448. [PubMed: 16028215]

40. Boeve BF, Silber MH, Saper CB, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodgenerative disease. Brain. 2007; 130:2770–2788. [PubMed: 17412731]

41. Arnulf I, Ferraye M, Fraix V, et al. Sleep induced by stimulationin in the human pedunculopontine nucleus area. Ann Neurol. 2010; 67:546–549. [PubMed: 20437591]

42. Naismith SL, Lewis SJG. "DASH" symptoms in patients with Parkinson's disease: red flags for early cognitive decline. J Clin Neurosci. 2011; 18:352–355. [PubMed: 21237647]

TABLE 1

Demographic and clinical characteristics (N =191)

Variable	Mean (SD) or Percentage
Demographics	
Age, years	63.1 (10.0)
Sex, % male	71.7
Race, % white	94.8
Education, years	16.4 (3.0)
Parkinson's Disease	
PD duration, years	6.4 (5.4)
Hoehn and Yahr, median[a]	2.0
UPDRS motor score[a]	21.6 (10.3)
Deep brain stimulation, % yes	11.5
Medications	
Levodopa LEDD, mg/day	501.2 (419.5)
Dopamine agonist, % yes	49.7
Anticholingeric, % yes	3.7
Amantadine, % yes	19.4
MAO inhibitor, % yes[a]	13.7
Psychosis	
Any psychotic symptom, % yes	21.5
Visual hallucinations, % yes	13.6
Auditory hallucinations, % yes	6.8
Illusions or misidentification, % yes	7.3
Paranoid ideation, % yes	4.7
Psychiatric	
Inventory for Depressive Symptomatology score[a]	18.5 (12.6)
State Anxiety Inventory score[b]	39.2 (14.5)
REM Behavior Disorder score[c]	1.0 (1.2)
Epworth Sleepiness Scale score[d]	9.9 (4.8)
Apathy Scale score[e]	11.7 (6.4)
Cognition	
Mini-Mental State Examination score	29.2 (0.80)

[a]N = 190;

[b]N = 186;

[c]N = 182;

[d]N = 179;

[e]N = 178.

Abbreviations: MAO, monoamine oxidase.

TABLE 2

Demographic and clinical correlates of psychosis

| Variable (Mean [SD] or %) | Groups by Psychosis Diagnosis | | Chi-Square (df), *t* Test (df), or Nonparametric Test; *P* Value |
| | Non-Psychotic | Psychotic | |
	(N = 150; 78.5%)	(N = 41; 21.5%)	
Demographics/clinical variables			
Age, years	62.8 (10.1)	64.0 (9.6)	−0.6 (189); 0.52
Sex, % male	70.7	75.6	0.4 (1); 0.53
Education, years	16.5 (3.1)	16.1 (3.0)	0.7 (189); 0.48
Parkinson's disease			
Duration of PD, years	5.8 (5.0)	8.5 (6.4)	−2.8 (189); 0.005
Hoehn and Yahr stage	2.0	2.5	$P = 0.05$
UPDRS motor score	20.8 (10.2)	24.7 (10.4)	−2.2 (188); 0.03
Deep brain stimulation, % yes	10.0	17.1	1.6 (1); 0.21
Medications			
Levodopa LEDD, mg/day	480.0 (411.6)	620.4 (434.8)	−1.9 (189); 0.06
Dopamine agonist use, % yes	47.3	57.1	1.6 (1); 0.20
Psychiatric tests			
Inventory for Depressive Symptomatology score	16.6 (11.9)	25.3 (13.0)	−4.1 (189); <0.001
State Anxiety Inventory score	37.2 (13.8)	46.2 (14.9)	−3.6 (184); <0.001
REM Behavior Disorder score	0.8 (1.1)	1.6 (1.4)	−3.3 (50.8); 0.002
Epworth Sleepiness Scale score	9.3 (4.8)	12.2 (4.3)	−3.5 (177); 0.001
Apathy Scale score	11.0 (6.5)	14.1 (5.8)	−2.7 (176); 0.008
Cognitive tests			
Mini-Mental State Examination score	29.3 (0.8)	29.1 (0.8)	1.7 (189); 0.09

TABLE 3

Logistic regression model examining predictors of psychosis

Variable	Statistical Analysis (B [SE]; *P* value)
Duration of PD, years	0.04 (0.04); 0.26
Hoehn and Yahr stage	0.72 (0.38); 0.06
L-dopa LEDD, mg/day	0.00 (0.00); 0.44
Inventory for Depressive Symptomatology score	0.04 (0.02); 0.01
REM Behavior Disorder score	0.38 (0.17); 0.03
Epworth Sleepiness Scale score	0.09 (0.05); 0.07
Mini-Mental State Examination score	−0.23 (0.27); 0.41

Abbreviations: B, B coefficient; SE, standard error.