Rapid Eye Movement Sleep Behavior Disorder Symptoms Correlate with Domains of Cognitive Impairment in Parkinson's Disease

Jin-Ru Zhang[1], Jing Chen[1], Zi-Jiao Yang[1], Hui-Jun Zhang[1], Yun-Ting Fu[1], Yun Shen[1], Pei-Cheng He[1], Cheng-Jie Mao[1], Chun-Feng Liu[1,2,3]

[1]Department of Neurology and Sleep Center, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215004, China
[2]Institute of Neuroscience, Soochow University, Suzhou, Jiangsu 215123, China
[3]Beijing Key Laboratory for Parkinson's Disease, Beijing 100053, China

Abstract

Background: Rapid eye movement (REM) sleep behavior disorder (RBD) may be a risk factor for cognitive impairment in patients with Parkinson's disease (PD). However, little is known regarding the relation between the severity of RBD and the different domains of cognitive impairment. The aim of this study was: (1) to investigate the domains of cognitive impairment in patients with PD and RBD, and (2) to explore risk factors for PD-mild cognitive impairment (PD-MCI) and the relationship between RBD severity and impairment in different cognitive domains in PD.

Methods: The participants were grouped as follows: PD without RBD (PD-RBD; $n = 42$), PD with RBD (PD + RBD; $n = 32$), idiopathic RBD (iRBD; $n = 15$), and healthy controls (HCs; $n = 36$). All participants completed a battery of neuropsychological assessment of attention and working memory, executive function, language, memory, and visuospatial function. The information of basic demographics, diseases and medication history, and motor and nonmotor manifestations was obtained and compared between PD-RBD and PD + RBD groups. Particular attention was paid to the severity of RBD assessed by the RBD Questionnaire-Hong Kong (RBDQ-HK) and the RBD Screening Questionnaire (RBDSQ), then we further examined associations between the severity of RBD symptoms and cognitive levels via correlation analysis.

Results: Compared to PD-RBD subjects, PD + RBD patients were more likely to have olfactory dysfunction and their Epworth Sleepiness Scale scores were higher ($P < 0.05$). During neuropsychological testing, PD + RBD patients performed worse than PD-RBD patients, including delayed memory function, especially. The MCI rates were 33%, 63%, 33%, and 8% for PD-RBD, PD + RBD, iRBD, and HC groups, respectively. RBD was an important factor for the PD-MCI variance (odds ratio = 5.204, $P = 0.018$). During correlation analysis, higher RBDSQ and RBDQ-HK scores were significantly associated with poorer performance on the Trail Making Test-B (errors) and Auditory Verbal Learning Test (delayed recall) and higher RBD-HK scores were also associated with Rey–Osterrieth complex figure (copy) results.

Conclusions: When PD-RBD and PD + RBD patients have equivalent motor symptoms, PD + RBD patients still have more olfactory dysfunction and worse daytime somnolence. RBD is an important risk factor for MCI, including delayed memory. Deficits in executive function, verbal delayed memory, and visuospatial function were consistently associated with more severe RBD symptoms.

Key words: Mild Cognitive Impairment; Parkinson's Disease; Rapid Eye Movement Sleep Behavior Disorder

Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by the loss of muscle atonia typically occurring during REM sleep, often leading to violent motor manifestations of undesirable dreams. Patients and relatives complain about RBD symptoms, such as shouting, gesturing, leaping out of bed, or punching bed partners. Longitudinal

© 2016 Chinese Medical Journal ¦ Produced by Wolters Kluwer - Medknow

Access this article online	
Quick Response Code:	**Website:** www.cmj.org
	DOI: 10.4103/0366-6999.176077

studies have shown that idiopathic RBD (iRBD) patients may eventually be diagnosed with an α-synucleinopathy such as Parkinson's disease (PD), multiple system atrophy, or dementia with Lewy bodies.[1-3] Additionally, approximately 35–50% of patients with PD have RBD (PD + RBD); these patients tend to have the akinetic-rigid dominant subtype of PD and exhibit severe nonmotor symptoms.[4]

PD with mild cognitive impairment (PD-MCI), as a transitional stage, identifies those individuals at increased risk for PD dementia.[5-7] Despite the lack of consensus criteria, 19–38% of nondemented PD patients have MCI.[8] Furthermore, in those individuals with PD for at least 10 years, the cumulative prevalence of PD dementia is approximately 75–90%.[9] Of note, most studies have demonstrated that the prevalence of MCI is significantly higher in PD + RBD patients than in PD without RBD (PD-RBD) individuals.[10] However, seldom study has investigated the relation between the severity of RBD and the different domains of cognitive impairment.

In this study, we performed extensive neuropsychological assessments based on the recommendations from 2011 Movement Disorder Society (MDS) Task Force[11] to compare the cognitive level and prevalence of MCI in PD + RBD patients, PD-RBD patients, iRBD patients, and healthy control (HC) subjects. Furthermore, we assessed the ability of clinical factors to predict MCI in PD patients and explored the specific domains affected by RBD.

METHODS

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University, and all patients provided informed written consent before participating. Overview of the methods has been described in Supplementary Material 1.

Subjects

A total of 125 subjects, including 74 PD patients (32 PD + RBD and 42 PD-RBD), 15 iRBD patients, and 36 age-, sex-, and education level-matched HC subjects were recruited from the Center of Parkinsonism and Movement Disorders from February 2014 to May 2015 in the Second Affiliated Hospital of Soochow University. The HC participants were partners or friends of PD patients.

All subjects were between 40 and 80 years old and had at least 5 years of schooling. The diagnosis of PD was established according to the clinical diagnosis criteria of the United Kingdom PD Society. To reduce the influence of confounding factors such as bradykinesia and tremor on cognitive scores, we only included those patients whose Hoehn-Yahr (H-Y) stage $\leq$ 2.5 and Unified Parkinson's Disease Rating Scale (UPDRS) part III score $\leq$ 35. Clinical RBD in patients with PD was diagnosed according to affirmative responses to the Mayo Sleep Questionnaire (MSQ),[12,13] as well as the RBD Screening Questionnaire (RBDSQ) (a sensitivity of 0.842, and

specificity of 0.962 for detecting RBD).[14] A cut-off score of 7 on the RBDSQ was used to differentiate PD + RBD ($\geq$ 7) patients from PD-RBD patients (< 7). All iRBD patients and 35 PD patients underwent video-polysomnography to confirm or refute the diagnosis of RBD. The diagnosis of RBD for these patients was determined using the clinical criteria established by the American Academy of Sleep Medicine (AASM), the International Classification of Sleep Disorders third edition.

A total of 16 subjects were excluded because of the presence of severe dementia (Mini-Mental State Examination [MMSE] score < 24 and diagnosis of dementia according to the MDS clinical diagnostic criteria).[15] Patients were also excluded if they had a major psychiatric disease (major depression or anxiety) diagnosed according to the Diagnostic Statistical Manual-IV criteria, or if they were unwilling to cooperate with the cognitive tests.

Neuropsychological assessment

All subjects underwent a neuropsychological examination. The PD patients completed the tests within 1–2 h after taking their usual medications. Tests of global cognition included the MMSE and montreal cognitive assessment (Beijing version). The comprehensive tests were grouped into 5 cognitive domains based on the MDS task force recommendations[11] and prior studies: (1) attention and working memory: Trail Making Test-A (TMT-A), Digit Span Forward, and Symbol Digit Modalities Test; (2) executive function: TMT-B, Digit Span Backward, and Stroop Color-Word Test (SCWT); (3) language: Semantic Verbal Fluency Test (SVFT) of animal naming or similarities in the former 15 s and latter 45 s; (4) memory: Auditory Verbal Learning Test (AVLT) (word list learning with immediate and delayed recall and recognition conditions) and Recall of Rey-Osterrieth complex figure (Rey-O figure); and (5) visuospatial function: Copying Rey-O figure and Clock Drawing Test.

We classified patients as having MCI if they scored $\geq$ 1.5 standard deviations (SDs) below the age- and education-corrected norms on at least two tests, either within a single cognitive domain or across different cognitive domains.[11]

Clinical assessment

The information of basic demographics, diseases and medication history, and comorbid diseases was obtained for all subjects. Motor manifestations of PD patients were evaluated in the "on" state. These manifestations included the UPDRS-total and subscales I–IV, the H-Y stage, and the levodopa-equivalent daily (LED) dose. Additionally, we defined the akinetic-rigid/tremor (AR/T) ratio according to the Schiess classification[16] and the axial-limb ratio as the sum of UPDRS III items 18, 19, 22, and 27–30 divided by UPDRS III items 20–26. The frequency of falls and freezing[17] was measured according to scores for questions 6 and 7 on part II of the UPDRS.

Nonmotor symptoms and quality of life were also assessed. The nonmotor symptoms questionnaire[18] was used as

the screening instrument for hypersalivation, olfactory dysfunction, constipation, and urinary urgency, with answers recorded as "present" or "absent". Daytime somnolence and quality of life were evaluated using the Epworth Sleepiness Scale (ESS) and the PD questionnaire (PDQ-39), respectively.

Manifestations of rapid eye movement sleep behavior disorder

The severity of RBD symptoms was assessed using the RBDQ-HK and the RBDSQ. For those patients who completed an overnight video-polysomnography study (Compumedics-E series, Australia) (35 PD and all iRBD patients), we calculated the tonic chin electromyography activity (tonic density) and the phasic chin electromyography density activity (phasic density) according to a previously published method[19] and the criteria of the AASM.

Statistical analysis

SPSS Software version 18.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. To reduce the influence of confounding factors such as bradykinesia and tremor on cognitive scores (e.g., on the TMT, SMT, and SCWT), we controlled for age, education, H-Y stage, and UPDRS part III score before conducting the statistical analyses. Descriptive data are presented as mean ± SD, median (interquartile range), or frequency (percentage). Comparisons were performed using independent Student's t-test and Chi-square test for PD clinical variables after adjusting for age, education, H-Y stage, and UPDRS part III score. One-way analysis of variance and *post-hoc* comparisons were conducted for results of demographics and neuropsychological test. Nonparametric Kruskal-Wallis or Mann-Whitney U tests were applied for variables that were not distributed normally. Associations between clinical factors and the presence of MCI were evaluated using binary logistic regression analyses. Pearson's and Spearman's correlations were used to analyze correlations between the severity of RBD and different cognitive tests. Statistical significance was defined as a $P < 0.05$.

RESULTS

Demographics and clinical characteristics

Twenty-four subjects refused to undergo the neuropsychological assessment, and 14 and 13 PD patients were diagnosed with PD dementia and depression, respectively. Thus, 125 subjects were ultimately included in our study. Of these subjects, 73 were men and 52 were women, with a mean age of 62.7 ± 8.1 years (range: 47–75 years) and mean education duration of 9.8 ± 2.7 years (range: 5–18 years). According to MSQ criteria and RBDSQ scores, the participants were divided into four groups: PD + RBD, PD-RBD, iRBD, and HC. Our RBD patients confirmed by PSG showed behavior/vocalization in REM sleep, or REM sleeps without atonia. The PD + RBD patients exhibited higher percentages of tonic (17.70 ± 9.20% vs. 3.73 ± 3.56%, $t = −5.66$, $P < 0.05$) and phasic EMG activities (18.54 ± 11.08% vs. 5.82 ± 5.29%, $t = −4.891$, $P < 0.05$) than PD-RBD patients.

Table 1 shows the demographic variables and disease-related information for the four groups. PD + RBD patients had a higher frequency of olfactory dysfunction (48% vs. 75%, $P = 0.017$) and higher ESS scores (5.00 [1.00–7.00] vs. 6.00 [4.00–12.00], $P = 0.035$) than PD-RBD patients. Compared to PD-RBD patients, PD + RBD patients exhibited higher values for several other variables, although the differences between groups did not achieve statistical significance: UPDRS total score, AR/T ratio; axial/limb ratio; frequency of falling, freezing, hypersalivation, constipation, urinary urgency, and anxiety scores.

Neurological test scores

The neurological test scores and results of analyses are presented in Table 2. MCI was diagnosed in 14 of the 42 PD-RBD patients (33%), 20 of the 32 PD + RBD patients (63%), 5 of 15 iRBD patients (33%), and 3 of the 36 HC subjects (8%). MCI was significantly more frequent in PD + RBD patients than in PD-RBD patients ($\chi^2 = 6.221$, $P = 0.013$).

Univariate and multivariate binary logistic regression analyses of clinical factors associated with minimal cognitive impairment

Table 3 displays the results of the regression analyses of factors associated with MCI. First, the colinearity among clinical factors was determined, and it was subsequently reduced by removing some factors. The remaining factors, which are shown in Table 3, were entered into the univariate regression analysis. Factors found to be significantly associated with MCI during univariate logistic regression analyses were included in the subsequent multivariate analyses. After adjusting for covariates, significant risk factors for MCI were education ($\beta = −0.372$, odds ratio [OR] [95% confidence interval (CI)]: 0.689 [0.523–0.908], $P = 0.008$), the presence of RBD ($\beta = 1.649$, OR [95% CI]: 5.204 [1.330–20.364], $P = 0.018$) and higher UPDRS III scores ($\beta = 0.118$, OR [95% CI]: 1.125 [1.040–1.217], $P = 0.003$).

Correlation analysis

We further examined associations between the severity of RBD symptoms and cognitive levels via correlation analysis. Table 4 shows that higher RBDSQ scores were significantly associated with poorer performance on the TMT-B (errors) ($r = 0.267$, $P = 0.026$) and AVLT (delayed recall) ($r = −0.313$, $P = 0.008$). Higher RBD-HK scores were associated with worse scores on the TMT-B ($r = 0.249$, $P = 0.038$), AVLT (delayed recall) ($r = −0.246$, $P = 0.040$), and Rey-O figure (copy) test ($r = −0.290$, $P = 0.015$). These effects were observed after controlling for age, education duration, and UPDRS part III score.

DISCUSSION

In this study, we used the standard diagnostic criteria for PD-MCI proposed by the MDS. Our results indicated that cognitive function, including delayed memory, was worse in PD + RBD patients than in PD-RBD patients. The number

Table 1: The demographics and clinical characteristics of all subjects in this study

Items	PD−RBD (*n* = 42)	PD+RBD (*n* = 32)	iRBD (*n* = 15)	HC (*n* = 36)	Statistical values	*P*
Male, *n* (%)	20 (48)	23 (72)	11 (73)	19 (53)	6.246*	0.100[†]
Age (years)	62.2 ± 8.3	64.9 ± 5.2	61.7 ± 12.7	62.7 ± 8.1	1.072[§]	0.364[†]
Education duration (years)	9.8 ± 2.6	9.5 ± 2.3	10.4 ± 3.7	9.9 ± 2.6	0.723[§]	0.540[†]
PD duration (years)	4.2 ± 2.7	4.0 ± 2.5	–	–	–	–
RBD duration (years)	–	6.1 ± 4.8	12.4 ± 14.5	–	–	–
Hoehn-Yahr stage	2.0 (1.5–2.5)	2.0 (1.5–2.5)	–	–	−0.920[‖]	0.358
UPDRS part III score	20.02 ± 9.57	19.84 ± 12.01	–	–	0.072[‡]	0.943
UPDRS total score	32.83 ± 15.60	35.03 ± 17.41	–	–	−0.569[‡]	0.571
LED (mg/d)	298.2 ± 237.2	292.3 ± 210.2	–	–	0.019[‡]	0.913
AR/T, *n* (%)	30 (71)	27 (84)	–	–	1.720[†]	0.190
Axial/limb ratio	0.64 (0.51–0.89)	0.85 (0.51–1.00)	–	–	−1.107[‖]	0.268
Falling, *n* (%)	6 (14)	7 (22)	–	–	0.722*	0.395
Freezing, *n* (%)	14 (33)	14 (44)	–	–	0.838*	0.360
Hypersalivation, *n* (%)	6 (14)	8 (25)	–	–	1.359*	0.244
Olfactory dysfunction, *n* (%)	20 (48)	24 (75)	–	–	5.649*	0.017
Constipation, *n* (%)	20 (48)	22 (69)	–	–	0.304*	0.069
Urinary urgency, *n* (%)	16 (38)	17 (53)	–	–	1.660*	0.198
Depression score	7.03 ± 5.37	7.15 ± 5.68	–	–	0.088[‡]	0.930
Anxiety score	2.00 (1.00–6.00)	4.00 (2.00–7.00)	–	–	−1.442[‖]	0.155
ESS score	5.00 (1.00–7.00)	6.00 (4.00–12.00)	–	–	−2.109[‖]	0.035
PDQ-39 score	9.00 (4.00–24.00)	10.00 (5.00–19.00)	–	–	−0.233[‖]	0.815

Values are shown as mean ± SD, *n* (%), or median (interquartile range). [†]These *P* values were calculated between four groups, others between PD−RBD and PD+RBD groups. These analyses were performed using *Chi-square test; [‡]Independent Student's *t*-test; [§]One-way analysis of variance, and [‖]Nonparametric tests. "–": Not applicable. AR/T: Akinetic rigid/tremor + mixed (Schiess classification); ESS: Epworth Sleepiness Scale; HC: Healthy controls; iRBD: Idiopathic rapid eye movement sleep behavior disorder; LED: Levodopa equivalent daily dose; PDQ-39: Quality of life questionnaire; RBD: Rapid eye movement sleep behavior disorder; PD−RBD: Parkinson's disease patients without rapid eye movement sleep behavior disorder; PD+RBD: Parkinson's disease patients with rapid eye movement sleep behavior disorder; UPDRS: Unified Parkinson's Disease Rating Scale; SD: Standard deviation.

of PD + RBD patients who screened positive for MCI was high, and our results indicated that RBD was a significant independent risk factor for MCI. We also observed clear associations between RBD symptoms and different domains of PD-MCI.

Many investigators have studied the clinical characteristics of patients with PD + RBD. Some studies found that RBD in PD was associated with a higher LED.[20] A recent study reported that PD + RBD was a special type of disease characterized by less of a tremor, higher frequency of falls, and a lower amplitude of response to medications dose.[4] Nonetheless, other studies reported different results. Rolinski *et al*.[21] found that PD + RBD patients did not differ from PD-RBD patients with respective to motor phenotype and scored comparably on objective motor scales; however, PD + RBD patients exhibited greater sleepiness, depression, and cognitive impairment. Given the influence that confounding factors such as bradykinesia and tremor can have on cognitive tests, we adjusted for age, education duration, PD duration, and UPDRS part III score in the current study. After these adjustments, we found that PD + RBD patients were more likely to have only olfactory dysfunction and daytime somnolence. The discrepancy between our results and those of previous studies was likely attributable to our adjustments because we found more akinetic rigid subtypes in the PD + RBD group before adjustment. Thus, when PD-RBD and PD + RBD patients

have equivalent motor symptoms, those with PD + RBD have a greater prevalence of olfactory dysfunction and daytime somnolence.

Previous studies examining associations between RBD and cognition in patients with PD used different tests and cut-offs to measure MCI, and not surprisingly, these studies have produced discrepant results. In most studies, PD patients performed worse in tasks of attention/executive functions.[22] In our results, we additionally found the lower performance on one of two tests of visuospatial function in PD-RBD patients compared to HC. Importantly, we found a verbal and visuospatial memory (Rey-O figure, recall) deficiency in PD + RBD patients, but not in PD-RBD patients, which was opposite to the findings reported by Gagnon *et al*.[10] Our results were consistent with those of previous studies, which indicated that verbal memory impairment plus executive dysfunction are associated with the development of dementia in patients with PD.[23] As the cognitive tests are inextricably linked, we did not observe dysfunction in one single domain in PD + RBD, but these patients are more likely to have delayed memory impairment.

The pathophysiological mechanism responsible for our findings of impaired cognitive function in PR + RBD patients is unclear. The pedunculopontine nucleus (PPN) plays an important role, providing the majority of cholinergic input to the thalamus, as well as cholinergic input to various other

Table 2: Cognitive performance on neurological test scores among the four groups

Items	PD−RBD (n = 42)	PD + RBD (n = 32)	iRBD (n = 15)	HC (n = 36)	Statistical values	P
MMSE	27.59 ± 1.75*	27.22 ± 1.86†	28.20 ± 1.27	28.42 ± 1.03	3.738	0.013
MOCA	24.59 ± 3.29	23.09 ± 2.98†§	25.00 ± 2.63	25.03 ± 2.13	2.586	0.056
Attention and working memory						
TMT-A, time	55.62 ± 19.11*	68.68 ± 25.12†§	45.30 ± 11.03	44.25 ± 10.66	10.989	<0.001
Digit span forward	11.88 ± 1.90*	11.84 ± 1.92†	12.47 ± 1.85	12.64 ± 1.10	1.853	0.141
SDMT	35.22 ± 11.39*	30.66 ± 8.34†§	42.60 ± 9.42	42.94 ± 9.62	11.558	<0.001
Executive function						
TMT-B, time	86.52 ± 29.73*	105.31 ± 45.89†§	78.40 ± 23.51	69.88 ± 20.01	5.302	0.002
TMT-B, errors	0.00 (0.00–0.00)	0.00 (0.00–2.00)†§	0.00 (0.00–1.75)‡	0.00 (0.00–0.00)	15.594	0.001
Digit span backward	5.78 ± 2.29*	5.52 ± 2.36†	6.53 ± 2.13	7.11 ± 2.36	3.556	0.017
SCWT, time	14.07 ± 7.31	14.33 ± 7.90	12.31 ± 8.39	12.29 ± 6.46	0.765	0.516
SCWT, errors	0.00 (0.00–3.00)	0.00 (0.00–3.00)	0.00 (0.00–2.75)	0.00 (0.00–1.00)	3.771	0.287
Language						
SVFT, former 15 s	8.05 ± 1.53	7.72 ± 1.55	8.08 ± 1.93	8.19 ± 1.83	0.485	0.693
SVFT, latter 45 s	7.10 ± 2.51	6.72 ± 2.54†	8.00 ± 2.89	8.03 ± 2.71	1.799	0.151
Memory						
AVLT, immediate recall	20.95 ± 3.79	19.16 ± 4.18†	20.25 ± 5.53	21.31 ± 3.98	1.758	0.159
AVLT, delayed recall	7.18 ± 2.03	5.78 ± 2.14†§	6.87 ± 2.77	7.28 ± 1.45	4.542	0.005
AVLT, recognition	10.83 ± 1.77	10.44 ± 1.56†	10.33 ± 1.44	11.31 ± 1.01	2.379	0.073
Rey-O figure, recall	15.96 ± 5.89	13.77 ± 4.60†§	18.80 ± 6.13	19.60 ± 3.98	9.085	<0.001
Visuospatial function						
Rey-O figure, copy	30.04 ± 3.98	28.36 ± 4.02†§	30.20 ± 2.44	30.33 ± 2.74	2.560	0.058
Clock Drawing Test	24.41 ± 4.57*	23.95 ± 3.56†	26.37 ± 2.27	26.42 ± 2.76	3.852	0.011

Values are shown as mean ± SD or median (interquartile range). The *P* value reflects differences among the four groups. The TMT-B (errors) and SCWT (errors) were nonparametric tests. *Significant difference between PD−RBD and HC groups; †Significant difference between PD+RBD and HC groups; ‡Significant difference between iRBD and HC groups; §Significant difference between PD−RBD and PD+RBD groups. AVLT: Auditory Verbal Learning Test; HC: Healthy controls; iRBD: Idiopathic rapid eye movement sleep behavior disorder; MMSE: Mini-Mental State Examination; MOCA: Montreal cognitive assessment; PD−RBD: Parkinson's disease patients without rapid eye movement sleep behavior disorder; PD+RBD: Parkinson's disease patients with rapid eye movement sleep behavior disorder; Rey-O figure: Rey-Osterrieth complex figure; SCWT: Stroop Color-Word Test; SDMT: Symbol Digit Modalities Test; SVFT: Semantic Verbal Fluency Test; TMT-A: Trail Making Test-A; TMT-B: Trail Making Test-B; SD: Standard deviation.

Table 3: Univariate and multivariate binary logistic regression analyses of clinical factors associated with mild cognitive impairment

Items	Univariate analysis			Multivariate analysis		
	β	P	OR (95% CI)	β	P	OR (95% CI)
Gender	0.065	0.892	1.067 (0.419–2.716)	−0.361	0.570	0.697 (0.201–2.420)
Age	0.004	0.897	1.004 (0.948–1.062)	−0.002	0.961	0.998 (0.920–1.083)
Education	−0.212	0.027	0.809 (0.670–0.976)	−0.372	0.008	0.689 (0.523–0.908)
UPDRS part III	0.087	0.002	1.091 (1.032–1.154)	0.118	0.003	1.125 (1.040–1.217)
AR/T	1.275	0.045	3.577 (1.029–12.433)	1.735	0.059	5.669 (0.939–34.238)
Axial/limb ratio	0.041	0.902	1.042 (0.544–1.933)	–	–	–
Hypersalivation	0.309	0.595	1.363 (0.436–4.263)	–	–	–
Olfactory dysfunction	0.161	0.738	1.175 (0.457–3.023)	–	–	–
Constipation	0.606	0.210	1.833 (0.710–4.732)	–	–	–
Urinary urgency	−0.131	0.782	0.877 (0.346–2.222)	–	–	–
Depression	0.052	0.252	1.054 (0.963–1.152)	–	–	–
RBD	1.303	0.009	3.682 (1.390–9.752)	1.649	0.018	5.204 (1.330–20.364)

AR/T: Akinetic rigid/tremor + mixed (Schiess classification); *CI*: Confidence interval; RBD: Rapid eye movement sleep behavior disorder; UPDRS: Unified Parkinson's Disease Rating Scale; "–": Not applicable; *OR*: Odds ratio.

structures, including the nucleus basalis of Meynert (nbM), striatum, substantia nigra, subthalamic nucleus, globus pallidus interna, cerebellum, and the spinal cord.[24] Cholinergic output is sent to the cerebral cortex and thalamic nuclei by the nbM. Degeneration of the PPN and nbM occurs in PD, with the degree of degeneration correlating with motor and cognitive impairment, respectively.[24] Furthermore, the PPN is involved in the influence of sleep-wake cycles by the basal ganglion,[25] and acetylcholine is released in areas of the brain related to consciousness and conscious awareness.[24]

Table 4: Correlation analysis of cognitive scores with severity of rapid eye movement sleep behavior disorder

Items	RBDSQ score		RBD-HK score	
	r	P	r	P
MMSE	−0.063	0.603	0.019	0.874
MOCA	−0.208	0.083	−0.151	0.211
Attention and working memory				
TMT-A, time	0.025	0.061	0.176	0.144
Digit span forward	−0.001	0.992	0.015	0.903
SDMT	−0.148	0.220	−0.172	0.154
Executive function				
TMT-B, time	0.210	0.081	0.141	0.245
TMT-B, errors	0.267	0.026	0.249	0.038
Digit span backward	−0.048	0.694	−0.052	0.671
SCWT, time	−0.060	0.620	−0.032	0.790
SCWT, errors	−0.074	0.540	−0.123	0.309
Language				
SVFT, former 15 s	0.001	0.991	−0.050	0.684
SVFT, latter 45 s	0.022	0.859	−0.029	0.814
Memory				
AVLT, immediate recall	−0.164	0.176	−0.119	0.328
AVLT, delayed recall	−0.313	0.008	−0.246	0.040
AVLT, recognition	−0.112	0.357	−0.173	0.151
Rey-O figure, recall	−0.131	0.278	−0.171	0.156
Visuospatial function				
Rey-O figure, copy	−0.160	0.185	−0.290	0.015
Clock Drawing Test	0.033	0.789	0.045	0.710

Adjusted for age, education duration, Hoehn-Yahr stage, and UPDRS part III score. AVLT: Auditory Verbal Learning Test; MMSE: Mini-Mental State Examination; MOCA: Montreal cognitive assessment; RBD-HK: Rapid eye movement sleep behavior disorder questionnaire-Hong Kong; RBDSQ: Rapid eye movement sleep behavior disorder Screening Questionnaire; Rey-O figure: Rey-Osterrieth complex figure; SDMT: Symbol Digit Modalities Test; SCWT: Stroop Color-Word Test; SVFT: Semantic Verbal Fluency Test; TMT-A: Trail Making Test-A; TMT-B: Trail Making Test-B.

The prevalence of MCI in our four groups ranged from highest in the PD + RBD group, followed in descending order by the PD-RBD, iRBD, and HC groups. Unlike some cohort studies, the prevalence was not high in those with iRBD.[10] In a recent study, MCI and depression did not clearly predict clinical neurodegeneration in iRBD,[26] but indicated transition to dementia. In our multivariate binary logistic regression analyses, except for education duration, scores on the UPDRS part III and RBD were the only risk factors for PD-MCI. The association between AR/T + mixed subtype and MCI did not quite achieve statistical significance ($P = 0.059$), and it is possible that this would have been significant with a larger number of subjects. In our study, patients with major depression and anxiety were excluded, which may have explained why we detected no association between MCI and depression during the multivariate logistic regression analysis. Our findings thus suggested that cognitive function could be aggravated by RBD and the severity of the motor manifestations.

In our study, correlation analysis showed that the severity of RBD symptoms was associated with impaired executive function and delayed memory. Poorer visuospatial function correlated with RBD-HK but not RBDSQ. The current leading two explanations for decreased cognitive performance in patients with PD and concomitant RBD are as follows: One explanation states that REM sleep is associated with memory consolidation and long-term stabilization,[27] therefore, disruptions of REM sleep could directly perturb memory function;[24] the other explanation states that interrupted REM sleep can lead to cholinergic deficits in PD patients. Our findings were consistent with the hypothesis that the severity and frequency of RBD could exacerbate cognitive impairments of executive function, verbal delayed memory, and visuospatial function.

Several limitations of this study should be taken into consideration. For example, the study had a relatively small sample size and a cross-sectional design. Second, many of the subjects did not undergo polysomnography. Third, the neuropsychological tests used to represent function within cognitive domains varied to some extent from those used in previous studies. For example, the SVFT was divided into language function in our study.[22]

In conclusion, we confirmed that RBD may be a marker of a specific subtype of PD, which is more likely to be characterized by olfactory dysfunction and daytime somnolence, when patients have equivalent motor symptoms. Moreover, RBD is a crucial risk factor for MCI, including delayed memory function. Furthermore, the clinical severity of RBD correlates with poorer performance in executive function, delayed memory, and visuospatial function.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology 2009;72:1296-300. doi: 10.1212/01.wnl.0000340980.19702.6e.
2. Iranzo A, Tolosa E, Gelpi E, Molinuevo JL, Valldeoriola F, Serradell M, *et al.* Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: An observational cohort study. Lancet Neurol 2013;12:443-53. doi: 10.1016/S1474-4422(13)70056-5.
3. Iranzo A, Molinuevo JL, Santamaría J, Serradell M, Martí MJ, Valldeoriola F, *et al.* Rapid-eye-movement sleep behaviour

disorder as an early marker for a neurodegenerative disorder: A descriptive study. Lancet Neurol 2006;5:572-7. doi: 10.1016/S1474-4422(06)70476-8.

4. Postuma RB, Gagnon JF, Vendette M, Charland K, Montplaisir J. REM sleep behaviour disorder in Parkinson's disease is associated with specific motor features. J Neurol Neurosurg Psychiatry 2008;79:1117-21. doi: 10.1136/jnnp.2008.149195.

5. Dalrymple-Alford JC, Livingston L, MacAskill MR, Graham C, Melzer TR, Porter RJ, et al. Characterizing mild cognitive impairment in Parkinson's disease. Mov Disord 2011;26:629-36. doi: 10.1002/mds.23592.

6. Pedersen KF, Larsen JP, Tysnes OB, Alves G. Prognosis of mild cognitive impairment in early Parkinson disease: The Norwegian ParkWest study. JAMA Neurol 2013;70:580-6. doi: 10.1001/jamaneurol.2013.2110.

7. Hu P, Li Y, Ma H, Xi C, Chen X, Wang K. Dissociation between source and item memory in Parkinson's disease. Chin Med J 2014;127:3224-8. doi: 10.3760/cma.j.issn.0366-6999.20140957.

8. Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, Kulisevsky J, et al. Mild cognitive impairment in Parkinson disease: A multicenter pooled analysis. Neurology 2010;75:1062-9. doi: 10.1212/WNL.0b013e3181f39d0e.

9. Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson disease. J Neurol Sci 2010;289:18-22. doi: 10.1016/j.jns.2009.08.034.

10. Gagnon JF, Vendette M, Postuma RB, Desjardins C, Massicotte-Marquez J, Panisset M, et al. Mild cognitive impairment in rapid eye movement sleep behavior disorder and Parkinson's disease. Ann Neurol 2009;66:39-47. doi: 10.1002/ana.21680.

11. Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, et al. MDS task force on mild cognitive impairment in Parkinson's disease: Critical review of PD-MCI. Mov Disord 2011;26:1814-24. doi: 10.1002/mds.23823.

12. Boeve BF, Molano JR, Ferman TJ, Smith GE, Lin SC, Bieniek K, et al. Validation of the mayo sleep questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. Sleep Med 2011;12:445-53. doi: 10.1016/j.sleep.2010.12.009.

13. Boeve BF, Molano JR, Ferman TJ, Lin SC, Bieniek K, Tippmann-Peikert M, et al. Validation of the mayo sleep questionnaire to screen for REM sleep behavior disorder in a community-based sample. J Clin Sleep Med 2013;9:475-80. doi: 10.5664/jcsm.2670.

14. Nomura T, Inoue Y, Kagimura T, Uemura Y, Nakashima K. Utility of the REM sleep behavior disorder screening questionnaire (RBDSQ) in Parkinson's disease patients. Sleep Med 2011;12:711-3. doi: 10.1016/j.sleep.2011.01.015.

15. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22:1689-707. doi: 10.1002/mds.21507.

16. Schiess MC, Zheng H, Soukup VM, Bonnen JG, Nauta HJ. Parkinson's disease subtypes: Clinical classification and ventricular cerebrospinal fluid analysis. Parkinsonism Relat Disord 2000;6:69-76. doi: 10.1016/S1353-8020(99)00051-6.

17. Romenets SR, Gagnon JF, Latreille V, Panniset M, Chouinard S, Montplaisir J, et al. Rapid eye movement sleep behavior disorder and subtypes of Parkinson's disease. Mov Disord 2012;27:996-1003. doi: 10.1002/mds.25086.

18. Yu B, Xiao ZY, Li JZ, Yuan J, Liu YM. Study of an integrated non-motor symptoms questionnaire for Parkinson's disease. Chin Med J 2010;123:1436-40. doi: 10.3760/cma.j.issn.0366-6999.2010.11.016.

19. Montplaisir J, Gagnon JF, Fantini ML, Postuma RB, Dauvilliers Y, Desautels A, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. Mov Disord 2010;25:2044-51. doi: 10.1002/mds.23257.

20. Nomura T, Inoue Y, Kagimura T, Nakashima K. Clinical significance of REM sleep behavior disorder in Parkinson's disease. Sleep Med 2013;14:131-5. doi: 10.1016/j.sleep.2012.10.011.

21. Rolinski M, Szewczyk-Krolikowski K, Tomlinson PR, Nithi K, Talbot K, Ben-Shlomo Y, et al. REM sleep behaviour disorder is associated with worse quality of life and other non-motor features in early Parkinson's disease. J Neurol Neurosurg Psychiatry 2014;85:560-6. doi: 10.1136/jnnp-2013-306104.

22. Poletti M, Frosini D, Pagni C, Baldacci F, Nicoletti V, Tognoni G, et al. Mild cognitive impairment and cognitive-motor relationships in newly diagnosed drug-naive patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;83:601-6. doi: 10.1136/jnnp-2011-301874.

23. Levy G, Jacobs DM, Tang MX, Côté LJ, Louis ED, Alfaro B, et al. Memory and executive function impairment predict dementia in Parkinson's disease. Mov Disord 2002;17:1221-6. doi: 10.1002/mds.10280.

24. Yarnall A, Rochester L, Burn DJ. The interplay of cholinergic function, attention, and falls in Parkinson's disease. Mov Disord 2011;26:2496-503. doi: 10.1002/mds.23932.

25. Mena-Segovia J, Bolam JP, Magill PJ. Pedunculopontine nucleus and basal ganglia: Distant relatives or part of the same family? Trends Neurosci 2004;27:585-8. doi: 10.1016/j.tins.2004.07.009.

26. Postuma RB, Gagnon JF, Bertrand JA, Génier Marchand D, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder: Preparing for neuroprotective trials. Neurology 2015;84:1104-13. doi: 10.1212/WNL.0000000000001364.

27. Ferini-Strambi L, Di Gioia MR, Castronovo V, Oldani A, Zucconi M, Cappa SF. Neuropsychological assessment in idiopathic REM sleep behavior disorder (RBD): Does the idiopathic form of RBD really exist? Neurology 2004;62:41-5.
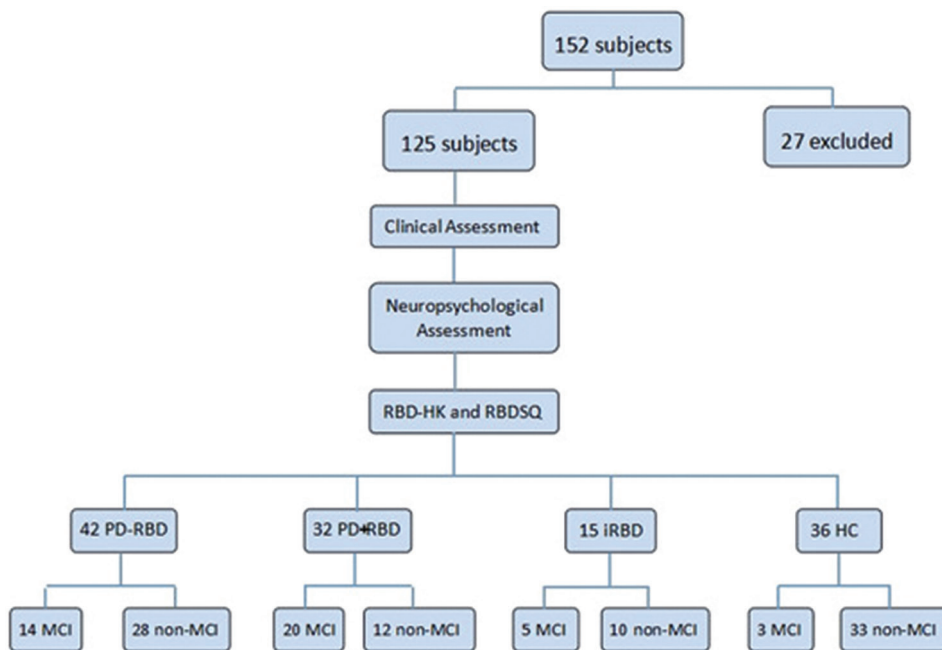
Supplementary Material 1: Flowchart of this study. RBDQ-HK: Rapid eye movement sleep behavior disorder Questionnaire-Hong Kong; RBDSQ: Rapid eye movement sleep behavior disorder Screening Questionnaire; PD−RBD: Parkinson's disease patients without rapid eye movement sleep behavior disorder; PD+RBD: Parkinson's disease patients with rapid eye movement sleep behavior disorder; iRBD: Idiopathic rapid eye movement sleep behavior disorder; HC: Healthy controls; MCI: Mild cognitive impairment.