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Earn CE REM Sleep Behavior Disorder in Parkinson's Disease: Change in Cognitive, Psychiatric, and Functional Outcomes from Baseline to 16–47-Month Follow-Up

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Abstract

Objective: Rapid Eye Movement Sleep Behavior Disorder (RBD) is common in Parkinson's Disease (PD) and is associated with cognitive impairment; however, the majority of the evidence on the impact of RBD on multidomain cognitive batteries in PD is cross-sectional. This study evaluated the longitudinal impact of probable RBD (pRBD) on cognitive, psychiatric, and functional outcomes in people with PD.

Method: Case–control study. A total of 65 people with PD completed the study protocol at baseline and 16-to-47-month follow-up. Participants were classified as pRBD+ (n = 25) or pRBD− (n = 40) based on an established cutoff of 6 on the RBD Sleep Questionnaire (RBDSQ). Participants also completed a) comprehensive cognitive testing, b) self-report measures of depression, anxiety, and apathy, and c) performance-based and other-report forms of instrumental activities of daily living.

Results: Baseline mean age was 67.8 (SD = 8.1; range = 45–86) and baseline mean years of education was 16.4 (SD = 2.1; range = 12–20). The two groups did not differ on measured demographic characteristics. Baseline mean T-scores for cognitive tests were in the average range (46–55). Hierarchical linear models tested group differences in cognitive and functional decline from baseline to follow-up, controlling for appropriate demographic and psychiatric variables. Compared to the pRBD− group, pRBD+ participants showed greater decline in attention/working memory ($r = -0.31$; $p = 0.01$) and UPSA financial skills ($r = -0.31$; $p = 0.01$). No other group differences approached significance.

Conclusions: RBD may differentially affect attention/working memory and financial abilities in PD. Results underscore the importance of regular RBD screening in older adults with PD in order to triage symptomatic patients to appropriate cognitive and medical interventions.

Keywords: Neuropsychology; Neurodegeneration; Movement disorders; Activities of daily living; Sleep

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Introduction

Parkinson's disease (PD) is a movement disorder that has traditionally been characterized by motor symptoms such as bradykinesia, rest tremor, and rigidity (Postuma et al., 2015). In recent years, the scope of PD research has broadened to include nonmotor symptoms such as cognitive impairment, sleep disturbance, and psychological distress, which increase mortality and reduce quality of life in people with the disease (Chaudhuri, Healy, & Schapira, 2006; Marras & Chaudhuri, 2016; Poewe, 2008; Schapira, Chaudhuri, & Jenner, 2017; Sveinbjornsdottir, 2016). Cognitive impairment is common in PD (Aarsland, 2016; Domellof, Ekman, Forsfren, & Elgh, 2015; Goldman et al., 2018; Pedersen, Larsen, Tsynes, & Alves, 2017), with approximately one quarter of nondemented PD patients meeting criteria for mild cognitive impairment (MCI; Aarsland et al., 2017), and a disproportionately high number of these individuals ultimately transitioning to a dementia diagnosis (Aarsland et al., 2017; Kehagia, Barker, & Robbins, 2010; Pedersen et al., 2017). Moreover, in the context of significant relationships between cognitive abilities and instrumental activities of daily living (IADLs) in older adults (Hanks, Rapport, Millis, & Deshpande, 1999; Jefferson, Paul, Ozonoff, & Cohen, 2006; Razani et al., 2007), patients with PD-MCI show measurable difficulties with IADLs as measured by performance-based tests (Pirogovsky et al., 2014; Sumida et al. 2021).

In conjunction with motor symptoms and cognitive impairment, sleep disturbances such as Rapid Eye Movement Sleep Behavior Disorder (RBD) are common in PD, with roughly one-third to one-half of PD patients meeting criteria for RBD (Gagnon et al., 2002; Rolinski et al., 2014; Sixel-Döring, Trautmann, Mollenhauer, & Trenkwalder, 2011). RBD is a parasomnia characterized by a lack of muscle atonia during REM sleep, resulting in physical dream enactments (Marques et al., 2010) and often occurring prodromal to the onset of motor symptoms in PD (Berg et al., 2014; Gagnon, Postuma, Mazza, Doyon, & Montplaisir, 2006). Idiopathic RBD is associated with cognitive impairment (Ferini-Strambi et al., 2004; Figorilli et al., 2020; Marques et al., 2010; Youn et al., 2016) and cognitive decline more broadly (Boeve, 2010). Additionally, some evidence suggests that RBD is associated with a faster rate of cognitive decline in PD (Folle, Paul, Bronstein, Keener, & Ritz, 2019), and the presence of comorbid RBD and MCI is related to a faster rate of progression of overall PD symptoms (Fereshtehnejad et al., 2015). Taken together, this suggests that early recognition of RBD is important for the identification of those PD patients who are at increased risk for later cognitive decline and disease progression (Lin & Chen, 2018).

A substantial cross-sectional literature suggests that PD patients with RBD (PD/RBD+) perform worse on cognitive batteries than PD patients without RBD (PD/RBD−; Mao et al., 2020), although limitations inherent in this methodology prevent a full understanding of the progression of PD/RBD and cognition over time. Specifically, past cross-sectional studies have shown that, compared to PD/RBD−, PD/RBD+ perform worse on measures of attention (Jozwiak et al., 2017; Zhang et al., 2016), visuospatial abilities (Jozwiak et al., 2017; Pagano et al., 2018; Vendette et al., 2007), learning (Jozwiak et al., 2017; Mahmood et al., 2020; Vendette et al., 2007; Zhang et al., 2016), memory (Jozwiak et al., 2017; Pagano et al., 2018; Vendette et al., 2007; Zhang et al., 2016), and executive functions (Jozwiak et al., 2017; Trout et al., 2020; Zhang et al., 2016). In contrast, the literature on RBD and psychiatric functioning in PD is mixed in that PD/RBD+ patients have not always differed from PD/RBD− in terms of depression, anxiety, and apathy (Jozwiak et al., 2017; Mahmood et al., 2020; Pagano et al., 2018; Xie, Shen, Zhou, & Xu, 2021). A large literature suggests that psychiatric symptoms are associated with both worse cognition (Robinson, Watkins, & Harmon-Jones, 2013) and lower quality sleep (Walker, 2009) in the general population, so it is important to account for psychiatric symptoms in investigations of cognition and RBD in PD.

The majority of the current research investigating the impact of RBD on multiple domains of cognition is cross-sectional, thereby diminishing prognostic utility. In contrast, longitudinal investigations could provide evidence regarding the predictive validity of RBD in PD with respect to cognitive outcomes. Unfortunately, this literature is sparse and so firm conclusions cannot yet be drawn from it. Postuma, Lang, Gagnon, Pelletier, and Montplaisir (2012) showed that RBD is a risk factor for later conversion to PD dementia, and three studies reported that PD/RBD+ was associated with more rapid cognitive decline over time than PD/RBD−, using the Mini-Mental State Examination or Montreal Cognitive Assessment (MoCA; De La Riva, Smith, Xie, & Weintraub, 2014; Folle et al., 2019; Pagano et al., 2018). Only one longitudinal study to our knowledge examined the effects of RBD on cognitive decline in PD with a multi-domain neuropsychological battery. Chahine et al. (2016) administered the RBD Screening Questionnaire (RBDSQ; Stiasny-Kolster et al., 2007), the MoCA, and an abbreviated 6-test battery to 423 nondemented PD patients, with multiple yearly follow-up assessments. They reported that baseline probable RBD (pRBD) correlated with later cognitive decline on the MoCA, one test of attention/processing speed, and delayed verbal memory (free recall). However, Chahine and colleagues did not measure aspects of executive functioning (e.g., verbal abstraction, problem solving, inhibitory control) or visual memory, and they did not report on longitudinal relationships among baseline pRBD and changes in psychiatric symptomatology or IADLs. Both dysexecutive (Dirnberger & Jahanshahi, 2013; Kudlicka, Clare, & Hindle, 2011; Zgaljardic et al., 2006) and psychiatric symptoms (Aarsland, Marsh, & Schrag, 2009; den Brok et al., 2015; Dissanayaka et al., 2017) are common in PD (including PD/RBD+) and contribute to disease burden, so it is important to understand the relationship between RBD and these symptoms. Moreover, the ability to complete IADLs is key to healthy,

autonomous aging, and yet IADLs have been understudied in PD/RBD; consequently, there is a need to further examine and report on these factors.

In the current study, we sought to expand on the results of Chahine et al. (2016) with a longitudinal investigation of the cognitive and functional effects of pRBD in PD, accounting for psychiatric symptomatology. We administered a comprehensive cognitive battery, measures of psychiatric symptoms, and tests of IADLs to PD patients at baseline and 16-to-47-month follow-up. Our primary hypothesis was that the baseline pRBD+ group would decline to a greater degree than the pRBD− group on tests of attention/working memory, visuospatial abilities, episodic memory, and executive functions. We also explored the impact of baseline pRBD+ on follow-up IADLs and symptoms of depression, anxiety, and apathy.

Methods

Participants and Procedure

We recruited participants from the community and the Movement Disorders Clinic at the *University of San Diego* and VA San Diego between 2009 and 2017 as part of a longitudinal parent study on cognitive decline in PD. Inclusion criteria for the current study were a) the completion of baseline RBDSQ and b) both baseline and a 16–47-month follow-up assessment of objective cognitive performance. Variability in follow-up duration occurred for several reasons, including missed appointments, transportation difficulties, and lack of patient availability for comprehensive research evaluations.

Board-certified neurologists specializing in movement disorders diagnosed PD based on the United Kingdom Parkinson's Disease Society Bank Criteria (Hughes, Ben-Shlomo, Daniel, & Lees, 1992). We excluded PD patients for the following reasons: 1) the presence of plausible secondary causes of parkinsonism at baseline, 2) a comorbid neurodegenerative illness, 3) untreated major depression and/or psychotic symptoms, 4) prior treatment for substance abuse, 5) positive screen for dementia based on a baseline score of <124 on the Mattis Dementia Rating Scale (MDRS; Llebaria et al., 2008; Schmidt et al., 1994), or 6) missing data from over half of the cognitive tests at both time points. Ultimately, 65 participants aged 48–86 (22 women; 12–20 years of education) met both inclusion and exclusion criteria (PD/pRBD+ = 25; PD/pRBD− = 40; see Table 1 for demographic characteristics), representing 38% of the sample reported in a cross-sectional analysis (Mahmood et al., 2020).

PD patients who were receiving dopaminergic therapy as part of their ongoing treatment completed the neurocognitive battery while on medication; levodopa equivalent dosage (LED) is presented in Table 1 (Mahmood et al., 2020). Motor symptoms were assessed using Part III of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS; Goetz et al., 2008) and a modified version of the Hoehn and Yahr rating scale (Goetz et al., 2004) to denote the disease stage. Of the 62 participants with available UPDRS-Part III data at baseline, 3% were "off" (i.e., overnight washout) medications and 97% were "on" (i.e., normal routine) medications during the UPDRS-Part III, with no differences between the PD/pRBD groups ($p = 0.521$). Of the 54 participants with available UPDRS-Part III data at follow-up, 100% were "on" at follow-up. PD-MCI status was based on Level II criteria of the Movement Disorder Society Task Force Guidelines (Litvan et al., 2012).

All 65 participants completed a comprehensive neuropsychological test battery (see Table 2) and additional psychiatric and clinical measures at baseline and 16–47-month follow-up. Participants provided informed consent and the local institutional review board approved the study.

Measures

RBD. The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ; Stiasny-Kolster et al., 2007) is a self-report measure of RBD symptom severity. Prior research suggests that a cutoff score of 6 has good sensitivity (0.842) and specificity (0.962) in identifying RBD in PD (Nomura, Inoue, Kagimura, Uemura, & Nakashima, 2011; Wang et al., 2015). We administered the RBDSQ and grouped participants into pRBD+ and pRBD− groups, as described in the Statistical Analyses section.

Cognitive performance. Participants underwent a comprehensive neuropsychological battery assessing attention/working memory, language, visuospatial functioning, learning, memory, and executive functions (Table 2), and comprised of tests that are frequently administered in PD patients (Pirogovsky-Turk et al., 2017). We calculated cognitive composites for the six cognitive domains by averaging T scores for tests within each domain, with the constraint that at least two individual measures were required to calculate a composite (Miller & Rohling, 2001; see Table 2).

Functional capacity. Participants completed the UCSD Performance-Based Skills Assessment (UPSA; Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001) finance subtest to assess financial management skills and the Medication Management

Table 1. Sample characteristics

	T1 PD/pRBD + Mean (SD) or n (%) ($n = 25$)	T1 PD/pRBD− Mean (SD) or n (%) ($n = 40$)	T2 PD/pRBD + Mean (SD) or n (%) ($n = 25$)	T2 PD/pRBD− Mean (SD) or n (%) ($n = 40$)
Demographic Characteristics				
Age (years)	68.20 (7.82)	67.50 (8.32)	70.56 (7.81)	69.83 (8.32)
Education (years)	15.84 (2.21)	16.80 (2.03)	–	–
Gender (% men)	64	68	–	–
Race/Ethnicity (% White)	92	95	–	–
Disease Characteristics				
Duration of PD (years)	5.82 (4.08)	5.93 (5.83)	8.29 (3.71)	8.09 (5.68)
UPDRS Part III[*]	12.88 (7.60)	17.70 (13.31)	17.09 (11.45)	22.09 (12.58)
Modified Hoehn and Yahr stage	1.69 (0.59)	1.77 (0.88)	2.07 (0.68)	2.03 (0.86)
Levodopa dosage equivalence	829.82 (336.56)	649.32 (628.95)	795.82 (410.09)	678.90 (355.73)
PD-MCI status (%)	4 (16%)	9 (23%)	12 (50%)	11 (28%)
Mood/Sleep Characteristics				
RBDSQ	8.64 (2.34)	3.18 (1.43)	8.88 (3.09)	4.82 (2.29)
Geriatric Depression Scale	7.20 (4.56)	5.23 (4.14)	6.48 (5.46)	5.53 (4.57)
Apathy Scale	11.72 (4.70)	10.23 (4.58)	11.60 (6.38)	10.27 (4.60)
State Anxiety (STAI)	35.00 (8.62)	32.55 (9.52)	36.52 (8.87)	35.16 (11.61)
Trait Anxiety (STAI)	34.96 (8.51)	33.30 (9.40)	36.16 (9.41)	34.03 (9.48)
Cognitive Functioning				
MDRS total score	139.16 (3.40)	139.03 (3.53)	135.52 (8.21)	138.25 (4.32)
Global Cognition	50.87 (6.91)	53.40 (5.37)	46.67 (9.14)	50.94 (7.93)
Attention/Working memory	45.87 (7.58)	46.77 (7.26)	40.39 (9.45)	45.13 (9.63)
Language	52.25 (9.96)	51.46 (9.99)	50.55 (10.32)	49.41 (10.51)
Visuospatial functioning	53.28 (7.58)	56.17 (9.23)	46.69 (12.07)	51.97 (10.33)
Learning	50.21 (9.90)	56.03 (7.23)	46.59 (11.52)	53.40 (9.67)
Memory	52.52 (8.70)	56.42 (7.46)	50.08 (10.18)	55.45 (9.25)
Executive Functioning	51.97 (8.32)	54.28 (5.82)	48.10 (9.88)	50.31 (9.85)
Functional Capacity				
MMAA	29.16 (5.15)	30.68 (3.65)	25.13 (8.20)	29.44 (5.73)
UPSA (Finance subscale)	10.12 (0.83)	10.03 (0.95)	8.96 (2.51)	10.14 (1.27)
IADL Scale	13.79 (2.59)	14.32 (2.06)	12.54 (4.20)	13.00 (3.38)

Global Cognition = global neuropsychological performance (calculated as an average of all individual cognitive measures); IADL = Instrumental Activities of Daily Living; MDRS = Mattis Dementia Rating Scale; MMAA = Medication Management Abilities Assessment; PD-MCI=Parkinson's disease-Mild Cognitive Impairment status; RBDSQ = REM Behavior Disorder Screening Questionnaire; STAI=State/Trait Anxiety Inventory; T1 = time point 1 (baseline); T2 = time point 2 (follow-up); UPDRS=Unified Parkinson's Disease Rating Scale; UPSA = UCSD Performance-Based Skills Assessment.

[*]No on versus off medication differences between groups.

All cognitive domains report results using T-scores ($M \pm SD = 50 \pm 10$, range 20–80), except for the MDRS total score, which is expressed as a total raw score (range 0–144).

Abilities Assessment (MMAA; Patterson et al., 2002) to measure the ability to take medications as instructed. PD patients' caregivers completed the Instrumental Activities of Daily Living Scale (IADL; Lawton & Brody, 1969). We analyzed total scores from these measures, with higher scores reflecting better performance and functioning.

Neuropsychiatric symptoms. We measured mood with the Geriatric Depression Scale (GDS; Yesavage et al., 1982), anxiety with the State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) Trait and State total scores (Barnes, Harp, & Jung, 2002), and apathy with the Apathy Scale (Starkstein et al., 1992). Empirical support exists for the psychometric properties of each of these measures in PD (Dissanayaka et al., 2017; Leentjens et al., 2008a, 2008b). Higher scores indicate more severe neuropsychiatric symptoms.

Statistical Analyses

We classified PD patients into PD/pRBD+ (n = 25) and PD/pRBD− (n = 40) using an established cutoff score of 6 on the RBDSQ (Nomura et al., 2011). Baseline sample and PD disease characteristics are summarized in Table 1. Four participants (three PD/pRBD−, one PD/pRBD+) were missing the IADL Scale at baseline, two (one PD/pRBD−, one PD/pRBD+) were missing the MMAA at follow-up, six (five PD/pRBD−, one PD/pRBD+) were missing the IADL Scale at follow-up, 12 (eight

Table 2. Neuropsychological assessment battery

Cognitive domain	Tests within domain	Normative data	Demographic adjustments
Attention/	CVLT-II Trial 1	Delis et al., 2000	Age, gender
Working Memory	DOT-A	Schiehser et al., in preparation	Gender
	DKEFS Color Naming	Delis et al., 2001	Age
Language	MDRS Similarities	Neurocognition Movement Lab norms	–
	DKEFS Category Fluency	Delis et al., 2001	Age
Visuospatial Functioning	JLOT	Schiehser et al., in preparation	Gender
	WMS-III Visual Reproduction Copy	Wechsler, 1997	Age, education
Learning	CVLT II Trials 1–5 Total	Delis et al., 2000	Age, gender
	WMS-III Logical Memory I Recall	Wechsler, 1997	Age, education
	WMS-III Visual Reproduction I Recall	Wechsler, 1997	Age, education
Memory	CVLT II Long Delay Free Recall	Delis et al., 2000	Age, gender
	WMS-III Logical Memory II Recall	Wechsler, 1997	Age, education
	WMS-III Visual Reproduction II Recall	Wechsler, 1997	Age, education
Executive Functioning	WCST Total Errors	Heaton & Staff, 1993	Age, education
	DKEFS Letter Fluency	Delis et al., 2001	Age
	DKEFS Color-Word Inhibition	Delis et al., 2001	Age
	DKEFS Inhibition/Switching	Delis et al., 2001	Age

CVLT-II = California Verbal Learning Test -Second Edition; DKEFS=Delis-Kaplan Executive Function System; DOT-A = Ascending Digit Order Test; JLOT = Judgment of Line Orientation Test; MDRS = Mattis Dementia Rating Scale; WCST = Wisconsin Card Sorting Test; WMS-III=Wechsler Memory Scale-Third Edition.

PD/pRBD−, four PD/pRBD+) were missing the GDS at follow-up, three (all PD/pRBD−) were missing the AS at follow-up, and two (both PD/pRBD−) were missing the STAI at follow-up.

Given variability in duration between baseline and follow-up assessment (16–47 months), study hypotheses were tested using hierarchical linear models (HLM) in R (R Core Team, 2020) with lme4 (Bates, Maechler, Bolker, & Walker, 2015). All available data were used for parameter estimates, via maximum likelihood estimation, in order to account for missing data (Schafer & Graham, 2002; Singer, Willett, & Willett, 2003). The random effect of intercept for individuals was included in all models; model convergence issues precluded the inclusion of the random effect of visit. Visit was modeled as a continuous parameter representing time in months. In addition to visit as the lower level predictor, we entered a dummy-coded variable representing the comparison between PD/pRBD− and PD/pRBD+ patients (coded as 0 and 1, respectively) as the higher order predictor variable (i.e., between person variables). The resulting group × visit cross-level interaction term represents the parameter of interest in the current study.

Based on established methods for covariate selection (Raab, Day, & Sales, 2000), bivariate Pearson/Spearman correlations determined that demographic characteristics (i.e., age, gender, education) and baseline severity of depression and apathy were significantly associated with cognitive outcomes; thus, these variables were included as covariates within the HLMs. Age emerged as the only statistically significant bivariate correlate of functional and psychiatric outcomes, with depression and apathy also emerging as a bivariate correlate of IADL scores. As such, these variables were included as covariates within their respective models. Time since PD diagnosis did not correlate with any outcomes of interest, so it was not included as a covariate in the models. Moreover, results from models covarying for LED were comparable to models that did not; as such, results from the latter are reported.

We performed backward selection elimination of covariates with $p > 0.05$ in the HLMs. Examination of model fit statistics (−2 log likelihood [−2LL], Akaike Information Criterion [AIC], and Schwarz's Bayesian Criterion [BIC]) determined that the inclusion of these additional covariates did not improve model fit. As such, data from the more parsimonious models are reported, with remaining covariates specified for each model. Estimate effect sizes for the HLM analyses are reported as r values (small = 0.10; medium = 0.30; large = 0.50; Cohen, 1992). Alpha was set a priori at $p < .05$.

Results

Baseline RBDSQ scores were as follows: PD/pRBD+: $M = 8.64$ ($SD = 2.34$), and PD/pRBD−: $M = 3.18$ ($SD = 1.43$). At baseline, there were no group differences on MDS-UPDRS Part III, $U = 381$, $p = 0.17$, Hoehn & Yahr stage $t(61) = 0.40$, $p = 0.69$, or time since PD diagnosis, $t(62) = 0.08$, $p = 0.94$; however, the groups differed on LED, $U = 703.5$, $p = 0.006$,

Table 3. Results of linear mixed effects models examining the effect of baseline probable RBD status on changes in cognitive and functional scores, and psychiatric symptom severity

Measures	PD/pRBD− vs. PD/pRBD+				
	B	SE	*t*	*p*	*r*
Cognitive Functioning[a]					
Global Cognition	−0.07	0.05	−1.62	0.11	−0.20
Attention/Working memory	−0.16	0.06	−2.61	**0.01**	−0.31
Executive Functioning	−0.02	0.07	−0.35	0.73	−0.04
Language*	0.02	0.08	0.21	0.84	0.03
Learning	−0.05	0.06	−0.85	0.40	−0.10
Memory	−0.07	0.06	−1.19	0.24	−0.15
Visuospatial Functioning	−0.10	0.08	−1.28	0.21	−0.16
Functional Capacity[b]					
MMAA	−0.05	0.05	−0.89	0.38	−0.12
UPSA (Finance subscale)	−0.03	0.01	−2.69	**0.01**	−0.31
IADL Scale**	−0.002	0.03	−0.08	0.94	−0.01
Symptom severity					
Geriatric Depression Scale[c]	−0.03	0.04	−0.78	0.44	−0.10
Trait Anxiety (STAI-T)[c]	0.03	0.06	0.42	0.68	0.05
Apathy Scale	−0.004	0.04	−0.01	0.92	−0.01

Note. IADL= Instrumental Activities of Daily Living; MMAA = Medication Management Abilities Assessment; PD/pRBD− = Parkinson's Disease, no REM Behavior Disorder; PD/pRBD+ = Parkinson's Disease, with REM Behavior Disorder; STAI = State Trait Anxiety Inventory; UPSA = UCSD Performance-Based Skills Assessment.

[a]Controlling for education and gender

[b]Controlling for age at baseline

[c]Controlling for gender

*also controlling for age at baseline

**also controlling for baseline depression severity

with PD/pRBD+ evidencing higher LED. Controlling for gender and education, the PD/pRBD+ group had lower learning at baseline, but the difference was not statistically significant, B = −4.08, $t(1, 84.27) = -1.89$, $p = 0.06$, $r = -0.20$. Similarly, after controlling for gender, depressive symptom severity was higher in the PD/pRBD+ group at baseline, but this difference was also not statistically significant, B = 2.01, $t(1, 96.61) = 1.80$, $p = 0.08$, $r = 0.18$. There were no other group differences at baseline.

Controlling for education and gender, PD/pRBD+ patients' global cognitive scores were not significantly different than those of PD/pRBD− patients' at follow-up, B = −0.07, $t(1, 65.62) = -1.62$, $p = 0.11$, $r = -0.20$, although the effect was in the prediction direction. Controlling for age and education, HLMs examining group-related change in individual cognitive domains revealed that PD/pRBD+ patients declined to a greater degree in attention/working memory performance than PD/pRBD− patients, B = −0.16, $t(1, 65.85) = -2.61$, $p = 0.01$, $r = -0.31$. No other group-related changes in individual cognitive domains were significant; however, all effects were in the predicted direction except for the language domain ($r = 0.03$; $p = 0.84$).

Controlling for the effects of age at baseline, PD/pRBD+ patients showed a greater decline in UPSA financial subscale scores than PD/pRBD− patients, B = −0.05, $t(1, 67.50) = -3.39$, $p = 0.001$, $r = -0.38$, and MMAA, B = −0.12, $t(1, 63.34) = -2.03$, $p = 0.046$, $r = -0.25$. Given non-normal residual distributions for the HLMs examining group-related differences in change in UPSA and MMAA scores, the models were rerun excluding outliers (six participants with an MMAA score of ≤9 at visit 2; three participants with an UPSA score ≤5 at visit 2). The UPSA results remained statistically significant, $p = 0.01$, $r = -0.31$, but the MMAA findings were no longer significant, $p = 0.38$, $r = -0.12$. No other group-related differences in change in functional or psychiatric outcomes were significant. Table 3 presents the parameter estimates, *p*-values, and effect sizes for the group × visit interaction for all HLM outcome measures.

Discussion

This study evaluated the longitudinal impact of PD/pRBD status on cognitive and functional outcomes, accounting for psychiatric symptomatology. Of the 65 participants, 25 (38.5%) met criteria for pRBD at baseline, which is consistent with prior prevalence estimates (Gagnon et al., 2002; Rolinski et al., 2014; Sixel-Döring et al., 2011). Partially consistent with a priori hypotheses, the PD/pRBD+ group declined to a greater degree in attention/working memory than did the PD/pRBD− group, with a medium effect size ($r = -0.31$). That is, while the PD/RBD− group mean T score remained in the average range

from time 1 (M = 46.77 [7.26]) to time 2 (M = 45.13 [9.63]), the PD/RBD+ group mean T score declined from the average range at time 1 (M = 45.87 [7.58]) to the low average range at time 2 (M = 40.39 [9.45]). Additionally, the PD/pRBD+ group also declined to a greater degree on a test of financial skills, with a medium effect size ($r = -0.31$). There were no other significant group differences in change in cognitive or functional outcomes from baseline to 16–47-month follow-up.

Our primary finding that the baseline PD/pRBD+ group declined more across time in attention/working memory than the PD/pRBD− group extends cross-sectional literature suggesting that PD/pRBD+ patients perform worse on measures of attention compared to PD/pRBD− patients (Jozwiak et al., 2017; Zhang et al., 2016). Our finding also partially aligns with evidence of more pronounced deterioration in attention/processing speed in a longitudinal investigation showing RBD-associated neuropsychological decline in PD (Chahine et al., 2016). Importantly, although we measured attention using different tests than Chahine et al. (2016), the sensitivity of this domain to PD/RBD+ in both studies suggests that it may be uniquely vulnerable to the additive impact of the RBD syndrome in PD. Consistent with this notion, broader literature suggests that attentional weaknesses are an early and prominent cognitive feature in patients with parkinsonian disorders (e.g., dementia with Lewy bodies) who have RBD and later develop MCI or dementia (Genier Marchand et al., 2018), and some evidence suggests that idiopathic RBD is associated with attentional deficits as well (Youn et al., 2016).

In addition to a more pronounced cognitive decline, the PD/pRBD+ group also declined to a greater degree than the PD/pRBD− group in an IADL specific to financial management skills (measured by the UPSA). Cognitive abilities are associated with IADLs (including UPSA performance) in a variety of clinical populations (e.g., Moore et al., 2017; Spitz, Ponsford, Rudzki, & Maller, 2012; Twamley et al., 2002), including PD (Holden et al., 2018; Pirogovsky et al., 2013, 2014). Moreover, attention and working memory have specifically been shown to share variance with performance-based functional capacity in older adults with varying degrees of cognitive impairment (Garcia-Alvarez, Gomar, Sousa, Garcia-Portilla, & Goldberg, 2019), suggesting that the RBD-associated decline in attention/working memory in the current study may have at least partially explained the decline in UPSA financial skills.

Aside from the attention/working memory domain, our hypotheses involving RBD-associated decline in neurocognition were largely unsupported, although results were generally in the predicted direction (i.e., greater decline in PD/pRBD+ compared to PD/pRBD−). In contrast, Chahine et al. (2016) demonstrated longitudinal decline in PD/pRBD+ compared to PD/pRBD− in general cognition and delayed recall. The authors did not measure visual memory or executive functioning, making the current study the only longitudinal investigation to our knowledge to assess the impact of these domains in PD/pRBD+ and PD/pRBD− groups. Overall, discrepancies between our focal cognitive results and other work suggesting widespread RBD-associated changes (e.g., Folle et al., 2019; Jozwiak et al., 2017; Zhang et al., 2016), may result from a confluence of factors, including our smaller sample size (compared to Chahine et al., 2016), and differences in sample characteristics, follow-up windows, RBD assessment, and disease duration.

Several important scientific and clinical implications follow from the current study findings. From a research perspective, when measuring cognition in longitudinal studies of PD, it is important to assess and account for RBD. Clinically, if RBD is present in evaluations of PD patients, neuropsychologists may expect a greater decline across time in attention/working memory and financial skills than they would if the patient did not have RBD. In the presence of PD and RBD, measurement of attention and working memory could be made a higher priority during test selection and the clinical interview could include detailed questions regarding finances, with the goal of identifying early signs of errors and loss of independence. Moreover, during feedback sessions, knowledge of possible future decline in attention/working memory and financial skills could inform psychoeducation and recommendations. For example, if clinically indicated, neuropsychologists might suggest that patients receive extra assistance with finances, and compensatory cognitive strategies could specifically target the domain of attention and working memory.

The current study has several limitations, and results should be interpreted in light of these factors. First, although multiple follow-up evaluations better elucidate temporal patterns of change, the current study was limited to baseline and a single follow-up visit. Second, our sample was relatively small and was comprised of predominantly white, highly educated participants, thereby reducing statistical power and generalizability. Although the gender distribution of our PD groups was imbalanced (approximately two-thirds men), this is consistent with previous demographic prevalence estimates in PD (Kim & Jeon, 2014; Van Den Eeden et al., 2003). Regarding ethnic/racial and socioeconomic diversity, recruitment took place primarily in the region surrounding the University of San Diego and VA San Diego, although efforts were made to recruit PD patients from the larger San Diego county area as well. To encourage PD patients of lower socioeconomic status to participate, all patients were offered free transportation to and from appointments. Still, the sample was relatively homogeneous in terms of race/ethnicity and education, and we have since widened our catchment area so as to recruit more diverse samples for our research program. Third, we excluded patients with comorbid neurodegenerative illnesses, dementia, and untreated major depressive disorder or psychotic symptoms, which further limits external validity. Finally, we assessed RBD with a self-report measure (the RBDSQ),

as opposed to objective polysomnography, and there are limitations to assessment of RBD via self-report (Stiasny-Kolster et al., 2015). Consequently, our interpretations are confined to probable RBD rather than definitive RBD.

The current study also has several strengths. First, in contrast to past cross-sectional work in PD/RBD and cognition, the current study's longitudinal design allowed us to assess the predictive validity of baseline pRBD symptoms on future cognitive decline. Specifically, as mentioned earlier, we only measured two time points, which limits our ability to draw conclusions about the slope of decline across many years; however, we can suggest that baseline pRBD confers a greater risk for decline in attention/working memory and financial skills in PD across a 1–4 year time interval. Second, we administered a comprehensive battery of cognitive, psychiatric, and functional tests, thereby allowing for a thorough evaluation of relevant covariates, potential confounds, and outcomes.

In summary, we found evidence that PD patients with pRBD declined to a greater degree over time in attention/working memory and UPSA financial skills than those with PD without pRBD. There were no other significant RBD-associated differences in longitudinal change rates. Our findings underscore the importance of regular RBD screening in older adults at risk for PD, in order to triage symptomatic patients to appropriate support and care. Specifically, identifying patients who are at greater risk for domain-specific cognitive and IADL change may allow for targeted behavioral and/or medical interventions. This may, in turn, improve cognitive functioning, stave off decline, and/or reduce the functional consequences of such decline in this patient population.

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Conflict of Interest

None declared.

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