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Research article

Multiple sleep disturbances are associated with apathy in individuals with Parkinson's disease

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ABSTRACT

Background: Parkinson's disease (PD) is associated with both sleep disturbances and apathy, and within PD, apathy has been associated with REM behavior disorder and excessive daytime sleepiness. Whether other forms of sleep disturbance are similarly associated with apathy in PD remains unclear. This study explored associations between a broad array of sleep disturbances and apathy in 50 individuals with idiopathic PD (PD) and 48 matched controls (MC).

Methods: Participants were adults aged 53–80 (*Mdn* = 67), 23 % female, and 96 % white. Sleep disturbances were measured with various questionnaires (ISI, PSQI, PROMIS-SD, ESS, PROMIS-SRI, RBDSQ). Mood was measured with the STAI and BDI-II. Apathy was evaluated using the Apathy Scale (AS). Spearman correlations and regression analyses were performed between measures of sleep disturbance and AS in the total sample and each group. Group correlations were compared using 2-sample Fisher's *z* test.

Results: The AS total score significantly correlated with PROMIS-SRI in the total sample and multiple measures of sleep disturbance in the PD group. The apathy subscales were each significantly correlated with sleep disturbance measures in the total sample, MC, and PD groups. The correlations between several sleep and apathy values were significantly stronger in the PD group than MC. When accounting for anxiety and depression most differences were no longer significant, only the PROMIS-SRI was significantly predictive of the behavioral apathy sub score.

Discussion: Evidence supports an association between sleep disturbances and apathy in individuals with PD. Specifically, insomnia severity, poor sleep quality, and daytime sleepiness were uniquely associated with apathy in this group. We did not find these associations in the matched control group. Anxiety and depression are likely involved in the association between sleep and apathy in PD. Experimental studies that manipulate or improve sleep may further elucidate the mechanisms underlying the association between sleep disturbance and apathy in PD.

Parkinson's disease (PD) is a progressive neurodegenerative disorder whose cardinal motor symptoms include bradykinesia, resting tremor, and rigidity [1]. At least 6.1 million individuals worldwide and 700,000 individuals in the United States have PD [2]. Individuals with PD also frequently experience non-motor symptoms, including alterations in sleep disturbances and motivation

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Table 1
Comparison of sample characteristics between patients with Parkinson's disease (PD) and matched controls (MC).

Characteristic	Total sample ($N = 98$)	MC ($n = 48$)	PD ($n = 50$)	*df*	$t/z/\chi^2$	*p-value*
Age[a], years	67.5 (7.3)	67.5 (7.4)	67.4 (7.2)	96	<0.01	0.946
Education[a], years	16 [14, 19]	17[15, 19]	16 [13, 18]	–	1.04	0.301
Female[a], *n*	23 (23 %)	11 (23 %)	12 (24 %)	1	0.02	0.899
White[a], *n*	94 (96 %)	46 (96 %)	48 (96 %)	2	<0.01	0.999
Married, *n*	86 (88 %)	43 (90 %)	43 (86 %)	1	3.63	0.604
Employed, *n*	23 (23 %)	13 (27 %)	10 (20 %)	2	1.51	0.470
ISI[a], total score	5 [2, 11]	4 [1, 7.5]	6.5 [3, 12]	–	−2.51	0.012*
AS, total score	10.2 (5.1)	9.9 (4.8)	10.5 (5.3)	96	−0.65	0.519
AS, cognitive subscore	4 [2, 6]	4 [2, 5]	5 [1, 7]	–	−1.01	0.313
AS, affective subscore	3 [1, 5]	2 [1, 4]	3 [1, 5]	–	−1.42	0.158
AS, behavioral subscore	1 [0, 2]	1 [0, 2]	1.5 [1, 3]	–	−3.22	0.001**
PROMIS-SD, total score	49 [41, 59]	45 [40, 58]	52 [45, 61]	–	−1.98	0.048*
PROMIS-SRI, total score	27 [21, 36]	23 [18, 29]	33 [26, 39]	–	−4.58	<0.001***
PSQI, total score	5 [3,9]	5 [3, 7]	6 [4, 10]	–	−2.27	0.023*
TST, minutes	420 [360, 450]	420 [390, 465]	420 [360, 450]	–	1.21	0.227
ESS, total score	7 [4, 11]	6 [4, 10]	8 [6, 13]	–	−2.29	0.022*
RBDSQ, total score	3.8 (2.8)	2.2 (1.6)	5.3 (2.9)	96	−6.47	<0.001***
STAI-State, total score	28 [23, 38]	24 [21, 30]	33 [24, 43]	–	−3.51	<0.001***
STAI-Trait, total score	30 [24, 38]	28 [23, 31]	34.5 [27, 42]	–	−3.09	0.002**
MMSE score[a]	29 [28, 30]	29 [28, 30]	29 [28, 30]	–	0.46	0.647
BDI-11, total score	4 [1, 7]	2 [1, 4]	6 [4, 11]	–	−5.13	<0.001***
PDQ-39[b], total score	–	–	32 [18, 48]	–	–	–
Hoehn-Yahr stage	–	–	1.8 (1.1)	–	–	–
Disease Duration, years	–	–	7.8 (4.9)	–	–	–
LED, mg	–	–	756 (493.6)	–	–	–

Note. M(SD), Median[Inter-quartile Range]; ISI = Insomnia Severity Index, AS = Apathy Scale, PROMIS-SD = Patient-Reported Outcomes Measurement Information System - Sleep Disturbance, PROMIS-SRI = Patient-Reported Outcomes Measurement Information System - Sleep-Related Impairment, PSQI = Pittsburgh Sleep Quality Index, TST = total sleep time, ESS = Epworth Sleepiness Scale, RBDSQ = REM Behavior Disorder Screening Questionnaire, STAI-State and STAI-Trait = State-Trait Anxiety Inventory, FSS = Fatigue Severity Scale, MMSE = Mini-Mental Status Exam, BDI-II = Beck Depression Inventory-II PDQ-39 = Parkinson's Disease Questionnaire-39, LED = Levodopa Equivalent Dose, mg = milligrams.
* $p < 0.05$, ** $p < 0.01$, ***p < 0.001.
[a] These sample characteristics have been reported previously in other papers [25].
[b] PDQ-39 was solely administered to the PD group.

(apathy) that are among the earliest symptoms of PD and in some cases appear decades before motor symptoms [3]. Sleep disturbances, including insomnia symptoms, daytime sleepiness, and rapid eye movement (REM) sleep behavior disorder (RBD) are more common in PD than the general population, affecting over 60 % of individuals with PD [4]. Apathy is characterized by a marked reduction of interest, enthusiasm, or concern. When accounting for comorbid depression or dementia, the prevalence of apathy in PD ranges from 3 to 48 % [5]. Recent studies indicate that apathy in conjunction with impulse control behaviors could be a risk factor in the development of levodopa-induced dyskinesia [6]. Moreover, both sleep disturbances and apathy impact an individual's quality of life as they are associated with impairments in activities of daily living and poorer quality of life [7,8]. Thus, due to the wide prevalence and deleterious impact of sleep disturbances and apathy within PD, investigating how these symptoms are associated is an important target area for research, as it may have implications for earlier detection of PD and improving an individual's quality of life.

Apathy has been described as a "lack of motivation", especially manifesting in diminished goal-directed behavior, including "diminished productivity, lack of effort, diminished initiative [and] lack of persistence" [9]. In the original diagnostic criteria for apathy, Marin proposed three theoretical components (i.e., affective, behavioral, and cognitive), as targets for study and intervention [10]. A conceptual relationship between sleep and apathy is widely assumed and some scholars have gone as far as to include sleep disturbance as a feature of apathy [11]. Early sleep researchers observed that the prevailing mood of participants following sleep deprivation is apathetic depression, characterized by reduced spontaneity, decreased interest in social interaction, and listlessness [12]. Conversely, individual differences in motivation could conceptually lead to changes in sleep behavior and health. For example, apathy may reduce engagement in daytime activity and sleep health recommendations, which may negatively impact sleep health. Some evidence suggests that sleep dysfunction and apathy have common underlying physiological mechanisms [13]. Indeed, sleep disturbance and apathy have been noted in several neurodegenerative diseases, including Alzheimer's disease and myotonic dystrophy [14,15]. Sleep disturbance symptoms are associated with increased levels of apathy in PD as well [16]. In a study on de novo, untreated individuals with Parkinson's disease, researchers found that those individuals with poor sleep at night experienced more apathy [17]. Some have proposed that the comorbidity between sleep disturbance and apathy within PD is due to early mesolimbic dysfunction associated with dopaminergic and neurological changes involved in PD [18–21]. Empirical research on the association between sleep and motivation is sparce, particularly in the context of PD.

Much of the research regarding sleep disturbance and apathy in PD has focused on associations between excessive daytime sleepiness, RBD and apathy [22]. Bargiotas and colleagues [22] found that within PD, RBD is associated with increased levels of apathy. The authors noted that sleep disturbance beyond RBD may account for this association. Another study failed to find greater

Table 2
Correlations between the Apathy Scale (AS) total score, Affective, Behavioral, and Cognitive subscale scores with other measures in the total sample ($N = 98$), individuals with Parkinson's disease (PD, $n = 50$), and matched controls (MC, $n = 48$).

	AS total score			Affective subscale			Behavioral subscale			Cognitive subscale		
Sleep measures	Total sample	PD	MC	Total sample	PD	MC	Total sample	PD	MC	Total sample	PD	MC
ISI, total score	0.17	0.38**+	−0.13	0.14	0.15	0.05	0.39*	0.47*	0.17	0.22*	0.40**+	0.04
PROMIS-SD, total score	0.20	0.32*	0.03	0.12	0.02	0.16	0.41*	0.52*	0.22	0.26*	0.32*	0.12
PSQI global score	0.13	0.19	−0.01	0.07	−0.03	0.10	0.36*	0.40*	0.18	0.24*	0.31*	0.08
TST, minutes	−0.03	−0.21	0.21	−0.03	0.03	−0.08	−0.24*	−0.43*+	0.06	−0.12	−0.31*+	0.18
RBDSQ, total score	<0.01	−0.07	−0.02	0.04	−0.09	0.04	0.23*	−0.04	0.16	−0.03	−0.07	−0.18
PROMIS-SRI, total score	0.37***	0.56***	0.22	0.26*	0.28	0.21	0.61*	0.71*+	0.39*	0.35***	0.49***	0.20
ESS, total score	0.15	0.42**+	−0.18	0.09	0.28*+	−0.21	0.33*	0.45*	0.07	0.14	0.33*+	−0.12
STAI-State, total score	0.27**	0.47***+	−0.05	0.22*	0.33*	0.05	0.48***	0.59***+	0.20	0.28**	0.38**	0.05
STAI-Trait, total score	0.41***	0.57***+	0.17	0.41***	0.47***	0.32*	0.52***	0.63***+	0.31*	0.33***	0.41**	0.09
BDI-II, total score	0.37***	0.47***	0.24	0.34***	0.33*	0.26	0.63***	0.59***	0.56***	0.34***	0.40**	0.21
PDQ-39, total score[a]	–	0.45**	–	–	0.19	–	–	0.63***	–	–	0.45**	–
Disease duration, months	–	−0.10	–	–	−0.10	–	–	−0.07	–	–	−0.14	–
LED	–	0.26	–	–	0.20	–	–	0.05	–	–	0.37**	–

Note:
+Fisher's z significant between groups at $p < 0.05$. [a]The PDQ-39 was only administered to patients with PD, thus the sample for these correlations was the PD group (n = 50). ISI = Insomnia Severity Index, PROMIS-SD = Patient-Reported Outcomes Measurement Information System - Sleep Disturbance, PSQI = Pittsburgh Sleep Quality Index, TST = Total Sleep Time, RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire, PROMIS-SRI = Patient-Reported Outcomes Measurement Information System - Sleep-Related Impairment, ESS = Epworth Sleepiness Scale, STAI-State, and STAI-Trait = State-Trait Anxiety Inventory, BDI-II = Beck Depression Inventory, PDQ-39 = Parkinson's Disease Questionnaire, LED = Levodopa Equivalent Dose, mg = milligrams.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

apathy in patients with both PD and RBD, which may have been due to the dopaminergic therapy administered for two months before the study [23]. Chan and colleagues [24] conducted a longitudinal study which assessed individuals with mild PD over the course of two years and observed that a worsening in EDS was also associated with increased levels of apathy. Although these preliminary results demonstrate that there seems to be an association between sleep disturbances and apathy within PD, examining how sleep disturbances beyond EDS and RBD are associated with apathy may further elucidate how these impairing symptoms interact within the context of PD.

This study aimed to examine how a broad array of self-reported sleep disturbances including insomnia severity, sleep quality, sleep duration, probable RBD, and daytime sleepiness, are associated with the three theoretical components (i.e., affective, behavioral, and cognitive components) of apathy in a sample of individuals with PD and matched controls. Such a study may have important implications in understanding how sleep and mood disturbances co-occur in the context of PD.

1. Methods

1.1. Participants and protocol

This paper is a secondary analysis of data collected from a previously published study where the methods are explained in detail [25]. Herein, we summarize only the basic methods essential to the present analyses. The sample size for the original study was determined a prior based on research on correlations between sleep and wake functioning in PD and older adults without PD [26–33]. Thestatistical software G*Power 3.1 (http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/) was used to estimate the sample size needed to obtain statistical significance across different domains of biopsychosocial functioning using multiple regression. The estimated range in sample size needed for statistical significance was between 70 and 180 subjects, for large to small effects, given

Table 3
Regressions for apathy total score, affective, behavioral, and cognitive sub-scores controlling for group.

	Model 1			Model 2			Model 3			Model 4		
	p	95 % *CI*	*β*	*p*	95 % *CI*	*β*	*p*	95 % *CI*	*β*	*p*	95 % *CI*	*β*
Group	0.434	[-3.04, 1.31]	−0.09	0.408	[-0.64, 1.57]	0.09	0.179	[-0.16, 0.87]	0.15	0.290	[-2.00, 0.60]	−0.12
ISI	0.534	[-0.32, 0.17]	−0.08	–	–	–	0.166	[-0.02, 0.11]	0.21	0.951	[-0.18, 0.19]	0.01
PROMIS-SD	–	–	–	–	–	–	0.061	[-0.04, 0.001]	−0.32	0.283	[-0.10, 0.03]	−0.22
Global PSQI	–	–	–	–	–	–	0.871	[-0.10, 0.09]	−0.02	0.348	[-0.14, 0.39]	0.17
TST	–	–	–	–	–	–	0.962	[<0.01, <0.01]	0.01	0.789	[-0.01, 0.01]	0.04
RBDSQ	–	–	–	–	–	–	0.144	[-0.16, 0.02]	−0.15	–	–	–
PROMIS-SRI	0.010*	[0.04, 0.32]	0.40	0.126	[-0.01, 0.09]	0.19	<0.001**	[0.04, 0.10]	0.63	0.029*	[0.01, 0.20]	0.41
ESS	0.857	[-0.22, 0.27]	0.02*	0.964	[-0.68, 2.93]	−0.01	0.299	[-0.02, 0.07]	0.10	0.881	[-0.16, 0.14]	−0.02

Note: Model 1 predicts Apathy Total Score. Model 2 predicts Apathy Affective sub-score. Model 3 predicts Apathy Behavioral sub-score. Model 4 predicts Apathy Cognitive sub-score. ISI = Insomnia Severity Index, PROMIS-SD = Patient-Reported Outcomes Measurement Information System - Sleep Disturbance, Global PSQI = Pittsburgh Sleep Quality Index, TST = Total Sleep Time, RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire, PROMIS-SRI = Patient-Reported Outcomes Measurement Information System - Sleep-Related Impairment, ESS = Epworth Sleepiness Scale.
β = standardized coefficient.
*p < 0.05, **p < 0.01.

Power = 0.8, alpha error prob = 0.05, and 10 predictors. A sample of 180 would have been ideal. However, due to feasibility constraints, a sample size of 100 was obtained, which allowed for detection of medium to large effects for the original aims of the study and the current secondary analyses.

Participants were aged 53–80 and included 50 individuals with idiopathic PD and 48 matched controls (MC) without PD, who were matched on age, self-reported sex, race, and education. Participants responded male or female to the question "What is your sex?" Participants with PD, who had a clinical diagnosis of idiopathic PD as defined by the United Kingdom PD Society Brain Bank were

Table 4
Regressions for apathy total score, affective, behavioral, and cognitive sub-scores controlling for group, trait anxiety, and depression.

	Model 1			Model 2			Model 3			Model 4		
	p	95 % *CI*	*β*	*p*	95 % *CI*	*β*	*p*	95 % *CI*	*β*	*p*	95 % *CI*	*β*
Group	0.102	[-3.81, 0.42]	−0.17	0.739	[-0.90, 1.27]	0.04	0.761	[-0.46, 0.62]	0.03	0.083	[-2.48, 0.15]	−0.21
ISI	0.191	[-0.38, 0.08]	−0.17	–	–	–	0.299	[-0.03, 0.10]	0.15	0.895	[-0.19, 0.17]	−0.02
PROMIS-SD	–	–	–	–	–	–	0.072	[-0.04, 0.002]	−0.31	0.401	[-0.10, 0.04]	−0.17
Global PSQI	–	–	–	–	–	–	0.897	[-0.10, 0.09]	−0.01	0.419	[-0.16, 0.37]	0.14
TST	–	–	–	–	–	–	0.799	[<-0.01, <0.01]	0.03	0.612	[-0.01, 0.01]	0.07
RBDSQ	–	–	–	–	–	–	0.556	[-0.12, 0.07]	−0.06	–	–	–
PROMIS-SRI	0.522	[-0.10, 0.19]	0.10	0.262	[-0.10, 0.03]	−0.16	0.018*	[0.01, 0.08]	0.63	0.429	[-0.06, 0.15]	0.16
ESS	0.596	[-0.15, 0.30]	0.06	0.863	[-0.11, 0.13]	0.02	0.198	[0.02, 0.09]	0.13	0.954	[-0.14, 0.15]	0.01
STAI-Trait	0.090	[-0.03, 0.33]	0.26	0.004**	[0.04, 0.22]	0.45	0.278	[-0.02, 0.06]	0.15	0.549	[-0.08, 0.14]	0.10
BDI-II	0.071	[-0.03, 0.61]	0.30	0.471	[-0.10, 0.22]	0.12	0.118	[-0.01, 0.12]	0.23	0.071	[-0.02, 0.38]	0.32

Note: Model 1 predicts Apathy Total Score. Model 2 predicts Apathy Affective sub-score. Model 3 predicts Apathy Behavioral sub-score. Model 4 predicts Apathy Cognitive sub-score. ISI = Insomnia Severity Index, PROMIS-SD = Patient-Reported Outcomes Measurement Information System - Sleep Disturbance, Global PSQI = Pittsburgh Sleep Quality Index, TST = Total Sleep Time, RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire, PROMIS-SRI = Patient-Reported Outcomes Measurement Information System - Sleep-Related Impairment, ESS = Epworth Sleepiness Scale, STAI-State/Trait = State and Trait Anxiety Inventory, and BDI-II = Beck Depression Inventory II.
β = standardized coefficient.
*p < 0.05, **p < 0.01.

recruited during routine visits or from an IRB-approved clinical research protocol. Matched controls were recruited through various methods including patient spouses, newspaper advertisements, local aging communities, fliers in the community, and mailed fliers. They were not required to be healthy beyond the exclusion criteria outlined below, and because many in the MC group had health problems, they represent a non-PD group, not a healthy control group. Exclusion criteria included dementia, severe psychiatric/health co-morbidities, diagnosis or treatment for periodic limb movement disorder (PLMD), obstructive sleep apnea (OSA), or restless leg syndrome (RLS), or the lack of bed partner who was able to document the absence of OSA, RLS, and PLMD. There were no exclusions for medication use. To screen for possible dementia, the Mini-Mental Status Exam (MMSE) was administered, with scores <25 as exclusionary. The demographic characteristics of this sample have been previously published [25]. In brief, participants were non-dementing, middle-aged to older adults ($M = 67$ years old, $SD = 7$ years), 23 % female, 96 % Caucasian, 88 % married, 23 % employed, and well-educated ($M = 16$ years). Sample characteristics are summarized in Table 1. Participants provided informed consent prior to entry into the study and were compensated for their participation.

Participants completed screening, a clinical sleep interview, and various questionnaires related to sleep and mood in a clinical testing room at the University of Florida or in participants' homes. Participants were informed of the risk of fatigue associated with the multiple tests and questionnaires. They were allowed breaks as needed. The participants scored in the normal range on the MMSE, a cognitive screener, with no difference between the groups. Participants completed the study while on their medications and rarely required assistance with completing the research protocol. All individuals with PD were assessed in the ON state (i.e., while medicated) and were stabilized on the medications for at least three months before participating. A modified clinical sleep interview was used to assess sleep history, psychosocial functioning, medical conditions, medications, and mental health. All study protocols were approved by the university's institutional review board. This study focused on measures pertinent to the present analyses.

1.2. Measures

1.2.1. Measures of sleep disturbance

Sleep measures used in this study were selected to allow comparison between the PD and MC groups. For this reason, PD specific sleep measures were not generally selected. Where possible, validated measures in both groups were used as outlined below. For those not yet validated in PD at the time of data collection (i.e., PROMIS-SD and SRI), we have previously published validation results for these measures in PD [34].

The Insomnia Severity Index (ISI) was used to assess insomnia severity over the past 2 weeks. The ISI is a widely used, well-validated, 7-item questionnaire of sleep quality and insomnia severity. Scores range between 0 and 28, with higher scores indicating more severe insomnia [35–37].

To characterize sleep quality and quantity, the Patient-Reported Outcomes Measurement Information System – Sleep Disturbance (PROMIS-SD) and the Pittsburgh Sleep Quality Index (PSQI) were administered. The PROMIS-SD is an item bank consisting of 27 items that has been previously validated in individuals with PD [34]. The total score was computed from these items, with higher scores indicating worse sleep quality. The PSQI is an 18-item, self-report questionnaire used to measure sleep quality over the past month. The PSQI total score was an indication of overall sleep disturbance. Item 4 of the PSQI, which asks the individual to report "how many hours of actual sleep" they got in the past month, was used to estimate an individual's Total Sleep Time (TST) in minutes. The PSQI has received a "recommended" status by a Movement Disorders Task Force for use in individuals with PD [38] and is a reliable and valid measure of sleep disturbance in older adult samples [39–41].

The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) was used to assess the presence of probable RBD in our PD sample. The RBDSQ is a well-validated 10-item screening questionnaire for RBD symptoms [42]. This questionnaire has been validated in individuals with PD and is widely used in individuals with PD for screening purposes [43,44]. A score of ≥ 5 was used to categorize participants as having probable RBD [42].

The Epworth Sleepiness Scale was used to assess daytime sleepiness. The ESS is an 8-item questionnaire that asks participants to rate the likelihood of dozing in eight different situations. The ESS total score was computed, with higher scores indicating greater daytime sleepiness. This scale is widely used and has been validated for use in older adults [40,41].

The PROMIS Sleep-Related Impairment (PROMIS-SRI) item bank was used to assess daytime sleep-related impairments. It is a measure that gets at sleepiness, alertness, and daytime tiredness, along with the perceived functional impairments associated with sleep problems. We used the total score from the full 16 items with higher scores indicating increased sleep-related impairment. The PROMIS-SRI has been previously shown to be a valid measure of sleep-related impairment in individuals with PD [34].

1.2.2. Mood measures

The Apathy Scale (AS) was used to assess overall apathy and its three components: affective, behavioral, and cognitive. The AS is a 14-item questionnaire that was originally designed to quantify apathy across affective, behavioral, and cognitive, domains [9]. The Apathy Scale (AS) has been validated in patients with PD [45] and has become one of the most widely used apathy scales in PD. Indeed, it the only apathy scale that received a "recommended" status by the Movement Disorder Society's taskforce on apathy scales for use with individuals with PD [46]. In this study, we used the AS total score to quantify overall apathy, with higher scores indicating greater apathy. The subscales were calculated by summing the items that loaded on previously validated latent factors of affect, behavior, and cognition [47]. The affective factor included questions 9,10,11,13, and 14 the behavioral factor was computed as the sum of questions 8 and 12, and the cognitive factor included questions 1,2,4,5,6, and 7.

The State and Trait Anxiety Scale - The State-Trait Anxiety Inventory (STAI) is a validated, 40-item scale that measures state anxiety and trait anxiety. Each item is rated on a 4-point scale, and higher scores indicate more anxiety [48]. This study will use questions 1–20

to measure state anxiety and 21–40 to measure trait anxiety. A previous meta-analysis provided evidence that the STAI-trait can be used to distinguish between individuals with an anxiety diagnosis and general anxiety (Cohen's d = 1.74), and the reliability of the STAI-trait for individuals with some anxiety disorder is around α = 0.9 [49]. A group analyzed the STAI for individuals with de novo Parkinson's disease and found good internal consistency for the state and trait (0.93 and 0.92, respectively), with decent validity [50].

The Beck Depression Inventory-II (BDI-II) was used to assess depressive symptoms over the previous two weeks. The BDI-II assesses various depressive symptoms that are consistent with the diagnostic criteria of depression and older adults were included in the original psychometric sample for the scale [51]. This scale has been validated for use in individuals with PD [52].

1.2.3. PD-specific measures

To characterize our PD sample, we obtained measures of PD-related impairment, disease duration, and PD medication dosage. The Parkinson Disease Questionnaire-39 (PDQ-39), a validated 39-item self-report questionnaire, was used to assess PD-related quality of life. The PDQ-39 asks participants, "Due to having Parkinson's disease, how often during the last month have you …" had difficulty with specific dimensions of daytime functioning including activities of daily living, cognition, communication, depression, functional mobility, quality of life, and interpersonal functioning [53]. We computed the total score of all 39 items. Disease duration of PD was measured in months from the time of PD diagnosis based on participant reports. Hoehn-Yahr scores were used to assess PD-related motor symptom severity [54]. To assess the impact of PD medications on measures in this study, we computed the Levodopa Equivalent Dose (LED) for each participant with PD. This calculated value uses conversion factors for different types of PD drugs and allows for direct comparisons to be made between them.

1.2.4. Statistical analyses

Data were analyzed with Stata SE 16. Descriptive statistics for all measures were reported using means and standard deviations or the median and interquartile range, as appropriate. Group comparisons between individuals with Parkinson's disease and matched-controls were computed using Mann-Whitney U or Student *t* tests. Spearman correlations were conducted between AS total score, subscale-scores (i.e., affective, behavioral, and cognitive), sleep measures (ISI, PROMIS-SD, PSQI, TST, RBDSQ, ESS, PROMIS-SRI), mood measures (STAI-State, STAI-Trait, BDI-II) and the PDQ-39 in the total sample and each group. The groups' correlations were compared using the 2-sample Fisher's *z* test. To identify which sleep variables predicted AS total score, affective, behavioral, and cognitive sub-scores, we ran four separate regressions with AS total score, and the three sub-scales as dependent variables. The additional predictors in each model were added based on their significant correlations with AS total score or any of the sub-scores. Finally, we ran the same models controlling for the group, depression, and anxiety in sensitivity analyses.

2. Results

2.1. Participants

See Table 1 for demographic information. There were no significant differences between the group with PD and the matched controls on age, education, self-reported sex, race, marital status, employment status, TST, and MMSE scores. Additionally, there were no significant differences between groups on AS total score or cognitive and affective subscales. There were significant differences between groups on the AS behavioral subscale, ISI, PROMIS-SD, PROMIS-SRI, PSQI, TST, RBDSQ, ESS, STAI-State, STAI-Trait, and BDI-II.

2.2. Correlational analyses

Correlations between the AS total score, affective subscale score, behavioral subscale score, and cognitive subscale score with the sleep and mood measures along with Fisher's z differences are reported in Table 2. The AS total score was significantly correlated with the PROMIS-SRI, STAI-State and Trait, and BDI-II in the total sample, and the ISI, PROMIS-SD, PROMIS-SRI, ESS, the three mood measures and PDQ-39 in the PD group. The affective subscale score was significantly correlated with the PROMIS-SRI and three mood measures in the total sample and the ESS and three mood measures in the PD group. The behavioral subscale was significantly correlated with the ISI, PROMIS-SD, PSQI, TST, RBDSQ, PROMIS-SRI, ESS and three mood measures in the total sample. In the PD group, the behavioral subscale was significantly correlated with all the above variables except for the RBDSQ and was also significantly correlated with the PDQ-39. In the MC group, the affective subscale was significantly correlated with the STAI-trait total score. The behavioral subscale was significantly correlated with the PROMIS-SRI, STAI-trait, and BDI-II. The cognitive subscale score was significantly correlated with ISI, PROMIS-SD, PSQI, PROMIS-SRI, and the three mood measures in the total sample and the ISI, PROMIS-SD, PSQI, TST, PROMIS-SRI, ESS, STAI-State & Trait, BDI-II, PDQ-39, disease duration, and LED in the PD group.

Fisher's z differences were used to compare the strength of the correlations between the PD and MC groups. For AS total score, the ISI, ESS, STAI-State and Trait demonstrated significantly higher correlations in the PD group, compared to the MC group. For the affective subscale score, ESS showed a significantly higher correlation in the PD group than the MC group. For the behavioral subscale score, TST, PROMIS-SRI, STAI-State and Trait showed significantly higher correlations in the PD group than the MC group. In the cognitive subscale score, ISI, TST, and ESS showed significantly higher correlations in the PD group than the MC group.

2.3. Regression analyses controlling for group

To identify which sleep variables predicted AS total score, affective, behavioral, and cognitive sub-scores, we initially ran four separate regressions (see Table 3). The predictors in each model were added based on their significant correlations with AS total score or any of the sub-scores while controlling for group. In Model 1, the PROMIS-SRI significantly predicted the AS total score ($b = 0.18$, $p = 0.010$), and the overall model predicted 10.74 % of the variance in total apathy. In Model 2, none of the predictors significantly predicted the affective sub-score. In Model 3, PROMIS-SRI significantly predicted the behavioral sub-scale ($b = 0.07$, $p < 0.001$) and PROMIS-SD almost reached significance ($b = -0.02$, $p = 0.061$) with the overall model predicting 39.51 % of the variance in the behavioral sub-score. In Model 4, PROMIS-SRI significantly predicted the cognitive sub-score ($b = 0.11$, $p = 0.029$), and the overall model predicted 10.79 % of the variation in the cognitive sub-score. Across the four models, the PROMIS-SRI was the only significant predictor for AS total score, behavioral and cognitive sub-scores after controlling for group and other sleep variables.

2.4. Regression analysis controlling for group, anxiety, and depression

The addition of anxiety and depression as controls in the models can be found in Table 4. While both state and trait anxiety were significantly associated with all aspects of apathy, including both in the model would have resulted in multicollinearity. As such, trait anxiety was included because it showed stronger correlations with the various apathy components. In Model 1, none of the predictors remained significant once anxiety and depression were accounted for. In Model 2, the STAI-trait significantly predicted the affective sub-score ($b = 0.13$, $p = 0.004$) and the model accounted for 22 % of the variability in affective apathy. In Model 3, the PROMIS-SRI was significantly predictive of the behavioral apathy sub-scale ($b = 0.05$, $p = 0.018$) while accounting for group, anxiety, and depression. The model accounted for 44 % of the variability in behavioral apathy. In Model 4, none of the variables significantly predicted cognitive apathy when controlling for group, anxiety, and depression.

3. Discussion

This study aimed to investigate associations between a broad array of sleep disturbances and apathy beyond RBD and EDS in individuals with PD and matched controls. We found that insomnia symptoms and general sleep disturbance in PD participants were significantly associated with apathy. We also found that sleep-related impairment, daytime sleepiness, state and trait anxiety, depression, and fatigue significantly correlated with apathy with PD. These findings agree with previous studies that suggest that daytime sleepiness and poor sleep in PD is associated with apathy [17,24]. Further, our study sample primarily consisted of individuals with early to middle-stage PD, which, similar to the literature, suggests that associations between sleep disturbances and apathy may be found relatively early in PD progression [17,55]. Unlike some previous studies, however, we did not find any strong associations between RBD and apathy in PD [22,56]. Our results agree with a recent study that similarly found no association between RBD and apathy [57].

To our knowledge, this study was the first to examine the relationship between sleep and the affective, behavioral, and cognitive aspects of apathy. We found that insomnia severity, sleep disturbance, sleep quality, and total sleep time were significantly correlated with cognitive components of apathy in the PD group. Other measures, such as sleep-related impairment, daytime sleepiness, anxiety and depression, consistently correlated with the affective, behavioral, and cognitive components of apathy in the PD group. Sleep-related impairments were also found to predict all tested aspects of apathy above and beyond other sleep disturbances. Interestingly, sleep disturbances were only significantly associated with components of apathy in the PD group, not the controls. These findings agree with other studies suggesting that sleep disturbance is related to apathy in individuals with PD [17] and add the unique finding that greater sleep impairment may affect affective, behavioral, and cognitive aspects of apathy not previously reported. When accounting for anxiety and depression, sleep related impairment remained predictive of behavioral apathy but not any other components of apathy which provides support for the idea that behavioral apathy may be distinct from depression while affective and cognitive apathy overlap with depressive symptoms.

Taken together, these results suggest that sleep disturbances, particularly daytime impairments associated with poor sleep, are negatively associated with motivation in PD patients. This may occur through a few mechanisms. A hypothesis set forth in the literature is that sleep disturbances may result in exacerbated sleep-related impairments, such as apathy, in individuals with neurodegenerative diseases like PD compared to individuals without neurodegenerative disease due to underlying differences in brain region functionality and connectivity [25]. Apathy in PD has been shown to have impairments in specific brain regions, such as the mesolimbic system [21,58] or the frontal-subcortical circuit [59,60] and brainstem [21]. Sleep disturbances, such as insomnia, have been demonstrated to relate to similar overlapping brain regions with apathy, such as the basal ganglia and the frontal medial and cingulate regions [61]. The presence of similarly impaired brain regions in sleep disturbances and apathy may suggest that PD uniquely affects brain regions that are associated with both ailments and thus may explain the significant associations between sleep-related impairment and apathy [62]. Another potential explanation for these associations lies in the potential impact of apathy on one's ability to follow healthy sleeping practices that could prevent sleep-related impairment. To our knowledge, however, there is no literature supporting the theoretical impact of apathy on sleep hygiene practices, but anxiety or depression may be playing a role with apathy in explaining this. On the other hand, there is ample literature, such as sleep deprivation studies, in greater favor of sleep, not apathy, driving the association [12]. More research is needed to clarify the potential impact of apathy on sleep disturbance in PD.

Our study has several limitations. The relatively small sample size of and the relatively large number of variables in this study limit the power of our findings. Despite this, the sample size was sufficiently large to detect significant correlations that have been

commonly demonstrated in the literature. Our results may also have been confounded by the presence of comorbidities of PD, such as restless leg syndrome, OFF-time related motor symptoms, other nocturnal movement disorders, that were not included in this study and that may have impacted the apathy and sleep disturbances of study participants. We also did not employ polysomnography or other units of measurement to evaluate sleep and the presence of comorbid sleep disorders, including obstructive sleep apnea. However, we believe the impact of comorbid sleep disorders was minimal due to our study excluding patients with a self-reported history or caregiver report of other sleep disorders. Beyond comorbidities, our study also did not evaluate the impact of PD medications on sleep and apathy due to the small sample size and feasibility of conducting a detailed evaluation of the potential involvement of specific medications at this time. Of note, the dataset includes patients that have probable RBD [63] and, therefore, our study is limited in how strongly we can attribute these significant correlations to the presence of PD alone. However, this study did not find significant associations between apathy and RBD in our specific sample, which makes these effects less likely. Additionally, our study did not employ PD-specific sleep measures; however, the measures we used have been validated in PD and allowed us to make comparisons between individuals with and without PD. Some other limitations are a lack of definitive diagnostic criteria for apathy, the paucity of group differences in apathy scores, the absence of behavioral and physiological measures of sleep, and a restricted range of PD severity. Future research aimed at elucidating the potential underlying mechanisms of apathy and sleep disturbances in PD may provide opportunities to therapeutically treat both apathy and sleep disturbances in affected individuals, as well as other related conditions, including anxiety. These conditions often present comorbidly in individuals with PD and better understanding their common and unique pathophysiology may provide researchers and clinicians with greater insight into how to jointly treat these complex disorders in PD.

Follow-up studies would benefit from investigating additional sleep measures, especially physiological or behavioral sleep characteristics (e.g., polysomnography and actigraphy), which may further elucidate underlying associations between sleep disturbances and apathy in PD. This would be particularly efficacious when finding samples of individuals with PD that have similar levels of depression, anxiety, and other related factors to best control for potential confounds. Another study design that could elucidate the relationship between the sleep disturbances and apathy would be having a longitudinal study to see if sleep disturbances predict apathy. Future studies could also investigate the impact of Cognitive Behavioral Therapy for Insomnia (CBT-I) on sleep quality and apathy in individuals with PD and evaluate how treating sleep disturbance ameliorates symptoms of apathy.

4. Conclusion

In recent years, studies have increasingly identified sleep disturbances and apathy as important symptoms of PD. This study adds to the literature focused on understanding the link between sleep disturbances and apathy in PD and presents novel findings related to how these symptoms are uniquely related in individuals with PD compared to individuals without PD. The results of this study suggest that the negative sequelae of sleep disturbance may worsen various aspects of apathy in PD. Addressing sleep disturbances in individuals with PD may improve apathy symptoms and more research needed to directly evaluate the beneficial impact of sleep on apathy in PD.

Ethics approval & informed consent

The original study was approved by the University of Florida IRB 117-2011. This secondary analysis study was reviewed and approved by Brigham Young University with the approval number: E16406, dated October 28, 2016. All participants provided written informed consent to participate in the study and for their data to be published.

Data availability

Data associated with this study have not been deposited into a publicly available repository. Data will be made available on request.

CRediT authorship contribution statement

Jolynn Jones: Writing – review & editing, Writing – original draft. **Spencer A. Nielson:** Writing – review & editing, Writing – original draft. **Jonathan Trout:** Writing – review & editing, Writing – original draft. **Jared J. Tanner:** Writing – review & editing, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Dawn Bowers:** Writing – review & editing, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization, Supervision, Methodology. **Daniel B. Kay:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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