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# Obstructive Sleep Apnea and Cognition in Parkinson's disease

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## ARTICLE INFO

## ABSTRACT

*Objective:* Obstructive sleep apnea (OSA) is very common in Parkinson's disease (PD). OSA is known to affect patients' cognition. The present study assessed whether PD patients with OSA (PD + OSA) score lower on cognitive measures than those without OSA (PD – OSA). In addition, this study evaluated whether treating the OSA with continuous positive airway pressure (CPAP) in PD + OSA patients results in an improved cognitive functioning.

*Methods:* Eighty-six patients with PD underwent an overnight polysomnography screen for OSA and were administered the Mini-Mental Status Exam (MMSE) and the Montreal Cognitive Assessment (MoCA). This resulted in 38 patients with PD + OSA who were randomly assigned to receive either therapeutic CPAP for 6 weeks ($n = 19$) or placebo CPAP for three weeks followed by therapeutic CPAP for three weeks ($n = 19$). Intervention participants completed a neurocognitive battery at baseline and 3- and 6-week time-points.

*Results:* Patients with PD + OSA scored significantly lower than PD – OSA on the MMSE and MoCA after controlling for age, education, and PD severity. OSA was a significant predictor of cognition (MMSE $p < 0.01$; MoCA $p = 0.028$). There were no significant changes between groups in cognition when comparing three weeks of therapeutic CPAP with 3 weeks of placebo CPAP. Comparisons between pre-treatment and 3-week post-therapeutic CPAP for the entire sample also revealed no significant changes on overall neuropsychological (NP) scores.

*Conclusions:* Findings suggest that PD patients with OSA show worse cognitive functioning on cognitive screening measures than those without OSA. However, OSA treatment after three or six weeks of CPAP may not result in overall cognitive improvement in patients with PD.

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## 1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting approximately 1% of individuals over the age of 60 years old and 4% of adults over the age of 80 [1]. Although PD is characterized as a movement disorder, non-motor symptoms of the disease are reported by nearly all patients with PD [2]. A study by Hely et al. suggested that non-motor symptoms such as cognitive dysfunction and sleep disturbances were more concerning to PD patients and more disabling than motor symptoms and were the major cause of morbidity and mortality [3]. The extent of cognitive dysfunction a patient with PD experiences, specifically, has been shown to predict rate of decline, caregiver stress, and nursing home placement [4].

Empirical evidence suggests that sleep disturbances in general can adversely affect cognitive function [5–8]. In PD, sleep disturbances have been found to impair quality of life and increase the level of disability [9]. Previous work in our laboratory showed that the presence of comorbid sleep disorders (ie, obstructive sleep apnea, restless legs syndrome, and REM sleep behavior disorder) in PD predicted increased sleep complaints, lower quality of life, increased depressive symptoms, increased fatigue, and poorer cognition [10]. Despite all of these findings, however, sleep-related problems in

patients with PD continue to be poorly recognized and inadequately treated.

A common sleep disorder in PD is obstructive sleep apnea (OSA). OSA is caused by obstruction of the upper airway leading to complete cessations (apneas) and/or partial decreases (hypopneas) in respiration during sleep. The prevalence of OSA in PD is estimated to be around 20–60% [11–15]. Consequences of OSA include cardiac arrhythmias, nighttime confusion, excessive daytime sleepiness, and functional decline [16,17]. OSA has also been documented as a high risk for motor vehicle accidents while driving [18]. Moreover, neuropsychological impairment and cognitive decline, especially in older adults, have also been frequently associated with OSA [19–21].

The most effective treatment for OSA is continuous positive airway pressure (CPAP). CPAP interventions have been shown to improve neuropsychological functioning among non-demented patients with OSA, specifically in the areas of nonverbal general intellectual functioning, attention, verbal memory, and construction [8,22,23]. Moreover, in a previous study investigating the effects of 3 weeks of CPAP treatment in patients with Alzheimer's disease and OSA, our research group found modest but statistically and clinically significant improvements in the cognitive domains of executive functioning and mental flexibility [24]. While our previous work showed that CPAP could be well tolerated by PD patients with OSA [25], the cognitive effects of treating OSA in PD have not yet been fully explored.

The purpose of the present study was to assess whether PD patients with OSA (PD + OSA) show worse cognitive performance on cognitive screening measures compared to PD patients without OSA (PD-OSA). In addition, this study implemented a double-blind placebo-controlled intervention to investigate the cognitive effects of CPAP treatment among PD patients with OSA. We hypothesized that patients with PD and OSA would exhibit worse cognitive performance relative to those without OSA (assessed by the Mini Mental Status Exam and the Montreal Cognitive Assessment). We further hypothesized that compared to patients treated with placebo CPAP, patients treated with therapeutic CPAP would show a global improvement in cognitive functioning (ie, have significantly higher composite neuropsychological scores across a test battery). We also explored whether specific cognitive tests would show a better response to CPAP treatment than others, thus resulting in significant differential cognitive improvement.

## 2. Methods

### 2.1. Participants

Patients with PD were recruited through San Diego Parkinson's Disease Association, University of California, San Diego (UCSD) Department of Neurosciences, referrals from private neurology clinics in the San Diego area, and through flyers and advertisements.

Inclusion criteria were (1) a clinical diagnosis of PD, (2) a Mini-Mental Status Exam (MMSE) score > 18, (3) age ≥ 50 years, (4) English Fluency, (5) willingness and the ability to remain on the same stable medication regimen for two months prior to enrollment in the study, and for participants randomized,(6) having an apnea–hypopnea index score (AHI) ≥ 10 and (7), continuing to remain on the same medication regimen for 6 weeks of the intervention.

Full exclusion criteria can be found in a previous study conducted by our group [10] and included (1) current treatment for OSA, (2) central sleep apnea, (3) current use of sleep medications, (4) current alcohol and/or drug abuse/dependence and/or (5) severe medical or psychiatric illnesses (eg, bronchospastic and symptomatic chronic obstructive pulmonary disease, symptomatic coronary or cerebral vascular disease, seizure disorder, or presence of a neurodegenerative disorder other than PD). The study was approved by the UCSD Human Research Protections Program and the Veterans Administration Healthcare System in San Diego, CA, USA. All participants provided written informed consent to participate.

### 2.2. Procedures

#### 2.2.1. Screening

Participants were administered a semi-structured interview by a physician (JL and JM) and were assessed by a board-certified neurologist using the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr (H&Y) for staging of the PD [26,27]. Information such as medication type, dose, frequency, time, reason, and duration of use was collected for each participant. The purpose of assessing this information was to allow comparisons among patients undergoing different types of dopaminergic therapy regimens. Drug dosage was converted to Levodopa Dosage Equivalents (LDE) using a computational formula outlined in a study by Hobson and colleagues [28]. Each patient was admitted to the Gillin Laboratory for Sleep and Chronobiology for one night of polysomnography (PSG) to screen for OSA, defined as an apnea–hypopnea index (AHI) ≥ 10. Full details of the polysomnographic evaluation can be found in Neikrub et al. (2014) [25]. All sleep recordings were scored by a scorer kept blind to treatment condition and all polysomnography records were staged and scored according to the criteria put forth by the American Academy of Sleep Medicine (AASM) [29]. Apneas were scored when there was a > 90% decrease in airflow amplitude from baseline lasting ≥10 sec, and hypopneas were scored when there was a 50–90% decrease in amplitude lasting ≥10 sec. An AHI ≥10 was used to define sleep apnea to be consistent with previous studies of sleep apnea in older adults [24].

#### 2.2.2. Global cognitive screening measures

All participants were evaluated with the MMSE, a valid and reliable 30-item brief cognitive screening test that assesses select constructs including orientation, attention, memory, and the ability to respond to verbal and written commands [30]. Scores ≤23 on this measure are indicative of significant cognitive impairment, whereas scores ≥24 suggest that individuals are more cognitively intact. The MMSE was administered once and used to assess cognition and to screen out patients who were considered too cognitively impaired to participate in this study (MMSE score <18).

Participants were also evaluated with the Montreal Cognitive Assessment (MoCA) [31], a valid tool used to help detect Mild Cognitive Impairment (MCI) that assesses attention and concentration, executive function, memory, language, visuospatial skills, conceptual thinking, calculations, and orientation. The MoCA is a 30-point test that takes approximately 10 min to administer.

#### 2.2.3. Randomization

Patients meeting criteria for OSA were randomized to receive therapeutic CPAP (tCPAP) for six weeks or placebo CPAP (pCPAP) for three weeks followed by therapeutic CPAP for three weeks. In the pCPAP condition, the CPAP mask had 10 1/4″ holes drilled into it for adequate gas exchange with a pressure reducer placed in the tubing between the CPAP unit and the modified mask [32,33]. To control for machine noise, a constant water pressure of 8 cm was set, thus making the noise level of the placebo CPAP indistinguishable from that of the therapeutic CPAP.

#### 2.2.4. Protocol

Detailed information regarding study procedures can be found in Neikrug et al [25]. Orientation and instructions on how to use CPAP were identical for all participants, and each participant and caregiver was kept blind to treatment assignment.

### 2.2.5. Neuropsychological (NP) tests

Wide Range Achievement Test-Third Edition (WRAT-III) reading scores were used to estimate participant's pre-morbid functioning. In order to evaluate treatment effects in a more detailed fashion, subjects were given a repeatable battery of neuropsychological (NP) tests at baseline and 3- and 6-week visits. This battery included the Digit Span, Digit Symbol, and Symbol Search subtests from the Wechsler Adult Intelligence Scale-Third edition (WAIS-III) [34]; Trail Making Tests A and B [35]; Continuous Performance Test-3 digit [36]; Benton Judgment of Line Orientation (JLO) [35]; Brief Visual-Spatial Memory Test-Revised [37]; Hopkins Verbal Learning Test-Revised [38]; Wisconsin Card Sorting Task–64 card version (conceptual level of responses) [39]; Stroop Color-Word Interference test (total words completed) [40]; and the Letter and Category (animals) Fluency test (total words generated) [41].

The NP test examiner was kept blind to the treatment conditions. Each test score was converted to a z-score. To represent the overall NP functioning, composite NP scores were calculated as the participant's mean z-scores across the test battery.

### 2.2.6. Statistical analyses

Demographic and disease characteristics of PD + OSA and PD – OSA groups were compared using independent *t*-tests for continuous and chi-squared tests for categorical variables. For some variables such as ethnicity and race, Hispanic versus Non-Hispanic and Caucasian versus Non-Caucasian groups were compared and Fisher's exact tests were calculated due to small cell sizes. Unadjusted differences in cognition (ie, MMSE and MoCA scores) between PD + OSA vs. PD – OSA groups were assessed using independent samples *t*-tests. The adjusted relationship between OSA and MMSE and OSA and MoCA scores was assessed using a univariate general linear model controlling for age, education, LDE, UPDRS, and H&Y.

For the PD + OSA intervention study, to examine if randomization achieved balance, the tCPAP and pCPAP groups were compared at baseline with independent *t*-tests for continuous variables, chi-squared tests for gender, and Fisher's exact tests for ethnicity (Hispanic versus Non-Hispanic), race (Caucasian versus Non-Caucasian), and H&Y staging (Stage 1 versus Stages 2 and 3) variables. Between-group analyses were conducted comparing three weeks of tCPAP to three weeks of pCPAP using independent *t*-tests. Within-group analyses were conducted in the tCPAP group comparing 6 weeks of therapeutic treatment to three weeks using paired *t*-tests. To make optimal use of all available data for estimating effect sizes, paired analyses were also conducted comparing three weeks of therapeutic CPAP in both groups. Significance was defined as $p < 0.05$, two tailed. When comparing individual NP test items, Bonferroni correction was applied.

Our power was based on the following: for a randomized controlled trial, with 18 participants per arm, we would have 80% power to detect an effect size of 1 (ie, standardized mean difference in composite score) between tCPAP and pCPAP arms, assuming a two-sided test with $\alpha = 0.05$. This hypothesized effect size was based on the study by Aloia et al. (2003) [42] which examined the effects of CPAP on the cognitive performance of adults with diagnosed sleep apnea and reported results that translate into effect sizes of approximately 1.2.

## 3. Results

### 3.1. OSA and cognition in PD patients

Of the 86 patients, 47 had an apnea–hypopnea index score (AHI) ≥ 10 (mean AHI = 22.67, standard deviation (SD) = 13.54) and 39 had an AHI <10 (mean AHI = 3.71, SD = 2.14). The MMSE and MoCA scores for each group were PD + OSA Mean MMSE score = 27.45, SD = 2.41; Mean MoCA score = 24.00, SD = 3.51 and PD – OSA Mean MMSE score = 28.41, SD = 1.82; Mean MoCA score = 25.29, SD = 3.16. The two groups did not significantly differ on any demographic variable (see Table 1). Without controlling for theoretically relevant

**Table 1**
Participant demographics at baseline.

| Variable | PD + OSA (n = 47) | PD – OSA (n = 39) | Therapeutic CPAP (n = 19) | Placebo CPAP (n = 19) |
|---|---|---|---|---|
| Age in years, mean (SD) | 68.09 (9.39) | 66.58 (8.02) | 66.68 (8.52) | 67.68 (10.02) |
| Education in years, mean (SD) | 16.77 (3.02) | 17.69 (2.81) | 16.63 (2.83) | 16.42 (3.37) |
| Female, n (%) | 13 (27.7%) | 16 (41.0%) | 7 (36.8%) | 5 (26.3%) |
| Ethnicity, n (%) | | | | |
| Hispanic | 4 (8.5%) | 1 (2.6%) | 4 (21.0%) | 0 (0.0%) |
| Non-Hispanic | 41 (87.2%) | 36 (92.3%) | 14 (73.7%) | 18 (94.7%) |
| Unknown | 2 (4.3%) | 2 (5.1%) | 1 (5.3%) | 1 (5.3%) |
| Race, n (%) | | | | |
| Caucasian | 45 (96.0%) | 36 (92.2%) | 17 (89.4%) | 19 (100.0%) |
| African American | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Asian American | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) |
| Pacific Islander | 1 (2.0%) | 0 (0.0%) | 1 (5.3%) | 0 (0.0%) |
| More than one race | 1 (2.0%) | 1 (2.6%) | 1 (5.3%) | 0 (0.0%) |
| Unknown | 0 (0.0%) | 1 (2.6%) | 0 (0.0%) | 0 (0.0%) |
| Body Mass Index, mean (SD) | 27.24 (4.15) | 26.27 (4.24) | 27.83 (4.65) | 27.21 (4.27) |
| Wide Range Achievement Test- Third Edition Reading Standard Score, n, mean, (SD)† | N/A | N/A | n = 14, 109.00 (5.94) | n = 13, 105.54 (13.23) |
| Apnea–hypopnea index, mean (SD) | 22.67 (13.54)* | 3.72 (2.14)* | 22.18 (15.77) | 22.41 (12.92) |
| Levodopa dosage equivalent (LDE) | 765.61 (550.77) | 763.85 (614.87) | 665.6 (407.1) | 917.2 (648.2) |
| UPDRS Total score | 35.29 (14.12) | 36.92 (12.25) | 33.56 (12.18) | 38.56 (15.47) |
| H&Y Staging | n = 42 | n = 38 | n = 18 | n = 18 |
| | 1: 14 (33.3%) | 1: 10 (26.3%) | 1: 9 (50.0%) | 1: 5 (27.8%) |
| | 2: 23 (54.7%) | 2: 21 (55.3%) | 2: 6 (33.3%) | 2: 11 (61.1%) |
| | 3: 5 (12.0%) | 3: 7 (18.4%) | 3: 3 (16.7%) | 3: 2 (11.1%) |
| Neuropsychological functioning composite score, n, mean (SD) | N/A | N/A | n = 19, –0.033 (0.63) | n = 18, 0.107 (0.78) |

*Abbreviations:* CPAP = continuous positive airway pressure; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale; H & Y = Hoehn and Yahr.
* *Note:*PD groups with and without OSA significantly differed on the apnea–hyponea index. For all of other variables, groups did not statistically differ from one another.
N/A = Only participants randomized to an intervention group were administered the WRAT-Third edition and the full neuropsychological battery.
† Normative mean is 100 ± 15; higher scores are indicative of better premorbid verbal intelligence.
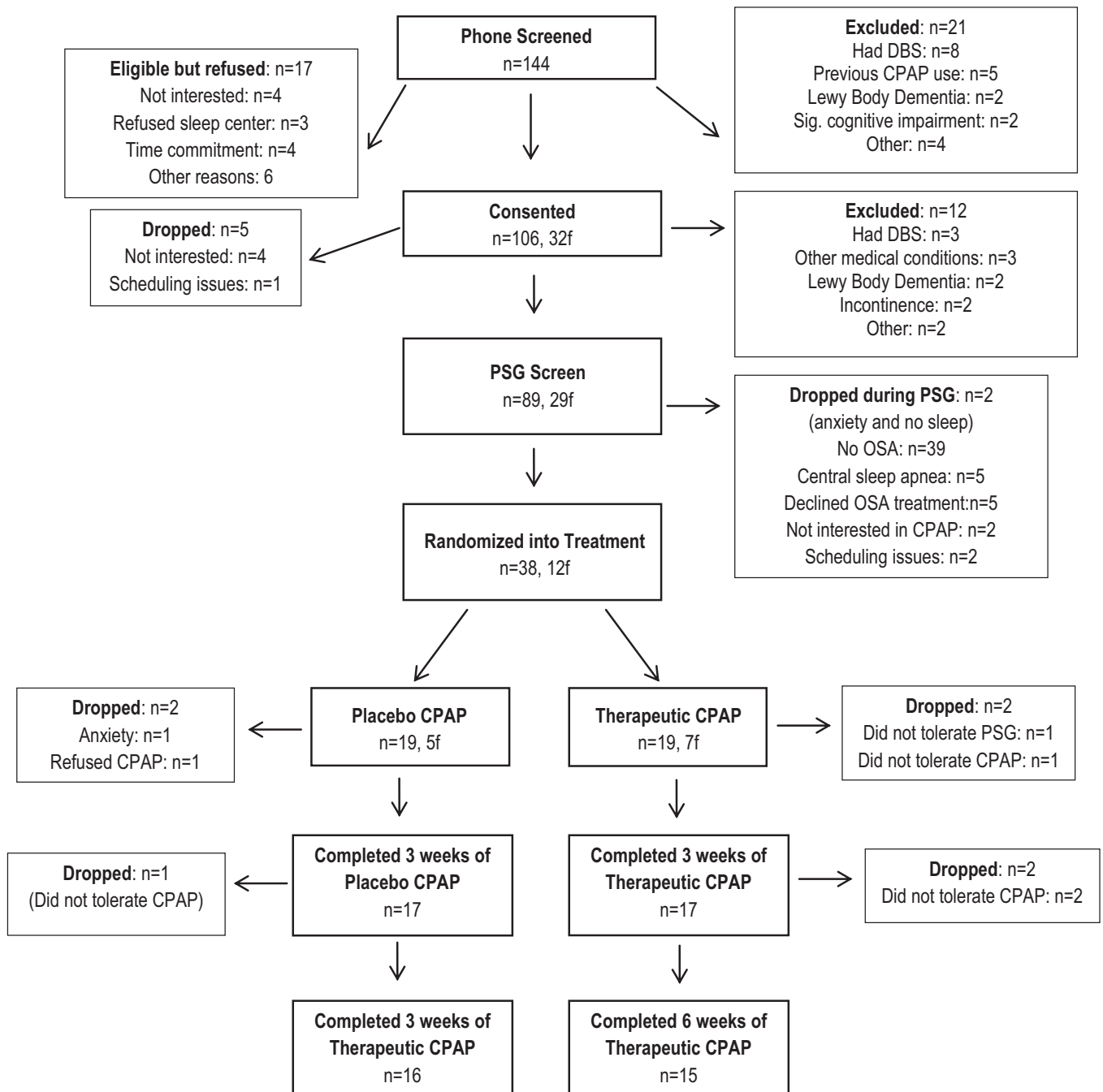
**Fig. 1.** CONSORT diagram showing the progression of participants through each stage of the intervention.

covariates, PD + OSA scored significantly lower than PD − OSA on the MMSE ($t(83.280) = 2.11$, $p = 0.038$), but not the MoCA cognitive screen ($t(83) = 1.76$, $p = 0.082$). However, using a univariate general linear model and controlling for age, education, levodopa dosage equivalent, Unified Parkinson's Disease Rating Scale, and Hoehn and Yahr staging, OSA was found to be a significant predictor of reduced MMSE ($F_{1, 78} = 7.189$, $p = 0.009$, $R$ [2] = 0.248) and MoCA scores ($F_{1, 78} = 5.042$, $p = 0.028$, $R$ [2] = 0.237). Post hoc analyses using a univariate general model and controlling for the same aforementioned covariates found significant differences between the OSA diagnostic groups in the areas of Visuospatial/Executive Functioning specifically (PD + OSA score = 3.95, SD = 1.02; PD −OSA score = 4.37, SD = 0.79; $F_{1, 78} = 6.504$, $p = 0.013$).

### 3.2. Intervention participant characteristics

Within the PD + OSA participants only, 19 participants were randomized to a pCPAP condition and 19 were randomized to a tCPAP condition (see Fig. 1).There were no significant differences between groups at baseline in age, gender, ethnicity, race, education, AHI, body mass index, WRAT-III scores, medications, disease severity, or NP composite $z$-scores (see Table 1). Of all participants screened and consented, seven dropped out before the end of the 6-week study (three participants in the pCPAP group and four participants in the tCPAP group). There were no significant differences in demographic or clinical characteristics between participants who dropped, and those who completed the study.

## 3.3. CPAP treatment adherence

To help optimize treatment adherence, research staff initially provided a full tutorial to the patient and their partner (if possible) on CPAP use when the patient was first given a CPAP machine. Patients were also contacted within the first week to address any issues or questions about the machine (eg, mask fit and feelings of claustrophobia). In addition, when collecting compliance information at the 3- and 6-week study visits, research staff was sent to the patient's house to further address any questions about the equipment.

At three weeks, adherence data were available for 16 participants in the tCPAP (94%) and 15 participants in the pCPAP group (88%). Participants in the pCPAP group used CPAP 88% of the nights for an average of 6.0 (SD = 1.7) hours per night. Participants in the tCPAP group used CPAP 82% of the nights for an average of 4.9 (SD = 1.5) hours. For the second 3-week time point (after crossover for those in the pCPAP group), participants in the pCPAP group used therapeutic CPAP 91% of the nights for an average of 5.4 (SD = 1.7) hours per night, while those in the tCPAP continued to use the CPAP on 89% of the nights for an average of 4.9 (SD =1.7) hours per night.

Effects of the CPAP treatment on AHI indices have been previously published (Neikrug et al., 2014 [28]). Specifically, at 3 weeks, compared to the pCPAP group (mean AHI = 20.00, SD = 14.3), the tCPAP group had significantly lower AHI levels (mean 5.2, SD = 8.1, $p = 0.01$). Moreover, after three weeks of therapeutic CPAP for all participants, AHI levels were significantly reduced from a baseline value of 21.1 (SD = 14.9) to 5.1 (SD = 7.2), $p < 0.01$.

## 3.4. NP outcomes

At 3 weeks, there were no significant differences between the tCPAP and pCPAP groups on composite NP scores ($t(34) = –0.172$, $p = 0.865$) or on any of the 13 individual NP tests. The mean and standard error for each of the 13 NP tests at each time point for each treatment group are presented in Table 2. Similarly, using paired samples $t$-tests, three weeks of therapeutic CPAP in both groups combined, compared to baseline, revealed no significant differences in composite score ($t(33) = –0.713$, $p = 0.481$); however, participants improved on the Continuous Performance Test-3 digit ($t(30) = –3.664$,

$p = 0.001$, Bonferroni adjusted $p = 0.013$). Within the treatment condition group, 6 weeks of CPAP did not reveal significant differences in composite scores compared to three weeks ($t(15) = –1.653$, $p = 0.119$) and participants seemed to perform worse at six weeks on the Trail Making A test ($t(14) = –3.797$, $p = 0.002$, Bonferroni adjusted $p = 0.026$).

## 3.5. Follow-up data

Within a subset of participants, we examined 3- ($n = 34$) and 6-month ($n = 25$) follow-up data comparing the NP functions in those participants who reported continued CPAP use to those who reported discontinued use. While no objective CPAP compliance data were available, there were no significant differences on composite scores or on any of the individual neuropsychological subtests between those who continued using CPAP and those who did not (this was assessed by subtracting follow-up data scores and scores at the end of the 6-week intervention study; data not shown).

## 4. Discussion

Results of this study suggest that PD patients with OSA have significantly worse cognitive function on screening measures than PD patients without OSA. However, in those with OSA, composite NP scores and most individual NP tests did not significantly improve with up to six weeks of CPAP treatment.

The finding that PD patients with OSA showed poorer cognitive performance is consistent with prior research suggesting that OSA in other populations correlates with cognitive impairment. Cognitive domains most likely affected by OSA include attention/vigilance, verbal and visual delayed long-term memory, visuospatial/constructional abilities, and executive dysfunction [43]. In our study, specifically, we found that PD patients with OSA scored significantly lower in the areas of visuospatial and executive functioning on the MoCA. We did not conduct extensive NP testing with PD patients without OSA; therefore, we have limited information as to what other specific cognitive domains might be impacted by OSA.

To our knowledge, this was the first study to explore whether implementing CPAP treatment in patients with PD and OSA, using

**Table 2**
Mean and Standard Errors for the neuropsychological tests at each time point for treatment and placebo groups.

| Treatment Group | Neuropsychological Test | Baseline | 3 weeks | 6 weeks | 3 months | 6 months |
|---|---|---|---|---|---|---|
| CPAP group | HVLT | 23.37 (1.5) | 22.67 (1.6) | 24.75 (1.7) | 26.44 (1.9) | 26.86 (2.9) |
| | BVMT | 17.33 (1.7) | 19.78 (1.7) | 18.56 (1.8) | 22.67 (1.9) | 23.86 (1.4) |
| | Trails A | 45.53 (6.7) | 44.78 (5.1) | 51.47 (14.5) | 39.28 (3.3) | 33.74 (3.7) |
| | Trails B | 111.37 (18.5) | 96.17 (19.3) | 94.00 (18.4) | 111.11 (30.1) | 81.29 (26.0) |
| | WCST | 30.47 (3.8) | 32.69 (4.3) | 37.86 (3.6) | 40.63 (5.0) | 43.14 (4.8) |
| | Stroop Color-Word | 31.24 (2.4) | 29.82 (2.5) | 33.67 (2.1) | 38.89 (4.7) | 35.29 (3.1) |
| | Letter Fluency FAS | 38.79 (2.6) | 41.06 (3.3) | 41.13 (3.4) | 42.89 (4.4) | 37.86 (4.5) |
| | Category Animals | 18.05 (1.2) | 17.28 (1.0) | 17.31 (1.3) | 17.33 (0.7) | 18.57 (1.6) |
| | Digit Span | 17.21 (1.0) | 16.72 (1.2) | 16.25 (1.4) | 17.22 (1.8) | 17.67 (1.7) |
| | Digit Symbol | 48.68 (3.3) | 48.33 (4.3) | 49.44 (4.2) | 46.22 (7.7) | 50.57 (4.7) |
| | Symbol Search | 21.95 (1.9) | 25.33 (2.1) | 25.75 (1.5) | 26.56 (2.7) | 32.00 (6.0) |
| | JLO | 23.24 (1.0) | 23.06 (1.3) | 24.31 (1.0) | 26.11 (1.2) | 24.86 (2.1) |
| | CPT 3 Digit | 1.82 (0.2) | 2.14 (0.2) | 2.11 (0.2) | 2.42 (0.3) | 2.66 (0.4) |
| Placebo Group | HVLT | 23.32 (1.7) | 22.26 (2.0) | 23.24 (1.8) | 22.80 (3.2) | 27.25 (5.4) |
| | BVMT | 18.28 (1.8) | 16.89 (1.7) | 16.56 (1.8) | 17.17 (3.5) | 17.20 (3.3) |
| | Trails A | 50.59 (5.1) | 55.32 (11.6) | 43.35 (4.3) | 40.50 (6.3) | 54.60 (13.6) |
| | Trails B | 128.94 (21.1) | 93.00 (15.0) | 94.00 (18.4) | 103.50 (28.5) | 116.20 (48.3) |
| | WCST | 27.11 (3.9) | 36.00 (3.7) | 34.82 (4.5) | 39.17 (5.6) | 33.20 (10.5) |
| | Stroop Color-Word | 34.24 (3.1) | 34.44 (3.4) | 37.76 (3.8) | 35.00 (4.8) | 37.80 (6.6) |
| | Letter Fluency FAS | 42.74 (3.2) | 44.28 (2.8) | 46.00 (3.5) | 47.60 (6.6) | 50.8 (5.4) |
| | Category Animals | 17.63 (1.4) | 18.06 (1.7) | 19.71 (1.7) | 21.80 (3.0) | 18.20 (3.1) |
| | Digit Span | 16.16 (1.0) | 16.00 (1.1) | 15.29 (0.7) | 17.33 (1.8) | 15.60 (2.5) |
| | Digit Symbol | 49.56 (4.6) | 48.71 (4.1) | 53.00 (4.6) | 54.17 (6.7) | 57.60 (10.2) |
| | Symbol Search | 23.63 (2.4) | 25.37 (2.4) | 25.65 (2.4) | 26.17 (3.2) | 26.60 (5.1) |
| | JLO | 23.89 (1.4) | 25.33 (1.0) | 25.44 (1.0) | 26.00 (1.0) | 26.00 (1.1) |
| | CPT 3 Digit | 1.75 (0.3) | 1.78 (0.2) | 2.21 (0.3) | 2.20 (0.4) | 2.49 (0.6) |

a randomized placebo-controlled design, was associated with cognitive changes. The overall trend toward non-significant outcomes in PD after CPAP use presents an interesting preliminary finding. Results from previous work suggest that other populations such as patients with only OSA and patients with AD and OSA show some improvements following CPAP use [24]. In a large-scale multicenter study (the APPLES study), Kushida et al. (2012) found improvement in measures of executive functioning for patients with severe OSA after two months of CPAP use (but no differences at the 6-month CPAP visit) [44]. We did not find significant differences in measures of executive functioning at any time point during our study. Therefore, there might be something unique about patients with PD that make them more resistant to cognitive improvements following CPAP use.

Regarding cognitive improvements in patients with AD and OSA following CPAP use, one possibility is that the patients with AD have higher levels of baseline cognitive impairment than those in the current study, giving them more room for improvement and making them more likely to show significant changes. This theory is probable as the PD patients in the present study had higher mean MMSE scores than those in our prior AD study [24]. Another possible explanation for why CPAP may not be as effective in PD patients relative to AD patients could be differences in the pathophysiology of the neurodegenerative processes. There is evidence that OSA promotes amyloid-β deposition, an important part of the pathophysiology of AD, through effects on hypoxic stress and inflammation [45]. Therefore, it is possible that CPAP treatment may help reverse the amyloid-β deposition in AD, which would lead to cognitive improvements in AD, but have minimal impact on cognition in PD. Another theory supported by recent studies is that less slow-wave sleep translates to more cognitive impairment and possibly more amyloid-β deposition in the brain [46]; therefore, CPAP treatment in AD patients may improve sleep and consequently some of the toxic accumulation of amyloid-β plaque. Notably, when explored post hoc, the PD + OSA and PD – OSA groups in our study did not show significant differences in slow-wave sleep architecture.

Overall, this study has several strengths. First, there is very limited research exploring the relationship between OSA and cognition in patients with PD. Furthermore, investigating the effects of CPAP treatment on cognitive outcomes in patients with PD and OSA contributes to an understudied area. Additional strengths of our study include a relatively low dropout rate, as well as very good CPAP adherence. It is also worth noting that the present study used a randomized double-blind cross-over design, thus reducing the influence of potential confounding covariates.

Despite these strengths, the small sample size in this study greatly limits power and conclusions that may be drawn. It is also worth noting that despite the fact that we found significant differences between patients with and without OSA on cognitive screening measures, the patients without OSA did not undergo full comprehensive NP testing, and therefore we have limited information about which specific areas of cognition differed between these two groups. Furthermore, when conducting analyses, we did not control for comorbid conditions in our study (eg, diabetes and cardiovascular disease) or non-dopaminergic medications, which may have an impact on cognition.

Given that our study was among the first to investigate OSA and cognition in PD and we found significant differences between groups on cognitive screening measures, it would be a welcome addition to the field for future researchers to administer more extensive NP testing to not only PD + OSA, but also PD – OSA groups to help explore which specific cognitive domains may be affected by OSA in patients with PD. Moreover, future studies should explore CPAP treatment over longer periods of time in larger samples of patients with PD and OSA to help determine if the treatment results in slower cognitive decline and/or whether it may lead to cogni-

tive improvements. Including larger samples of patients with PD and OSA and implementing CPAP interventions for longer durations may increase power to detect meaningful changes. In addition, future studies that look within PD patients with a severe degree of apnea/hypoxia burden are warranted to help determine whether CPAP treatment may result in cognitive improvements. Improving or stabilizing cognition in older adults with PD is a worthy goal as it can reduce health-care costs, help patients remain more independent and improve patient quality of life.

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## Conflict of interest

None. The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2016.01.001.

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