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Original Article

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Neurocognitive functioning in comorbid insomnia and sleep apnea patients is better after positive airway pressure therapy, but worse after cognitive behavioral therapy for insomnia: exploratory analysis of cognitive outcomes from the Multidisciplinary Approach to the Treatment of Insomnia and Comorbid Sleep Apnea study

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Abstract

Study Objectives: Neurocognitive impairments in comorbid insomnia and sleep apnea (COMISA) are not well documented. We explored neurocognitive functioning and treatment effects in individuals with COMISA as an ancillary study to a randomized clinical trial.

Methods: Participants with COMISA (n = 45; 51.1% female; mean age = 52.07 ± 13.29 years), from a 3-arm randomized clinical trial combining cognitive behavioral therapy for insomnia (CBT-I) and positive airway pressure (PAP) concurrently (CBT-I+PAP) or sequentially, completed neurocognitive testing at baseline, and post-treatment. Using Bayesian linear mixed models, we estimated effects of CBT-I, PAP, or CBT-I+PAP, compared to baseline, and CBT-I+PAP compared to PAP on 12 metrics across five cognitive domains.

Results: This COMISA sample had worse neurocognitive performance at baseline than reported for insomnia, sleep apnea, and controls in the literature, though short-term memory and psychomotor speed performance appears intact. When comparing PAP to baseline, performance on all measures was better after treatment. Performance after CBT-I was worse compared to baseline, and only performance in attention/vigilance, executive functioning via Stroop interference and verbal memory was better with moderate–high effect sizes and moderate probability of superiority (61–83). Comparisons of CBT-I+PAP to baseline generated results similar to PAP and comparing CBT-I+PAP to PAP revealed superior performance in only attention/vigilance via psychomotor vigilance task lapses and verbal memory for PAP.

Conclusions: Treatment combinations involving CBT-I were associated with poorer neurocognitive performance. These potentially temporary effects may stem from sleep restriction, a component of CBT-I often accompanied by initially reduced total sleep time. Future studies should examine long-term effects of individual and combined COMISA treatment pathways to inform treatment recommendations.

Clinical trial: This was an ancillary study from a clinical trial (Multidisciplinary Approach to the Treatment of Insomnia and Comorbid Sleep Apnea (MATRICS), which was preregistered at www.clinicaltrials.gov (NCT01785303)).

Key words: COMISA, insomnia, sleep apnea, CBT-I, PAP, neurocognitive functioning

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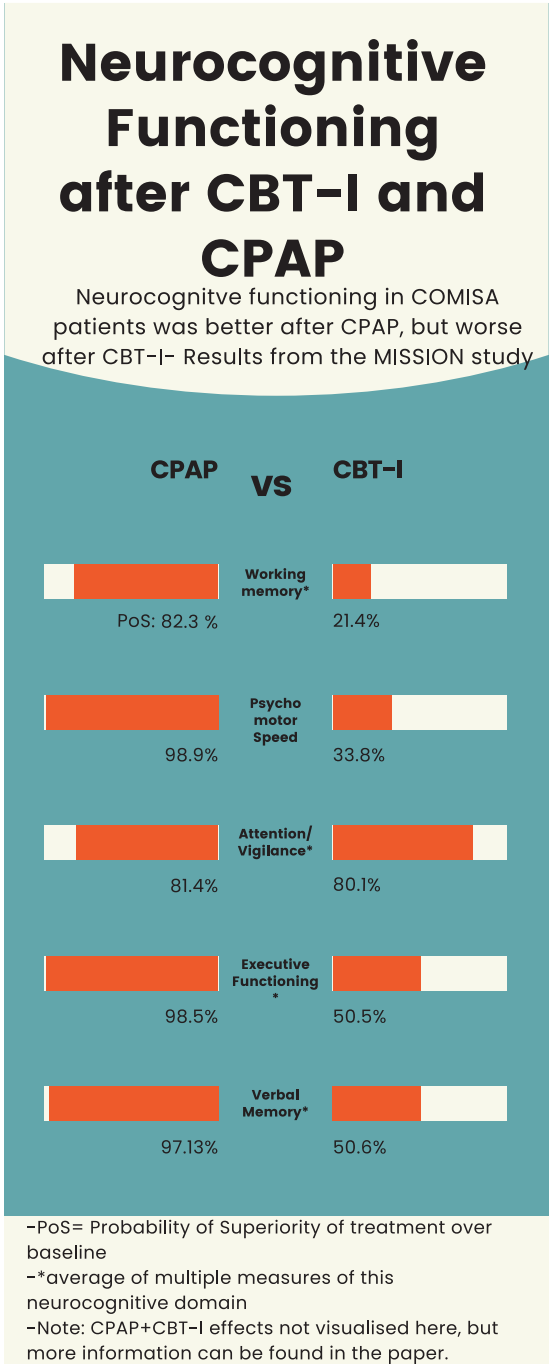
Graphical Abstract



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Statement of Significance

Impairments in neurocognitive functioning domains like memory, or attention can have a significant impact on quality of life or safety of the individual. Sleep disturbances like those seen in insomnia or obstructive sleep apnea, can lead to neurocognitive impairments. In patients with both sleep disorders (comorbid insomnia and sleep apnea, or COMISA), the impact may be further exacerbated; however, studies documenting functioning in the COMISA population are sparse. Treatments such as positive airway pressure therapy (PAP) or cognitive behavioral therapeutics for insomnia (CBT-I) may be beneficial in reversing the negative sequelae in COMISA; however, no research study of their efficacy in COMISA exists. This is the first study to document both baseline neurocognitive functioning of COMISA patients and the impact of CBT-I, PAP therapy, and combined treatment approaches.

Introduction

Insomnia and obstructive sleep apnea (OSA) are the two most common sleep disorders. Insomnia disorder, which affects approximately 10%–18% of the population, is characterized by difficulty initiating or maintaining sleep, while OSA, is a sleep-related breathing disorder that affects about 10%–20% of adults [1, 2]. Both insomnia and OSA are sleep disorders that include nocturnal sleep disturbances, as well as impairments to daytime functioning [1, 2]. OSA and insomnia cooccur more commonly than would be expected given the paradoxical nocturnal sequelae of the two disorders and the population estimates of each disorder. As with individual disorders, the prevalence of comorbid insomnia and sleep apnea (COMISA) varies by diagnostic criteria and sample population. Reports from sleep disorder clinics indicate that between 30%–40% of insomnia and 30%–50% of OSA patients meet criteria for COMISA [3–5]. COMISA has been associated with several public health concerns such as higher risk for psychiatric and medical conditions [6–10], reduced quality of life [6], excessive daytime sleepiness [6, 11], absenteeism from work [12], and more recently increased risk of all-cause mortality [13, 14]. Additionally, in the context of OSA, comorbid insomnia creates clinical challenges in the management of the disorder [15, 16].

Individuals with COMISA experience the additive detrimental nighttime and daytime symptoms of each disorder. It is presumed that this is the case with the daytime consequence of cognitive impairment; however, it has not been fully examined and the empirical evidence is scant. The profile of cognitive deficits in OSA and insomnia separately have been summarized in several systematic reviews and meta-analyses [17–20]. These studies have suggested that individuals with OSA exhibit deficits in the cognitive domains of attention/vigilance, delayed visual and verbal memory, executive functioning, and to a lesser extent visuospatial/constructional abilities [18, 20], while individuals with insomnia exhibit deficits in attention, memory, and executive functioning [17, 19]. Thus, research has shown a possible overlap in cognitive impairments with both OSA and insomnia separately reporting impairments in the domains of attention/vigilance, memory, visuospatial/constructional abilities, and executive functioning [17–20]. Considering the high prevalence rates of COMISA and the associations with higher self-reported daytime impairment, it is important to conduct an in-depth examination of the neuropsychological functioning of individuals with COMISA as well as the impact of treatment. To date, only two studies have examined neurocognitive impairment in COMISA patients [21, 22]. Stone et al. noted minimal differences, but poorer performance on memory, set-shifting, and attention tasks compared to those with insomnia alone [22], and Gooneratne et al. noted that those with COMISA had longer psychomotor reaction times, indicating possible poor sustained/vigilant attention compared to those with neither disorder [21]. However, Gooneratne et al. only examined attention/vigilance and both studies only examined neurocognitive functioning at baseline.

Many of the studies on the effect of positive airway pressure (PAP) therapy on neurocognitive functioning in patients with OSA indicate small improvements; however, study quality needs to be improved in order to conclusively determine the beneficial impact of PAP therapy on neurocognitive functioning [23]. In contrast, many studies that have evaluated the impact of CBT-I on objective cognitive performance demonstrate no meaningful change in functioning for patients with insomnia [24, 25], and some even report short-term impairment in functioning [26]. The impairment may be due to the implementation of Sleep Restriction Therapy (SRT), which has been linked to a reduction in objective total sleep time, increased daytime sleepiness, and impaired vigilance [27]. Implementing SRT in COMISA patients may lead to an even greater impairment than those seen in insomnia patients. Combining CBT-I with PAP therapy might offer a protective effect; however, this hypothesis remains untested, since to date, no study has examined the impact of treatment on cognitive functioning in COMISA patients. Examining the individual and combined effects of standard treatment for both conditions is thus important to provide guidance for practitioners as to what to expect when providing CBT-I to COMISA patients. This paper reports on the ancillary neurocognitive study of a large randomized control trial with main effects reported elsewhere [28, 29], which provides a unique opportunity to examine the neurocognitive profile of individuals with COMISA at baseline and to evaluate the relative effects of CBT-I, PAP, and combined treatment on neurocognitive performance in a subset of participants. As such, this was an exploratory study with the purpose of guiding future research.

Methods

Study design

This was an ancillary study of a 3-arm randomized clinical trial conducted at two sites (Rush University Medical Center and Northwestern University Feinberg School of Medicine), using a partial factorial design, examining the impact of concomitant treatments using cognitive behavioral therapy for insomnia (CBT-I) and PAP for individuals with COMISA (see [28]). This ancillary study added a neurocognitive assessment battery to explore the neurocognitive profile in this comorbid sample and to assess the relative benefit of different treatment combinations on neurocognitive functioning. The study design of the parent study is described elsewhere (see [30]). Briefly, after baseline assessment eligible individuals were randomized to one of the three treatment arms, each containing two phases (see Figure 1 for study design and flow diagram). In Arm A individuals received CBT-I in phase I followed by PAP in phase II, designed to test the impact of treating insomnia prior to the initiation of PAP (sequential treatment model). In arm B, individuals self-monitored their sleep with a diary in phase I followed by concurrent CBT-I and PAP in phase II, designed to test the impact of treating insomnia concurrently with PAP at home (concurrent treatment model). In arm C, individuals completed a sleep diary in phase I, followed by receiving PAP alone in phase II, which was designed to test the impact of current standard care without direct intervention on insomnia (standard treatment model). In individuals who consented to take part in the ancillary study, neurocognitive performance was assessed at three-time points: (1) at baseline (prior to treatment initiation), (2) after 1 month of either CBT-I or self-monitoring with a sleep diary, and (3) after a month of PAP therapy with or without concurrent CBT-I. Making use of the factorial design, we identified three different groups to enable the evaluation of the relative benefits of each individual as well as combined treatment on neurocognitive performance (see Figure 1). Group 1 were participants receiving only CBT-I [arm A, phase I], group 2 were participants who received both PAP and CBT-I [arm B, phase II], and group 3 were individuals who received PAP only [arm C, phase II].

Participants

Participants were invited to take part in this ancillary study between May 2015 and April 2018. Details on recruitment and screening procedures for the parent study and other secondary outcome measures have been previously described [28–30] and

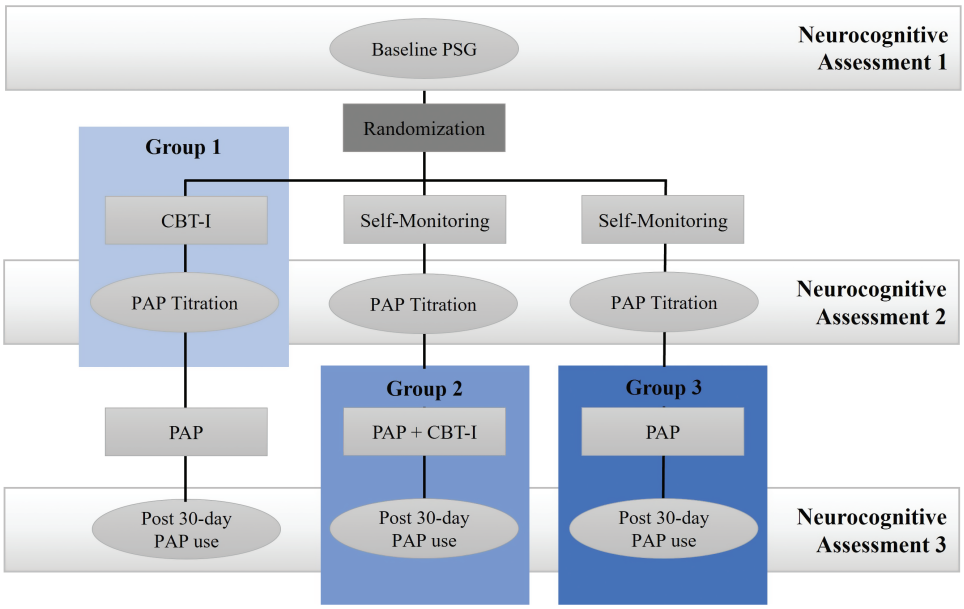

Figure 1. Overview of study design and flow. Caption- group 1: receiving CBT-I alone, group 2: receiving combined CBT-I and PAP therapy, and group 3: receiving PAP alone.

the parent study, a clinical trial, was preregistered at www.clinicaltrials.gov (NCT01785303). We included individuals who were eligible for the parent study (adults over the age of 18 who met criteria for insomnia disorder and OSA and excluded those with acute medical, psychiatric conditions. or suicidal ideation requiring immediate treatment, individuals with severe OSA requiring immediate treatment, those with an active use of sedative-hypnotics, and those with excessive daytime sleepiness see [30] for full inclusion and exclusion criteria). Additional exclusion criteria for this ancillary study were:

1. Comorbid psychiatric/medical conditions judged to interfere with the neurocognitive assessment including developmental disorders, learning disabilities, history of brain trauma, head injury, or any neurologic disorder, including stroke, and encephalitis.
2. Current use of medications that are known to alter cognition (e.g. benzodiazepines, opiates, tricyclic antidepressants, and anticonvulsants) and/or sleep (e.g. bronchodilators).

Written informed consent was obtained from all participants at the beginning of the in-person interview for the parent study. Participants could opt in or out of this ancillary study without impact on their participation in the parent study.

One hundred and eleven participants consented to participate in the neurocognitive evaluation. After screening, four were deemed ineligible for the neurocognitive evaluation because of issues that would impact cognition (e.g. previous concussion). After screening for the parent study, 58 were deemed ineligible (e.g. presence of PLMDs, no OSA on baseline PSG, active suicidality) and thus did not continue with the parent study nor complete the neurocognitive evaluation. A further four participants were not included in the analysis because of insufficient effort on cognitive tasks as estimated by the study neuropsychologist. Thus, a total of 45 participants met study criteria and completed baseline analyses. The treatment data presented in the results only includes data from 39 participants, since six participants were excluded from the parent study post-randomization because their baseline PSG indicated a need for immediate treatment of their OSA.

Procedure

Each participant completed neurocognitive testing administered by a study neuropsychologist or trained researchers according to standardized protocols on three occasions: the morning after the baseline PSG, morning after the PAP titration study, and morning of the 1-month follow-up visit. To ensure assessments were standardized relative to the individual's sleep phase, neurocognitive testing was completed within 2 hours of participants' habitual wake time. All testing was completed in a quiet secure room, and all tests were administered in a standardized manner by trained study personnel. The neurocognitive assessment battery contained a mix of traditional paper and pencil and tablet-based tasks evaluating domains shown to be sensitive to sleep deprivation and either insomnia, OSA, or both. The battery consisted of five separate tests (see below) and took approximately 30–45 minutes to administer. The study was approved by the local Institutional review board at both sites (Rush University #11090801-IRB01; Northwestern University # STU00203478).

Measures

Neurocognitive assessment measures

Verbal paired associates.

The verbal paired associates (VPA) task is a subtest of the Wechsler Memory Scale that evaluates hippocampal-dependent declarative memory via verbal memory for associated word pairs [31]. A list of 14-word pairs (e.g. laugh/stand) is read to the participant; after the complete list is read, the participant is asked to provide the associated word (stand) when presented with the first word (laugh) of the pair. The task is repeated for four trials and the order of items from the list is varied across trials, but the pairs remain the same. After a 20- to 30-minute delay, the participant is asked to recall the paired word without cuing with the full list ("what word goes with laugh") and complete a yes/no recognition

test of the word pairs (e.g. was "laugh/stand" one of the word pairs you heard?). Scores for VPA included Total Recall, measured as the total number of pairs recalled (with list cueing) across the four learning trials; Delayed recall, measured as the number of pairs recalled (without list cueing) following a 20- to 30-minute delay; and delayed recognition, measured as number of correctly identified word pairs. Although there are inconsistencies, research suggests that both individuals with OSA and individuals with insomnia have impaired declarative memory [17–20].

Psychomotor vigilance task.

The psychomotor vigilance task (PVT) assesses sustained attention/vigilance. The tablet-based PVT instructs individuals to respond to a stimulus (visual/auditory) that appears on the screen at random intervals. The PVT is a widely used measure of alertness as performance on this task is highly sensitive to both acute and chronic sleep deprivation [32]. The most often reported metrics of the PVT are reaction time in milliseconds, and number of lapses (defined as no reaction, or a reaction time greater than 500 milliseconds). While evidence regarding impairment in the PVT and similar attention/vigilance tasks are reported less often in insomnia [17, 33], there is strong evidence to suggest that this area is impaired in OSA [20].

Digit symbol substitution test.

The digit symbol substitution test (DSST) is a frequently used measure of psychomotor speed [34]. The DSST presents individuals with a key that links digits with symbols and asks them to use the key to match a series of symbols to the corresponding digits. The aim is to match as many symbols as possible within the allotted time (120 seconds). Scores on the DSST are the number of correctly matched symbols in the time allotted. This task is negatively affected by sleep deprivation [35, 36] and OSA is associated with impairments on this task specifically [37]. One study has indicated an improvement with PAP treatment [37], but to the best of our knowledge, no studies have examined the effect of CBT-I on performance on the DSST.

Stroop color/word test.

The stroop color/word task (color/word) is a portion of the Stroop Color and word test [38] that measures executive functioning. The stroop color/word test consists of three tasks word, color, and color/word. For the word task participants are asked to read names of colors (Red, Green, etc…) written in black ink on a white page down each column aloud as quickly and accurately as possible within the time allotted (45 seconds). For the color task, participants are asked to name the color of "XXXX"s (e.g. For "XXXX" written in red ink, the correct answer would be red) again down the column aloud as quickly and accurately as possible in the time allotted (45 seconds). For the color/word task individuals are asked to name the color of the ink a word is printed in, while ignoring the word that is printed (i.e. when the word Red is printed in green ink, the correct response is green) also down the column aloud as quickly and accurately as possible in the time allotted (45 seconds). The word and color tasks require attention, while the color/word task requires an individual to inhibit the natural response of reading the word for the more appropriate response of naming the ink color. Scores on the Stroop task include the number of correctly read stimuli for each subtest (color, word, and color/word). Analyses in this study focus on the color/word task as research indicates that the color/word task is impaired in both OSA and insomnia [17–20].

Digit span.

Digit span (DS) is a task included in the working memory domain of the Wechsler's Intelligence Scale, which focuses on the ability to repeat a list of numbers as presented and in the reverse order [34]. For DS forward, which measures attention and short-term memory, individuals are asked to repeat, in the correct order, digits that are verbally presented to them (ex. the correct answer for the sequence 123 is 123). For DS backwards, individuals are asked to repeat the digits that are verbally presented to them in reverse order (ex. the correct answer for the sequence 123 is 321). The number of digits presented increases sequentially for both digits forward and digits backward until the participant either correctly repeats a nine-digit sequence or incorrectly repeats two sequences of the same span length. The final score is the number of correctly repeated sequences (number correct) and the longest digit sequence correctly repeated (longest span) for each. Working memory has been reported to be impaired using these tasks in both the sleep apnea and insomnia populations [39–41].

Covariates

Gender was based on self-report at time of enrollment. Age (in years) was computed from self-reported birth date and date of enrollment in the study. Education was based on self-reported years of regular schooling. Race was based on self-report using the 1990 US Census categories. Objective baseline total sleep time from the diagnostic PSG and daytime sleepiness measured with the Karolinska Sleepiness Scale [42] were also included as covariates.

Analytic strategy

Continuous variables are presented as mean (standard deviation). To examine the relative impact of the different treatments, we analyzed our data using Bayesian linear mixed models. We had four comparisons of interest that assessed the effect of each treatment—comparing CBT-I, PAP, and CBT-PAP to baseline, and the combined treatment to PAP alone. These comparisons necessitated a mix of within and between comparisons, as all participants were present at baseline, but not in each of the treatment arms. Cognitive performance was presented through 12 neurocognitive performance metrics, which was each score garnered from the five neurocognitive tasks explored separately. We used an estimated marginal means approach, taking the average of the predicted scores in each treatment group, as well as at baseline. Our mixed models had a random effect on participant, meaning that the estimated marginal means incorporated information regarding the placement of individuals across baseline and treatment conditions.

Our Bayesian models yielded a distribution for each of the estimated means in each treatment condition, which we then compared via simple subtraction. The means of treatment and comparator were calculated, as well as the mean difference and the corresponding 95% lower and upper credible bounds for this difference. The probability of superiority (the probability that the difference between the treatment and comparator was greater than zero) was computed for each neurocognitive marker and each of the four comparisons (CBT-I vs. baseline, PAP vs. baseline, CBT-I+PAP vs. baseline, and CBT-I+PAP vs. PAP alone). Superior performance on the neurocognitive tests will be reported as "worse" or "better" performance. However, it is important to note that this does not suggest an improvement or worsening of functioning with treatment, because (1) the comparisons include a mix of within and between participant comparisons, and (2) the differences were computed from estimated marginal means, and so represent the covariate-adjusted

average effects within each condition, and thus these are not true pre-post comparisons.

Given the exploratory nature of the study, Cohen's d was also generated, and any effect that was larger than 1, was deemed noteworthy. We set this cutoff to avoid over-interpreting smaller effects in such a relatively small sample. We fitted a separate model for each of sub-measures, entering all covariates and the interaction between study arm and time point, and collected the estimated marginal means. Any Bayesian analysis requires a prior distribution for the model parameters (i.e. the covariates and time point by study arm interaction). We used very wide weakly informative priors on the parameter distributions of the coefficients, centered on zero with a very large variance. These prior specifications mean the priors exert almost no influence on the estimates. Models were estimated using the Bambi package in the Python language.

Results

Demographics

Among the 45 participants who met study criteria, six were referred for immediate treatment and thus only provided baseline data. Additionally, three individuals were missing data at baseline; however, their randomization arm allowed for pre- and post-treatment analyses (e.g. had data in-group 2 or 3) and these individuals were included in subsequent analyses. Therefore, data are presented on 42 participants with complete baseline data and 39 participants with data from the post-treatment time points who were randomized to one of the treatment arms. The total sample was 51.1% female, had a mean age of 52.1 (SD = 13.3) years, and a mean education attainment of 15.9 (2.33) years (Table 1).

Baseline neurocognitive functioning

At baseline study participants, as a whole, correctly recalled 21.17 ± 11.55 unrelated word pairs in total across the four trials of the immediate recall portion of the VPA test, and correctly recalled 8.69 ± 3.16 unrelated word pairs in the single trial of the delayed recall portion of the test. In the color/word trial of the stroop participants were able to name the color of the ink correctly, while inhibiting the natural inclination to read the word for an average of 34.57 ± 2.98 words. Participants were able to recall an average of 7.31 ± 1.37 strings of numbers for DS Forward and 4.19 ± 1.79 for DS Backward correctly. For the PVT, participants had a mean reaction time of 365.66 ms ± 157.39 and an average of 9.70 lapses ±16.16. In the Digit Symbol Substitution task, the average amount of symbols correctly paired within 120 seconds was 68.83 ± 12.33. Table 2 shows the baseline mean scores in this COMISA sample, and approximations from the literature for mean scores in either insomnia or OSA separately, as well as mean scores for those without sleep issues [39, 41, 43–46] . Supplementary Table S1 shows the means by treatment arm.

Effects of treatment on neurocognitive functioning

Among the 39 participants who were randomized to one of the three treatment arms (10-sequential treatment/Arm A; 15-concurrent treatment/Arm B; 14-standard treatment/Arm C) there were three participants with missing data that precluded analysis. The missing data were from one participant in Arm B and one participant in Arm C who only had baseline data, and one individual in Arm C without 1-month follow-up. The data from these individuals was not included; therefore, data are presented on the remaining 36 participants. Age, educational attainment, and proportions of age, race, and OSA severity were similar across Arms/treatment groups (see Table 1).

Effects of PAP.

After treatment with PAP alone, mean performance was better than baseline for all cognitive domains measured (see Table 3).

Table 1. Sample Characteristics

	Total sample (*n* = 45)*	Arm A (*n* = 10)*	Arm B (*n* = 15)*	Arm C (*n* = 14)*	*p*
Age (*M* ± SD)	52.1 ± 13.3	50.5 ± 10.1	54.8 ± 12.9	46.2 ± 14.9	.23
Gender (*n*, %)					.69
Male	22, 48.9%	4, 40%	7, 46.7%	8, 57.1%	
Female	23, 51.1%	6, 60%	8, 53.3%	6, 42.9%	
Race (*n*, %)					.67
Asian	1, 2.2%	0, 0%	0, 0%	1, 7.1%	
Black or African American	18, 40.0%	4, 40%	6, 40%	6, 42.9%	
White	25, 55.6%	6, 60%	9, 60%	6, 42.9%	
More than one race	1, 2.2%	0, 0%	0, 0%	1, 7.1%	
Education Years (*M* ± SD)	15.9 ± 2.3	15.4 ± 1.9	15.7 ± 2.6	16.2 ± 2.6	.72
BMI (*M* ± SD)	33.7 ± 9.1	37.6 ± 9.6	32.2 ± 10.4	32.5 ± 6.6	.30
OSA severity (*n*, %)					.80
Mild (AHI ≥ 5 and <15)	21, 46.7%	6, 60%	7, 46.7%	7, 50%	
Moderate/severe (AHI ≥15)	19, 42.2%	4, 40%	8, 53.3%	7, 50%	
Insomnia severity measured by ISI (*M* ± SD)	17.6 ± 4.5	17.6 ± 5.0	17.5 ± 3.8	17.8 ± 5.2	.98
Average *N* of psychiatric comorbidities	1.7 ± 1.7	2.3 ± 2.2	1.7 ± 1.7	1.1 ± 1.4	.28
Average *N* of physical comorbidities	1.4 ± 1.6	2.0 ± 2.1	1.1 ± 1.4	1.1 ± 1.5	.36

*Six participants completed baseline analyses but were not randomized into an arm of the study (hence, the total for those randomized is 39). AHI, Apnea–Hypopnea Index, ISI, Insomnia Severity Index. Arm A: CBT→PAP, Arm B: CBT+PAP and Arm C: PAP alone.

The magnitude of this difference was considerable, with effect sizes above Cohen's $d = 1$ for all domains except working memory, which was still high, but below our predefined cutoff, (DS Forward Correct Trials – PAP = 10.39 vs. Baseline = 9.65, Cohen's $d = 0.866$, ProS = 76.3; DS Forward Span Length – PAP = 7.67, Baseline = 7.26, Cohen's $d = 0.849$, ProS = 74.3. Table 3 includes the details of all comparisons. The probability of superiority (a higher score after treatment) was high, indicating a high degree of confidence that performance after treatment is better than after baseline.

Effects of CBT-I.

After treatment with CBT-I alone, mean performance was typically worse than performance at baseline, see Table 4, this was the case for tasks of working memory, psychomotor speed, executive functioning (Stroop color/word trial only), and verbal memory (delayed recall and recognition only). However, only the effect sizes for working memory indicated a noteworthy magnitude of difference (Cohen's $d = -1.11$ and -1.24). Additionally, the probability that performance after CBT-I was superior was low (14.2 and 18.6 for DS backward and forward, respectively).

Mean performance after CBT-I was better than baseline for attention/vigilance, executive functioning via Stroop interference, and immediate recall for verbal memory. Only the effect size for attention/vigilance via number of lapses on the PVT was noteworthy and the probability of superiority was high (ProS = 83.1). The probability of superiority for the other metrics were low (ProS = 61–77) Details of each comparison can be seen in Table 4.

Table 2. Comparison of Current COMISA Sample and Reported Mean Scores in Insomnia, OSA and No Sleep Issues

	Current COMISA sample	OSA | Insomnia separately*		No sleep issues range*	
Digit span backwards	4.19 ± 1.79	4.96 ± 1.23	6.76 ± 1.94	5.86 ± 1.38	6.42 ± 2.29
Digit span forward	7.31 ± 1.37	6.63 ± 1.63	8.42 ± 2.08	7.41 ± 1.60	8.63 ± 2.08
Digit symbol substitution	68.83 ± 12.33	47.00 ± 12.29	52.43 ± 11.68	54.21 ± 12.44	61.56 ± 11.43
†PVT reaction time	365.66 ± 157.39	347.85 ± 159.47	313.81 ± 46.34	297.04 ± 106.55	299.71 ± 36.89
PVT lapses	9.70 ± 16.17	4.82 ± 6.93	2.02 ± 2.57	3.74 ± 7.36	0.60 ± 0.84
Stroop Color/word trial	34.57 ± 2.98	37.55 ± 11.52	51.42 ± 10.46	41.70 ± 8.83	51.04 ± 10.07
Verbal paired associates immediate	27.17 ± 11.55	30.31 ± 12.88	23.43 ± 8.70	33.01 ± 14.87	26.53 ± 9.06
Verbal paired associates delayed	8.69 ± 3.16	10.67 ± 3.87	8.10 ± 2.41	10.00 ± 2.63	8.68 ± 1.81

*Mean Scores for Insomnia/OSA Separately and No Sleep Issues approximated from the literature [47] COMISA, comorbid insomnia and sleep apnea
†Higher Score indicates poorer performance.

Table 3. Effects of PAP Alone on Neurocognitive Performance

Cognitive domain	Measure	Treatment mean	Comparator mean	Mean difference	Lower	Upper	ProS*	Cohen's d^
Working memory	DS backwards: number of correct trials	**5.41**	4.15	1.26	−0.70	3.51	88.5	**1.508**
	DS backwards: longest span	**5.22**	4.32	0.90	−0.50	2.29	90.2	**1.716**
	DS forwards: number of correct trials	**10.39**	9.65	0.74	−1.28	2.82	76.3	0.866
	DS forwards: longest span	**7.67**	7.26	0.42	−0.92	1.63	74.3	0.849
Psychomotor speed	Digit symbol substitution task: number Correct	**79.20**	69.66	9.54	1.36	17.74	98.9	**2.776**
Attention/ vigilance	†PVT: mean reaction time	**305.30**	364.59	−59.29	−182.61	70.50	82.2	**-1.123**
	PVT: number of lapses	**4.65**	10.10	−5.45	−17.72	7.52	80.6	**-1.156**
Executive functioning	Stroop: color/word trial	**50.14**	35.63	14.51	8.13	21.32	100	**5.309**
	Stroop: interference score	**5.20**	−2.28	7.49	0.12	15.49	97.1	**2.48**
Verbal memory	VPA: total immediate recall	**39.73**	28.13	11.60	2.25	21.91	98.9	**2.738**
	VPA: delayed recall	**11.84**	8.89	2.95	0.19	5.92	97.8	**2.442**
	VPA: recognition	**39.48**	37.21	2.27	−0.58	5.05	94.7	**1.96**

For these comparisons, the comparator was everyone's baseline. Bold in the treatment/comparator columns indicates better performance. ProS, Probability of Superiority.
*Converted so that higher % indicates superiority of treatment.
†Higher Score indicates poorer performance for this measure. Cohen's d^ greater than 1 are bolded^ Cohen's d > 1 are in bold

Table 4. Effects of CBT-I Alone on Neurocognitive Performance

Cognitive domain	Measure	Treatment mean	Comparator mean	Mean difference	Lower	Upper	ProS*	Cohen's d^
Working memory	Digit span backwards: number of correct trials	3.31	**4.15**	−0.85	−2.71	1.04	18.6	**−1.112**
	Digit span backwards: longest span	3.91	**4.32**	−0.41	−1.66	0.83	26.1	−0.839
	Digit span forwards: number of correct trials	8.67	**9.65**	−0.98	−2.91	0.77	14.2	**−1.238**
	Digit span forwards: longest span	6.90	**7.26**	−0.35	−1.41	0.81	26.9	−0.783
Psychomotor speed	Digit symbol substitution task: number correct	68.08	**69.66**	−1.58	−8.51	6.06	33.8	−0.484
Attention/vigilance	†Psychomotor vigilance task: mean reaction time	**321.47**	364.59	−43.13	−150.43	68.52	77.1	−0.881
	†Psychomotor vigilance task: number of lapses	**4.46**	10.10	−5.64	−16.54	6.15	83.1	**−1.29**
Executive functioning	Stroop: Color/Word trial	34.81	**35.63**	−0.82	−6.84	4.91	39	−0.321
	Stroop: interference score	**−1.34**	−2.28	0.95	−5.50	8.08	61.1	0.345
Verbal memory	Verbal paired associates: total immediate recall	**29.83**	28.13	1.71	−6.71	9.88	65.3	0.439
	Verbal paired associates: delayed recall	8.74	**8.89**	−0.15	−2.64	2.36	45.4	−0.137
	Verbal paired associates: recognition	36.94	**37.21**	−0.27	−2.59	2.33	41.3	−0.256

For these comparisons, the comparator was everyone's baseline. Bold in the treatment/comparator columns indicates better performance. ProS, Probability of Superiority.
*Converted so that higher % indicates superiority of treatment.
†Higher Score indicates poorer performance for this measure. Cohen's d^ greater than 1 are in bold.

Table 5. Effects of CBT-I+PAP on Neurocognitive Performance

Cognitive domain	Measure	Treatment mean	Comparator mean	Mean difference	Lower	Upper	ProS*	Cohen's d^
Working memory	Digit span backwards: number of correct trials	**5.17**	4.15	1.02	−0.78	2.89	86.7	**1.384**
	Digit Span backwards: longest span	**4.95**	4.32	0.63	−0.65	1.88	84.2	**1.336**
	Digit span forwards: number of correct trials	**10.07**	9.65	0.42	−1.43	2.09	68.5	0.556
	Digit span forwards: longest span	**7.42**	7.26	0.16	−0.88	1.24	62.1	0.377
Psychomotor speed	Digit symbol substitution task: number correct	**74.90**	69.66	5.24	−1.77	12.20	92.3	**1.714**
Attention/vigilance	†Psychomotor vigilance task: mean reaction time	**314.38**	364.59	−50.21	−155.08	57.71	82.4	**−1.092**
	Psychomotor vigilance task: number of lapses	**3.03**	10.10	−7.07	−18.64	3.69	89.9	**−1.663**
Executive functioning	Stroop: color/word trial	**42.71**	35.63	7.09	1.73	12.65	99.4	**2.911**
	Stroop: interference score	**1.28**	−2.28	3.56	−2.80	10.23	86.4	**1.361**
Verbal memory	Verbal paired associates: total immediate recall	**40.06**	28.13	11.94	3.74	19.76	99.7	**3.252**
	Verbal paired associates: delayed recall	**11.19**	8.89	2.30	−0.06	4.69	97.1	**2.158**
	Verbal paired associates: recognition	**38.81**	37.21	1.60	−0.70	3.97	91.4	**1.595**

For these comparisons, the comparator was everyone's baseline. Bold in the treatment/comparator columns indicates better performance. ProS, Probability of Superiority.
*Converted so that higher % indicates superiority of treatment.
†Higher Score indicates poorer performance for this measure. Cohen's d^ greater than 1 are in bold.

Effects of combined treatments.

After treatment with CBT-I+PAP mean performance was better than baseline, with only digits forward not reaching a noteworthy effect size (Cohen's d = 1.092 –3.252). The probability that performance after combined treatment was higher compared to baseline was also high for all tasks except digits forward (ProS = 82.4–99.7). The details of these comparisons are depicted in Table 5. Mean performance after treatment with CBT-I+PAP was

Table 6. Effects of CBT-I+PAP Versus Effects of PAP Alone on Neurocognitive Performance

Cognitive domain	Measure	Treatment mean	Comparator mean	Mean difference	Lower	Upper	ProS*	Cohen's d^
Working memory	Digit span backwards: number of correct trials	5.17	**5.41**	−0.24	−2.86	2.56	43.7	−0.241
	Digit span backwards: longest span	4.95	**5.22**	−0.27	−1.95	1.42	37.9	−0.43
	Digit span forwards: number of correct trials	10.07	**10.39**	−0.32	−3.15	2.40	40.8	−0.319
	Digit span forwards: longest span	7.42	**7.67**	−0.25	−1.77	1.39	37.6	−0.433
Psychomotor speed	Digit symbol substitution task: number correct	74.90	**79.20**	−4.30	−15.02	7.63	22.9	**−1.062**
Attention/vigilance	†Psychomotor vigilance task: mean reaction time	314.38	**305.30**	9.08	−163.56	183.84	45.8	0.146
	Psychomotor vigilance task: number of lapses	**3.03**	4.65	−1.62	−16.95	14.31	58.6	−0.287
Executive functioning	Stroop: color/word trial	42.71	**50.14**	−7.43	−16.86	1.08	5.3	**−2.285**
	Stroop: interference score	1.28	**5.20**	−3.93	−14.05	5.49	21.5	**−1.105**
Verbal memory	Verbal paired associates: total immediate recall	**40.06**	39.73	0.34	−14.23	13.73	53.1	0.067
	Verbal paired associates: delayed recall	11.19	**11.84**	−0.65	−4.69	3.14	37.3	−0.454
	Verbal paired associates: recognition	38.81	**39.48**	−0.67	−4.65	2.91	35.8	−0.492

For these comparisons, the comparator was PAP alone. Bold in the treatment/comparator columns indicates better performance. ProS, Probability of Superiority.
*Converted so that higher % indicates superiority of treatment.
†Higher Score indicates poorer performance for this measure. Cohen's d^ greater than 1 are in bold.

worse than after treatment with PAP alone. This was the case for tasks of working memory, psychomotor speed, attention/vigilance via PVT mean reaction time, executive functioning, and verbal memory delayed recall and recognition. The effect size was noteworthy for psychomotor speed and executive functioning and the probability that combined treatment was superior to PAP alone was low (probability of superiority = 5.3–22.9). Mean performance after combined treatment was better than after treatment with PAP alone for attention/vigilance via number of lapses on the PVT and immediate recall for verbal memory. The effect sizes for this difference were not large (Cohen's d = −0.2 and 0.07, respectively). The probability of superiority was also not high (ProS = 58.6 and 53.1, respectively). Detailed results for these comparisons are in Table 6.

Discussion

The aim of this exploratory study was to assess neurocognitive functioning in COMISA patients at baseline and examine the impact of different treatment combinations (PAP alone, CBT-I alone, and CBT-I+PAP) on performance. At baseline, overall mean scores of the COMISA patients in this trial indicate larger deficits in some domains compared to what has been reported in the literature for insomnia and OSA separately, as well as healthy controls without sleep problems and published norms. Individuals with COMISA performed worse than individuals with insomnia alone or OSA alone and health controls in the areas of cognitive control, attention/vigilance, executive functioning, and immediate and delayed verbal memory. Individuals with COMISA appear to retain working memory abilities. Additionally, those with COMISA performed better than those with either insomnia or OSA alone on the measure of psychomotor speed.

These neurocognitive impairments may be a result of the combined effects of hypoxia (OSA [47],) and sleep fragmentation/deprivation (OSA and insomnia [47, 48],). Impairments in these areas are significant, as this may lead to an increased risk of motor vehicle accidents [26, 49, 50], poor decision-making [50–52], increases symptoms of psychiatric disorders like depression and anxiety [53, 54], and decreased quality of life [55, 56]. The impairments in cognitive performance observed in this exploratory study, especially in vigilance, suggest a need for future examinations of changes in a broader range of daytime functioning/impairment outcomes in patients with COMISA to include cognitive functioning and the impact on public health matters like driving performance.

Within this COMISA sample, there were differential treatment effects on neurocognitive functioning based on treatment modality. Participants who received treatment via PAP had better performance on all neurocognitive performance metrics after treatment compared to everyone's baseline. Neurocognitive impairment is seen in many patients with and is listed among the most prominent adverse consequences associated with OSA [18]. Unfortunately, research is inconsistent with regard to the influence of PAP treatment on neurocognitive functioning, with the majority reporting improvement after PAP, but from low-quality study designs [23]. The domains of attention and executive functioning are most often associated with improvement in the literature [23, 57]. This is consistent with the findings in this exploratory study with a COMISA sample with the Stroop color-word test (executive functioning) and the DSST (psychomotor speed and attention) having the highest effect sizes. It has been suggested that level of adherence and severity of OSA are factors that strongly influence the effectiveness of PAP in enacting change in neurocognitive performance [57]. This relationship might help to explain variations in treatment results across studies. With the

small sample size in the current study, we were limited in the number of covariates to include. Future studies should take OSA severity and PAP adherence into account when examining treatment impacts on cognitive functioning.

The individuals receiving CBT-I had a different pattern of performance when compared to baseline. Only number of lapses on the PVT in the CBT-I alone group demonstrated improvement with a noteworthy effect size and high probability of superiority. While a few other neurocognitive performance metrics showed better performance after treatment, performance was poorer after CBT-I compared to baseline. Participants demonstrated worse performance after CBT+PAP treatment when compared to treatment with PAP alone as well. These results are consistent with previous research on the influence of CBT-I on cognitive performance in insomnia. Over half of the randomized controlled trials exploring the influence of CBT-I on objective cognitive performance find no evidence of beneficial change [24–26, 58]. The most likely candidate for a mechanism that would lead to poorer neurocognitive response in some domains after treatment with CBT-I is Sleep Restriction Therapy (SRT). SRT is a component of CBT-I that involves restricting a patient's time in bed to match their current sleep duration, then titrating it up to core sleep requirement [26, 59]. SRT decreases opportunity to sleep across several nights, it also builds homeostatic sleep pressure, dampens pre-sleep cognitive and physiological arousal, and stabilizes circadian rhythms [60], which leads to shorter sleep latencies, and more consolidated uninterrupted sleep [27, 61–65]. Given the reduction in opportunity to sleep across several nights, and the prohibition of napping inherent in SRT, it is advised that during the initial phases of implementation, increases in daytime sleepiness may occur and result in a transient worsening of daytime functioning [27, 65, 66]. Research has indicated that acute SRT is associated with slower reaction times and increased lapses in the PVT [27, 59]. Additionally, OSA is commonly associated with elevated daytime sleepiness, which leads to concerns that SRT in COMISA may produce a more marked increase in daytime sleepiness that could potentially be dangerous given the demonstrated risk of motor vehicle accidents [26, 49–52]. In the parent study, however, we did not see any significant increased adverse events in the treatment arms that included CBT-I [28]. Given the public health concerns of increased accidents related to OSA, and therefore, COMISA, the increase in sleepiness and impairment in vigilance when implementing CBT-I (whether alone or in conjunction with PAP), it is imperative that clinicians are aware of the potential negative effects of CBT-I on neurocognitive functioning in this patient population. CBT-I in COMISA patients should be provided with caution and a recommendation to avoid operating heavy machinery and motor vehicles during treatment. These effects may of course only be temporary (our follow-up was only 30 days which is shorter than the traditional 6-8 week treatment session) and these results need to be replicated over longer periods.

There were several strengths of the study. First, this study used a comprehensive neurocognitive battery of tests that assessed five cognitive domains shown to be impaired by sleep deprivation, insomnia, and/or, sleep apnea. Secondly, data were utilized from a relatively diverse, balanced-by-gender sample that was a part of a randomized clinical trial, providing opportunity to assess neurocognitive performance after treatment. Finally, the use of Bayesian analysis allows for the comparison of performance without the pitfalls of frequent approaches. The Bayesian approach is a distribution of likely differences, which allowed for the use of the idea of probability of superiority—how likely one treatment is better than another is (or in this case, baseline). This ability to state simply how probable it is that treatment is better than baseline, allows for more informed discussions regarding future recommendations for personalized approaches and treatment plans.

There are also some limitations of the study. First, the results are based on a volunteer cohort that may not be representative of the US population in education or lifestyle. For instance, our results may be affected by the relatively high educational status of our sample, which might reflect a healthier population with a higher level of cognitive reserve/resilience. One of the exclusion criteria was excessive daytime sleepiness (see [30] for more details); future research should include samples with excessively sleepy COMISA patients. Additionally, since this was an exploratory study, the sample size was relatively small. By using Bayesian methods, which are more conservative in small sample sizes, we circumvent the false positives typically seen in small samples when using frequent analyses. However, the small sample size did prevent us from including additional covariates such as adherence to sleep restriction/stimulus control or reduction in total sleep time, improvements in sleepiness/disease severity, or the duration and severity of comorbidities. Also, the time frame for assessing neurocognitive changes was relatively short (but comparable to other studies on neurocognitive functioning) and might be insufficient to capture the changes associated with treatment. Furthermore, we did not measure duration of disease/onset of symptoms or family history of neurodegenerative disease, which may have had an impact on how one would interpret the neurocognitive scores. Lastly, in our analyses, we did not directly compare the COMISA sample to those with OSA, those with insomnia, or those without sleep issues. Though our comparisons include approximations of mean scores from the literature, future studies are necessary to provide a conclusive answer regarding the differences in neurocognitive functioning in COMISA, and the long-term effects of treatment on neurocognition (e.g. 6 months or greater).

In conclusion, the results of this exploratory study indicate that neurocognitive performance in COMISA patients appears to be impaired compared to normative data in samples with insomnia-alone, OSA alone, and neither condition. Furthermore, neurocognitive functioning was differentially affected by treatment combination. Particularly those combinations that involve CBT-I might lead to an increased temporary impairment that is in need of attention and monitoring. However, PAP therapy is associated with improvements in neurocognitive functioning across various domains. Further studies are needed in order to determine the long-term impact of CBT-I on neurocognitive functioning in COMISA patients.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Data Availability Statement

The data that support the findings of the study are available on request from the authors (JCO) upon reasonable request. The data are not publicly available because ethical approval for open access data was not obtained at the time.

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