Title: Cognitive and neuroimaging correlates of Insomnia symptoms in obstructive sleep apnea: a pilot-study

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Abstract

We aim to determine the sleep correlates of age-related brain loss in a sample of middle-aged to older males with obstructive sleep apnea. We evaluated consecutive treatment naïve male patients with OSA (AHI≥15 events/hr) without dementia, stroke or heart disease, from January to November of 2019. We collected demographic variables, vascular risk factors, and sleep questionnaires. We also obtained computerized neurocognitive testing with the Go-No-Go Response Inhibition Test, Stroop Interference Test, Catch Game Test, Staged Information Processing Speed Test, Verbal Memory Test and Non-Verbal Memory Test. We derived age and education adjusted domain-specific *Z*-scores for global cognition, memory, attention, processing speed and executive function. We used brain MRI T1-weighted images to derive total hippocampal and gray matter volumes. Partial correlations evaluated associations between the ISI, AHI, and oxygen level during sleep, with cognitive domains and brain volumes. Sixteen participants, age 40-76 years, 73% Hispanic/Latino, with mean AHI=48.9±25.5 and mean oxygen saturation of 91.4±6.9% during sleep. Hypertension was seen in 66% and diabetes in 27%. We observed that ISI and oxygen level during sleep had strong correlations with brain volumes and cognition. These preliminary findings may aid in developing future strategies to improve age-related brain loss in OSA.

Introduction

Emerging research points to a critical role for sleep in cognition and the risk for Alzheimer's disease (AD).[1] Sleep disturbances can accelerate the aging process [2-6] [7-9] and increase the risk for AD.[8, 10-14] For example, obstructive sleep apnea (OSA),a common sleep disorder found in more than 25% of adults,[15] is associated with cognitive decline and increased AD risk (HR 1.2 to 2.4)..[16, 17] Of interest, chronic insomnia is the most common sleep disorder in the general population and of high prevalence in patients with OSA.[18] Chronic insomnia is also associated with cognitive impairment, [19, 20] cognitive decline[21] and AD. [22] .Comorbid insomnia can affect up to 58% of OSA patients. Insomnia with OSA may represent a severe phenotype at increased risk for of age-related cognitive decline and brain loss. However, there is a paucity of studies evaluating the cognitive and neuroimaging correlates of brain loss associated to insomnia symptoms in OSA patients.[18]

Of importance, structural brain characteristics may be indicative of neuronal injury and neurodegeneration that can precede the clinical deterioration commonly observed in AD. Recent use of advanced imaging techniques provides detailed information about the rate of brain tissue loss in specific brain regions associated with AD, such as the hippocampus. [23, 24] In addition, gray matter volumes correlate with cognitive functioning, but there is a paucity of information on cognitive domains that correlate with brain volumes in newly diagnosed OSA patients. There is even less known about whether comorbid insomnia symptoms may add to these cognitive and brain volume deficits seen in individuals with OSA alone.

In this pilot-study we examined the feasibility of obtaining cognitive and neuroimaging markers of brain health in a diverse sample of middle-aged to older males from South Florida that include

a large proportion of Hispanic/Latino adults. We assessed brain volumes and cognitive performance in newly diagnosed OSA patients.[25] For this analysis, we aimed to characterize the magnetic resonance imaging brain volumes and cognitive domains that correlate with insomnia symptoms in patients with OSA. More specifically, we tested the hypothesis that greater insomnia symptoms and OSA severity (apnea-hypopnea Index (AHI) and hypoxic burden) are associated with poorer cognitive function (global cognition, executive function, memory and processing speed) and greater global brain tissue loss in AD susceptible regions.

Materials and Methods

Population

We recruited consecutive patients referred to an academic sleep center from January 1, 2019 to November 30, 2019. The inclusion criteria were being male, ≥40 years of age with a new diagnosis of moderate to severe obstructive sleep apnea (AHI≥15 events/hr.), not previously treated for a sleep disorder. We excluded participants with chronic lung disease, history of stroke or transient ischemic attack, coronary artery disease, cardiac arrhythmia, cardiac failure or history of carotid/intracranial arterial stenosis. We also excluded participants with polysomnography defined central or complex sleep apnea,[26] oxygen requirement, periodic limb movement disorder,[27] referred for primary insomnia, use of sleep medication or benzodiazepines, obesity hypoventilation syndrome, or narcolepsy. In addition, we excluded participants unable to communicate verbally, or carried a diagnosis of dementia; current or prior history of neurological disease associated with cognitive impairment or with loss of gray or white matter, neurodevelopmental disorders, and claustrophobia. We obtained the cognitive and neuroimaging outcomes (explained below) during the same research visit. We instructed the participants to avoid caffeine, tobacco or medications that could interfere with the results of cognitive testing or brain

magnetic resonance imaging. We used questionnaires and review of medical records to obtain demographic information (age, years of education, body mass index), health behaviors (tobacco, caffeine, alcohol use), medical history (diabetes mellitus, hypertension) and medication use. The study was approved by the Institutional Review Board at the University of Miami, Miller School of medicine. All participants signed an informed consent form.

Outcomes: *Cognitive Function*

We assessed cognitive function using a customized computerized-based cognitive assessment battery (NeuroTrax[tm][28] supervised by a licensed neuropsychologist or trained neuropsychometrician.[29] We assessed attention, executive functioning, verbal and visual memory, and speed of information processing. [30] We used the following subtests: the Go-No-Go Response Inhibition Test, Stroop Interference Test, Catch Game Test, Staged Information Processing Speed Test, Verbal Memory Test and Non-Verbal Memory Test. [30] The computerized scoring software calculated an overall Global, Composite, and Cognitive Functioning Score and the examiner assured completion of all parts of the assessment and reviewed all test findings. Final cognitive scores where normalized to age and years of education. The cognitive assessment also included validated depression [31, 32] and anxiety scales.[33, 34]

Brain magnetic resonance imaging (MRI)

All participants underwent MRI scanning using a 3T MRI scanner (skyra, Siemens Healthcare). Brain parcellation was obtained using a 3D T1-weighted sequence (MPRAGE) with 1.0 mm isotropic resolution, 2300 ms repetition time, 2.4 ms echo time, 930 ms inversion time, and 9-degree flip angle. [35] Total hippocampal volume was the sum of volumes of all subfields. In

addition, the following regions were measured from the T1-weighted images, the total hippocampal volume, the intracranial volume (ICV), gray matter (GM), white matter (WM) and total brain tissue (i.e. GM+WM) volumes using FreeSurfer 5.3 (http://surfer.nmr.mgh.harvard.edu). All brain volumes where normalized to intracranial volume. The respiratory rate, oxygen saturation and heart rhythm were monitored during the MRI.

Main exposures:

Sleep Symptoms

Participants completed the Insomnia Severity Index (ISI), a 7-item instrument measuring the individual's perception of his insomnia symptoms.[36] The ISI is a widely used instrument which queries the presence or absence of insomnia syndrome (nocturnal and daytime symptoms) over the previous two weeks that has been validated in both English and Spanish.[27] We also obtained the Epworth Sleepiness Scale (ESS),[37] a widely-used tool with a validated Spanish version that assesses the likelihood of falling asleep in eight common situations. Also, the Pittsburgh Sleep Quality Index (PSQI)[38] which is a 19-item self-administered questionnaire with high internal consistency (r=0.83), test-retest reliability (r=0.85), diagnostic validity and a validated Spanish version. The questionnaires were completed in the participant's preferred language (English or Spanish).

Obstructive sleep apnea

We identified participants with obstructive sleep apnea that had either in-laboratory video polysomnography (PSG; SandMan Elite), or a type-three home sleep apnea test (Embletta MPR) in our sleep center. Overnight PSG used a standard sleep montage, including electroencephalographic, electromyography (EMG), and electrooculography monitoring for an in-laboratory overnight video-PSG. Sleep stages, arousals, and sleep-related events and AHI, were

recorded according to the established practice parameters of the American Academy of Sleep Medicine (AASM).[39] Home sleep apnea studies used a self-applied type three device according to established AASM guidelines. A certified sleep technologist scored all records, manually edited artifacts, identified periods of sleep, and annotated each respiratory event using standardized techniques and the recommended scoring rules for apneas and hypopneas with its associated oxyhemoglobin desaturation. Moderate to severe OSA was defined with an AHI ≥ 15 using the number of apneas and hypopneas/hour of sleep with 3% oxygen desaturation. We also obtained measures of hypoxemic burden with the mean oxygen saturation during sleep, oxygen nadir during sleep and time spent with oxygen saturation in <90% (T90).

Statistical analysis

All data was inspected to ensure values were within expected ranges. Descriptive statistics defined mean, median and range across all continuous variables, while we used proportions for categorical variables. Pearson correlation was used to determine correlations between the ISI with demographic (age, years of education, body mass index), sleep variables (ESS, PSQI, AHI and hypoxemia measures), cognitive domains, neuroimaging, as well as depression and anxiety scales. We further adjusted for years of education (partial correlation) when evaluating the ISI, AHI with the cognitive domains, and adjusted for age when evaluating the neuroimaging outcomes. All partial correlations adjusted for multiple testing. We evaluated correlations at $p<0.05$ and $p<0.1$ In addition, we created an interactive dashboard to allow readers to visualize and interact with the data. The dashboard includes a (1) codebook of collected variables available for analyses, (2) a platform for generating descriptive statistics (e.g. means, medians, and standard deviations) for all participants as well as by their linguistic preference (English and Spanish), (3) correlation plots to examine bivariate associations (correlations) between pairs of variables of interest; both linear and

non-parametric fit lines can also be superimposed on the generated scatter plots, and (4) partial correlations tables to examine adjusted associations between variables of interest; partial correlations are calculated using the `ppcor` package in R. [40] The dashboard was created using R software with the shiny package. The application can be accessed at https://sanarlab.shinyapps.io/Ramos_OSA_MRI/

Results

We recruited 16 male participants 40-76 years of age. Table 1 shows the demographic and main characteristics of the participants. The data from the sleep instruments indicated that our sample had a mean Insomnia Severity Index of 10.3, reflecting sub-clinical insomnia on average. Five participants reported difficulties falling asleep, while eight participants reported difficulties staying sleep and four participants reported waking up too early.

The average Epworth Sleepiness Scale was normal, with a mean score of 8.2. Additionally, the average score of the Pittsburg Sleep Index was 5.4, reflecting poor sleep quality. In the PSQI, four participants reported difficulties falling asleep and 11 participants endorsed difficulties staying asleep or early awakening.

We observed a bivariate correlations between the ISI with the Epworth sleepiness scale, (r= 0.68, p=0.0037), and with the average oxygen saturation (r= -0.53, p = 0.036).

The ISI had a negative correlation with attention score (r= -0.66, p= 0.015), adjusting for education and multiple comparison. The ISI did not correlate with other cognitive domains.

Of interest, the AHI correlated with memory (r= -0.70, p=0.01), while the Epworth score was negatively correlated with attention (r= -0.69, p=0.02), adjusting for education and multiple comparisons. We also observed that mean oxygen saturation during sleep had positive correlation with memory (r= 0.64), attention (r=0.69) and global cognition (r=0.57), but these were attenuated

when adjusting for years of education. We also evaluated differences in verbal and visual memory subdomains and their relationships with the AHI. We observed that visual memory had a statistically significant inverse correlation with AHI (rho= -0.65, p<0.01), but not with verbal memory functioning The PSQI did not correlate with cognition.

Correlations Between ISI, Sleep Variables with Brain Volumes

After adjusting for age and multiple comparisons, the ISI had negative correlations with the caudal anterior cingulate cortex (r= 0.31, p= 0.04) and the inferior parietal gyrus (r= -0.75, p=0.01); while the Epworth sleepiness had correlations with the lateral ventricles (r=0.83, p=0.002). In addition, we observed age-adjusted partial correlations between average oxygen saturation during sleep and total cortical volume, lateral and medial orbitofrontal cortex, middle temporal cortex and precuneus, Table 2.

We did not observe correlations between the AHI and the PSQI with brain volumes. In addition, the ISI did not correlate with demographic (age, education, BMI), depression and anxiety scales.

Discussion

In this pilot-study of treatment naïve middle-aged to older males with OSA, we observed correlations between the ISI with decreased attention. In addition, we observed a positive correlation between the ISI with the anterior cingulate gyrus (ACC). Similar to our findings, patients with primary insomnia had increased brain volumes in the ACC[41], which has been associated with increased sleep-onset latency and wake after sleep onset.[41] The ACC help process cognitive and emotional information.[41] The correlation between the ACC and insomnia in OSA patients provide an opportunity to further examine the neuroimaging substrates that may explain cognitive difficulties in OSA patients with comorbid insomnia symptoms.

While most of our OSA patients had insomnia symptoms, the small sample size and pilot nature of our study precluded us from disentangling the effect of the ISI's nocturnal from daytime symptoms. [18] The ISI's daytime symptoms can reflect sleep fragmentation associated with OSA, while increased nocturnal symptoms suggest comorbid insomnia. Future studies should incorporate a nocturnal sub-score, when using the ISI.[18]

We did not observe a correlation between the AHI and brain volumes. The AHI is the main diagnostic and treatment metric for OSA. However, average sleep oxygen levels correlated with brain volumes in AD susceptible regions (e.g. temporal lobe structures). In a large population based study, oxygen levels during sleep correlated with brain volumes in the hippocampus–amygdala complex and other cortical regions sensitive to hypoxemia.[42] These findings suggest that nocturnal oxygenation or hypoxemia may serve as better predictors of brain health. In addition, we observed that daytime sleepiness, as measured by the Epworth sleepiness scale (ESS), had positive correlations with the lateral ventricles, suggesting an increment in ventricular volume with increase daytime sleepiness. Of interest, increased ventricular volumes was associated with a 46% increased dementia-risk in the Atherosclerosis Risk in Communities Study cohort.[43] Daytime sleepiness in OSA could be the manifestation of hypoxemia-related brain damage,[44] [45] [46, 47] which may explain the correlation with ventricular volume in our sample.

Our findings implicate gross cerebral compromise, and more specifically, the potential impact to the medial temporal lobe, where both learning and general memory functions reside.[48] The correlations between insomnia symptoms and sleepiness with cognitive and neuroimaging measures suggest a dysfunction of the frontal-temporal network.

Our findings suggest that advanced neuroimaging measures of brain health and cognition can serve as outcomes in OSA patients. Of importance, symptoms and metrics beyond the AHI are necessary

to identify at risk individuals, as well as to determine the interventions that improve OSA to inform treatment studies that can help reduce the impact of age-related cognitive decline and dementia. The strengths of our pilot study include the systematic measurement of cognition and neuroimaging obtained during the same research day, along with validated sleep questionnaires. We also applied a stringent inclusion, exclusion criteria to maintain the internal validity of our study. Limitations include the small sample size, no comparison group, the cross-sectional design, and limited adjustment for main confounders. The increased prevalence and severity of OSA in middle-aged males, coupled with better cognitive measures in females, limited us to examine males in our pilot study to avoid sex as a confounder. In our study, participants had either type III sleep home studies or polysomnography. Compared to polysomnography home sleep apnea studies can underestimate the frequency of respiratory events, as well as preclude the assessment of sleep macro-or micro-architecture.[49] However, type III sleep studies are an accepted method to diagnose OSA patients. Finally, our findings may not apply to females and need to be reproduce in a larger and heterogeneous sample.

In conclusion, we observed that insomnia symptoms, oxygen levels during sleep, and daytime sleepiness had strong correlations with cognition and neuroimaging measures of brain health in middle-aged to older OSA patients. Future studies can consider interventions that improve these brain metrics to mitigate the risk of late-life cognitive decline and the transition to dementia in obstructive sleep apnea.

Table 1. Sample Characteristics of treatment naïve patients with moderate to severe sleep apnea

Continuous Variables					
	Mean	SD	Median	Range	
Age, years	59.7	9.4	60.8	43.9	76.59
Years of Education	16.4	3.9	16.5	6.0	22.0
Body Mass Index	29.9	4.5	29.4	22.4	36.4
Insomnia Severity Index	10.3	4.7	8.0	6.0	19.0
Epworth Sleepiness Scale	8.2	5.9	8.0	0.0	23.0
Pittsburgh Sleep Quality Index	5.4	4.8	3.5	1.0	17.0
Depression score	2.5	2.9	2.0	0.0	10.0
Anxiety Score	29.3	5.9	28.5	21.0	42.0
Apnea-hypopnea index	52.6	28.2	53.4	15.7	119.0
Mean night-time oxygen, %	91.4	6.9			
Oxygen nadir, %	75.1	11.4			
Time with less than 90% oxygen saturation	32.9	35.6			
Categorical variables					
Language	%	-	-	-	-
English	41	-	-	-	-
Spanish	53	-	-	-	-
Hispanic background	71	-	-	-	-
Hypertension	59	-	-	-	-

Diabetes Mellitus	24	-	-	-	-
Coffee, cups per day		-	-	-	-
None	18	-	-	-	-
1-2 cups	65	-	-	-	-
3-5 cups	12	-	-	-	-
Current Tobacco	6	-	-	-	-

Table 2. Correlations between insomnia, sleepiness and oxygen during sleep with brain volumes

MRI brain Volumes r (p value)	Anterior cingulate cortex	Total cortical volume	Lateral orbitofrontal cortex	Medial orbitofrontal cortex	Middle temporal cortex	Precuneus	Inferior parietal gyrus
Insomnia	0.31 (0.04)	-	-	-	-	-	-0.75 (0.01)
Average oxygen during sleep	-	0.65 (0.06)	0.82 (0.003)	0.64 (0.07)	0.77 (0.01)	0.64 (0.07)	-

Partial correlations adjusted for age and multiple comparison

Institutional Review Board Statement:

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Miler School of Medicine, University of Miami. (protocol code 20160996)

Informed Consent Statement:

Informed consent was obtained from all subjects involved in the study

Data Availability Statement: The data is available upon request to the investigators.

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