

Association of Obstructive Sleep Apnea with Episodic Memory and Cerebral Microvascular Pathology: A Preliminary Study

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Objectives: To evaluate the impact of obstructive sleep apnea (OSA) on neurocognitive function and brain morphology in older adults with depression and cognitive impairment. **Methods:** We prospectively screened OSA with the STOP-Bang questionnaire in the last 25 patients enrolled into the Donepezil Treatment of Cognitive Impairment and Depression (DOTCODE) trial. High and low probability of OSA were defined as a STOP-Bang score of ≥ 5 (h-OSA) and of < 5 (l-OSA), respectively. Baseline magnetic resonance imaging (MRI) was used to evaluate brain morphology. The initial 16 weeks of antidepressant treatment were part of the DOTCODE trial. **Results:** After 16 weeks of antidepressant treatment, the h-OSA group performed significantly worse on the Selective Reminding Test delayed recall task than the l-OSA group, controlling for baseline performance ($F = 19.1$, $df = 1,22$, $p < 0.001$). In 19 of 25 participants who underwent brain MRI, the h-OSA group had significantly greater volumes of MRI hyperintensities in deep white matter, periventricular white matter, and subcortical gray matter compared with the l-OSA group. There was no significant association between OSA and hippocampal or entorhinal cortex volumes in our sample, even after controlling for intracranial volume. **Conclusions:** OSA is associated with impaired verbal episodic memory and microvascular damage in older adults with depression and cognitive impairment. One possibility is that by contributing to cerebral microvascular damage, OSA may exacerbate progressive memory decline. (Am J Geriatr Psychiatry 2017; 25:316–325)

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Obstructive sleep apnea (OSA) is caused by repeated partial or complete upper airway collapse, despite an ongoing effort to breathe during sleep. It is estimated that 22 million Americans suffer from OSA, including 24% of men and 9% of women in the middle-aged population (aged 30–60 years),¹ and 40%–60% of older adults (aged 65+ years).² Epidemiological studies consistently report a high prevalence of depression among individuals with OSA.^{3–5} The exact prevalence of cognitive impairment associated with OSA is difficult to estimate. Results from two independent meta-analysis studies provided evidence that individuals with OSA were significantly impaired on attention/vigilance, executive function, and verbal episodic memory.^{6,7} Emerging evidence demonstrates that older adults with OSA may be at greater risk of developing cognitive impairment or Alzheimer disease (AD) compared with age- and sex-matched healthy controls.^{8,9} Current structural imaging data suggest that hippocampal atrophy and microvascular damage (e.g., white matter hyperintensities, white matter integrity abnormalities, and gray matter loss), are accompanied by OSA,^{10–12} although a few studies failed to identify such structural changes.^{13,14}

Late-life depression and cognitive impairment are the most common neuropsychiatric disorders in the older adult populations. We reported the first epidemiological data showing that depression was associated with an increased risk of converting to AD during a 3-year follow-up period (relative risk [RR]: 2.9, 95% confidence interval [CI]: 1.76–4.91, $p < 0.001$).¹⁵ A meta-analysis suggested that depression was an independent risk factor for AD.¹⁶ Conversely, a recent epidemiological study revealed that the association of depression with prevalent dementia and with progression from MCI to dementia was stronger for vascular dementia than for AD.¹⁷ Whether depression shares common pathologic mechanisms with AD-related pathology remains controversial.^{18,19} On the other hand, a large body of imaging research has demonstrated the vascular and neural bases for these disorders. Although OSA is known for its destructive nature in the cerebral vascular and neural systems, whether OSA plays

an important role in the cognitive deteriorating process in older adults with amnesic mild cognitive impairment (aMCI) and depression is not clear. No study to date has evaluated the impact of OSA in this population.

As a sub-study in the Donepezil Treatment of Older Adults with Cognitive Impairment and Depression trial (DOTCODE, NCT01658228),²⁰ we used the widely validated STOP-Bang questionnaire²¹ as an add-on instrument to assess the probability of OSA. Using standard methods, a score of 5 or greater was defined as a high probability of OSA (h-OSA) and a score of less than 5 was defined as a low probability of OSA (l-OSA).^{22–25} We examined 1) baseline brain morphology, specifically microvascular damage and regions of interest (hippocampus and entorhinal cortex), which play critical roles in predicting conversion to dementia, and 2) changes in cognitive performance following 16 weeks of open antidepressant treatment (DOTCODE phase 1). We hypothesized that participants with h-OSA would exhibit more severe microvascular damage and poorer cognitive performance, particularly verbal episodic memory (primary outcome measure), than those with l-OSA.

METHODS

Participants

This study consisted of the last 25 participants enrolled to the DOTCODE trial²⁰ at the Late-life Depression and Memory Disorders Clinics at New York State Psychiatric Institute. Participants were eligible for this add-on study if they met the inclusion/exclusion criteria for the DOTCODE trial. Salient inclusion criteria included age 55–95 years, study criteria for cognitive impairment as measured by 1) subjective memory or other cognitive complaints and 2) score of 11 or less on the Logical Memory II (Delayed Paragraph Recall, Paragraph A) test from the Wechsler Memory Scale—Revised²⁶ or a score 1.5 SD or more below norms on the Free and Cued Selective Reminding Test²⁷ immediate or delayed recall, Folstein Mini

Mental State Exam²⁸ (MMSE) score of 21 or more out of 30, and study criteria for depression that required DSM-IV symptom criteria for Major Depression or Dysthymic Disorder for a minimum of 6 months (2-year duration DSM-IV TR criterion not required for dysthymic disorder in this study) and a 24-item Hamilton Rating Scale of Depression (HRSD)²⁹ score of 14 or greater. Salient exclusion criteria included clinical stroke with residual neurological deficits, DSM-IV criteria for dementia or probable Alzheimer disease (NINCDS-ADRDA criteria); DSM-IV TR criteria for schizophrenia, schizoaffective disorder, psychotic depression, bipolar disorder or other psychosis; alcohol or substance dependence or abuse (current or within past 6 months); active suicidal ideation or suicidal attempt in the last 6 months; or an acute, severe, or unstable medical condition at the evaluation visit. Participants who were taking benzodiazepines in lorazepam equivalents greater than or equal to 2 mg daily, narcotics, or anticholinergics were ineligible to participate because these medications are known to have a negative impact on cognition. Participants taking warfarin or monoamine oxidase inhibitors were also ineligible to participate. Brain research magnetic resonance imaging (MRI) scan was optional and done at baseline. All DOTCODE participants were required to have the capacity to provide informed consent and sign the institutional review board–approved informed consent form. Local and State regulations for consent were followed. The institutional review board of the New York State Psychiatric Institute at Columbia University Medical Center approved this add-on pilot study.

Treatment

The DOTCODE trial phase 1 consisted of an open antidepressant treatment phase (initial 16 weeks). Participants first underwent an 8-week treatment period with the selective serotonin reuptake inhibitor citalopram, starting with 10 mg/day for the first week, then increasing to 20 mg/day thereafter. At the week 8 visit, citalopram responders (those with a 50% reduction from baseline HRSD) were instructed to continue citalopram treatment, and participants who failed to respond to citalopram began an 8-week venlafaxine treatment period, starting with 37.5 mg/day for the first week, then increasing to 225 mg/day for the fifth to eighth week. If deemed clinically necessary by the study physician, 300 mg/day was

prescribed. At the end of the eighth week, venlafaxine responders (those with a 50% reduction from baseline HRSD) were instructed to continue venlafaxine treatment. At the end of the sixteenth week, nonresponders to both citalopram and venlafaxine received antidepressant based on the doctor's choice in consultation with the patient. A flexible dosing schedule was used throughout the study, based on the physician's assessment of the efficacy and tolerability of the medication. Phase 2 was not part of this pilot sub-study. Protocol details have been published elsewhere.²⁰

Measures

OSA

OSA severity is determined by number of apneas and hypopneas per hour of sleep (apnea/hypopnea index, AHI) and is usually categorized as: mild (AHI 5–15), moderate (AHI 15–30), and severe (AHI \geq 30).³⁰ We selected the STOP-Bang scale to assess pre-test probability of having moderate to severe OSA because it has the highest methodological metrics and has shown sensitivity in predicting moderate to severe OSA, as compared with other OSA screening questionnaires.³¹ The STOP-Bang scale consists of eight yes/no question items with total scores ranging from 0 to 8, 1 point for each question, including four items in the STOP (loud Snore, Tired, Observed apnea, and high blood Pressure) category and four items in the BANG (BMI, Age, Neck size, and Gender) category.²¹ The sensitivity of scores greater than or equal to 3 to detect moderate and severe OSA is 93% and 100%, respectively; a STOP-Bang score of 5–8 is associated with a high probability of moderate to severe OSA.²² The correlation between STOP-Bang score and severity of OSA as diagnosed by PSG has been further validated in several studies with large sample sizes.^{23–25} The STOP-Bang Questionnaire has been widely used in the general population, including with medical, surgical, and psychiatric patients.³²

In this preliminary study, a STOP-Bang score of 5 or greater was defined as having high probability of moderate to severe OSA (the h-OSA group), and a STOP-Bang score of less than 5 was defined as having low probability of moderate to severe OSA (the l-OSA group). Study physicians also assessed OSA-related medical comorbidities.

Depression

Depressive symptoms were assessed with the 24-item HRSD.

Neuropsychological Evaluation

In addition to the inclusion criteria, we assessed other neuropsychological domains. Verbal Episodic Memory (primary outcome measure): 12-item six-trial Selective Reminding Test (SRT).³³ Processing speed: Trail Making Test-Part A (Trail A). Executive Function: Trail Making Test—Part B (Trail B), and WAIS-III Digit Symbol,³⁴ which also tapped into processing speed. Visual Memory: Wechsler Memory Scale-III visual reproduction subtest (WMS-III; Wechsler, 1997). Language skills: Verbal Fluency (Letter and Animal Naming, 60-second trials).

MRI

MRI study was part of the DOTCODE trial. MRI was obtained at baseline and acquired on a GE Signa 3 Tesla whole body scanner with the following sequences. Three-Plane Localizer Repetition Time (TR) = 23.4 msec, Echo Time (TE) = 1.7 msec, Flip angle = 30°, Bandwidth = 31.3 MHz, field of view (FOV) = 24 × 24 cm, thickness = 5.0 mm, Spacing = 1.5 mm, 9 slices per volume (3 axials, 3 sagittals, 3 coronals), Matrix 256 × 128. Scan Time: 10 sec. 3D SPGR Anatomical Sequence TI 500 msec, TR 5 msec, TE Minimum (1.3 ms), Flip angle 11°, Band width 31.25 MHz, FOV 26 × 26, Slice thickness 1.1 mm, spacing 0.0, 128 slices per volume, 1 NEX images × 2 (acquisitions averaged off line), Matrix 256 × 256. This sequence was acquired in the coronal orientation aligned to the long axis of the hippocampus, and these nearly isotropic images were easily reformatted into any plane for definition of regions of interest (ROIs). T2 FLAIR: 2D IR axial images with TR = 10,000 msec, TE = 122 msec, TI = 2,000 msec, FOV = 24, Matrix = 320 × 256, NEX = 1, Slice thickness = 5 mm, 31 slices. Scan Time: 4.4 minutes.

Quantification of whole brain MRI signal hyperintensity volume used the MRICro software.³⁵ The procedure has been described in our previous study.³⁶ We used the modified Rating Scale to assess the severity of microvascular lesions.³⁷ Periventricular white matter hyperintensity (PVH) was graded as 0 (absent), 1 ("caps," or pencil-thin lining), 2 (smooth "halo"), or

3 (irregular periventricular hyperintensities extending into the deep white matter). Deep white matter hyperintensity (DWMH) was graded as 0 (absent), 1 (punctate foci), 2 (beginning confluence of foci), or 3 (large confluent areas). Subcortical gray matter hyperintensity (SCG) was scored as 0 (absent), 1 (punctate), 2 (multipunctate), or 3 (diffuse).

ROIs, chosen a priori, were based on our previously published study identifying regions that predicted increased risk of dementia in aMCI.³⁸ The anatomical boundaries for hippocampus and entorhinal cortex tracings have been described elsewhere;³⁸ the inter-rater and intra-rater reliability were 0.90 and 0.92 for hippocampus volume, and 0.98 and 0.99 for entorhinal cortex volume, respectively. An experienced technician, who was trained and maintains reliability with expert raters, rated all scans and drew ROIs using atlas-based approaches to define the hippocampus and entorhinal cortex.

Statistical Analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS version 23.0). A 5% level was used to determine statistical significance. No adjustments were made to account for multiple testing.

Clinical and Neuropsychological Data Analyses

Patient demographic and clinical features were compared between the h-OSA group and the l-OSA-group using χ^2 tests or Fisher's exact tests for categorical variables, and two-tailed t tests for continuous variables. Differences in HRSD between the two groups were assessed at both baseline and week 16 using t tests. Change in HRSD within each group was assessed using paired t tests. Difference in changes in HRSD between the two groups was assessed by fitting a linear regression model having HRSD at week 16 as the outcome with baseline HRSD and OSA group as predictors. We tested the slope coefficient of OSA to assess differences between the groups in changes in HRSD over 16 weeks. To assess differences between the two groups on baseline cognitive measures we fit 1) linear regression models with each cognitive measure as the outcome and OSA as the predictor and 2) the same models, adjusting for baseline HRSD. We tested the slope coefficient for

OSA in each model to assess differences between the two groups on these baseline measures. To assess differences between the two groups on changes in cognitive measures we fit 1) linear regression models with each cognitive measure at week 16 as the outcome and had the corresponding baseline measure and OSA group as the predictors and 2) the same models, adjusting for HRSD at week 16. We tested the slope coefficient for OSA in each model to assess differences between the two groups on changes in each cognitive measure over 16 weeks.

Baseline MRI Data Analyses

The severity of microvascular lesions was dichotomized into two categories: grade 0–1 and grade 2–3 lesions. Associations between the two groups and binary lesion severity were assessed using Fisher’s exact test. Differences between the two groups with respect to DWMH, PVH, and SCG were assessed using the Mann-Whitney U test. The Mann-Whitney U test was also used to assess differences between OSA groups with respect to hippocampal volume and entorhinal cortex volume. To control for intracranial volume, we took the ratios of hippocampal volume/intracranial volume and entorhinal cortex volume/intracranial volume and used the Mann-Whitney U test to assess differences between the two groups with respect to these ratios.

RESULTS

Baseline Demographic and Clinical Features

Among 25 participants, there were 10 in the h-OSA group and 15 in the l-OSA group. As shown in Table 1, age, education, depression severity, and the MMSE were not significantly different between the two groups, whereas body mass index was significantly higher in the h-OSA group. The h-OSA group had higher proportions of men, hypertension, and vascular risk factors than the l-OSA group. No participants received any form of OSA treatment before or during this study.

MRI

Nineteen of 25 participants underwent MRI scan. For volume of MRI hyperintensities (see Table 2), we used Mann-Whitney U tests to compare the two groups. The h-OSA group had greater volumes of DWMH ($Z = 2.60$, $p = 0.009$), PVH ($Z = 2.24$, $p = 0.025$), and SCG ($Z = 2.28$, $p = 0.023$) compared with the l-OSA group. For microvascular lesion severity, the h-OSA group had higher proportions of grade 2–3 lesions in DWMH (33% versus 0%), PVH (83.3% versus 46.2%), and SCG (33% versus 0%), though the differences were not statically significant between the two groups. For volumes of hippocampus and entorhinal cortex, there were no

TABLE 1. Demographic and Clinical Features of Older Adults with Both Depression and Cognitive Impairment

Baseline	Total Sample N = 25		h-OSA Group N = 10		l-OSA Group N = 15		<i>p</i> ^a
	Mean	SD	Mean	SD	Mean	SD	
Continuous variables							
Age, years	70.6	9.1	69.9	8.0	71.1	10.0	0.75
Education, years	14.9	4.0	14.9	4.1	14.9	4.1	0.98
Body mass index	26.2	6.2	30.6	6.0	23.1	4.5	0.01
MMSE (30 items)	27.8	1.8	27.2	1.7	28.3	1.6	0.14
Categorical variables	N	%	N	%	N	%	<i>p</i> ^b
Sex, female	12	(48)	2	20	10	67	0.03
Hypertension	18	53	10	100	8	53	0.02
Diabetes mellitus	3	12	9	90	1	7	0.71
Vascular risk factor ≥ 2	8	40	9	90	2	13	0.01

Notes: MMSE: Mini-Mental Status Exam; HRSD: Hamilton Rating Scale for Depression.

^a*p* values from two-sample *t* test, comparing high probability OSA (h-OSA) group and low probability OSA (l-OSA) group, *df* = 23.

^b*p* values from either χ^2 test (*df* = 1) or Fisher’s exact test, comparing h-OSA group and l-OSA group.

TABLE 2. Comparison of Baseline MRI indices of Cerebral Microvascular Damage Between Participants with High and Low Probability of Obstructive Sleep Apnea

Volume Measures	h-OSA Group (N = 6)		l-OSA Group (N = 13)		p
	Median	Range	Median	Range	
DWM hyperintensities	4.35	(0.10–14.30)	0.20	(0.00–2.40)	0.009
PVH hyperintensities	23.90	(0.40–125.90)	2.20	(0.30–12.80)	0.025
SCG hyperintensities	0.45	(0.00–1.20)	0.00	(0.00–0.20)	0.023

Notes: Mann-Whitney U test used to compare distributions in h-OSA and l-OSA groups. h-OSA: high probability of OSA; l-OSA: low probability of OSA; DWM: deep white matter; PVH: periventricular white matter; SCG: subcortical gray matter.

statistically significant differences between the two groups, even after controlling for intracranial volume.

Depression

At baseline, there was no significant difference in HRSD between the two groups. After 16 weeks of antidepressant treatment, depression severity significantly improved in both groups (h-OSA group: $t = 7.99$, $df = 9$, $p < 0.001$; l-OSA group: $t = 5.42$, $df = 14$, $p < 0.001$). There was no difference in depression severity at week 16 between the two groups, even after controlling for baseline depression severity.

Neuropsychological Performance

At baseline, there were no statistically significant differences in performance across all cognitive domains, including attention/psychomotor, executive function, and verbal memory, between the two groups and the results remained nonsignificant after controlling for baseline depression severity. As shown in Table 3, performance on executive function tasks (Trails B and Digital Symbol) improved in both groups following antidepressant treatment; performance on processing speed tasks (Trails A) and verbal episodic memory tasks (SRT total and delayed recall) improved in the l-OSA group but worsened in the h-OSA group. With the exception of performance on verbal delayed recall tasks, these changes were not significantly different between the two groups, even after controlling for both baseline cognitive performance and week 16 depressive symptom severity. There was a 1-point average decrease in verbal delayed recall in the h-OSA group and a 2-point average increase in the l-OSA group (see Figure 1); the difference between the two groups was observed only after acute depressive symptoms were

treated ($F = 19.1$, $df = (1,22)$, $p < 0.001$), and the results remained significant after controlling for both baseline performance and week 16 depression severity. No participants dropped out or stopped antidepressant treatment during this study period.

DISCUSSION

The goals of this add-on preliminary study to the DOTCODE Trial (phase 1) were to investigate the impact of OSA on brain morphology and cognitive performance in older adults with both depression and MCI. We found that 1) there was a significant association between OSA and severity of microvascular damage as identified on MRI; 2) the association between OSA and hippocampal or entorhinal cortex volume was not significant, even after controlling for intracranial volume; and 3) following 16 weeks of antidepressant treatment, changes in cognitive measures across multiple domains were not statistically significant between the groups, with the exception of verbal episodic memory.

As hypothesized, we found that the h-OSA group had significantly greater volumes of DWMH, PVH, and SCG, as well as a higher proportion of severe microvascular lesions when compared with the l-OSA group. In previous studies, greater white matter damage and more advanced microvascular lesions were associated with an increased risk for more rapid cognitive decline and new onset of AD in patients with aMCI.^{39–41} One possible explanation for our findings is that OSA may facilitate additional neural injury (e.g., beyond that which is seen in AD pathology alone) and accelerate cognitive decline. Consequently, cognitive deficits accompanying OSA may persist or progress if OSA is left untreated. Recent imaging studies showed that OSA

TABLE 3. Comparison of Antidepressant Treatment Outcomes between High and Low Probability of Obstructive Sleep Apnea Groups

Outcome Variables	Baseline						Week 16					
	Mean (SD)		Unadjusted ^a		Adjusted ^b		Mean (SD)		Unadjusted ^c		Adjusted ^d	
	h-OSA	l-OSA	F _(1, 23)	p value	F _(1, 22)	p value	h-OSA	l-OSA	F _(1, 22)	p value	F _(1, 21)	p value
Depression^c												
HRSD-24 items	20.9 (4.1)	24.5 (7.2)	2.03	0.17	-	-	7.7 (4.3)	11.2 (4.7)	3.88	0.06	-	-
Primary outcomes												
Verbal Memory-SRT^c												
Total Immediate Recall	33.8 (5.2)	41.3 (11.5)	3.72	0.07	2.70	0.11	33.2 (9.0)	45.1 (11.0)	3.77	0.06	2.97	0.10
Delayed Recall	4.7 (2.1)	5.1 (2.8)	0.17	0.68	0.11	0.74	3.7 (1.7)	7.1 (2.0)	19.10	<0.01	13.17	<0.01
Delayed Recognition	13.4 (4.3)	16.7 (7.9)	1.48	0.24	0.96	0.34	6.7 (2.5)	6.0 (2.1)	0.46	0.51	0.04	0.85
Secondary outcomes												
Processing speed												
Trail A (time) ^f	51.0 (23.3)	52.8 (17.1)	0.05	0.83	0.04	0.84	53.4 (28.4)	47.9 (17.5)	1.67	0.21	0.71	0.41
Digit Symbol ^g	36.1 (11.3)	39.1 (15.1)	0.28	0.60	0.35	0.56	38.5 (12.6)	39.9 (15.5)	0.55	0.47	1.28	0.27
Executive Functions												
Trail B (time) ^f	147.1 (73.0)	138.4 (63.7)	0.10	0.76	0.02	0.89	138.0 (71.7)	132.2 (56.8)	0.01	0.91	0.31	0.58
Verbal fluency^g												
Letter	32.3 (11.2)	43.8 (15.9)	3.93	0.06	2.51	0.13	26.9 (9.2)	44.3 (17.4)	3.66	0.07	2.15	0.16
Animal	14.4 (3.6)	16.3 (5.8)	0.88	0.36	0.39	0.54	13.4 (4.3)	16.7 (7.9)	0.59	0.45	0.69	0.41
Visual memory^g												
WMS-R-VR imRecall	29.1 (6.9)	32.8 (6.9)	1.72	0.20	1.70	0.21	28.4 (8.8)	27.0 (9.6)	4.26	0.05	5.39	0.03
WMS-R VR deRecall	17.2 (12.5)	17.9 (11.0)	0.02	0.88	<0.01	0.94	15.3 (13.0)	20.0 (11.8)	1.21	0.28	0.47	0.50

Notes: OSA: obstructive sleep apnea; h-OSA: high probability of OSA; l-OSA: low probability of OSA; HRSD: Hamilton Rating Scale for Depression; SRT: Selective Reminding Test; WMS-R-VR imRecall: Wechsler Memory Scale-Revised-Visual Reproduction immediate recall; WMS-R VR deRecall: Wechsler Memory Scale-Revised-Visual Reproduction delayed recall.

^aDependent variables at baseline predicted by OSA groups. p values are for F test of the coefficient of OSA in the unadjusted model; df (1, 23).

^bDependent variables at baseline predicted by OSA groups. p values are for F test of the coefficient of OSA in the models adjusting for baseline depression severity (HRSD); df (1, 22).

^cDependent variables at week 16 predicted by OSA groups controlling for dependent variable at baseline. p values are for F test of the coefficient of OSA in the unadjusted model; df (1, 22).

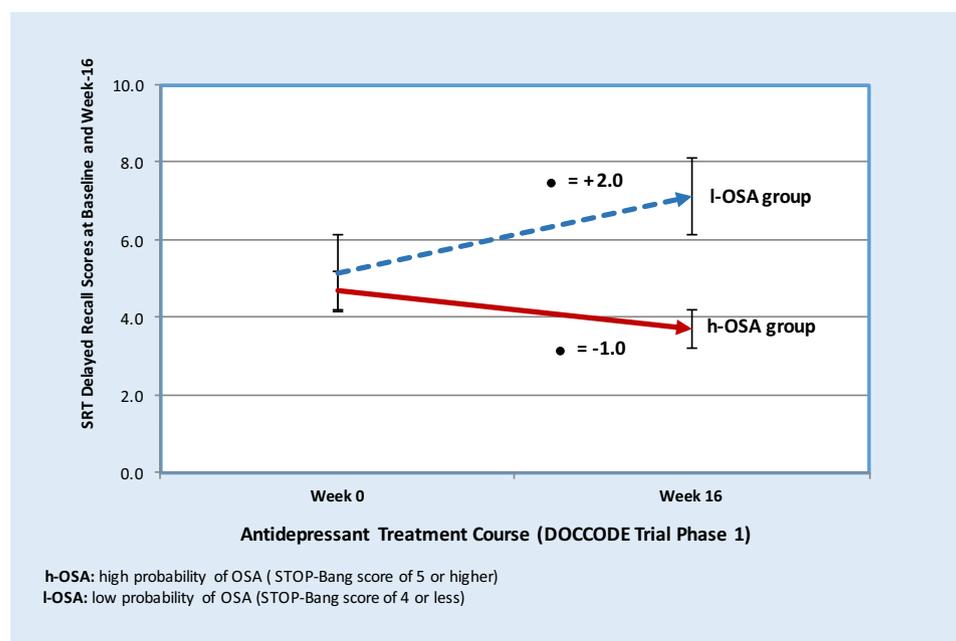
^dDependent variables at week 16 predicted by OSA groups controlling for dependent variable at baseline. p values are for F test of the coefficient of OSA in the models adjusting for baseline depression severity (HRSD); df (1, 21).

^eA higher score indicates more or worse depressive symptoms.

^fA longer time needed to complete the test indicates worse cognitive performance.

^gA higher score indicates better cognitive performance.

FIGURE 1. Comparison performance on delayed recall tasks following antidepressant treatment between high and low probability of obstructive sleep apnea. h-OSA: high probability of OSA (STOP-Bang score of 5 or higher); l-OSA: low probability of OSA (STOP-Bang score of 4 or less).



treatment may lead to improvement in indices of microvascular and neural damage, and may result in improved cognitive functioning.

Several studies found that OSA patients had smaller hippocampi than patients without OSA.^{10,42} We conducted exploratory analyses on baseline hippocampal volume and entorhinal cortical volume and did not find significant differences between the two groups. Several possibilities may explain our findings. First, our participants had aMCI at baseline; thus, the impact of OSA might not prevail over the effects of AD pathology on hippocampal volume in our study sample. Second, the overall effect of OSA on hippocampal volume depends on the severity and chronicity of OSA.^{43,44} As such, disentangling the pure effects of OSA on hippocampal volume in our participants, who were likely to have had AD pathology, would be difficult. Third, episodic memory impairment could be, in part, the result of an indirect effect on hippocampal functioning through remote functional disruption, which may be disassociated from hippocampal volume's impact on memory.⁴⁵ An imaging study demonstrated that damage to white matter

fiber tracts within Papez's memory circuit caused aberrant connectivity with hippocampal structures, which might contribute to aMCI.⁴⁶ Nonetheless, our small MRI sample size might have limited our ability to observe differences in hippocampal volume and may have affected the results.

Following 16 weeks of antidepressant treatment, performance on a verbal delayed recall task declined in the h-OSA group. Taking into account potential practice effects, the worsening performance suggested a true cognitive deficit in h-OSA group. This result raises the important question of whether antidepressants influence the severity of OSA, which might, in turn, affect episodic memory. Several studies have examined the effectiveness of antidepressants as a drug treatment option for OSA. The rationale was that serotonin plays a critical role in maintaining upper airway patency during sleep, and antidepressants might increase upper airway dilator muscle tone, thus reducing its collapsibility during sleep in patients with OSA.⁴⁷ Some showed that antidepressant treatment reduced OSA severity (AHI) compared with placebo, whereas others reported that no benefits were observed.⁴⁷ Therefore,

the use of citalopram or venlafaxine was not likely to have caused worsening of OSA. On the other hand, because of worsening verbal episodic memory despite successful treatment of depression in the h-OSA group, the presence of depression at baseline may have masked the impact of OSA on cognition. Therefore, screening for OSA in this type of patient has potentially important clinical utility.

Strengths and Limitations

To our knowledge, this is the first study that has explicitly examined the association between OSA, cognition, and brain structural abnormalities in older adults with aMCI and depression. In comparing changes in cognitive performance between the h-OSA group and l-OSA group after depression was successfully treated, this study design allowed us to begin to disentangle the effects of confounding variables that are frequently present in patients with both depression and aMCI. Our findings add to the growing body of literature suggesting that a mixture of AD and microvascular pathologies may heighten one's risks of progressive cognitive deterioration and developing dementia.⁴⁸

On the other hand, because of several limitations, caution is needed for the interpretation of our preliminary findings. First, the "gold standard" diagnostic method for OSA is polysomnography (PSG). In this preliminary study, we used the STOP-Bang questionnaire to assess probability of moderate to severe OSA. A score of 5 or greater was classified as h-OSA and a score of less than 5 was classified as l-OSA; this clinical classification led to strong associations with

cognitive and MRI-derived variables. Nevertheless, expanded studies using PSG to diagnose OSA are warranted. Other limitations include our small sample size and the lack of control for multiple statistical comparisons, thus increasing the likelihood of a type I error among our exploratory analyses.

CONCLUSIONS

In older adults with aMCI and depression, the presence of OSA was associated with microvascular damage and impaired verbal episodic memory, which are consistent with the existing literature on nondepressed and middle-aged OSA patients. One possibility is that by contributing to cerebral microvascular pathologies, OSA exacerbates progressive memory decline, despite successful treatment of depression. Therefore, cognitive deficits accompanying OSA may persist or progress if OSA is left untreated. Clinical trials are needed to determine whether OSA treatment can change the trajectory of cognitive deterioration in older adults who are at a high risk of developing dementia.

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References

1. Young T, Palta M, Dempsey J, et al: The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; 328:1230-1235
2. Ancoli-Israel S, Klauber MR, Butters N, et al: Dementia in institutionalized elderly: relation to sleep apnea. *J Am Geriatr Soc* 1991; 39:258-263
3. Ohayon MM: The effects of breathing-related sleep disorders on mood disturbances in the general population. *J Clin Psychiatry* 2003; 64:1195-1200, quiz 1274-1196
4. Wheaton AG, Perry GS, Chapman DP, et al: Sleep disordered breathing and depression among U.S. adults: National Health and Nutrition Examination Survey, 2005-2008. *Sleep* 2012; 35:461-467
5. Peppard PE, Szklo-Coxe M, Hla KM, et al: Longitudinal association of sleep-related breathing disorder and depression. *Arch Intern Med* 2006; 166:1709-1715
6. Beebe DW, Groesz L, Wells C, et al: The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. *Sleep* 2003; 26:298-307
7. Wallace A, Bucks RS: Memory and obstructive sleep apnea: a meta-analysis. *Sleep* 2013; 36:203-220
8. Osorio RS, Gumb T, Pirraglia E, et al: Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology* 2015; 84:1964-1971
9. Yaffe K, Laffan AM, Harrison SL, et al: Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* 2011; 306:613-619
10. Macey PM, Henderson LA, Macey KE, et al: Brain morphology associated with obstructive sleep apnea. *Am J Respir Crit Care Med* 2002; 166:1382-1387

11. Macey PM, Kumar R, Woo MA, et al: Brain structural changes in obstructive sleep apnea. *Sleep* 2008; 31:967-977
12. Zimmerman ME, Aloia MS: A review of neuroimaging in obstructive sleep apnea. *J Clin Sleep Med* 2006; 2:461-471
13. Davies CW, Crosby JH, Mullins RL, et al: Case control study of cerebrovascular damage defined by magnetic resonance imaging in patients with OSA and normal matched control subjects. *Sleep* 2001; 24:715-720
14. Kiernan TE, Capampangan DJ, Hickey MG, et al: Sleep apnea and white matter disease in hypertensive patients: a case series. *Neurologist* 2011; 17:289-291
15. Devanand DP, Sano M, Tang MX, et al: Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Arch Gen Psychiatry* 1996; 53:175-182
16. Ownby RL, Crocco E, Acevedo A, et al: Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry* 2006; 63:530-538
17. Richard E, Reitz C, Honig LH, et al: Late-life depression, mild cognitive impairment, and dementia. *JAMA Neurol* 2013; 70:374-382
18. Byers AL, Yaffe K: Depression and risk of developing dementia. *Nat Rev Neurol* 2011; 7:323-331
19. Wilson RS, Boyle PA, Capuano AW, et al: Late-life depression is not associated with dementia-related pathology. *Neuropsychology* 2016; 30:135-142
20. Pelton GH, Andrews H, Roose SP, et al: Donepezil treatment of older adults with cognitive impairment and depression (DOTCODE study): clinical rationale and design. *Contemp Clin Trials* 2014; 37:200-208
21. Chung F, Subramanyam R, Liao P, et al: High STOP-Bang score indicates a high probability of obstructive sleep apnoea. *Br J Anaesth* 2012; 108:768-775
22. Chung F, Abdullah HR, Liao P: STOP-Bang Questionnaire: a practical approach to screen for obstructive sleep apnea. *Chest* 2016; 149:631-638
23. Chung F, Liao P, Farney R: Correlation between the STOP-Bang score and the severity of obstructive sleep apnea. *Anesthesiology* 2015; 122:1436-1437
24. Farney RJ, Walker BS, Farney RM, et al: The STOP-Bang equivalent model and prediction of severity of obstructive sleep apnea: relation to polysomnographic measurements of the apnea/hypopnea index. *J Clin Sleep Med* 2011; 7:459-465B
25. Luo J, Huang R, Zhong X, et al: Value of STOP-Bang questionnaire in screening patients with obstructive sleep apnea hypopnea syndrome in sleep disordered breathing clinic. *Chin Med J* 2014; 127:1843-1848
26. Wechsler WD: Memory Scale-revised: Manual. San Antonio, TX: The Psychological Corporation, 1987
27. Buschke H: Cued recall in amnesia. *J Clin Neuropsychol* 1984; 6:433-440
28. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189-198
29. Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56-62
30. Ruehland WR, Rochford PD, O'Donoghue FJ, et al: The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index. *Sleep* 2009; 32:150-157
31. Abrisshami A, Khajehdehi A, Chung F: A systematic review of screening questionnaires for obstructive sleep apnea. *Can J Anaesth* 2010; 57:423-438
32. Alam A, Chengappa KN, Ghinassi F: Screening for obstructive sleep apnea among individuals with severe mental illness at a primary care clinic. *Gen Hosp Psychiatry* 2012; 34:660-664
33. Buschke H, Fuld PA: Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology* 1974; 24:1019-1025
34. Joy S, Kaplan E, Fein D: Speed and memory in the WAIS-III Digit Symbol-Coding subtest across the adult lifespan. *Arch Clin Neuropsychol* 2004; 19:759-767
35. Rorden C, Brett M: Stereotaxic display of brain lesions. *Behav Neurol* 2000; 12:191-200
36. Sneed JR, Culang-Reinlieb ME, Brickman AM, et al: MRI signal hyperintensities and failure to remit following antidepressant treatment. *J Affect Disord* 2011; 135:315-320
37. Coffey CE, Figiel GS, Djang WT, et al: Subcortical hyperintensity on magnetic resonance imaging: a comparison of normal and depressed elderly subjects. *Am J Psychiatry* 1990; 147:187-189
38. Devanand DP, Pradhaban G, Liu X, et al: Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. *Neurology* 2007; 68:828-836
39. Bilello M, Doshi J, Nabavizadeh SA, et al: Correlating cognitive decline with white matter lesion and brain atrophy magnetic resonance imaging measurements in Alzheimer's disease. *J Alzheimers Dis* 2015; 48:987-994
40. Maillard P, Carmichael O, Fletcher E, et al: Coevolution of white matter hyperintensities and cognition in the elderly. *Neurology* 2012; 79:442-448
41. Tosto G, Zimmerman ME, Carmichael OT, et al: Predicting aggressive decline in mild cognitive impairment: the importance of white matter hyperintensities. *JAMA Neurol* 2014; 71:872-877
42. Canessa N, Castronovo V, Cappa SF, et al: Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. *Am J Respir Crit Care Med* 2011; 183:1419-1426
43. Rosenzweig I, Kempton MJ, Crum WR, et al: Hippocampal hypertrophy and sleep apnea: a role for the ischemic preconditioning? *PLoS ONE* 2013; 8:e83173
44. Rosenzweig I, Glasser M, Polsek D, et al: Sleep apnoea and the brain: a complex relationship. *Lancet Respir Med* 2015; 3:404-414
45. Chetelat G, Desgranges B, de la Sayette V, et al: Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. *Brain* 2003; 126:1955-1967
46. Villain N, Desgranges B, Viader F, et al: Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease. *J Neurosci* 2008; 28:6174-6181
47. Mason M, Welsh EJ, Smith I: Drug therapy for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* 2013; (5):CD003002
48. Gorelick PB, Scuteri A, Black SE, et al: Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; 42:2672-2713