Obstructive Sleep Apnea and Age

A Double Insult to Brain Function?

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Rationale: Healthy aging is associated with cognitive deficits similar to those found in obstructive sleep apnea (OSA). As in OSA, older adults show compensatory cerebral activation during cognitive demands in the face of neurocognitive decline.

Objectives: The current study examines whether the combination of increasing age and sleep apnea will lead to a stronger compensatory response than either factor alone, or overwhelm the brain's capacity to compensate.

Methods: A total of 14 treatment-naïve patients with sleep apnea (aged 25–59 yr) and 14 age-matched healthy control subjects were each divided into two age groups of young (<45 yr) and middle-aged (≥ 45 yr). All underwent a sleep study, followed the next morning by a functional magnetic resonance imaging session that included a sustained attention and a verbal encoding task. *A priori* contrast analyses compared middle-aged patients with OSA to young patients, young control subjects, and middle-aged control subjects.

Measurements and Main Results: Middle-aged patients with OSA showed reduced performance for immediate word recall and slower reaction time during sustained attention compared with the other three groups (middle-aged control, young sleep apnea, and young control). For both tasks, decreased activation was detected for middle-aged sleep apnea relative to the other groups in task-related brain regions.

Conclusions: These results suggest that the presence of both sleep apnea and increasing age overwhelmed the brain's capacity to respond to cognitive challenges with compensatory recruitment and to maintain performance. The findings that sleep apnea impairs performance and brain function at a younger age than what might ordinarily be expected underscore the importance of early diagnosis and treatment of sleep apnea.

Keywords: obstructive sleep apnea; functional magnetic resonance imaging; age; cognition

Obstructive sleep apnea (OSA) is characterized by repeated cessations of breathing during sleep. OSA is recognized as a significant public health problem, and imposes substantial neurocognitive morbidities (1). The estimated prevalence of sleep-disordered breathing among middle-aged adults is 9% for women and 24% for men (2), and prevalence continues to increase in older adults (3).

Functional magnetic resonance imaging (fMRI) studies have reported increased brain activation and intact cognitive performance in untreated patients with OSA relative to healthy control subjects during episodic encoding (i.e., memorization

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Individuals with obstructive sleep apnea show cognitive deficits similar to those often associated with aging. Like patients with sleep apnea, older adults show compensatory cerebral activation during cognitive tasks in order to cope with cognitive demand in the face of neurocognitive decline.

What This Study Adds to the Field

This study assessed the combined effect of obstructive sleep apnea and age on cognitive performance and brain activation. The findings, that the combination of sleep apnea and age can lead to further impairments beyond either factor alone, suggest that patients with sleep apnea may be particularly vulnerable to cognitive and cerebral impairment earlier than middle-aged individuals without sleep apnea.

of nouns). In OSA, greater activation was associated with better recall, suggesting compensatory recruitment of additional cerebral resources to maintain performance (4). In contrast, decreased brain activation in OSA, often with impaired performance, was reported for response inhibition (i.e., ability to withhold responses to target stimuli) (5), sustained attention (6), and working memory (i.e., ability to simultaneously store and process information) (7). Cognitive deficits similar to those found in OSA are also associated with aging (8–13). Similarly, like patients with OSA, older adults show compensatory cerebral activation during cognitive tasks when performance is preserved (14). In both populations, recruitment of additional brain regions to cope with cognitive demand in the face of neurophysiological decline (e.g., gradual anatomical and other physiological changes) may suggest a functional response to such decline. These parallels between aging and OSA raise the question of whether the combination of increasing age and OSA will lead to a stronger compensatory response that maintains performance (as is seen in each individually), or will overwhelm the brain's capacity to compensate, and lead to impaired performance.

Despite the striking similarities between OSA and aging, few studies have examined whether age modifies the effects of OSA on cognitive function. Alchanatis and colleagues (15) reported that middle-aged patients with OSA showed cognitive decline in comparison to age-matched control subjects, whereas cognitive performance of younger patients with OSA on attention tasks was similar to age-matched control subjects. This suggests that age plus OSA may pose a double insult for which the brain may be not able to compensate. Another study assessing attention in young and middle-aged patients with OSA and control subjects, however, found both OSA-related and aging-related cognitive deficits, but

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did not demonstrate that age interacts with OSA to make cognitive deficits worse (16, 17). Given prior work in both OSA and aging, showing that cerebral responses to cognitive challenges influence performance, it is important to examine such cerebral responses when evaluating the combined effects of OSA and age, as that may help explain the discrepant findings reviewed here.

Previously, we examined group differences between OSA and control subjects in performance and brain activation (4, 6). Here, we extend those analyses by specifically examining the combined impact of increasing age and OSA on cognition and brain activation. Hypotheses include: (1) during verbal learning, age plus OSA would produce impaired performance and decreased brain activation; and (2) during sustained attention, age plus OSA would produce impaired performance and decreases in brain activation.

Some of the results related to the verbal learning task have been previously reported in the form of an abstract (18).

METHODS

A total of 14 treatment-naïve patients with OSA (aged 25–59 yr) and 14 age-matched healthy control subjects were studied (13 males and 1 female in each group). Inclusion criteria were: OSA, apnea–hypopnea index 10 or greater; control, apnea–hypopnea index less than 5; and free of psychiatric and medical disorders. Exclusion criteria were: hypertension greater than 180/110; diabetes; weight greater than 300 lbs; and sleep disorders other than OSA. For more detail, see Reference 4. There were no significant demographic differences between the patients and control subjects (Table 1), and there was no significant difference between the young and middle-aged OSA groups in apnea–hypopnea index. The study was approved by the University of California San Diego institutional review board, and all participants provided written informed consent.

Participants had an overnight polysomnography to confirm OSA diagnosis and rule out sleep disorders other than OSA (4). Apnea was defined as any drop of more than 80% in respiratory amplitude lasting longer than 10 seconds. Hypopnea was defined as any drop of more than 30% in respiratory amplitude lasting longer than 10 seconds plus either more than 3% desaturation or arousal (19). Apnea–hypopnea index was calculated representing the number of apnea and hypopnea events per hour of sleep. Participants underwent an fMRI session 2–3 hours after waking the next morning.

The fMRI session took place in a 3T scanner (General Electric, Waukesha, WI). During the session, participants performed a “Go-NoGo” task (6) and a verbal learning task. The Go-NoGo task alternated between active blocks and resting blocks. During active blocks, four shapes were presented sequentially. Participants were instructed to press a button as fast as possible every time they saw three of the shapes (“Go” stimuli), but to withhold a response when they saw the “NoGo” stimulus.

The verbal learning (VL) task (4) contained memorization blocks in which participants were instructed to learn nouns for an immediate free-recall test, and baseline blocks in which participants indicated whether a noun was printed in all capital or all lowercase letters, and did not memorize them. During the entire task, nouns were presented one at a time.

The fMRI contrasts of interest and main behavioral outcome variables were as follows. Go-NoGo: Go trials (compared with fixation trials, in which participants viewed a cross in the center of the screen) indexed sustained attentional processing; mean reaction time to the GO shapes was the behavioral outcome; VL: memorization blocks (compared with resting blocks) indexed encoding of verbal information (immediate free recall immediately measured verbal memory); Sensorimotor, active blocks compared with resting blocks indexed visual and sensory processes.

Individual fMRI data were processed and analyzed as described elsewhere (4). To test our hypothesis that the combination of age and OSA would produce significantly reduced cerebral responses, we performed an *a priori* contrast analysis to compare the middle-aged (≥ 45 yr) OSA group to the other three groups (young OSA [< 45 yr]; middle-aged control [≥ 45 yr]; young control [< 45 yr]). The mean age of 45 years served as a cutoff.

The fMRI analysis for VL and Go-NoGo tasks employed a whole-brain approach. To protect against type I error in the whole-brain analysis, we used a cluster threshold method (20), requiring significant clusters to include at least 12 contiguous voxels (768 mm^3), each significant at a *P* value less than 0.05. Hence, all clusters reported are equal to or larger than the single largest cluster of activation expected by chance at an α of 0.05.

Group analyses for the behavioral data tested the same *a priori* contrast used to evaluate imaging data.

RESULTS

Performance

The *a priori* contrast comparing middle-aged patients with OSA to the other three groups (middle-aged control, young OSA, and young control) revealed significantly reduced immediate free recall on the verbal learning task ($P < 0.001$), and sustained attention on the Go-NoGo task ($P < 0.001$) in the middle-aged OSA group (see Figures 1A and 1B).

Brain Activation

Verbal encoding. The middle-aged OSA group, relative to the other groups, showed decreased activation in task-related brain regions, including the left inferior and middle frontal gyrus, bilateral parahippocampal gyrus, and bilateral areas within the basal ganglia and cerebellum (see Table 2 and Figure 2).

Sustained attention. When assessing the combined effect of OSA and age on brain activation in response to the sustained

TABLE 1. SAMPLE CHARACTERISTICS

Characteristics	Young CTRL (<i>n</i> = 7)	Middle-Aged CTRL (<i>n</i> = 7)	Young OSA (<i>n</i> = 5)	Middle-Aged OSA (<i>n</i> = 9)
Age, yr*	37.9 (7.8)	49.4 (4.5)	32.0 (7.6)	53.2 (3.6)
Body mass index	29.5 (4.2)	27.8 (2.6)	28.9 (6.8)	31.5 (5.2)
Blood pressure, systolic, mm Hg	120.6 (12.4)	117.7 (12.9)	125.2 (17.8)	125.7 (13.4)
Blood pressure, diastolic, mm Hg	78.3 (7.6)	70.0 (11.3)	78.0 (9.4)	75.3 (11.7)
Education, yr	15.4 (1.9)	16.6 (4)	16.8 (2.4)	15.4 (2.9)
Apnea–hypopnea index*	1.7 (1.5)	2.4 (2.5)	36.5 (22.9)	33.5 (20.1)
Minutes below 90% SpO ₂	4.9 (12.2)	0.9 (1.3)	23.1 (32.4)	26.7 (44.6)
Lowest SpO ₂ *	93.5	90.2	78.6	80.6
Arousal index*	5.6 (2.4)	9.6 (5.1)	46.7 (28.7)	30.4 (15.9)
No. of words recalled	8.4 (2.4)	7.7 (2.8)	7.8 (4)	5.7 (3.2)
Go reaction time, ms	829.9 (92)	779.8 (89)	796.8 (88)	897.3 (113)

Definition of abbreviations: CTRL = control; OSA = obstructive sleep apnea; SpO₂ = oxygen saturation as measured by pulse oximetry.

Data presented are means ($\pm$ SD).

* $P < 0.01$ (one-way analysis of variance).

Figure 1. Immediate word recall on the verbal learning task (A) and average reaction time on the sustained attention task (B) for middle-aged patients with obstructive sleep apnea (OSA) compared with the other three groups (middle-aged control, young OSA, and young control). Go RT = reaction time to the “Go” stimuli.

attention challenge, decreased activation was detected for the middle-aged OSA group relative to the other groups in the right middle frontal gyrus, right inferior parietal lobe, right thalamus, and bilateral caudate. Increased activation was detected in left superior frontal gyrus and right anterior cingulate (see Table 3 and Figure 3).

DISCUSSION

This article examined the combined effects of age plus OSA on cognitive performance and cerebral activation in middle-aged (i.e., 45–59-yr-old) patients with OSA compared with young patients with OSA, middle-aged control subjects, and young control subjects across two cognitive domains. Previous studies have demonstrated that OSA (4, 5) and age (21, 22) each individually have similar effects on performance and cerebral responses during cognitive challenges in these domains, but few studies have examined the combined effects of age and OSA. Here, we report that the combined effects of both age and OSA produced significant impairments in behavioral performance and cerebral responses beyond that of either variable alone.

We have previously shown that, during this same verbal encoding task, patients with OSA showed intact performance

and increased brain activation compared with control subjects (4). This is consistent with the literature on compensatory recruitment in the context of aging (14). For example, studies have reported that both OSA and aging were associated with increased activation (relative to control/young subjects) that was associated with intact performance (23, 24). Here, we report that the combination of increasing age and OSA, compared with either one alone, led to worse immediate word recall that was associated with decreased activation in task-related brain regions. These findings suggest that the presence of both increasing age and OSA overwhelmed the brain’s capacity to compensate and maintain performance.

For the sustained attention challenge, middle-aged patients with OSA also showed significantly decreased activation relative to middle-aged control subjects, younger patients with OSA, and younger control subjects. Although reaction times during this task were not significantly different between OSA and control subjects (6), when adding the effect of age, middle-aged patients with OSA showed more slowing in reaction times than the other three groups. This again supports our hypothesis that the combination of increasing age and OSA has a more deleterious effect on brain activation and cognition than the effects of age and OSA alone. The middle-aged patients with OSA also showed focal increases in activation during this task in regions related to response competition and inhibition, possibly reflecting that this group experienced increased cognitive demands in these domains during task performance.

Taken together, our findings suggest that, on a task in which OSA alone or age alone typically led to increased, compensatory brain activation and intact performance, the combination of age and OSA led to an overwhelming effect on the brain’s ability to compensate. The result was impaired cerebral responses in task-related brain areas and diminished performance in patients with both OSA and advancing age. Also, on a task in which OSA alone led to decreased activation and impaired performance, the combination with age led to further decreases in activation and a more profound performance impairment. The idea that OSA affects some cognitive domains (such as sustained attention), but not others (such as verbal abilities and short-term memory), is well documented (1). However, although OSA may differentially impact various brain regions and/or cognitive processes, our results suggest that the double insult of OSA with increasing age more consistently leads to impaired brain activation and performance across tasks.

Our behavioral findings are consistent with previous reports that OSA does not impair performance relative to age-matched control subjects until patients reach middle-age (15). The authors of that study concluded that OSA-related factors, such as sleep fragmentation or brain damage due to hypoxia for many years, may lead to these cognitive differences, and that patients with OSA are particularly vulnerable to cognitive impairment when they reach middle age. Our findings further support the conclusion that OSA interferes with cognitive function and alters cognitive performance more strongly as patients age. Importantly, though, neither our participants nor those in the study by Alchanatis and colleagues (15) were in the range normally considered “older.” Rather, they were all under 65 years of age. This suggests that OSA may produce cognitive and cerebral impairments well before the time at which age-related deficits are typically thought to begin. Although our findings support those of Alchanatis and colleagues, they are not consistent with those by Mathieu and colleagues, reporting no interaction between age and OSA (16, 17). Differences in methodology, including patient age range, OSA severity, cognitive tasks used, and statistical analyses, may explain these discrepant findings.

TABLE 2. BRAIN REGIONS SHOWING COMBINED EFFECTS OF AGE (YOUNG VERSUS OLD) AND GROUP (OBSTRUCTIVE SLEEP APNEA VERSUS CONTROL) DURING VERBAL ENCODING

Anatomical Location	BA	Volume (mm ³)	Center			Max eta ²
			X	Y	Z	
Inferior and middle frontal	L45, 9	1,408	45	21	23	.37
Middle frontal	L6	1,728	33	2	47	.32
	L9 and precentral gyrus	1,024	37	17	39	.48
Postcentral gyrus	L	2,752	5	-37	12	.40
Precentral	L	1,728	28	-21	54	.46
	L6	960	44	-8	40	.30
Parahippocampal gyrus	R	1,728	-34	-2	-24	.41
	L30	960	13	-36	-6	.43
Uncus	L	896	34	0	-26	.37
Fusiform	L37	5,440	38	-48	-17	.44
Precuneus	L	9,472	23	-59	35	.47
	R, superior parietal/7	3,712	-23	-69	48	.42
Caudate, head, putamen, lentiform	B	14,464	0	13	8	.51
	R	960	-14	11	0	.32
Culmen/Tuber	R	6,592	-35	-52	-22	.44
Declive	L	1,920	17	-72	-19	.31

Definition of abbreviations: BA = Brodmann area; eta² = eta squared effect size (variance accounted for by the combined effects of age and group).

The combination of age and OSA may increase the risk of medical comorbidities, such as cardiovascular events, stroke, and transient ischemic attack, and can be a serious deterrent to the health of patients. Our data suggest that the combination of age and OSA also adversely impacts the cerebral response to cognitive challenges, even in relatively healthy patients with OSA, without evidence of the medical comorbidities mentioned previously here. It is possible that the additional presence of such a medical condition could further impair brain function. Independent of that possibility, though, our data have implications for everyday function in middle-aged patients with OSA. For example, given the slowed reaction times in the middle-aged patients with OSA reported here, one might predict concentration difficulties in these patients, or potentially increased risk of accidents when response time is important (e.g., some driving situations). Our finding of impaired word recall in middle-aged patients with OSA might suggest learning and memory deficits that could be mistaken for mild cognitive impairment and/or cognitive aging.

The findings we report here are also consistent with findings from studies assessing the effect of intermittent hypoxia on young and aging rats. Gozal and colleagues (25) showed that

aging rats exposed to room air or intermittent hypoxia displayed significant spatial learning impairments compared with similarly exposed young rats, and that the decrements in performance between room air and intermittent hypoxia were markedly greater in older compared with younger rats. These changes in performance of older rats were associated with larger intermittent hypoxia-induced decreases in cyclic AMP response element binding phosphorylation, proteasomal activity, and neural apoptosis in the older rats (25). These findings of increased vulnerability of the aging rodent brain to intermittent hypoxia, along with our finding of poorer performance in middle-aged patients with OSA compared with younger patients with OSA or middle-aged control subjects, support the notion of a “double insult” resulting from the combination of increasing age and OSA. Although we do not suggest a possible mechanism for the observed behavioral and cerebral changes reported here, Gozal’s study may shed some light on the possible involvement of long-term, intermittent hypoxia in the mechanism that leads to these changes. Regardless of the mechanism, our results, taken together with the literature on the effects of OSA and age on brain function, lend support to the idea that OSA potentiates and/or accelerates what are typically reported as age-related declines in performance and

TABLE 3. BRAIN REGIONS SHOWING COMBINED EFFECTS OF AGE (YOUNG VERSUS OLD) AND GROUP (OBSTRUCTIVE SLEEP APNEA VERSUS CONTROL) DURING SUSTAINED ATTENTION

Anatomical Location	BA	Volume (mm ³)	Center			Max eta ²
			X	Y	Z	
Middle frontal	R9, precentral gyrus	2,688	-40	14	41	.36
	R46	1,216	-48	20	23	.29
Superior Frontal	L8	1,152	17	26	49	.24
Anterior cingulate	R32	768	-6	45	6	.27
Inferior parietal	R	768	-40	-59	47	.26
Superior temporal	R	1,152	-49	-42	2	.37
Middle occipital	L19	1,408	28	-64	8	.39
	R	1,408	-35	-64	8	.30
	L19, fusiform gyrus	1,216	44	-67	-8	.23
Thalamus	R medial dorsal	832	-5	-15	6	.40
Caudate + body	R	5,440	-16	-3	19	.40
	L	960	8	3	19	.27

Definition of abbreviations: BA = Brodmann area; eta² = eta squared effect size (variance accounted for by the combined effects of age and group).

Figure 2. Brain regions showing combined effects of age (young versus old) and group (obstructive sleep apnea [OSA] versus control) during verbal encoding (see Table 2). The *panel* shows sagittal and axial slices with numbers corresponding to Talairach and Tournoux coordinates (L = left; R = right; S = superior). For all images, clusters surviving our cluster threshold method are overlaid in color on top of the group average anatomical image. The color corresponds to the effect size η^2 , corresponding to the amount of variance accounted for by the combined effects of age and group. (A) bilateral caudate nucleus, left middle frontal gyrus, right superior temporal gyrus. (B) Left middle frontal gyrus, right caudate, left lentiform, bilateral superior temporal gyrus. (C) Right superior parietal lobe, left precuneus, left middle temporal gyrus, left declive. (D) Right cerebellum, fusiform, superior temporal gyrus. (E) Right parahippocampal gyrus, inferior and superior parietal lobe. (F) Left middle and inferior frontal gyri, fusiform, pre- and postcentral gyri.

brain function. However, the idea that age effects start earlier in patients with OSA needs to be explored further.

Implications

OSA is known to have a negative impact on cognition in elderly patients. For example, worse cognitive functioning in community-dwelling elderly with higher apnea indices, and significant correlations between sleep apnea severity and all subscales on the dementia rating scale, have been reported (26). Similarly, epidemiological studies have found relationships between symptoms of OSA and both cognitive impairment and dementia in older adults (27, 28), and it has been

Figure 3. Brain regions showing combined effects of age (young versus old) and group (obstructive sleep apnea [OSA] versus control) during sustained attention (see Table 3). The *panel* shows sagittal and axial slices, with numbers corresponding to Talairach and Tournoux coordinates (L = left; R = right; S = superior). For all images, clusters surviving our cluster threshold method are overlaid in color on top of the group average anatomical image. The color corresponds to the effect size η^2 , corresponding to the amount of variance accounted for by combined effects of age and group. (A) Right middle frontal gyrus, precentral, inferior parietal lobe. (B) Right middle temporal gyrus, right middle frontal gyrus, inferior parietal lobe. (C) right anterior cingulate, caudate, thalamus, lingual gyrus. (D) Right anterior cingulate. (E) Right middle and superior frontal gyrus, right precentral gyrus, left superior frontal gyrus.

hypothesized that sleep apnea may contribute to cognitive decline in dementia (29).

The apparent connection between OSA and impaired cognition in the elderly, the growing aging population, and the fact that the prevalence of OSA in the elderly is higher than in younger adults (3) highlight the importance of the findings reported here. In particular, our findings that OSA impairs performance and brain function at a younger age (here, 45–59 yr of age) than what might ordinarily be expected, suggest that these data have immediate implications for the importance of early diagnosis and treatment of OSA.

Continuous positive airway pressure (CPAP) has been shown to diminish sleep fragmentation, increase nocturnal oxygen saturation, and improve cognitive functioning (30–33). Studying the effects of CPAP compliance on neuropsychological functioning in older adults with OSA, Aloia and colleagues (34) reported that CPAP-compliant older adults showed more

improvement on tests of psychomotor speed and nonverbal learning that noncompliant users of CPAP (34). Similarly, greater cognitive improvements were reported in middle-aged patients with OSA showing optimal CPAP treatment compliance compared with those showing poor compliance (35). Two recent fMRI studies have also suggested improvement in brain function after treatment (36, 37). These findings suggest that early identification and treatment of OSA may help reduce the double insult-related impairments that we report here.

Limitations

One limitation in the current study was the difficulty in determining the number of years an individual had been suffering from OSA before diagnosis was made. Clearly, to support the idea that OSA-related factors, such as sleep fragmentation or hypoxia for many years, lead to the cognitive and cerebral changes, longitudinal data are necessary.

In addition, as we studied young and middle-aged adults, the findings of this study cannot be directly applied to an older population. However, because the changes that we report here are already visible at a relatively young age (45–59 yr), one could expect that the deleterious effects of OSA on cognition would be even more profound with increasing age. In that respect, the effects of OSA may be parallel to those seen in the Alzheimer's literature, where early changes in brain activation predict a subsequent decline in cognition (38). In addition, a recent study assessing cognition, gray matter density, and cerebral metabolic levels in middle-aged patients with OSA suggests that cerebral changes may precede the onset of notable neuropsychological consequences (39). Therefore, the questions addressed in this study should be assessed more directly in a sample of older adults.

Clearly, as our sample size is relatively small, further studies with larger sample sizes are needed to confirm the results reported here. We took several steps to protect against type I error, including minimizing the number of hypotheses tested. One result of this is that we only report the most robust effects here.

Nonetheless, our findings highlight the importance of an early detection and treatment of OSA. Treatment may reverse the negative effects of OSA, prevent potential long-term exposure to intermittent hypoxia and cortical arousals, and prevent cognitive deterioration. This may be especially important in older adults, whose brains are also facing age-related physiological changes that affect cognition. Because OSA can be easily and effectively treated, treating OSA as one strategy for improving cognition in middle-aged and older adults may be a simpler mission than trying to reverse other correlates of the aging process that can impair cognition.

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References

- Beebe DW, Groesz L, Wells C, Nichols A, McGee K. The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. *Sleep* 2003;26:298–307.
- Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230–1235.
- Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep disordered breathing in community-dwelling elderly. *Sleep* 1991;14:486–495.
- Ayalon L, Ancoli-Israel S, Klemfuss Z, Shalauta MD, Drummond SPA. Increased brain activation during verbal learning in obstructive sleep apnea. *Neuroimage* 2006;1:1817–1825.
- Ayalon L, Ancoli-Israel S, Drummond SPA. Altered brain activation during response inhibition in obstructive sleep apnea. *J Sleep Res* 2009;8:204–208.
- Ayalon L, Ancoli-Israel S, Aka A, McKenna B, Drummond SPA. Relationship between obstructive sleep apnea severity and brain activation during a sustained attention task. *Sleep* 2009;32:371–383.
- Thomas RJ, Rosen BR, Stern CE, Weiss JW, Kwong KK. Functional imaging of working memory in obstructive sleep-disordered breathing. *J Appl Physiol* 2005;98:2226–2234.
- Tombaugh TN, Hubley AM. Rates of forgetting on three measures of verbal learning using retention intervals ranging from 20 min to 62 days. *J Int Neuropsychol Soc* 2001;7:79–91.
- Verhaeghen P, Marcoen A, Goossens L. Facts and fiction about memory aging: a quantitative integration of research findings. *J Gerontol* 1993;48:157–171.
- McDowd JM. Inhibition in attention and aging. *J Gerontol B Psychol Sci Soc Sci* 1997;52:265–273.
- Zacks R, Hasher L. Cognitive gerontology and attentional inhibition: a reply to Burke and McDowd. *J Gerontol B Psychol Sci Soc Sci* 1997;52:274–283.
- Moscovitch M, Winocur G. The neuropsychology of memory and aging. In: Craik FIM, Salthouse TA, editors. *Handbook of aging and cognition*. Hillsdale, NJ: Erlbaum Associates; 1992. pp. 315–372.
- West RL. An application of prefrontal cortex function theory to cognitive aging. *Psychol Bull* 1996;120:272–292.
- Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging* 2002;17:85–100.
- Alchanatis M, Zias N, Deligiorgis N, Liappas I, Chroneou A, Soldatos C, Roussos C. Comparison of cognitive performance among different age groups in patients with obstructive sleep apnea. *Sleep Breath* 2008;12:17–24.
- Mathieu A, Mazza S, Decary A, Massicotte-Marquez J, Petit D, Gosselin N, Malo J, Montplaisir J. Effects of obstructive sleep apnea on cognitive function: a comparison between younger and older OSAS patients. *Sleep Med* 2008;9:112–120.
- Mathieu A, Mazza S, Petit D, Decary A, Massicotte-Marquez J, Malo J, Montplaisir J. Does age worsen EEG slowing and attention deficits in obstructive sleep apnea syndrome? *Clin Neurophysiol* 2007;118:1538–1544.
- Ayalon L, Ancoli-Israel S, Klemfuss Z, Drummond SPA. Brain function in obstructive sleep apnea: an association with age [abstract]. *Sleep* 2006;29:A169.
- Redline S, Budhiraja R, Kapur V, Marcus CL, Mateika JH, Mehra R, Parthasarathy S, Somers VK, Strohl KP, Sullit LG, et al. The scoring of respiratory events in sleep: reliability and validity. *J Clin Sleep Med* 2007;3:169–200.
- Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic-resonance-imaging (fMRI)—use of a cluster-size threshold. *Magn Reson Med* 1995;33:636–647.
- Dolcos F, Rice HJ, Cabeza R. Hemispheric asymmetry and aging: right hemisphere decline or asymmetry reduction. *Neurosci Biobehav Rev* 2002;26:819–825.
- Grady CL. Cognitive neuroscience of aging. *Ann N Y Acad Sci* 2008;1124:127–144.
- Hazlett EA, Buchsbaum MS, Mohs RC, Spiegel-Cohen J, Wei TC, Azueta R, Haznedar MM, Singer MB, Shihabuddin L, Luu-Hsia C, et al. Age-related shift in brain region activity during successful memory performance. *Neurobiol Aging* 1998;19:437–445.
- Morcom AM, Good CD, Frackowiak RSJ, Rugg MD. Age effects on the neural correlates of successful memory encoding. *Brain* 2003;126:213–229.
- Gozal D, Row BW, Kheirandish L, Liu R, Guo SZ, Qiang F, Brittan KR. Increased susceptibility to intermittent hypoxia in aging rats: changes in proteasomal activity, neuronal apoptosis and spatial function. *J Neurochem* 2003;86:1545–1552.
- Ancoli-Israel S, Klauber MR, Butters N, Parker L, Kripke DF. Dementia in institutionalized elderly: relation to sleep apnea. *J Am Geriatr Soc* 1991;39:258–263.
- Dealberto MJ, Pajot N, Courbon D, Alperovitch A. Breathing disorders during sleep and cognitive performance in an older community sample: the EVA Study. *J Am Geriatr Soc* 1996;44:1287–1294.
- Foley DJ, Monjan AA, Masaki KH, Enright PL, Quan SF, White LR. Associations of symptoms of sleep apnea with cardiovascular disease,

- cognitive impairment, and mortality among older Japanese-American men. *J Am Geriatr Soc* 1999;47:524–528.
29. Bliwise DL. Is sleep apnea a cause of reversible dementia in old age? *J Am Geriatr Soc* 1996;44:1407–1409.
 30. Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, Redline S, Henry JN, Getsy JE, Dinges DF. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep-apnea. *Am Rev Respir Dis* 1993;147:887–895.
 31. McMahon JP, Foresman BH, Chisholm RC. The influence of CPAP on the neurobehavioral performance of patients with obstructive sleep apnea hypopnea syndrome: a systematic review. *WMJ* 2003;102:36–43.
 32. Valencia-Flores MD, Bliwise L, Guilleminault C, Cilveti R, Clerk A. Cognitive function in patients with sleep apnea after acute nocturnal nasal continuous positive airway pressure (CPAP) treatment: sleepiness and hypoxemia effects. *J Clin Exp Neuropsychol* 1996;18:197–210.
 33. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999;159:461–467.
 34. Aloia MS, Illiczyk N, Di Dio P, Perlis ML, Greenblatt DW, Giles DE. Neuropsychological changes and treatment compliance in older adults with sleep apnea. *J Psychosom Res* 2003;54:71–76.
 35. Zimmerman ME, Arnedt JT, Stanchina M, Millman RP, Aloia MS. Normalization of memory performance and positive airway pressure adherence in memory-impaired patients with obstructive sleep apnea. *Chest* 2006;130:1772–1778.
 36. Castronovo V, Canessa N, Strambi LF, Aloia MS, Consonni M, Marelli S, Iadanza A, Bruschi A, Falini A, Cappa SF. Brain activation changes before and after PAP treatment in obstructive sleep apnea. *Sleep* 2009;32:1161–1172.
 37. Aloia MS, Sweet LH, Jerskey BA, Zimmerman M, Arnedt JT, Millman RP. Treatment effects on brain activity during a working memory task in obstructive sleep apnea. *J Sleep Res* 2009;18:404–410.
 38. Bookheim SY, Strojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, Small GW. Patterns of brain activation in people at risk for Alzheimer's disease. *N Engl J Med* 2000;343:450–456.
 39. Yaouhi K, Bertran F, Clochon P, Mezenge F, Denise P, Foret J, Eustache F, Desgranges B. A combined neuropsychological and brain imaging study of obstructive sleep apnea. *J Sleep Res* 2009;18:36–48.