

# Nocturnal sleep apnea/hypopnea is associated with lower memory performance in *APOE* $\epsilon$ 4 carriers

**Abstract**—The authors investigated the relationship between obstructive sleep apnea/hypopnea (OSAH) and cognition in 36 older adults, 18 *APOE*  $\epsilon$ 4 carriers, and 18 non-carriers. Greater numbers of respiratory events negatively impacted memory function in  $\epsilon$ 4 carriers only. This is the first study to provide preliminary evidence for a negative interaction of *APOE*  $\epsilon$ 4 and OSAH on memory in older adults, which may have important implications for treating cognitive decline and delaying dementia onset.

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The *APOE*  $\epsilon$ 4 allele is a genetic risk factor for Alzheimer disease (AD)<sup>1</sup> and is associated with cognitive decline in non-demented, community-dwelling older adults.<sup>2</sup> However, presence of the  $\epsilon$ 4 allele alone is not sufficient to produce cognitive decline. The *APOE*  $\epsilon$ 4 allele appears to be a susceptibility factor that interacts with other genetic or environmental influences to increase the risk of cognitive deterioration. One such factor may be obstructive sleep apnea/hypopnea (OSAH). Presence of the  $\epsilon$ 4 allele may confer as much as a twofold increased risk for the development of OSAH.<sup>3</sup> OSAH is also associated with cognitive impairment, particularly deficits in delayed recall ability.<sup>4</sup> Impairments in delayed recall are consistently associated with the  $\epsilon$ 4 allele. This raises the question of whether OSAH may account, in part, for the association between cognitive decline and *APOE*  $\epsilon$ 4 allele among non-demented individuals. We investigated the relationship between level of OSAH and cognitive function in 36 community dwelling, non-demented older adults, 18 with and 18 without the  $\epsilon$ 4 allele.

**Methods.** *Study subjects.* Thirty-six community-dwelling older adults were recruited from an ongoing investigation of the relationship between the  $\epsilon$ 4 allele and cognition. Eighteen had an  $\epsilon$ 4

allele, and 18 were non-carriers, as we targeted  $\epsilon$ 4 carriers from the original sample so as to have an equal number of carriers and non-carriers. The genotypes were 3  $\epsilon$ 4/ $\epsilon$ 4, 13  $\epsilon$ 3/ $\epsilon$ 4, 2  $\epsilon$ 2/ $\epsilon$ 4, and 18  $\epsilon$ 3/ $\epsilon$ 3. Twelve men and 24 women participated. All were over age 60, with a mean age of 70.6 (SD = 8.1), a mean of 16.1 (SD = 2.4) years of education, and a mean Mini-Mental State Examination (MMSE) of 28.7 (SD = 1.2; range 27 to 30). The mean body mass index (BMI) was 25.9 (SD = 4.5). The protocol was approved by the Institutional Review Board at Stanford University, CA, and written informed consent was obtained from each participant.

Genomic DNA was extracted from frozen whole blood samples and *APOE* genotyping was performed using the Hixson and Verner restriction isotyping protocol (see appendix E-1 on the *Neurology* Web site at [www.neurology.org](http://www.neurology.org)).

All subjects were administered the following cognitive tests before being assessed for OSAH: the MMSE; the Rey Auditory Verbal Learning Test of immediate verbal recall (RAVLT1); short-term free recall (RAVLT6) and 30-minute delayed free-recall (RAVLT Delayed); the Stroop Color and Word (SCW) measure of attention and cognitive flexibility; and the Symbol-Digit Modalities Test (SDMT) of information processing speed (see appendix E-2).

OSAH was evaluated in subjects' homes using portable recordings with the EdenTrace Model II ambulatory monitoring system, recording nasal/oral airflow (thermistor), finger pulse oximetry, heart rate, chest wall impedance, snoring, and body position. All recordings produced at least 4 hours of usable data, and were hand-scored using standard definitions. Apneas were defined as at least 10 seconds interruption of oronasal airflow, associated with at least 3% oxyhemoglobin desaturation. Hypopneas were defined as at least 10 second decrements in airflow, followed by at least 3% decrease in oxygen saturation. We calculated the apnea-hypopnea index (AHI), i.e., the average number of apneas or hypopneas per hour of estimated sleep, to measure OSAH severity in each subject. Studies using this approach find highly reproducible data ( $r = 0.94$ ) that is well correlated with OSAH severity (AHI) assessed with in-laboratory polysomnography ( $r = 0.96$ ).<sup>5</sup> AHI served as the independent variable. The Epworth Sleepiness Scale (ESS) was included to measure self-reported daytime sleepiness (see appendix E-3).

**Statistical analysis.** We compared the  $\epsilon$ 4 and non- $\epsilon$ 4 groups on demographic, self-reported daytime sleepiness, respiratory and cognitive variables using *t* tests. We employed the homogeneity of correlation test, based upon Fisher's *z*-transformation,<sup>6</sup> to compare the relationship of OSAH to cognition for the  $\epsilon$ 4 carriers with that for the non- $\epsilon$ 4 carriers. Similar analyses examined the relationship of ESS and minimum oxygen saturation ( $\text{minSaO}_2$ ) to cognition in  $\epsilon$ 4 and non- $\epsilon$ 4 carriers.

**Results.** No significant differences were observed between the  $\epsilon$ 4 and non- $\epsilon$ 4 groups with respect to demographic, self-reported daytime sleepiness, respiratory, and cognitive variables (table 1). No significant association was observed between ESS and any cognitive measure, and no differences existed between the  $\epsilon$ 4 and non- $\epsilon$ 4 carriers with respect to the association of ESS to cognition. However, the homogeneity of correlation test found the relationship be-

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**Table 1** Comparison between APOE  $\epsilon 4$  carriers and non-carriers on demographics, self-reported daytime sleepiness, respiratory, and cognitive variables (mean [SD]; *t* test *p* value)

	$\epsilon 4$ Carriers, n = 18	Non-carriers, n = 18	<i>p</i> Value
Age, y	69.6 (5.8)	71.6 (10.2)	0.47
Sex	12 F, 6 M	12 F, 6 M	0.99
Education	16.1 (1.6)	16.1 (3.05)	0.99
BMI	27.3 (4.8)	24.4 (3.8)	0.06
AHI	9.1 (8.1)	6.2 (6.6)	0.13
MinSaO <sub>2</sub> , %	88.4 (6.4)	86.3 (4.8)	0.28
Desaturation per apnea, %	4.7 (2.2)	4.2 (3.1)	0.59
Desaturation per hypopnea, %	4.1 (0.9)	4.1 (0.6)	0.78
ESS	6.6 (4.1)	7.1 (5.0)	0.74
MMSE	28.8 (1.3)	28.6 (1.1)	0.48
RAVLT 1	6.6 (1.4)	6.0 (2.9)	0.46
RAVLT 6	10.1 (3.2)	8.9 (4.4)	0.35
RAVLT delayed	9.1 (3.3)	8.9 (4.5)	0.87
SCW	142.2 (33.5)	144.2 (27.4)	0.85
SDMT	50.7 (7.2)	46.4 (10.6)	0.16

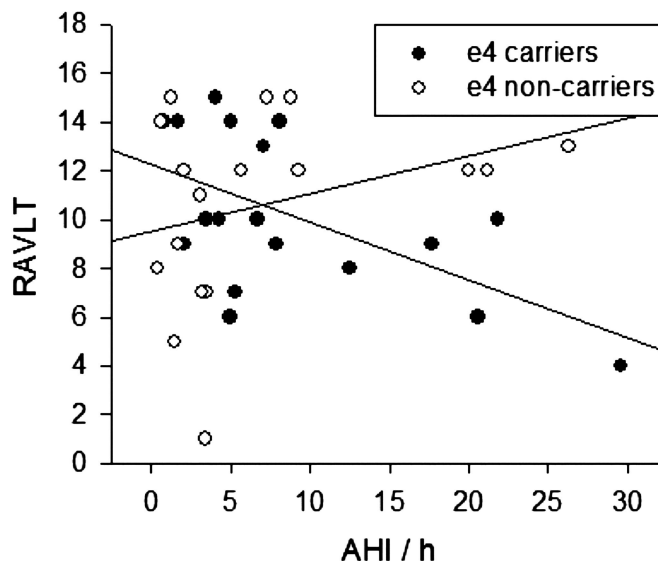
BMI = body mass index; AHI = apnea/hypopnea index; MinSaO<sub>2</sub> = minimum oxygen saturation; ESS = Epworth Sleepiness Scale; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; SCW = Stroop Color and Word Test; SDMT = Symbol-Digit Modalities Test.

tween AHI and the delayed recall and short-term recall components of the RAVLT to be significantly different in the  $\epsilon 4$  vs non- $\epsilon 4$  carriers. Higher levels of AHI were associated with lower memory scores in the  $\epsilon 4$  carriers only (AHI vs RAVLT6;  $r = -0.49$  in  $\epsilon 4$  vs  $r = 0.24$  in non- $\epsilon 4$  carriers; table 2, figure). MinSaO<sub>2</sub> was not significantly different in the  $\epsilon 4$  groups, but was lower than 90% in both, indicating hypoxia had occurred. MinSaO<sub>2</sub> was not associated with cognition, although there was a non-significant trend for minSaO<sub>2</sub> to negatively impact memory in the  $\epsilon 4$

**Table 2** Relationship of apnea/hypopnea index to cognition in APOE  $\epsilon 4$  carriers compared to non-carriers (homogeneity of correlation test, *r* values)

	$\epsilon 4$ Carriers, n = 18	Non-carriers, n = 18	<i>p</i> Value
MMSE	-0.15	-0.15	0.98
RAVLT delayed (30 minute delayed recall)	-0.46	0.21	0.05
RAVLT 6 (short-term free recall)	-0.49	0.24	0.03
RAVLT 1 (immediate recall)	-0.29	-0.09	0.59
SCW	0.12	0.08	0.91
SDMT	-0.08	-0.26	0.59

MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; SCW = Stroop Color and Word Test; SDMT = Symbol-Digit Modalities Test.



**Figure.** Graph of the Rey Auditory Verbal Learning Test (RAVLT) plotted against the apnea/hypopnea index per hour of estimated sleep (AHI/hour) in APOE  $\epsilon 4$  carriers compared to non-carriers.

carriers only (minSaO<sub>2</sub> vs RAVLT delayed:  $r = 0.32$  in  $\epsilon 4$  vs  $r = -0.18$  in non- $\epsilon 4$  carriers).

**Discussion.** The results of this preliminary investigation suggest that APOE  $\epsilon 4$  and OSAH may interact to impair cognition in non-demented, older adults. Our data indicate a significant negative relationship between the number of respiratory events and memory performance only in  $\epsilon 4$  carriers. This suggests that OSAH may account, in part, for the association of APOE  $\epsilon 4$  allele to cognitive decline in community-dwelling, older adults. This finding is of particular clinical importance considering the high prevalence of OSAH in this age group<sup>7</sup> and the high carrier frequency of APOE  $\epsilon 4$  in the general population (25%).

The mechanism by which the  $\epsilon 4$  allele and OSAH may interact to impact cognition is unclear.<sup>8</sup> The  $\epsilon 4$  allele may increase neuronal vulnerability to oxidative stress reducing the brain's response to the hypoxia experienced during respiratory events. Hypoxia negatively impacts neuronal integrity in several brain regions, including the hippocampus which subserves delayed recall,<sup>9</sup> and is vulnerable to deleterious effects of the  $\epsilon 4$  allele in older adults.<sup>10</sup> The hypoxia associated with OSAH may interact with the  $\epsilon 4$  allele to negatively impact cognition. In our study, minSaO<sub>2</sub> displayed a tendency to negatively impact memory in  $\epsilon 4$  carriers only, but the actual number of respiratory events was more strongly associated with lower memory in the  $\epsilon 4$  carriers. Some argue that apnea-associated sleep disruption rather than hypoxia negatively impacts cognition.<sup>4</sup> Since we did not employ EEG to obtain a direct measure of sleep we were unable to address this issue. However, we observed no impact of self-reported daytime sleepiness, which often accompanies sleep fragmentation, on

cognitive function. Future studies should incorporate appropriate measures of sleep to more fully explore these competing explanations.

Our preliminary investigation had several additional limitations which temper our conclusions and should be addressed in future investigations. The sample size is small. The recording technique lacked nasal airway pressure or pleural pressure measurements and could not detect increased upper airway resistance. Also, it was not possible to exclude the possibility of a central mechanism for a few recorded apneas/hypopneas, although the great majority of events were of obstructive nature.

However, this preliminary study provides evidence for a significant negative interaction of *APOE*  $\epsilon$ 4 and OSAH on memory in older adults. Larger longitudinal studies are required to investigate whether *APOE*  $\epsilon$ 4 increases vulnerability to the negative effect of OSAH on cognition, or whether the relationship between *APOE*  $\epsilon$ 4 and cognition is due to the higher prevalence of OSAH in those with the  $\epsilon$ 4 allele.

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