ELSEVIER

Sleep Medicine 7 (2006) 498–507

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Original article

Obstructive sleep apnea–hypopnea and neurocognitive functioning in the Sleep Heart Health Study

Stuart F. Quan [a,*], Ron Wright [b], Carol M. Baldwin [c], Kristine L. Kaemingk [d], James L. Goodwin [e], Tracy F. Kuo [f], Alfred Kaszniak [g], Lori L. Boland [h], Elise Caccappolo [i], Richard R. Bootzin [j]

[a] *Department of Medicine, Arizona Respiratory, Sleep Disorders and General Clinical Research Centers, University of Arizona College of Medicine, 1501 North Campbell, Room 2305 Tucson, AZ 85724, USA*
[b] *Department of Psychiatry and General Clinical Research Center, University of Arizona College of Medicine, Tucson, AZ, USA*
[c] *College of Nursing (Southwest Borderlands), Arizona State University, Tempe, AZ, USA*
[d] *Department of Pediatrics, Steele Memorial Children's Research and General Clinical Research Centers, University of Arizona College of Medicine, Tucson, AZ, USA*
[e] *Department of Medicine and Arizona Respiratory Center, University of Arizona College of Medicine, Tucson, AZ, USA*
[f] *Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA*
[g] *Department of Psychology, University of Arizona, Tucson, AZ, USA*
[h] *Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN, USA*
[i] *Department of Neurology, Columbia University, New York, NY, USA*
[j] *Departments of Psychology and Psychiatry, Sleep Disorders Center, University of Arizona, Tucson, AZ, USA*

Received 19 October 2005; received in revised form 8 February 2006; accepted 12 February 2006
Available online 3 July 2006

Abstract

Background and purpose: Obstructive sleep apnea–hypopnea (OSAH) is associated with sleep fragmentation and nocturnal hypoxemia. In clinical samples, patients with OSAH frequently are found to have deficits in neuropsychological function. However, the nature and severity of these abnormalities in non-clinical populations is less well defined.

Patients and methods: One hundred and forty-one participants from the Tucson, AZ and New York, NY field centers of the Sleep Heart Health Study completed a battery of neuropsychological tests for 9–40 months (mean = 24 months, SD = 7 months) after an unattended home polysomnogram. Sixty-seven participants had OSAH (AHI > 10) and 74 did not have OSAH (control (CTL), apnea–hypopnea index (AHI) < 5). In addition to the individual tests, composite variables representing attention, executive function, MotorSpeed and processing speed were constructed from the neuropsychological test battery.

Results: There were no significant differences in any individual neuropsychological test or composite variable between the OSAH and CTL groups. However, when time spent with O_2 saturations less than 85% was dichotomized into those participants in the top quartile of the distribution and those in the lower three quartiles, motor speed was significantly impaired in those who were more hypoxemic. In addition, poorer motor speed (model adjusted $R^2 = 0.242$, $P < 0.001$) and processing speed performance (model adjusted $R^2 = 0.122$, $P < 0.001$) were associated with more severe oxygen desaturation even after controlling for degree of daytime sleepiness, age, gender and educational level.

Conclusions: Mild to moderate OSAH has little impact on the selected measures of attention, executive function, motor speed and processing speed. However, hypoxemia adversely affects both motor and processing speed. These results suggest that in middle-aged to elderly adults the neuropsychological effects of clinically unrecognized mild to moderate OSAH are neither global nor large.

Keywords: Sleep disordered breathing; Obstructive sleep apnea; Neuropsychologic function; Hypoxemia; Neurocognitive function; epidomiology

* Corresponding author. Tel.: +1 520 626 6115; fax: +1 520 626 6970.
E-mail addresses: squan@arc.arizona.edu (S.F. Quan), wrightr@u.arizona.edu (R. Wright), carol.baldwin@asu.edu (C.M. Baldwin), kaemingk@peds.arizona.edu (K.L. Kaemingk), jamieg@arc.arizona.edu (J.L. Goodwin), tracykuo@stanford.edu (T.F. Kuo), kaszniak@email.arizona.edu (A. Kaszniak), boland@epi.umn.edu (L.L. Boland), ec668@columbia.edu (E. Caccappolo), bootzin@u.arizona.edu (R.R. Bootzin).

1389-9457/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.sleep.2006.02.005

1. Background

Obstructive sleep apnea–hypopnea (OSAH) is now recognized as a major public health problem due to its high prevalence, increased morbidity and mortality, high medical costs and increased public safety risk [1–3]. The impact of OSAH is potentially profound and wide-ranging with a number of studies noting adverse effects on physical, emotional, and intellectual capacities [4–7], as well as functional quality of life [8,9]. Some of the most serious symptoms that have been associated with OSAH include attention deficits, impaired concentration, and memory problems [10].

A number of studies have found patients diagnosed with OSAH to have poorer cognitive outcomes [11–16]. For example, Montplaisir et al. reported executive and psychomotor deficits, as well as attention and memory problems associated with impaired vigilance [14]. Greenberg et al. reported deficits on measures of motor and perceptual-organization ability [12]. Memory deficits have been related to the number of apneas and hypopneas per hour of sleep, while typical frontal lobe-related abnormalities appeared consistent with the level of nocturnal hypoxemia [15,16].

Several studies suggest that cognitive deficits persist despite standard interventions for OSAH. Valencia-Flores et al. examined OSAH patients on their neuropsychological test performance prior to and immediately after successful treatment with continuous positive airway pressure (CPAP) [17]. Analyses showed that the effects of severe OSAH appear to impair functions that were not easily modified by treatment with continuous positive airway pressure (CPAP), such as sustained attention in repetitive arithmetic tasks. In their re-evaluation study of attention, short-term memory span, learning abilities, planning capacities, categorizing activities, and verbal fluency 4–6 months following CPAP treatment, Naegele et al. noted that patients had normalized their cognitive executive and learning problems; however, short-term memory impairment persisted [16]. More recently, a meta-analytic review of the neuropsychological effects of OSAH indicated that vigilance, motor coordination and executive functions ranged from moderately to markedly affected, while intelligence, verbal and visual-perceptual abilities were not affected in adults with untreated OSAH [18].

Reports of cognitive impairment have not been limited only to patients with severe OSAH. Redline et al. found that in comparison to controls, individuals with mild sleep apnea performed more poorly on a visual vigilance task and the digits backward test of working memory [19]. Notably, Kim et al. found that mild OSAH was equivalent to a reduction in psychomotor efficiency associated with five additional years of age, or to half of the decrement related to use of hypnosedatives [20].

Although, there is evidence to suggest that cognitive deficits occur in both clinical and non-clinical samples with varying levels of OSAH severity, neuropsychological findings differ in type and/or degree as well as their association with the number of OSAH events and/or severity of hypoxemia. These inconsistencies could be due to the sensitivity of tests used to assess neuropsychological function, sample size, and/or criteria used to assess the severity of OSAH [21]. Whether the results of the preceding studies are generalizable to untreated community-based persons with mild to severe OSAH remains unclear. The intent of the present study is to characterize the effect of mild to severe OSAH on neuropsychological functioning in a subset of persons from the Sleep Heart Health Study (SHHS), a community-dwelling cohort recruited to investigate the cardiovascular consequences of OSAH. It is hypothesized that persons with OSAH will manifest neuropsychological deficits compared to persons who do not have OSAH, and the deficits will be proportional with the severity of the OSAH.

2. Methods

2.1. Recruitment and participants

Participants were recruited from the Tucson, AZ and New York, NY sites of the SHHS. The SHHS is a multicenter prospective cohort study implemented by the National Heart, Lung, and Blood Institute to investigate the cardiovascular consequences of OSAH. The specific aims, design and participant characteristics of the SHHS have been previously reported [22,23]. They are also available at www.jhucct.com/shhs. In brief, SHHS subjects were recruited from ongoing parent cohort studies of cardiovascular or respiratory disease. Inclusion criteria were age 40 years or older, no history of treatment of sleep apnea with CPAP, no tracheostomy and no current home oxygen therapy.

The demographic characteristics of participants at the Tucson and New York sites have been reported [24]. All prospective participants had to be between the ages of 40 and 75 years. Because final scoring of an unattended polysomnogram (PSG) was not available for months after the study had been completed, potential index cases (OSAH group) were identified based on preliminary scoring of the PSG. Preliminary scoring of the PSG defined the apnea hypopnea index (AHI) as the number of apneas or hypopneas associated with a 3% oxygen desaturation per hour of total sleep time (AHI3%). Initial assignment to the OSAH group was based on participants having an AHI3% between 10 and 50. However, after final PSG scoring, only participants with a sufficient number of apneas or hypopneas associated with a 4% oxygen desaturation per hour of total sleep time (AHI4%) were included in the OSAH group (vide infra). A total of 97 women and 245 men were identified as potential index-case subjects who met OSAH selection criterion. Potential control participants were persons who

had an AHI3% <5, with a total of 559 women and 380 men identified as possible control cases (CTL group).

To control for important confounding conditions that may contribute to neuropsychological impairments, potential participants were excluded if they were currently being treated for cancer and/or in remission for <5 years, on antipsychotic or anticonvulsant medication or being treated for OSAH, had a history of alcohol-related problems that interfered with work and/or personal life, myocardial infarction within the last 3 years, stroke, head injuries, or surgical treatment for OSAH. Potential participants were recruited by telephone. In Tucson, recruitment also included a mailed SHHS newsletter announcement.

A brief phone screen was conducted to determine whether or not a prospective subject met selection criteria after he/she expressed interest in participating. In order to maximize the potential of finding group differences, an effort was made to enroll cases with the highest AHIs first. Recruitment then moved downward toward the lower end of the AHI cutoff. Recruitment of the CTL subjects was staggered and on average lagged behind the OSAH subjects by 4 months. A total of 144 persons (107:46 women and 61 men from Tucson; and 37; 17 women and 20 men from New York) were enrolled. As previously discussed, recruitment was based on a preliminary determination of the AHI (AHI3%). Thus, one Tucson participant and two New York participants ultimately were excluded because their final AHI (AHI4%) was between 5 and 10, which did not meet selection criteria. Therefore, the final sample consisted of 67 OSAH (53% male) and 74 CTL participants (63% male). Non-Hispanic Whites represented 86.5% of the study population. The remaining participants were primarily of African-American (7.8%) or Hispanic (5.0%) descent.

2.2. Polysomnography

As part of the SHHS protocol, all participants underwent unattended PSG at home prior to the neuropsychological testing. The average time lag between the PSG and the neuropsychological testing was 24 months (SD = 7, range = 9–40 months). A questionnaire on sleep habits, requesting information on snoring history, sleep apnea symptoms, diagnosis and treatment, and daytime sleepiness assessed by the Epworth sleepiness scale (ESS) was administered prior to the PSG [25]. Detailed descriptions of the home visit and the methods used for unattended PSG have been previously published [22,23]. In summary, overnight PSG was performed using the Compumedics Portable PS-2 System (Abottsville, AU) [23]. Sensors were placed and equipment was calibrated during an evening visit by a certified technician. Data collection included C3/A2 and C4/A1 electroencephalograms (EEGs); right and left electrooculograms (EOGs); a bipolar submental electromyogram (EMG); thoracic and abdominal excursions (inductive plethysmography bands); 'airflow' (detected by a nasal-oral thermocouple (Protec, Woodinville, WA)); oximetry using finger pulse oximetry (Nonin, Minneapolis, MN); electrocardiogram (ECG) and heart rate (using a bipolar ECG lead); body position (using a mercury gauge sensor); and ambient light (on/off, by a light sensor secured to the recording garment). Following equipment retrieval, the data, stored in real time on Personal Computer Memory Card International Association (PCMCIA) cards, were downloaded to the computers at each respective clinical site, locally reviewed, and forwarded to the central SHHS Reading Center (Case Western Reserve University, Cleveland, OH). Sleep stages were scored according to the guidelines developed by Rechtschaffen and Kales [26]. Stages 3 and 4 were combined and classified as 'slow wave sleep'. Arousals were identified according to American Sleep Disorders Association criteria [27]. An apnea was defined as a complete or almost complete cessation of airflow (at least <25% of baseline), as measured by the amplitude of the thermocouple signal, lasting >10 s. Hypopneas were identified if the amplitude of a measure of flow or volume (detected by the thermocouple or thorax or abdominal inductance band signals) decreased to <70% of the amplitude of 'baseline' breathing for >10 s, but did not meet the criteria for apnea. For this study, only apneas or hypopneas associated with ≥4% oxyhemoglobin desaturation were considered in the calculation of the AHI (AHI4%). In addition to the AHI4%, the number of arousals per hour (arousal index, AI) was used as a measure of sleep disruption. The percentage of sleep time in which oxygen saturation was <85% (O_2SAT85) was used as an index of hypoxemia. Variables representing sleep architecture included total sleep time (TST), sleep efficiency, and percent of stages 1, 2, 3/4, and REM sleep.

2.3. Neuropsychological assessment

After successful recruitment, participants were scheduled for a neuropsychological screening conducted by trained psychometricians that employed commonly used measures dependent on attention, processing speed, executive function and motor speed. Measures included the Wechsler Adult Intelligence Test-Third Edition (WAIS-III) Picture Completion, Digit Span, Letter-Number Sequencing, Digit Symbol Coding, and Symbol Search subtests [28]; the Stroop Color and Word Test [29]; the Trail Making Test [30]; and the Grooved Pegboard [31].

Picture Completion, Digit Span, and Letter-Number Sequencing are commonly used measures of attention [28,32,33]. They require the ability to identify missing elements of pictures, repetition of numbers (forward and reverse order), and recall letters and numbers in order (numerical, alphabetical), respectively. Digit Symbol Coding and Symbol Search are measures of processing speed that assess rapid copying of symbols and scanning speed and accuracy, respectively [28,32]. Both measures are timed and require a motor response. These Wechsler measures have a mean of 10 and SD of 3. Executive function

was measured using the Interference *T*-score (mean = 50, SD = 10) from the Stroop [29]. This score is an indicator of response inhibition and a commonly used measure of executive function [32,33]. The time to complete Trail Making Part B (in seconds) was also used to assess executive function [30]. This measure of executive skills requires rapid sequencing and alternating attention [32,33]. Motor speed was assessed with Grooved Pegboard [31], a task that requires rapid placement of pegs in holes with the dominant hand and then the non-dominant hand. Completion time with each hand was used as the dependent measure.

2.4. Data analysis

In order, to focus on specific components of neuropsychological function, we created composite variables for (a) attention (Attention), (b) processing speed (Procspeed), (c) executive function (Execfunct) and (d) motor speed (MotorSpeed). The composite variable for the Attention domain combined data from the Picture Completion, Digit Span, and Letter-Number Sequencing tests. Procspeed combined Digit Symbol Coding and Symbol Search. Execfunct was a composite of the Stroop Interference *T*-score and the time to complete the Trail Making B test. Motorspeed was assessed by summing the scores on the Grooved Pegboard. In order to give every component variable equal weight in the composite, each component was first standardized and these *Z*-scores were averaged to create the composite variables. Within a given composite, component variables were positively correlated, and composites retained the original direction for the construct. Thus, high scores indicated better performance for the Attention and Procspeed composites, while low scores indicated better performance for the ExecFunct and MotorSpeed composites.

Although, the overall AHI4% distribution here was bimodal (hence, non-normal) by study design, in past research, AHI4% has generally not been normally distributed, and the usual practice is to apply a logarithmic transformation prior to analysis. We have followed that procedure as well (LogAHI4%). For cases in which AHI4% was 0, the value 0.07 was used. This represents a trivial number that is 50% of the lowest non-zero value of AHI4%. In addition, the difference in the median AHI4% between the OSAH and CTL groups was assessed utilizing the Mann–Whitney *U*-test. Student's unpaired *t*-test was employed to compare mean differences between the OSAH and CTL groups. The χ^2 statistic was used to compare proportions between nominal variables.

The relationships between the four composite variables of neuropsychological function (Attention, Procspeed, Execfunct and Motorspeed), and potential explanatory and demographic variables were explored using simple and multiple linear regression. For each composite variable, performance was assessed in the following models: (1) AHI group (OSAH vs. CTL) alone, and in combination with the covariates age, educational level and gender because each potentially could affect neuropsychological performance; (2) LogAHI4% alone, and in combination with age, educational level and gender; (3) O_2SAT85 alone, and in combination with age, educational level and gender; (4) ESS alone and in combination with age, educational level and gender; (5) ESS with either LogAHI4% or O_2SAT85, and age, educational level and gender; and (6) each of models 1 and 3–5 within both AHI groups individually. In preliminary analyses, AI was found to predict worse Motorspeed performance. Thus, AI was included along with age, educational level and gender in prediction models for only this composite variable. No other sleep architecture or demographic variables were related to neuropsychological performance on exploratory analyses. Models including both LogAHI4% and O_2SAT85 were not constructed because there were no instances where both variables in a simple regression predicted performance on any of the composite variables.

Analyses were performed using Systat (Version 10, Systat Software, Inc., Richmond, CA) and SPSS for Windows, Version 11.5, SPSS, Inc., Chicago, IL).

Table 1
Participant characteristics

	CTL, *N* = 74: 39 men 35 women		OSAH, *N* = 67: 42 men 22 women		*P* value
	Mean	SD	Mean	SD	
Demographics					
Age (years)	57.4	9.2	59.4	9.2	n.s.
Education (years)	14.9	2.7	15.2	2.6	n.s.
Ethnicity (% non-hispanic white)	85.1		88.1		n.s.
Body mass index (kg/m^2)	25.9	4.3	30.8	6.2	<001
Married (%)	62.4		73.8		n.s.
Right handed (%)	67.6		76.1		n.s.
Habits					
Usual caffeine intake	3.7	4.4	2.8	2.8	n.s.
Current smoker (%)	5.4		9.0		n.s.
Daytime sleepiness					
Epworth sleepiness scale	7.0	4.3	9.1	4.9	.007

3. Results

Table 1 shows the demographic and social characteristics of the CTL and OSAH groups. Persons with OSAH had higher ESS scores and body mass index (BMI). Otherwise, there were no significant differences between groups.

Data pertaining to sleep and respiration for the CTL and OSAH groups are displayed in Table 2. Except for a slightly greater percentage of stage 1 sleep in persons with OSAH, no differences were observed between the two groups in sleep architecture. However, OSAH participants had a greater number of arousals. By definition, the AHI4% was higher in the OSAH group and as might be expected, greater amounts of oxygen desaturation (higher O_2SAT85) were observed in the OSAH group as well.

The mean actual and *Z*-scores for individual neuropsychological tests are displayed in Table 3. There were no significant differences between the OSAH and CTL groups.

Table 4 shows the mean *Z*-scores for the composite variables Motorspeed, Execfunct, Procspeed and Attention for the OSAH and CTL groups as well as for a comparison of the upper quartile of O_2SAT85 against the lower three quartiles. Although, no differences were observed between AHI groups in any of the composite variables, Motorspeed performance was significantly impaired in those with greater amounts of oxygen desaturation.

Table 5 shows selected multiple regression models illustrating the important relationships between the four composite neuropsychological domains and age, educational level, gender, AHI Group, LogAHI4% and O_2SAT85 for all participants. With respect to covariates, increasing age was observed to be associated with worse performance on tests of Motorspeed and Execfunct and slightly better function in Procspeed. Educational level was a significant factor only for Attention and for the effect of LogAHI4% on Procspeed. Men scored slightly worse in Motorspeed and better in Procspeed. More notably, severity of nocturnal oxygen desaturation was found to be predictive of worse performance in the domains of motor speed and Procspeed. Furthermore, regression analyses within each AHI Group (CTL and OSAH) confirmed that severity of oxygen desaturation within OSAH participants was responsible for the adverse impact on Motorspeed ($\beta = 0.081 \pm 0.034$, $P = 0.02$) and Procspeed ($\beta = 0.080 \pm 0.038$, $P = 0.04$) in the models using all participants. In order to assess the contribution of oxygen desaturation in explaining the variance in the models of Motorspeed and Procspeed, the unadjusted coefficient of variation (R^2) was calculated for these models including only the covariates age, education and gender. Comparison was then made with the R^2 of models with oxygen desaturation included. For Motorspeed, adding O_2SAT85 to the regression model increases R^2 from 0.234 to 0.264 ($P = 0.02$). For Procspeed, adding O_2SAT85 increases R^2 from 0.113 to 0.148 ($P = 0.02$). Thus, although small in absolute terms, oxygen desaturation accounts for 12.8 and 31.0% of the explained variance in our models. Sleepiness was found to be predictive of poorer performance only for Procspeed ($\beta = -0.044 \pm 0.014$; $P = 0.004$). In contrast, neither the AHI Group nor LogAHI4% was found to be predictive of performance in any of the four domains of neuropsychological function. In addition, AI was unrelated to Motorspeed performance in multivariate analyses ($\beta = 0.001 \pm 0.007$, $P =$ n.s.).

4. Discussion

This study investigated the effects of OSAH on performance of commonly used measures of attention, executive function, motor speed and processing speed in a sample of adults from the community-based Sleep Heart Health Study. Excessive daytime sleepiness was more severe in persons with OSAH and affected processing speed function. However, the presence of mild to moderate OSAH was not associated with impaired performance on any of the measures of neuropsychological function used in this study. In contrast, severity of hypoxemia adversely impacted both processing speed and motor speed performance.

Table 2
Sleep architecture and sleep disordered breathing

	CTL, $N=74$: 39 men 35 women		OSAH, $N=67$: 42 men 22 women		*P* value
	Mean	SD	Mean	SD	
Sleep architecture					
Total sleep time (min)	352	67	356	76	n.s.
Sleep efficiency (%)	82	9	81	12	n.s.
Stage 1 (%)	4.7	3.5	6.5	6.1	<05
Stage 2 (%)	58.4	10.7	60.5	9.4	n.s.
Stages 3 and 4 (%)	16.5	11.5	14.6	10.3	n.s.
Stage REM (%)	20.4	5.9	18.5	6.6	n.s.
Arousal index	16.2	8.6	24.8	10.6	<001
OSAH measures					
Median AHI	0.7	–	22.4	–	0.001
LogAHI4 %	−0.6	1.1	3.1	0.4	0.001
O_2SAT<85% (% of TST)	0.0002	0.002	1.5	2.8	0.001

Table 3
Actual and Z-scores for individual neuropsychological tests

	Actual scores		Z-scores	
	CTL (SD)	OSAH (SD)	CTL (SD)	OSAH (SD)
Picture completion[a]	11.8 (2.7)	12.0 (2.4)	−0.042 (1.04)	0.012 (0.929)
Letter numbering[a]	11.8 (3.0)	11.5 (2.4)	0.058 (1.10)	−0.073 (0.890)
Digit span[a]	11.3 (2.7)	10.8 (2.8)	0.010 (1.02)	−0.032 (0.976)
Digit symbol coding[a]	11.0 (3.0)	10.9 (2.8)	0.097 (0.977)	−0.092 (1.02)
Symbol search[a]	11.3 (2.4)	11.2 (2.4)	0.006 (0.997)	−0.018 (1.01)
Stroop interference T[b]	48.2 (15.5)	49.5 (8.6)	−0.021 (1.17)	0.079 (0.646)
Trail making B[c]	73.8 (26.8)	77.9 (37.4)	−0.043 (0.820)	0.083 (1.14)
Pegboard dominant[c]	80.9 (17.0)	81.0 (13.7)	−0.022 (1.07)	−0.017 (.865)
Pegboard non-dominant[c]	86.0 (17.7)	92.0 (19.5)	−0.164 (0.936)	0.155 (1.03)

[a] Reported as scale scores with a mean = 10 and SD = 3.
[b] Reported as a scale score with a mean = 50 and SD = 10.
[c] Scores reported in seconds.

Our finding that persons with OSAH had evidence of greater daytime sleepiness on the ESS is not surprising, and is consistent with previous studies [34–36], including analyses performed in another subset of the SHHS cohort [25]. Nevertheless, despite a large disparity in AHI4% between the CTL and OSAH groups, the difference in mean ESS was not large. This observation reinforces the concept that the presence of OSAH is not necessarily synonymous with subjective sleepiness, especially in a non-clinical population [37,38].

We observed that OSAH had little negative impact on the measures of neuropsychological function employed in this study. In contrast, studies in untreated populations of individuals referred for evaluation of OSAH have demonstrated an adverse effect on a variety of neuropsychological domains including attention, working memory and executive function using assessment measures such as the Paced Auditory Serial Addition Task, Trails B, Digit Span and Purdue Pegboard (reviewed in [10,18]). In addition, CPAP treatment of OSAH has been shown to improve neuropsychological function (reviewed in [10]), although some studies indicate that there may be persistent deficits [13,14,16,39,40]. However, in non-clinical populations, the impact of OSAH on neuropsychological function is not as clear, with studies showing inconsistent results [11,20,41–45]. Some of these studies did not directly assess OSAH, using snoring as a surrogate [11,42]. Others investigated only elderly individuals who may have had other medical problems adversely impacting neuropsychological function [43–45]. There were also significant differences in the neuropsychologic assessment measures used across studies. Nevertheless, even in the studies using a younger age range of individuals and in whom there were physiologic assessments of the degree of OSAH, the effect of OSAH on neuropsychological function has not been uniform [20,41,46,47]. In the middle-aged participants of the Wisconsin Sleep Cohort, Kim et al. found that scores on a psychomotor efficiency factor, which included some tests used in the current study, were inversely correlated with more severe OSAH [20]. Similarly, Adams et al. found that OSAH was linearly related to three composite factors in a middle-aged cohort without other co-morbid medical problems: 'declarative memory', 'signal discrimination', and 'working memory' [46]. In contrast, Boland and co-workers in the Atherosclerosis Risk in Communities cohort (mean age: 62.3 years, range: 52–75 years) of the SHHS did not find any relationship between OSAH and verbal learning and fluency, and only a very weak association with a test of psychomotor ability [41]. Furthermore, in the Finnish Twin Cohort, Telakivi et al. found little evidence of worse neuropsychological function in snorers with evidence of periodic breathing [47]. As a whole, these studies suggest that the impact of mild to moderate OSAH on neuropsychological function is modest. Thus, although there are differences in the variety of neuropsychological tests administered, our results are similar to these studies performed in non-clinical populations in whom there was both documentation of the severity of OSAH and testing of neuropsychological

Table 4
Z-scores for composite neuropsychological variables index saturation

	Apnea–hypopnea index		Percent time < 85% saturation	
	CTL	OSAH	Lower three quartiles	Upper quartile
Attention	0.01 ± 0.85	−0.01 ± 0.68	−0.02 ± 0.58	−0.02 ± 0.58
Executive function	0.03 ± 0.73	−0.03 ± 0.68	−0.04 ± 0.71	0.11 ± 0.72
Processing speed	0.07 ± 0.88	−0.08 ± 0.93	0.08 ± 0.90	−0.21 ± 0.88
Motor Speed	0.01 ± 0.85	0.10 ± 0.89	−0.14 ± 0.93	*0.42 ± 0.80

*$P = 0.002$ vs. lower three quartiles.

Table 5
Selected regression models for composite

Neuropsychological outcomes	β	SE	P
Motor speed			
Effect of LogAHI4%			
$N=139$, adjusted $R^2=0.211$, $P<0.001$			
Age	0.045	0.008	<0.001
Education	−0.032	0.027	n.s.
Gender	0.298	0.245	0.043
LogAHI4%	−0.002	−0.003	n.s.
Effect of O_2Sat85			
$N=138$, adjusted $R^2=0.242$, $P<0.001$			
Unadjusted $R^2=0.264$, full model			
Unadjusted $R^2=0.234$; age, education, gender only			
Age	0.045	0.008	<0.001
Education	−0.032	0.026	n.s.
Gender	0.279	0.143	0.053
O_2Sat85	0.077	0.033	0.022
Processing speed			
Effect of LogAHI4%			
$N=139$, adjusted $R^2=0.094$, $P=0.002$			
Age	0.026	0.008	0.002
Education	0.058	0.028	0.04
Gender	−0.371	0.150	0.014
LogAHI4%	−0.038	0.037	n.s.
Effect of O_2Sat85			
$N=138$, adjusted $R^2=0.122$, $P<0.001$			
Unadjusted $R^2=0.148$, full model			
Unadjusted $R^2=0.113$, age, education, gender only			
Age	0.024	0.008	0.002
Education	0.058	0.027	n.s.
Gender	−0.360	0.148	0.016
O_2Sat85	−0.081	0.034	0.020
Attention			
Effect of O_2Sat85			
$N=138$, $R^2=0.114$, $P=0.032$			
Age	0.004	0.007	n.s.
Education	0.078	0.024	0.002
Gender	−0.056	0.130	n.s.
O_2Sat85	−0.021	0.030	n.s.
Effect of LogAHI4%			
$N=139$, $R^2=0.046$, $P=0.036$			
Age	0.005	0.007	n.s.
Education	0.077	0.024	0.002
Gender	−0.062	0.130	n.s.
LogAHI4%	−0.007	0.032	n.s.
Executive function[a]			
Effect of LogAHI4%			
$N=130$, adjusted $R^2=0.047$, $P=0.034$			
Age	0.023	0.006	<0.001
Education	−0.014	0.022	n.s.
Gender	0.164	0.119	n.s.
LogAHI4%	−0.051	0.029	n.s.
Effect of O_2Sat85			
$N=129$, adjusted $R^2=0.086$, $P=0.004$			
Age	0.022	0.006	<0.001
Education	−0.015	0.022	n.s.
Gender	0.154	0.120	n.s.
O_2Sat85	−0.038	0.030	n.s.

[a] The variable Execfunct was constructed by combining scores on the Stroop Interference T (Stroop) and the Trail Making B (Trails B) tests. However, unlike component variables for the other scales, which correlated positively with one another (+0.22 to +0.71), the components of the Execfunct scale were uncorrelated ($r=0.001$). Individually, performance on the Stroop and the Trails B was predicted by O_2SAT85, but in opposite directions. LogRDI4% was associated with better performance on the Stroop, but did not predict scores on the Trails B.

function. Furthermore, they provide additional data extending these findings to a cohort with a broader age range.

Although, we observed little impact of OSAH by itself on selected measures of neuropsychological function, hypoxemia was associated with decrements in motor and processing speed performance. In clinical populations, OSAH patients with hypoxemia have been found to be more cognitively impaired than persons without hypoxemia [12,48]. Some studies performed in non-clinical samples have also found a relationship between severity of hypoxemia and neuropsychological function [46,47]. There are some differences, however. Adams et al. found that hypoxemia was associated with worse performance on a wider spectrum of neuropsychological functioning than our data [46]. In contrast, Telakivi et al. noted only an impairment in verbal memory, an area we did not examine [47]. Nevertheless, our observations are consistent with a more limited impact of hypoxemia on neuropsychological function. The reason for these discrepancies is not clear, but differences in the age range of participants, the severity of hypoxemia and the types of tests administered are possible explanations (e.g. no visuospatial or memory tests were used) [21].

The underlying mechanism responsible for neuropsychological deficits associated with OSAH is still undecided. Nocturnal hypoxemia is a commonly proposed causative factor (reviewed in [49]), and our data would support this theory at least in those persons with mild to moderate OSAH. Intermittent hypoxia in experimental paradigms has been shown to result in worse neurobehavioral function in rodents and correlates with evidence of cellular dysfunction and apoptosis in the hippocampus [50]. Alternatively, sleep fragmentation with resultant sleepiness and diminished vigilance may be responsible (reviewed in [49]). Although, we observed a slight increase in stage 1 sleep and a higher arousal index among persons with OSAH, these factors were not correlated with neuropsychological performance. A number of studies have implicated sleepiness as an important factor affecting neuropsychological function [46,47,51]. However, our data do not completely support this hypothesis. Although, the ESS did predict processing speed, our results with respect to both motor and processing speed persisted after controlling for the ESS. Perhaps, the most parsimonious explanation is that both hypoxemia and the consequences of sleep fragmentation are responsible for the adverse effects of OSAH on neuropsychological function [49], and the relative impact will depend on the severity of OSAH, degree of hypoxemia and the affected individual.

In our regression models, we controlled for the effects of age, education and gender. In most models, these variables were not significant predictors of our composite outcome variables. However, as might be expected, increasing age was associated with worse performance in Motorspeed and Execfunct, and higher educational achievement predicted better scores on Execfunct. Nevertheless, why increasing age would result in better Procspeed performance and why there are gender differences in Procspeed and Motorspeed is unexplained.

We acknowledge that our study has some limitations. First, the neuropsychological testing was done some months after the PSG was performed. Thus, it is possible that the severity of OSAH was greater at the time of the neuropsychological testing, leading to some misclassification. Although, OSAH severity can increase in some individuals over time, this is not a universal finding (discussed in [52]). Furthermore, in the absence of weight change, worsening of OSAH over several years is slight [53]. Because assignment to the control group was limited to those with a AHI4% <5 and to the OSAH group to those with a AHI4% >10, we believe that there was a minimal misclassification. Moreover, we found LogAHI4%, a continuous variable, was not predictive of neuropsychological performance. Second, although this cohort was recruited from several large non-clinical cohorts, there is some inherent survivor bias in the sample used in this analysis as well as in the component cohorts of SHHS [22]. This may be particularly true in the Tucson participants where individuals are the survivors of a 25-year longitudinal cohort study. They are perhaps healthier than their counterparts in the general population, and they have a history of 'volunteering' for participation in this study. It is also possible that individuals with better neuropsychological functioning were more likely to agree to participate, thus biasing the results towards the null hypothesis. Therefore, we acknowledge that our results may not be representative of those that might be found in a general population sample. Third, it is difficult to compare our results to others given that there are differences in types of neuropsychological tests administered and because we aggregated test results into four domains. However, except for Execfunct, individual test components correlated with each other suggesting that our approach was reasonable. Fourth, in comparison to the overall SHHS cohort, the sample size selected for testing is small and thus limits statistical power. Irrespective of this latter limitation, we nonetheless were able to detect a significant effect related to hypoxemia.

Despite these limitations, however, our study has several strengths. First, in contrast to a number of studies that have used snoring as a surrogate for OSAH and/or have used symptoms as an indicator of neuropsychological function, it is one of the few studies in a non-clinical sample in which OSAH has been directly measured and neuropsychological testing has been utilized. Second, as a non-clinical sample, participants were not being treated or evaluated for OSAH, and, thus, our results may be more reflective of the neuropsychological consequences of clinically unrecognized OSAH. Third, our participants were middle-aged to elderly persons and thus are representative of the age range with the highest prevalence of OSAH.

5. Conclusions

We found that mild to moderate OSAH had minimal impact on selected measures of attention, executive function, motor speed and processing speed. However, hypoxemia modestly affected both motor and processing speed. These results suggest the neuropsychological effects of clinically unrecognized mild to moderate OSAH in middle-aged to elderly adults are neither uniform nor large, and are primarily related to hypoxemia.

Acknowledgements

This work was supported by National Heart, Lung and Blood Institute cooperative agreements U01HL53940 (University of Washington), U01HL53941 (Boston University), U01HL53938 (University of Arizona), U01HL53916 (University of California, Davis), U01HL53934 (University of Minnesota), U01HL53931 (New York University), U01HL53937 and U01HL64360 (Johns Hopkins University), U01HL63463 (Case Western Reserve University), and U01HL63429 (Missouri Breaks Research). In addition, statistical support for this analysis was provided by the University of Arizona General Clinical Research Center.

Sleep Heart Health Study (SHHS) acknowledges the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), the Cornell/Mt. Sinai Worksite and Hypertension Studies, the Strong Heart Study (SHS), the Tucson Epidemiologic Study of Airways Obstructive Diseases (TES) and the Tucson Health and Environment Study (H&E) for allowing their cohort members to be part of the SHHS and for permitting data acquired by them to be used in the study. SHHS is particularly grateful to the members of these cohorts who agreed to participate in SHHS as well. SHHS further recognizes all of the investigators and staff who have contributed to its success. A list of SHHS investigators, staff and their participating institutions is available on the SHHS website (www.jhucct.com/shhs).

References

[1] Baumel MJ, Maislin G, Pack AI. Population and occupational screening for obstructive sleep apnea: are we there yet? Am J Respir Crit Care Med 1997;155:9–14.

[2] Kapur V, Blough DK, Sandblom RE. The medical cost of undiagnosed sleep apnea. Sleep 1999;22:749–55.

[3] Kryger MH, Roos L, Delaive K, et al. Utilization of health care services in patients with severe obstructive sleep apnea. Sleep 1996; 19:S11–S16.

[4] Aikens JE, Caruana-Montaldo B, Vanable PA, et al. MMPI correlates of sleep and respiratory disturbance in obstructive sleep apnea. Sleep 1999;22:362–9.

[5] Bliwise DL, Yesavage JA, Sink J, et al. Depressive symptoms and impaired respiration in sleep. J Consult Clin Psychol 1986;54:734–5.

[6] Kales A, Caldwell AB, Cadieux RJ. Severe obstructive sleep apnea-II: associated psychopathology and psychosocial consequences. J Chron Dis 1985;38:427–84.

[7] Pillar G, Lavie P. Psychiatric symptoms in sleep apnea syndrome: effects of gender and respiratory disturbance index. Chest 1998;114: 697–703.

[8] Baldwin CM, Griffith KA, Nieto FJ, et al. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. Sleep 2001;24:96–105.

[9] Finn L, Young T, Palta M, Fryback DG. Sleep-disordered breathing and self-reported general health status in the Wisconsin sleep cohort study. Sleep 1998;21:701–6.

[10] Engleman HM, Kingshott RN, Martin SE, Douglas NJ. Cognitive function in the sleep apnea/hypopnea syndrome (SAHS). Sleep 2000; 23:S102–S8.

[11] 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: 1287–94.

[12] Greenberg GD, Watson RK, Deptula D. Neuropsychological dysfunction in sleep apnea. Sleep 1987;10:254–62.

[13] Kotterba S, Rasche K, Widdig W, et al. Neuropsychological investigations and event-related potentials in obstructive sleep apnea syndrome before and during CPAP-therapy. J Neurol Sci 1998;159:45–50.

[14] Montplaisir J, Bedard MA, Richer F, Rouleau I. Neurobehavioral manifestations in obstructive sleep apnea syndrome before and after treatment with continuous positive airway pressure. Sleep 1992;15: S17–S19.

[15] Naegele B, Thouvard V, Pepin JL. Deficits of cognitive executive functions in patients with sleep apnea syndrome. Sleep 1995;18: 43–52.

[16] Naegele B, Pepin JL, Levy P, et al. Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSA) after CPAP treatment. Sleep 1998;21:392–7.

[17] Valencia-Flores M, Bliwise DL, Guilleminault C, et al. 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.

[18] 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.

[19] Redline S, Strauss ME, Adams N. Neuropsychological function in mild sleep-disordered breathing. Sleep 1997;20:160–7.

[20] Kim HC, Young T, Matthews CG, et al. Sleep-disordered breathing and neuropsychological deficits: a population-based study. Am J Respir Crit Care Med 1997;156:1813–9.

[21] Weaver TE. Outcome measurement in sleep medicine practice and research. Part 2: assessment of neurobehavioral performance and mood. Sleep Med Rev 2001;5:223–36.

[22] Quan SF, Howard BV, Iber C, et al. The Sleep Heart Health Study: design, rationale, and methods. Sleep 1997;20:1077–85.

[23] Redline S, Sanders MH, Lind BK, et al. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep 1998;21:759–67.

[24] Lind BK, Goodwin JL, Hill JG, et al. Recruitment of healthy adults into a study of overnight sleep monitoring in the home: experience of the sleep heart health study. Sleep Breath 2003;7:13–24.

[25] Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 1992;15:376–81.

[26] Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Washington, DC: US Government Printing Office; 1968.

[27] American Sleep Disorders Association Taskforce. EEG arousals; scoring rules and examples: a preliminary report from the atlas task force of the American Sleep Disorders Association. Sleep 1992;15: 173–84.

[28] Wechsler D. Wechsler adult intelligence scale-third edition (WAIS-III). San Antonio: The Psychological Corporation; 1997.
[29] Golden C. Stroop color and word test: a manual for clinical and experimental uses. Wood Dale, IL: Stoelting Company; 1978.
[30] Reitan R, Wolfson D. The Halstead-Reitan neuropsychological test battery. Tucson, AZ: Neuropsychology Press; 1985.
[31] Lafayette I. Instruction/owner's manual for the grooved pegboard test. Lafayette, IN; 1989.
[32] Lezak MD. Neuropsychological assessment. 3rd ed. London: Oxford University Press; 1995.
[33] Spreen ES. A compendium of neuropsychological tests. New York: Oxford University Press; 1998.
[34] Gottlieb DJ, Whitney CW, Bonekat WH, et al. Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. Am J Respir Crit Care Med 1999;159:502–7.
[35] Goncalves MA, Paiva T, Ramos E, Guilleminault C. Obstructive sleep apnea syndrome, sleepiness, and quality of life. Chest 2004;125:2091–6.
[36] Chung KF. Use of the Epworth Sleepiness Scale in Chinese patients with obstructive sleep apnea and normal hospital employees. J Psychosom Res 2000;49:367–72.
[37] Chervin RD, Aldrich MS. The Epworth Sleepiness Scale may not reflect objective measures of sleepiness or sleep apnea. Neurology 1999;52:125–31.
[38] Benbadis SR, Mascha E, Perry MC, et al. Association between the Epworth sleepiness scale and the multiple sleep latency test in a clinical population. Ann Intern Med 1999;130:289–92.
[39] Bedard MA, Montplaisir J, Malo J, et al. Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). J Clin Exp Neuropsychol 1993;15:330–41.
[40] Barnes M, McEvoy RD, Banks S, et al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med 2004;170:656–64.
[41] Boland LL, Shahar E, Iber C, et al. Measures of cognitive function in persons with varying degrees of sleep-disordered breathing: the Sleep Heart Health Study. J Sleep Res 2002;11:265–72.
[42] Jennum P, Hein HO, Suadicani P, Gyntelberg F. Cognitive function and snoring. Sleep 1993;16:S62–S4.
[43] Hayward L, Mant A, Eyland A, et al. Sleep disordered breathing and cognitive function in a retirement village population. Age Ageing 1992;21:121–8.
[44] Berry DT, Phillips BA, Cook YR, et al. Sleep-disordered breathing in healthy aged persons: possible daytime sequelae. J Gerontol 1987;42:620–6.
[45] Foley DJ, Monjan AA, Masaki KH, et al. Associations of symptoms of sleep apnea with cardiovascular disease, cognitive impairment, and mortality among older Japanese–American men. J Am Geriatr Soc 1999;47:524–8.
[46] Adams N, Strauss M, Schluchter M, Redline S. Relation of measures of sleep-disordered breathing to neuropsychological functioning. Am J Respir Crit Care Med 2001;163:1626–31.
[47] Telakivi T, Kajaste S, Partinen M, et al. Cognitive function in middle-aged snorers and controls: role of excessive daytime somnolence and sleep-related hypoxic events. Sleep 1988;11:454–62.
[48] Findley LJ, Barth JT, Powers DC, et al. Cognitive impairment in patients with obstructive sleep apnea and associated hypoxemia. Chest 1986;90:686–90.
[49] Engleman HM, Douglas NJ. Sleep. 4: sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. Thorax 2004;59:618–22.
[50] Row BW, Liu R, Xu W, et al. Intermittent hypoxia is associated with oxidative stress and spatial learning deficits in the rat. Am J Respir Crit Care Med 2003;167:1548–53.
[51] Roehrs T, Merrion M, Pedrosi B, et al. Neuropsychological function in obstructive sleep apnea syndrome (OSAS) compared to chronic obstructive pulmonary disease (COPD). Sleep 1995;18:382–8.
[52] Quan SF. Evolution of OSA. Thorax 1998;53:532.
[53] Peppard PE, Young T, Palta M, et al. Longitudinal study of moderate weight change and sleep-disordered breathing. J Am Med Assoc 2000;284:3015–21.