Cognitive Function and Sleep Related Breathing Disorders in a Healthy Elderly Population: the Synapse Study

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Study Objectives: Sleep related breathing disorders (SRBD) are risk factors for cognitive dysfunction in middle-aged subjects, but this association has not been observed in the elderly. We assess the impact of SRBD on cognitive performance in a large cohort of healthy elderly subjects.
Design: Cross-sectional study examining the association between subjective memory test, neuropsychological battery testing and SRBD in the elderly.
Setting: Community-based sample in home and research clinical settings.
Participants: 827 subjects, 58.5% women, aged 68 y at study entry, participated in the study. All were free of previously diagnosed SRBD, coronary heart disease, and neurological disorders, including stroke and dementia. Clinical interview, neurological assessment, polygraphy, and extensive cognitive testing were conducted for all participants.
Intervention: N/A
Measurement and Results: SRBD (apnea-hypopnea index [AHI] > 15 events/h) was diagnosed in 445 (53%) subjects, 167 (37%) of them with AHI > 30. Minimal daytime sleepiness was found in the group; 9.2% of the population had an Epworth Sleepiness Scale score > 10. No significant association was found between AHI, nocturnal hypoxemia, and cognitive scores. Comparison of mild *vs* severe cases showed a trend toward lower cognitive scores with AHI > 30, affecting delayed recall and Stroop test.
Conclusions: The impact of undiagnosed SRBD on cognitive function appeared quite limited in a generally older healthy population, and only slightly affected severe cases. The implication of undiagnosed SRBD on the cognitive impairment in elderly subjects remains hypothetical and needs to be prospectively studied.
Clinical Trial Information: Autonomic Nervous System Activity, Aging and Sleep Apnea/Hypopnea (SYNAPSE); Registration #NCT 00766584 (This study is ongoing, but not recruiting participants.); URL - http://clinicaltrials.gov/ct2/show/NCT00766584?term=NCT+00766584&rank=1
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RECENT META-ANALYSIS STUDIES[1,2] ON THE NEUROPSYCHOLOGICAL DYSFUNCTION ASSOCIATED WITH SLEEP RELATED BREATHING DISORDERS (SRBD) and obstructive sleep apnea syndrome (OSAS) indicate that attention and executive functions[3,4] are substantially affected, with sleep fragmentation, apnea recurrence, and nocturnal hypoxemia[5,6] being the most contributory factors. Since aging modifies cognitive abilities[7] and induces a greater incidence of SRBD[8] with associated vascular comorbidities,[9] an important issue is whether age increases susceptibility to cognitive dysfunction in SRBD patients.

A first epidemiological survey, i.e., the Sleep Heart Health Study (SHHS)[10] has not revealed any evidence of a dose-response relationship between the respiratory disturbance index and cognitive function score in a cohort of 837 men and 923 women over 60 years of age. Other studies examining the impact of SRBD elderly subjects referred for clinical evaluation have given conflicting results; some authors have reported a relationship between cognitive impairment and SRBD,[11,12] while others have not.[13,14] Differences in results may be explained by the differences in cognitive testing, the limited number of patients examined and the worsening in sleep quality in the oldest patients recorded in the laboratory. Despite these factors, it is not known if cognitive alterations related to SRBD in older populations are a specific entity[15] or whether the presence of SRBD exaggerates the physiological changes in the upper airways[16] and cognitive abilities[17] associated with increasing age. Yet, accurate identification of a pathological degree of SRBD and neuropsychological impairments in the elderly is crucial for the clinical identification of patients who really need treatment.

In the present cross-sectional study, complete cognitive function measures were obtained from 827 community-dwelling healthy subjects free of clinically diagnosed SRBD and dementia. The homogeneity of age at the inclusion time, the large sample, and the extended cognitive assessment were chosen to identify whether a cognitive decline in elderly SRBD subjects occurs and if this decline is related to SRBD severity.

A commentary on this paper appears in this issue on page 423.

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METHODS

Sample

Subjects for the study were selected from the participants of the PROgnostic indicator OF cardiovascular and cerebrovascular events study (PROOF study), an ongoing study on the prognostic value of autonomic nervous system activity indicators on brain and on cardiac morbidity and mortality. Details of the PROOF study have been described previously.[18] Briefly, subjects were recruited amongst the inhabitants of the city of Saint-Etienne, France, from 2001 to 2003 and were eligible if aged 65 y at the inclusion date. Among 3983 eligible participants, 11% declined participation, 67% did not reply and 1.2% were ineligible. The sample was completed by 48 participant's spouses and 132 voluntary subjects. The final study population includes 1011 subjects, a sample size allowing detection of any increased incidence of fatal and non-fatal cardiac events due to reduced heart rate variability, with a statistical power of 80% and a statistical significance of 5%. Cardiological assessment including 12-leads ECG, ECG Holter, echocardiography and ambulatory blood pressure monitoring was done in all participants to exclude myocardial infarction and heart failure. Clinical interview, neurological examination, and magnetic resonance imaging allowed exclusion of stroke and other neurological disorders in the study sample. An ancillary study addressing the association between SRBD, assessed by at-home polygraphic study, and cardiovascular and cerebrovascular morbidity during 7-y follow-up was proposed to participants (SYNAPSE study). Of the original sample of 1011, a total of 851 subjects (58.5% women) participated in the SYNAPSE study between March 2003 and June 2005. Failure of polygraphic recording and refusal to perform a second sleep study led to the exclusion of 24 subjects. The final sample included 827 participants (484 women [58.5%] and 343 men [41.5%]; 68 ± 1.8 y). When compared to those who refused polygraphy, the final sample did not differ in any variables, including educational level, gender, daytime sleepiness, and incidence of prior disease.

The PROOF and SYNAPSE studies were approved by the local Ethics Committee (CCPRB Rhone-Alpes Loire) and all subjects gave written consent to study participation.

Cognitive Self-Assessment

Cognitive self-assessment was explored with the short form of the French version of the Mac Nair scale.[19] This self-rating scale has been designed to explore cognitive difficulties in everyday life, and consists of 26 questions that essentially assess memory and attention difficulties in daily life activities over a period of three weeks. Each item was scored on a 5-point scale according to its frequency (from "never" (0 point) to "very often" (4 points). Total score varies from 0 to 104 points.

Cognitive Measures

An extensive neuropsychological battery assessing principally memory and executive functions was administered to all subjects within one month after overnight polygraphy. The tests were administered in the same order to all subjects by the same examiner, as listed below:

- **The Mini-Mental-State Examination (MMSE)**[20] to evaluate global cognitive functioning. This test of 30 items measures different cognitive components including orientation, attention, immediate and short-term recall, language, and the ability to follow commands, with possible scores ranging from 0 to 30.
- **The French Version of the Free and Cued Selective Reminding Test (FCSR)**[21] was used to explore episodic memory. This test allows to control the encoding phase by including semantic processing and combines free and cued recall trials. The test comprises 3 successive free and cued recall trials of a 16-word list, followed by a recognition task of the target words presented among distractor elements. A delayed recall of the list is then asked 20 minutes later. Four measures were used in the following analyses: total immediate recall, recognition score, total delayed recall and free delayed recall.
- **Visual Memory** was assessed with the Benton visual memory test (form C).[22] This test consists of 15 stimulus cards and 15 multiple choice cards. The subjects are presented with the card for 10 s, and are then asked to choose the initial figure among four options. Possible scores range from 0 to 15.
- **The Digit Span Test (DST)**[23] explores attention and part of executive functions. Subjects must assign the correct symbol to digits ranging from 1 to 9 according to a code table displaying digits and symbols. The time is limited to 90 s. Possible scores range from 0 to 93. In digit spans exploring working memory, the experimenter recites a set of digits (at the rate of one digit per second) that the participant has to repeat in the correct order (forward span) and the reverse order (backward span). The first set of digits consists of 2 digits and the set size increases by one digit every 2 trials. The test stops when the subject presents 2 consecutive errors at any given set size or when 2 successful trials at set size 8 are reached. Success at each set size is determined by successful completion of 1 out of the 2 trials administered.
- **The Memory Span and Tracking Baddeley Dual Task**[24] presented participants with a chain of 80 ± 0.5 cm^2 boxes laid out on an A4 page to form an irregular chain. Participants were asked to place a cross in each box as rapidly as possible during 2 minutes. The second single task component was a digit span task in which participants were required to memorize strings of digits of increasing length. After establishing the participants' digit span forward through presenting digit strings of increasing length, sequences of digits at the determined length were presented and tested continuously for 2 min. In the dual task component, participants crossed boxes while simultaneously recalling sequences of digits at their span, for a 2-min period. A measure of overall dual task decrement (mu%) was obtained by calculating dual task performance as a percentage of single task performance.
- **The Trail Making Test A and B**[25] assesses attention and speed of exploration (version A), but also shifting capacity in part B; the first part consists of connecting randomly located letters in alphabetical order as fast as possible. In the second part, the task connects alternately numbers and letters in their respective sequences.
- **The Stroop Test**[26] was designed to investigate the inhibition processes. This test consists of three cards printed in color. The Color subtask consists of color dots; the Word subtask consists of color names written in black; in the color-word subtask assessing inhibition abilities, the subject is presented

with a card displaying color names printed in contrasting inks. The subject has to ignore the meaning of the word and to name the ink color as quickly as possible.

- In the Alphabetic Fluency Tasks,[27] participants were instructed to generate verbally as many words as possible that began with the letter P in a 2-min period. Proper nouns were scored as incorrect. Similarly, for the Category Fluency Test, participants were instructed to generate animal examples within a 2-min time period. The score variables were total number of correct P and animal exemplars.
- Finally, the Wechsler Adult Intelligence Scale (WAIS) Similarities Test[28] was administered to explore abstractive reasoning ability and semantic knowledge. In this test subjects were asked to explain in what way 2 things are similar (e.g., "dog-lion"). Nineteen pairs of words were presented to the subject. A score of 2 points was given for an abstract generalization, and one point if a response was a specific concrete likeness (except for the 5 first items, in which the maximal score is 1 point). Possible scores range from 0 to 33.

Depression and Anxiety

Depressive symptomatology was measured using the Pichot (QD2A) questionnaire[29] of 13 questions. QD2A scores ranged from 0 to 13 points, and subjects with a score > 7 were considered as having depressive symptoms. Anxiety was assessed using the French version of the Goldberg scale,[30] a 9-item scale with scores ranging from 0 to 9. Individuals with a score > 4 were considered as anxious.

Daytime Sleepiness

The impact of sleepiness during the day was evaluated using the Epworth Sleepiness Scale (ESS), a 4-grade scale (0, non napping; 3, high chance for napping) in that a maximum of 24 points could be achieved. The presence of an excessive daytime sleepiness was retained for a score > 10.

Sleep Study

Nocturnal unattended home-sleep study was performed in all subjects using a polygraphic system (HypnoPTT, Tyco Healthcare, Puritan Bennett), which included the following parameters: sound measurement, electrocardiogram, pulse transit time, R-R timing, airflow by nasal pressure, thoracoabdominal respiratory efforts by one inductance plethysmography, and body position. Oxygen saturation (SpO_2) was measured by pulse oximetry. A software package was used for downloading and analysis of tracings. A recording was considered acceptable if ≥ 5 h of recording without missing data on respiratory signals or SpO_2 was obtained. A second night of monitoring was performed when subjective sleep latency exceeded 2 hours on the first night, sleep duration was < 5 h or when the respiratory recording was considered as not acceptable. Hypopnea was defined as ≥ 50% reduction in airflow from baseline value lasting ≥ 10 s and associated with ≥ 3% oxygen desaturation. Apneas were defined as the absence of airflow on the nasal cannula lasting > 10 s. The absence of rib cage movements associated with an apnea defined the event as central, while progressive increase in pulse transit time and respiratory efforts allowed definition of the event as obstructive. The apnea + hypopnea index (AHI) was established as the ratio of the number of apneas and hypopneas per hour of recording. Indices of nocturnal hypoxemia were the following: mean SpO_2; % of recording time below 90%; minimal SpO_2 value recorded during sleep and the oxygen desaturation index (ODI) i.e., the number of episodes of oxygen desaturation per hour of recording time during which blood oxygen fell by ≥ 3%. Pulse transit time was continuously monitored, and an autonomic respiratory-related and total arousal index (AAI) was calculated according to previously defined criteria.[31] To minimize potential overestimation of sleep duration, subjects completed a sleep diary to exclude from the analysis wakefulness before lights-off and to establish subjective total sleep time. An AHI > 15 was considered diagnostic of SRBD.[32] Cases were stratified as mild (AHI between 15 and 30) and moderate to severe (AHI > 30).

Statistical Analyses

The subjects' characteristics were summarized as means ± SD for continuous variables, and counts and percentages for categorical variables. Comparisons were performed using the χ^2 test for categorical variables and Student *t*-test for normally distributed variables. One-way analysis of variance was used to consider the variation in cognitive scores among groups separately defined by SRBD severity using AHI. Pearson correlation coefficients were calculated for continuous sleep data, anthropometric parameters, and cognitive function scores.

Multiple linear regression analysis was used to evaluate further differences in mean cognitive function scores by severity of AHI and ODI. All regression models were adjusted for confounding variables such as gender, BMI, diabetic status, hypertension, education level, anxiety and depression scores, ESS, blood pressure, and self-reported sleep time at the moment of polygraphy.

All statistical analyses were conducted using the SPSS statistical software package (SPSS for Windows, version 12.0, SPSS, Chicago, IL). After Bonferroni correction for multiple comparison, 2-tailed P values < 0.05 were considered to indicate statistical significance.

RESULTS

The general characteristics of the subjects' group according to presence of SRBD and to AHI severity are presented in Table 1. The sample included a higher proportion of women (58.5%) compared to men (41.5%), with a mean age of 68 ± 1.8 y, and a mean educational level of 11.0 ± 2.9 y. The average AHI was 20.4 ± 12.6 and the mean ODI 9.4 ± 9.5, which is a modest level of hypoxemia severity. Overall, incidence of sleepiness was low, 75 subjects (9.2%), 40 men and 35 women, reporting an ESS > 10, i.e., pathological sleepiness. An AHI > 15 was found in 53.8% of subjects: 33.6% of these subjects had an AHI between 15 and 30, and 20.2% had an AHI > 30. Subjects with SRBD had greater BMI and neck circumference, both significantly different in subjects with an AHI > 30. Comparison between groups according to AHI stratification revealed that subjects with AHI > 30 had greater BMI and neck circumference and higher ESS score.

Table 2 shows the cognitive scores in the total group and in subjects with an AHI > 15 (SRBD+) and with an AHI < 15 (SRBD−). Comparison of subjects with and without SRBD did not show any statistically significant differences between groups in all measures of attention, memory, and executive function,

Table 1—Clinical, anthropometric, and polygraphic data for the entire group of subjects and for the sample with (AHI > 15) and without (AHI < 15) SRBD according to gender (mean ± SD)

	Total			Without SRBD		With SRBD	
Clinical data	**Total (n = 827)**	**AHI < 15 (n = 382)**	**AHI > 15 (n = 445)**	**Men (n = 118)**	**Women (n = 264)**	**Men (n = 225)**	**Women (n = 220)**
Education, y	11.0 ± 2.9	11.1 ± 2.8	11.0 ± 2.9	11.5 ± 3.3	11.3 ± 2.5	11.3 ± 3.2	10.9 ± 2.7
BMI, kg/m^2	25.5 ± 3.8	24.6 ± 3.5	26.2 ± 3.9*	24.9 ± 2.8	24.5 ± 3.7	26.4 ± 3.0	26.1 ± 4.6
Neck cirumference, cm	37.1 ± 4.0	35.7 ± 3.6	38.2 ± 3.9*	39.6 ± 3.0	34.1 ± 2.3*	40.8 ± 2.7	35.4 ± 3.0***
Depression score	2.59 ± 2.7	2.57 ± 2.8	2.60 ± 2.6	1.75 ± 1.8	2.92 ± 3.1***	1.92 ± 2.0	3.30 ± 3.0***
Anxiety score	3.4 ± 2.8	3.47 ± 2.9	3.29 ± 2.8	2.56 ± 2.5	3.87 ± 3.0**	2.48 ± 2.5	4.13 ± 2.9**
ESS score	5.7 ± 3.6	5.1 ± 34	6.2 ± 3.7	5.6 ± 3.45	4.8 ± 3.5	7.0 ± 3.7	5.5 ± 3.6**
Sleep study							
AHI n/h	20.4 ± 14.7	8.67 ± 4.1	30.4 ± 13.1***	9.29 ± 3.8	8.41 ± 4.2	32.9 ± 14.4	27.8 ± 11.0***
ODI n/h	9.4 ± 9.5	3.9 ± 3.4	14.0 ± 10.4***	4.3 ± 3.4	3.7 ± 3.4	15.8 ± 11.0	12.2 ± 9.5*
Mean SpO_2 %	95.4 ±1.6	95.5 ± 1.8	95.2 ± 1.4	95.2 ± 2.4	95.7 ± 1.5	95.1 ± 1.5	95.3 ± 1.4
Time SpO_2 % < 90% min	1.90 ± 5.7	1.2 ± 5.7	2.5 ± 7.7	0.67 ± 7.0	0.31 ± 5.1*	6.2 ± 6.8	5.1 ± 6.4
Nadir SpO_2 %	89.7 ± 4.1	91.2 ± 2.8	88.4 ± 4.6**	90.8 ± 3.2	91.5 ± 2.6	88.1 ± 4.8	88.7 ± 4.3

AHI, apnea plus hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; *P < 0.05; **P < 0.01; ***P < 0.001; *comparison between participants with (SRBD+) and without (SRBD−) sleep related breathing disorders. *t*-test or χ^2 test, as appropriate.

Table 2—Scores of cognitive function tests of participants (mean ± SD) in the total group of cases and in subjects with and without SRBD

	Total	AHI < 15	AHI > 15	P*
Subjective cognitive difficulties	27.9 ± 1.9	27.2 ± 1.9	28.6 ± 2.0	ns
MMSE (score)	28.6 ± 1.5	28.4 ± 1.7	28.6 ± 1.3	0.06
FCSR				
Total Immediate recall	15.3 ± 0.9	15.4 ± 0.9	15.3 ± 0.9	ns
Total Delayed recall	15.6 ± 1.0	15.6 ± 0.9	15.5 ± 1.1	0.04
Free Delayed recall	12.1 ± 2.4	12.2 ± 2.2	12.0 ± 2.5	0.01
Recognition score	15.8 ± 0.6	15.8 ± 0.6	15.8 ± 0.5	ns
Visual memory	12.5 ± 1.7	12.5 ± 1.6	12.4 ± 1.8	0.07
DST				
Digit span forward	5.5 ± 1.0	5.5 ± 1.0	5.5 ± 1.1	ns
Digit span backward	4.2 ± 1.0	4.2 ± 1.0	4.2 ± 1.0	ns
Baddeley dual task				
Dual task decrement	93.8 ± 10.7	93.5 ± 10.0	93.0 ± 11.2	ns
Trail Making				
Trail Making Test A (speed)	47.5 ± 15.8	48.2 ± 16.3	46.9 ± 15.4	ns
Trail Making Test A (errors)	0.11 ± 0.4	0.10 ± 0.4	0.11 ± 0.5	ns
Trail Making Test B (speed)	103.5 ± 48.8	103.1 ± 47.7	103.9 ± 49.8	ns
Trail Making Test B (errors)	0.45 ± 0.9	0.45 ± 1.0	0.44 ± 0.8	0.07
Semantic memory				
Verbal fluency Phonemic	19.3 ± 6.6	19.3 ± 6.5	19.3 ± 6.7	ns
Verbal fluency Semantic	29.9 ± 8.1	29.5 ± 7.8	30.3 ± 8.4	ns
Stroops				
Word (score)	97.7 ±14.1	98.1 ± 13.7	97.4 ± 14.4	0.09
Color (score)	70.2 ± 11.1	70.6 ± 10.7	69.7 ± 11.4	ns
Color word (score)	49.2 ± 8.1	49.3 ± 7.7	49.1 ± 8.4	0.07
WAIS Similarities test	16.9 ± 5.5	16.7 ± 5.4	17.1 ± 5.5	ns

FCSR, Free and cued selective reminding test; DSST, digit symbol substitution test. **t*-test comparison between participants with and without SRBD.

except delayed recall. A tendency to impaired Benton and Stroop tests in SRBD+ subjects was noted, without, however, statistically significant differences. Overall, after adjustment for BMI, gender, diabetic status, hypertension, education level, anxiety and depression scores, ESS, blood pressure, and self-reported sleep time, we found no strong relationship between objective cognitive scores, severity of SRBD, and ESS. The AHI was related to delayed recall ($r = -0.113$, $P = 0.001$) and color Stroop test score ($r = -0.097$, $P = 0.005$) without any significant relation with other cognitive scores. When we considered ODI, a marker of nocturnal hypoxemia, we found a relationship between ODI, immediate ($r = -0.088$, $P = 0.01$) and delayed recall ($r = -0.091$, $P = 0.001$), word ($r = -0.120$, $P = 0.001$) and color ($r = -0.083$, $P = 0.02$) Stroop test. No significant relationship was found between daytime sleepiness and objective cognitive scores, subjective cognition score ($r = 0.51$, $P < 0.001$) and MMSE ($r = 0.37$, $P = 0.005$) being the only variables associated to ESS.

To investigate whether the use of AHI as a marker of severity of SRBD predicts differences between groups, comparison analyses were conducted using three categories of AHI severity as predictors (0-14.9, 15-30, > 30) (Table 3). No significant differences were obtained among subgroups, except for immediate recall and the color Stroop test which was lower in subjects with an AHI > 30. Analyses were also conducted using cut-off points for the ODI (< 15 and > 15). The majority of comparisons between SpO_2 and cognitive impairment were not statistically significant except for the color Stroop test, on which subjects with ODI > 15 had lower scores ($P < 0.05$).

DISCUSSION

In the present study we aimed to examine the relationship between cognitive functions and SRBD in

a large, healthy, elderly population. In general, this cross-sectional study demonstrated lack of significant differences in the majority of cognitive functions in active elderly subjects having SRBD compared to those without respiratory sleep disorders. The most relevant aspects of our study are: (1) the majority of attention, memory and executive cognitive function tests showed no significant changes when comparing subjects with and without SRBD; (2) no significant or strong relationship was found between cognitive scores at the neuropsychological testing and AHI, ESS, and ODI, suggesting that with age other shared risk factors might explain the association between cognition and sleep disorders. Using extended objective cognitive testing in a large population, our results demonstrate that in the elderly, the altered cognitive functioning related to SRBD is quite different compared to that of middle-aged patients and, probably, affected by other factors outside respiratory sleep disorder.

Despite the prevalence of SRBD increasing with age,[33,34] there is a debate as to whether the significance of the disease in older adults is equal to that of SRBD in middle-aged adults.[9,14,35,36,37] Few large-scale studies have examined the association between SRBD, a disease highly prevalent in older populations, and cognitive dysfunction, and the results are contradictory. While some studies have reported little or no association of SRBD with sleepiness, hypertension, or diminished cognitive functioning,[38,39,40,41] others[9,10,42,43,44] have reported diminished vigilance capability and reduced MMSE and cognition score in older adults. These contradictory findings could be due to study differences, including sample size and sensitivity of tests.[45] A limitation of previous studies is that they have used the MMSE as a measurement tool. This tool is a global general measure of cognition and is not sufficiently sensitive or specific to detect any effect of SRBD on specific cognitive domains.[45] In addition, as demonstrated in our sample, a subjective overestimation of cognitive impairment may be described even when no objective decline is assessed. Moreover, the use of limited cognitive testing without evaluation of attentional process may introduce methodological bias in cognition assessment, attention affecting executive function.[3] The major strength of our study is that it includes a large and homogeneous number of elderly subjects with a wide range of SRBD, not referred to a sleep center, and free of underlying neurological or medical disorders that might impact on cognitive function. Moreover, the extensive cognitive assessment we chose may help to clarify the question as to whether SRBD alone contributes to an accelerated general decline in aging as revealed by MMSE, or whether the sleep disorder predisposes to specific alterations in memory and executive function. The first interesting finding of our study is that despite the use of an extensive battery testing, we failed to reveal any significant differences in attention, memory and executive function, the majority of cognitive scores being similar in elderly subjects with and without SRBD. Second, the presence of marginal differences in episodic delayed memory and Stroop test, more evident in severe cases, suggests that in older populations the presence of a pathological AHI may not have the same associated functional consequences seen in young and middle-aged adults.[15,35,37] Cognitive dysfunction in the elderly probably is a more complex and dynamic process influenced by several factors including greater individual susceptibility to sleep disruption.[46,47]

It is relatively unknown why elderly subjects with SRBD are less susceptible to the negative consequences of apneas and whether, in the elderly, SRBD is an entirely different disorder or merely a variant in severity of the disease. Phenotypic differences between middle-aged and older subjects in symptom profiles, comorbidities, and behavioral consequences suggest differences in underlying neurobiological mechanisms. Replicating the results obtained in a clinical setting,[13] we found that attention, memory and executive functions are preserved in our elderly subjects, with light disturbances found only in severe cases. Moreover, a lower incidence (9%) of sleepiness was reported by our subjects, probably as a consequence of limited sensitivity of ESS to detect vigilance impairment in the elderly.[42,48] Although speculative, our data support the "cognitive reserve" hypothesis.[49,50,51] According to this hypothesis, individual compensatory mechanisms, i.e., alternative brain pathways or functional plasticity,[7] may act as an adaptive compensatory mechanism for

Table 3—Scores of cognitive function tests (mean ± SD) of participants according to apnea-hypopnea index (AHI)

	AHI < 15 (n = 382)	AHI 15-30 (n = 278)	AHI > 30 (n = 167)	*P
Subjective cognitive difficulties	29.1 ± 1.9	29.2 ± 1.9	29.1 ± 2.0	ns
MMSE (score)	28.4 ± 1.7	28.7 ± 1.4	28.6 ± 1.2	ns
FCSR				
Total Immediate recall	15.4 ± 0.9	15.4 ± 0.8	15.2 ± 1.1	ns
Total Delayed recall	15.6 ± 0.9	15.6 ± 0.8	15.2 ± 1.3	0.02
Free Delayed recall	12.2 ± 2.2	12.1 ± 2.3	11.7 ± 2.8	0.04
Recognition score	15.9 ± 0.4	15.9 ± 0.4	15.8 ± 0.6	0.06
Visual memory	12.5 ± 1.6	12.4 ± 1.8	12.4 ± 1.8	ns
DST				
Digit span forward	5.5 ± 1.0	5.5 ± 1.1	5.4 ± 1.1	ns
Digit span backward	4.2 ± 1.0	4.2 ± 0.9	4.2 ± 1.0	ns
Baddeley dual task				
Dual task decrement	93.5 ± 10.1	93.0 ± 10.5	92.9 ± 12.2	0.08
Trail Making				
Trail Making Test A (speed)	47.5 ± 15.8	46.5 ± 15.4	47.5 ± 15.4	ns
Trail Making Test A (errors)	0.10 ± 0.3	0.10 ± 0.4	0.13 ± 0.4	ns
Trail Making Test B (speed)	103.5 ± 48.8	104.3 ± 50.6	103.2 ± 48.5	ns
Trail Making Test B (errors)	0.45 ± 0.9	0.47 ± 0.7	0.46 ± 0.9	ns
Semantic memory				
Verbal fluency Phonemic	19.3 ± 6.5	19.2 ± 6.4	19.5 ± 7.2	ns
Verbal fluency Semantic	29.5 ± 7.8	30.0 ± 8.3	30.6 ± 8.5	ns
Stroops				
Word (score)	98.1 ± 13.7	97.9 ± 13.9	96.5 ± 15.2	ns
Color (score)	70.7 ± 10.7	70.6 ± 11.2	68.1 ± 11.5	0.03
Color word (score)	49.3 ± 7.7	49.2 ± 8.3	49.0 ± 8.6	ns
WAIS Similarities test	16.9 ± 5.5	16.9 ± 5.5	17.3 ± 5.5	ns

FCSR, Free and cued selective reminding test; DSST, digit symbol substitution test.
*One-way Anova

accumulated hypoxemia and sleep loss. Therefore, as in middle-aged healthy volunteers,[5] our healthy elderly appear to be less vulnerable to the deleterious effects of sleep disruption and hypoxemia. This has been recently confirmed[52] by the absence of focal cortical gray matter loss in a subset of our SRBD subjects. Further extensive prospective studies are needed to determine whether these cognitive alterations have a clinical significance, and to identify which subjects need treatment[53] and, of these, how many may be helped by efficacious therapy.[54]

There is a lack of consensus as to whether the reduced performance of cognitive tasks in patients with SRBD is associated with intermittent night-time hypoxemia or with excessive sleepiness that results from sleep fragmentation.[1,2,11] In line with recent studies on sleepiness in the elderly,[47,48] our study shows a lack of association between ESS and objective cognitive scores, with, in contrast, a linear relationship with subjective cognitive and MMSE scores. Although our study does not provide a final conclusion with respect to mechanisms acting on cognitive dysfunction, our exploratory analysis suggests that, in the elderly, hypoxemia may be the most important factor,[1] sleepiness acting only on subjective cognitive decline.

Some methodological limitations need to be considered in the interpretation of our results. First, participants were recruited from a cross-sectional community-based study and strict exclusion criteria considering associate medical disorders were applied. The cross-sectional nature of the study precluded inference of causality, and exclusion criteria may limit our evaluation to "very healthy" elderly. Therefore, one cannot exclude the possibility that our study design makes this cohort different from the general population, and results cannot be extrapolated to clinic-based samples. However, a major advantage of our study design is that we investigated subjects with the same age and we have a control group, drawn from the same sample, not significantly different from subjects with SRBD. These two elements exclude the interference of the associated medical disorders on cognitive dysfunction. This has, to our knowledge, never been done before, and, despite our limitations, we believe that our results are valid. Second, we defined the presence of SRBD on the basis of an AHI > 15 even when subjects did not report other complaints such as sleepiness. Although sleepiness is frequently reported in SRBD patients,[36] previous studies on the association between SRBD and sleepiness in the elderly have demonstrated that sleepiness is not always associated with SRBD.[38,46-48] Associated sleep disorders and health problems that decreased nocturnal sleep efficiency may affect sleepiness,[38,47,48] diabetes, BMI and depression being more important than SRBD to explain sleepiness in older populations.[46,55] Finally, we found SRBD to be common among our elderly subjects, half of the studied population (53.8%) having an AHI > 15. Two explanations may be proposed. Firstly, interscorer reliability for scoring respiratory events, particularly hypopneas, is affected by the degree of reduction in the amplitude of the measured signal, the type of sensor used, i.e., thermistor vs nasal pressure, and the level of associate desaturation.[56,57] When we consider previous community studies,[33,34] thermocouples were frequently used and oxygen desaturation > 4% was applied to scoring hypopneas; both of these factors may lead to underestimation of hypopneas. Second, compared to previous studies, we used ambulatory polygraphy, which may induce an overestimation by inclusion of respiratory events occurring during wakefulness or transitional sleep stages. Several published papers have demonstrated the validity of ambulatory polygraphy[55,58,58] in middle-aged[59] and elderly patients,[55] with sensitivity ranging from 75% to 98% and specificity from 68% to 97%. Although we have not performed a validation study comparing polygraphy vs polysomnography in our population, the published results on polygraphy make us confident with results.

In conclusion, in a healthy community-dwelling elderly population, the impact of undiagnosed sleep related breathing disorder on cognitive functioning appeared quite moderate, no differences being detected in cognitive tests between subjects with and without SRBD. Some objective cognitive scores were weakly correlated with ODI and AHI, without any effect of sleepiness. These results suggest the role of other factors such as cognitive reserve, individual susceptibility and shared medical disorders on cognitive functions in older SRBD. Prospective studies are needed to investigate further the relationship between SRBD and age-related changes in cognition, and to assess whether cognitive decline preceded or is a consequence of the respiratory sleep disorder.

ABBREVIATIONS

AAI, autonomic arousal index
AHI, Apnea + hypopnea index
DSST, Digit Symbol Substitution test
ESS, Epworth sleepiness scale
FCSR, Free and Cued Selective Reminding test
MMSE, Mini Mental State examination
ODI, oxyhemoglobin desaturation index
OSAS, obstructive sleep apnea syndrome
SRBD, sleep related breathing disorders

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DISCLOSURE STATEMENT

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