SLEEP DISORDERED BREATHING

Increased Muscle Sympathetic Nerve Activity and Impaired Executive Performance Capacity in Obstructive Sleep Apnea

Thiago T. Goya, BS[1]; Rosyvaldo F. Silva, BS[2]; Renan S. Guerra, BS[3]; Marta F. Lima, MD, PhD[3]; Eline R.F. Barbosa, BS, MD[3]; Paulo Jannuzzi Cunha, PhD[4,5]; Denise M.L. Lobo, BS[3]; Carlos A. Buchpiguel, MD, PhD[6]; Geraldo Busatto-Filho, MD, PhD[4,5]; Carlos E. Negrão, PhD[3,7]; Geraldo Lorenzi-Filho, MD, PhD[3]; Linda M. Ueno-Pardi, PhD[2,5]

[1]Master Program in Experimental Physiopathology, HCFMUSP, São Paulo, Brazil; [2]School of Arts Sciences and Humanities, USP, São Paulo, Brazil; [3]InCor-HCFMUSP, São Paulo, Brazil; [4]Laboratory of Psychiatric Neuroimaging, Department of Psychiatry, HCFMUSP, São Paulo, Brazil; [5]Center for Interdisciplinary Research on Applied Neurosciences (NAPNA, USP), São Paulo, Brazil; [6]Institute of Radiology, HCFMUSP, São Paulo, Brazil; [7]School of Physical Education and Sport, USP, São Paulo, Brazil

Study Objectives: To investigate muscle sympathetic nerve activity (MSNA) response and executive performance during mental stress in obstructive sleep apnea (OSA).

Methods: Individuals with no other comorbidities (age = 52 ± 1 y, body mass index = 29 ± 0.4, kg/m^2) were divided into two groups: (1) control (n = 15) and (2) untreated OSA (n = 20) defined by polysomnography. Mini-Mental State of Examination (MMSE) and Inteligence quocient (IQ) were assessed. Heart rate (HR), blood pressure (BP), and MSNA (microneurography) were measured at baseline and during 3 min of the Stroop Color Word Test (SCWT). Sustained attention and inhibitory control were assessed by the number of correct answers and errors during SCWT.

Results: Control and OSA groups (apnea-hypopnea index, AHI = 8 ± 1 and 47 ± 1 events/h, respectively) were similar in age, MMSE, and IQ. Baseline HR and BP were similar and increased similarly during SCWT in control and OSA groups. In contrast, baseline MSNA was higher in OSA compared to controls. Moreover, MSNA significantly increased in the third minute of SCWT in OSA, but remained unchanged in controls ($P < 0.05$). The number of correct answers was lower and the number of errors was significantly higher during the second and third minutes of SCWT in the OSA group ($P < 0.05$). There was a significant correlation ($P < 0.01$) between the number of errors in the third minute of SCWT with AHI ($r = 0.59$), arousal index ($r = 0.55$), and minimum O_2 saturation ($r = -0.57$).

Conclusions: As compared to controls, MSNA is increased in patients with OSA at rest, and further significant MSNA increments and worse executive performance are seen during mental stress.

Clinical Trial Registration: URL: http://www.clinicaltrials.gov, registration number: NCT002289625.

Keywords: executive performance, mental stress, muscle sympathetic nerve activity, obstructive sleep apnea

Citation: Goya TT, Silva RF, Guerra RS, Lima MF, Barbosa ER, Cunha PJ, Lobo DM, Buchpiguel CA, Busatto-Filho G, Negrão CE, Lorenzi-Filho G, Ueno-Pardi LM. Increased muscle sympathetic nerve activity and impaired executive performance capacity in obstructive sleep apnea. *SLEEP* 2016;39(1):25–33.

Significance

Patients with OSA have deficits in sustained attention, inhibitory control, and increased sympathetic response during SCWT that contribute for cognitive decline and increased cardiovascular risk in this group. Further studies are needed to demonstrate the effect of OSA treatment on these parameters.

INTRODUCTION

Obstructive sleep apnea (OSA) is common and is characterized by recurrent episodes of apnea and hypopnea during sleep caused by upper airway obstruction.[1,2] OSA is recognized as a significant public health problem that results in substantial occupational and social failures. OSA may be associated with poor cardiovascular outcome[3] and impaired neuropsychological functioning.[4–6]

Sympathetic overactivity may play a role in the genesis of cardiovascular alterations associated with OSA[7,8] and contribute to a risk of hypertension[9,10] and cardiovascular morbidity.[11,12] Transient asphyxia[13] and recurrent arousals triggered by OSA[14] cause acute increases in muscle sympathetic nerve activity (MSNA).[15] Patients with OSA have increased MSNA while awake,[7] which indicates that sympathetic overactivity during sleep carries over into the daytime. Sympathetic overactivity is involved directly or indirectly in several other OSA effects, including oxidative stress,[16] lipid dysfunction,[17,18] inflammation,[19] endothelial dysfunction,[16,20,21] and accelerated atherosclerosis.[22] Despite the role of sympathetic overactivity, few studies have attempted to evaluate the MSNA response to situations that cause mental challenge and mild levels of stress that are common during daily activities. Previous studies have shown contradictory results regarding the MSNA responses to tests that mimic social stress including increases,[23] decreases, or no change in MSNA.[24] It has been reported that factors that could influence MSNA and cardiovascular adjustments to mental tasks include the type of cognitive task, absolute level of task difficulty, the individual's performance,[25] and pathologies, such as hypertension, heart failure, and obesity.

The Stroop Color Word Test (SCWT) has been used for many years[26] to explore the conflict between a well-learned or automatic behavior (read) and a decision rule that requires this behavior to be inhibited.[27] SCWT is a tool used to evaluate executive function, which is characterized by a set of skills (including selective attention and inhibitory control) that allow the individual to direct the behavior of targets, performing self-organized actions to choose the most effective strategies to resolve the task.[28] Essentially, inhibitory control is the ability to suppress the processing or expression of information that would disrupt the efficient completion of the goal at hand. This key executive function influences an individual's ability to cope with the stress of everyday life and allows the complex control between cognition and behavior that is essential for more effective social interaction.[29] Also, the SCWT is often associated with a social stress, depending on the protocol of the experiment.

In the current study, we hypothesized that MSNA is increased in OSA at rest, and further significant increments and worse executive performance will occur during mental stress in patients with OSA compared with a control group.

METHODS

Subjects

Male and female individuals, 40 to 65 y of age from the Sleep Laboratory, who had recently undergone a sleep study, were recruited for this protocol. The controls for the study were recruited from the Heart Institute Hospital staff or relatives and friends. All subjects were healthy as confirmed by medical history and physical examinations, blood profile, echocardiographic evaluation, and were not taking medications. All non-menopausal women were studied between the first and the fifth day after the onset of menstruation, because hormonal variability during the regular menstrual cycle may affect blood pressure (BP) or perception of a task as being difficult. Patients with hypertension were carefully excluded. All subjects had at least three office BP measurements obtained by one investigator. Three out-of-office BP measurements were also obtained to confirm the BP levels. Study subjects who had body mass index (BMI) > 40 kg/m^2, cardiopulmonary disease, chronic renal disease, diabetes mellitus, atrial fibrillation, pacemaker, renal failure, echocardiographic evidence of impaired left ventricular function (ejection fraction < 45%), history of psychiatric disorders, dementia or other neurodegenerative disorders, history of smoking or alcohol abuse (two or more drinks per day), any sleep apnea treatment, history of circadian desynchrony (e.g., shift workers), less than 2 y of formal education, resting BP higher than 140/90 mm Hg were excluded from the study. The institutional committee (0833/10) on human research approved the study, and all subjects gave written informed consent.

Screening of Cognitive Functions

The shortened Mini-Mental State Examination that tests global cognition and covers domains such as orientation, memory, registration, recall, constructional ability, language, and the ability to understand and follow commands[30] was administered. The Mini-Mental State Examination test is not very sensitive to minor changes in cognitive function. It is designed to identify dementia and more severe cognitive impairment.

Estimated Coefficient of Intelligence (IQ)

Intelligence was evaluated by the Wechsler Abbreviated Scale for Intelligence using vocabulary and matrices subtests.[31]

Anxiety

Anxiety symptoms over the previous 2 w were assessed by means of the Beck Anxiety Inventory that consists of 21 questions; each question has four possible answers.[32]

Depression

Depressive symptoms over the previous 2 w were assessed by means of the Beck Depression Inventory that consists of 21 items, whose intensity varies from 0 to 3.[33]

Daytime Sleepiness

To evaluate the level of general sleepiness with regard to the past few weeks, patients completed the Epworth Sleepiness Scale.[34] Normal values range between 2 and 10; scores > 14 are indicative of a high level of daytime sleepiness.

Sleep Study

All participants underwent overnight polysomnography (Embla N7000, Medcare Flaga, Reykjavik, Iceland) as previously described.[35–37] Sleep stages, apneas, hypopneas, and arousals were defined and scored as previously described.[36,37] Briefly, apnea was defined as complete cessation of airflow for at least 10 sec. Hypopnea was defined as a reduction in respiratory signal ≥ 50% from baseline for at least 10 sec associated with oxygen desaturation ≥ 3%. The apnea-hypopnea index (AHI) was calculated by the total number of respiratory events (apneas and hypopneas) per hour of sleep. OSA was defined as a cessation of respiratory airflow for 10 sec with thoracoabdominal effort, which was detected by using a piezo respiratory effort sensor. Individuals with > 70% obstructive events were defined as individuals with OSA.

Muscle Sympathetic Nerve Activity

The MSNA was directly recorded from the peroneal nerve using microneurography (662C-4 Nerve Traffic Analysis System, The University of Iowa, Iowa City, IA, USA).[35,38] Muscle sympathetic bursts were identified by visual inspection conducted by a single investigator, blinded to the study protocol, and are expressed as burst frequency (bursts per min) and bursts per 100 heartbeats.

Hemodynamic Measures

Heart rate (HR) was continuously evaluated by eletrocardiogram. BP was monitored noninvasively with an automatic ankle blood pressure cuff (nondominant ankle) with an automated oscillometric device (DX 2022, Dixtal Biomedics, Manaus, AM, Brazil). The systolic, diastolic, and mean blood pressures were registered every minute of the protocol.

Stroop Color Word Test

A modified version of SCWT[39,40] was conducted using a 3-min period after a 4-min resting baseline. During SCWT, subjects were shown a series of names of colors written in a different colored ink from the color specified. Subjects were asked to identify the color of the ink, not read the word. Throughout SCWT, subjects were pressed to respond quickly. On completion of the protocol, each subject was asked to assess stress perception using a scale ranging from 0 to 5 points (0, not stressful, 1 very mildly stressful, 2 mildly stressful, 3 moderately stressful, 4 very stressful, and 5 extremely stressful).

Cardiopulmonary Exercise Test

Maximal exercise capacity was determined by means of a maximal progressive cardiopulmonary exercise test (SensorMedics – Vmax Analyzes Assembly, Encore 29S) on an electromagnetically braked cycle ergometer (Via Sprint 150P, Ergoline, Bitz, Germany), within work-rate constant increments (5 to 20 W/min) at 60 to 70 rpm until exhaustion as

previously described.[35] Peak oxygen uptake (VO_2) was defined as the maximum attained VO_2 at the end of the exercise period in which the subject could no longer maintain the cycle ergometer velocity at 60 rpm.

Experimental Protocol

All subjects abstained from caffeine for 24 h before the study. All studies were performed during the postabsorptive state with the exception of blood sample collection. The study was performed in a quiet, temperature-controlled room (21–22°C) in the morning at approximately the same time each day. The right leg was positioned for microneurography. After an adequate nerve-recording site was obtained, the subject rested quietly for 10 min. Baseline MSNA, BP, and HR were then recorded continuously for 4 min at baseline and during the 3 min period of SCWT.

Statistical Analysis

The data are presented as mean ± standard error or median (range). The correct answers during SCWT were analyzed as the number of answers − number of errors per minute. The MSNA responses to SCWT were analyzed by relative and absolute differences (each minute of the SCWT − mean baseline) for both groups. A χ^2 (sex), unpaired Student *t*-test (age, BMI, body fat, estimated IQ, anxiety, depression, metabolic and functional parameters, baseline cardiovascular parameters, AHI, minimum O_2 saturation), or Mann-Whitney *U* test (y of education, Mini-Mental State Examination, arousal index) were used to compare differences between groups. Two-way analysis of variance with repeated measures was used to compare within and between group differences at baseline and during 3 min of mental challenge (MSNA, HR, mean BP). In the case of significance, *post hoc* comparisons were performed by Tukey honest significant difference test. An unadjusted Poisson regression model was used to examine the association between errors during SCWT and sleep parameters. Poisson regression models were also adjusted for sex, age, educational level, and BMI. $P \leq 0.05$ was considered statistically significant. All statistical analysis was performed using STATISTICA 12 software.

Table 1—Baseline characteristics in controls and patients with obstructive sleep apnea.

	Control (n = 15)	OSA (n = 20)	P
Sex, female/male	8/7	11/9	0.99
Age, y	51 ± 2	54 ± 2	0.19
BMI, kg/m^2	27 ± 1	30 ± 1	0.02*
Body fat, %	28 ± 3	30 ± 2	0.49
Education, y	11 (5–20)	11 (5–18)	0.68
Mini-Mental State Examination	29 (23–29)	27 (21–30)	0.14
Estimated IQ	90 ± 4	89 ± 3	0.82
BAI score	7 ± 2	7 ± 1	1.00
BDI score	8 ± 2	6 ± 1	0.20
Metabolic and Functional Parameters			
Fasting glucose, mg/dL	99 ± 2	104 ± 2	0.06
Total cholesterol, mg/dL	204 ± 11	201 ± 8	0.82
Peak VO_2, mL/kg/min	25 ± 6	23 ± 1	0.36
Cardiovascular Parameters			
LVEF, %	71 ± 1	69 ± 1	0.21
Heart rate, beats/min	69 ± 3	66 ± 2	0.32
Systolic BP, mm Hg	119 ± 3	122 ± 3	0.51
Diastolic BP, mm Hg	78 ± 2	79 ± 1	0.71
MSNA, bursts/min	28 ± 2	41 ± 3	0.01*
MSNA, bursts/100 heartbeats	41 ± 3	62 ± 4	0.01*

Sex was not significantly different among groups. There was no significant difference in age, body fat, estimated intelligence quotient (IQ), fasting glucose, total cholesterol, oxygen uptake (VO_2); left ventricular ejection fraction (LVEF), heart rate, brachial systolic and diastolic blood pressure (BP), Beck Anxiety Inventory (BAI) score, Beck Depression Inventory (BDI) score among groups. Body mass index (BMI) was higher in patients with OSA than in controls. The baseline muscle sympathetic nerve activity (MSNA) in bursts per min or bursts per 100 heartbeats was higher in patients with OSA when compared with controls. Unpaired Student *t*-test. Values are means ± standard error or median (range). *P < 0.05, OSA versus control. There was no significant difference in y of education, Mini-Mental State Examination using Mann-Whitney *U* test. Sex was tested by χ^2 test. OSA, obstructive sleep apnea.

RESULTS

Baseline Measures

The final sample consisted of 15 controls and 20 patients with OSA (AHI ≥ 15 events per hour of sleep). Controls and patients with OSA were not taking medications 2 mo prior to the experimental protocol. Characteristics of OSA and control groups are shown in Table 1. There were no significant differences in sex, age, y of education, Mini-Mental State Examination, IQ, Beck Anxiety Inventory score, Beck Depression Inventory score, body fat, metabolic parameters, and peak VO_2 between OSA and control groups. Left ventricular function, and HR and BP levels did not differ between groups. BMI was higher in patients with OSA compared with that in the control group. The daytime sleepiness score did not differ between OSA and the control group (11.6 ± 7 versus 12.1 ± 6 for mean ± standard deviation, P = 0.83), respectively. The baseline MSNA in bursts per min or bursts per 100 heartbeats was higher in the OSA group when compared with that in controls. Regarding the sleep pattern (Table 2), AHI was higher and minimum O_2 saturation lower in the OSA group compared with that in the control group. Arousal index was greater in the OSA group compared with that in the control group.

Responses to SCWT

The stress perception after SCWT was moderate and did not differ between OSA and the control groups (3.1 ± 1.4 versus 2.7 ± 1.2 for mean ± standard deviation, P = 0.16), respectively. Figure 1A indicates statistically significant differences between groups observed in MSNA values during the SCWT. There was a significant increase in MSNA during the

third minute of SCWT (time × group interaction; $P < 0.05$). Also, delta MSNA (each minute of SCWT – baseline) showed significant differences between groups with a significant increase in MSNA in the OSA group (within group) during the third minute of SCWT compared with the baseline value (Figure 1B). Figure 2 shows examples of MSNA in control and OSA patients at baseline and in the third minute of the SCWT. HR significantly increased in both controls and patients with OSA (Figure 3). HR response during the first minute of SCWT was higher compared with HR in the second and third minutes of SCWT in both control and OSA groups. The mean BP significantly increased during the second and third minutes of SCWT in both control and OSA groups (Figure 4). An abrupt decrease in the number of answers during the second and third minute of SCWT was observed in the OSA group compared with that in the control group (Figure 5A). The number of errors significantly increased in the third minute of SCWT in the OSA group (Figure 5B). The number of correct answers significantly decreased in the second and third minute of SCWT in the OSA group compared with that in the control group (Figure 5C). In addition, a significant correlation was found between the number of errors in the third minute of SCWT and AHI ($r = 0.59$; $P < 0.001$; Figure 6A), the number of errors in the third minute of SCWT, and the arousal index ($r = 0.55$; $P < 0.001$; Figure 6B); the number of errors in the third minute of SCWT and minimum O_2 saturation ($r = -0.57$; $P < 0.01$; Figure 6C). Adjustment for sex, age, educational level, and BMI strengthened the association. No linear correlation was found between the number of errors in the third minute of SCWT and systolic BP ($r = -0.20$; $P > 0.05$), diastolic BP ($r = -0.25$; $P > 0.05$) or HR ($r = -0.013$; $P > 0.05$).

Table 2—Sleep pattern in controls and patients with obstructive sleep apnea.

	Control (n = 15)	OSA (n = 20)	P
AHI, events/h	8 ± 1	47 ± 7	0.01*
Arousals, events/h	21 (10–28)	27 (14–67)	0.005*
Minimum O_2 saturation, %	90 ± 1	76 ± 2	0.01*

Arousal index was greater in patients with OSA when compared with the control group. AHI and arousals were higher and minimum O_2 saturation lower in OSA when compared with the control group. Unpaired Student *t*-test. Values are means ± standard error or median (range). *P < 0.05, OSA versus control. Arousal index was tested by Mann-Whitney *U* test. AHI, apnea-hypopnea index; OSA, obstructive sleep apnea.

DISCUSSION

The main and new findings of the current study are that: (1) patients with OSA presented a time delay until impairment of MSNA during SCWT; (2) executive performance during a continued task involving inhibitory control, as evaluated by SCWT, is reduced in patients with OSA; (3) SCWT performance is inversely associated with sleep apnea severity parameters, including sleep fragmentation and hypoxia during sleep.

Our results are also in line with results in previous studies reporting that patients with OSA have increased baseline MSNA[7] compared with controls. The mechanisms explaining such findings are multiple and include chemoreceptor overactivity[15] and depressed sympathetic baroreflex sensitivity.[41] A previous study[42] reported a significant decrease in the

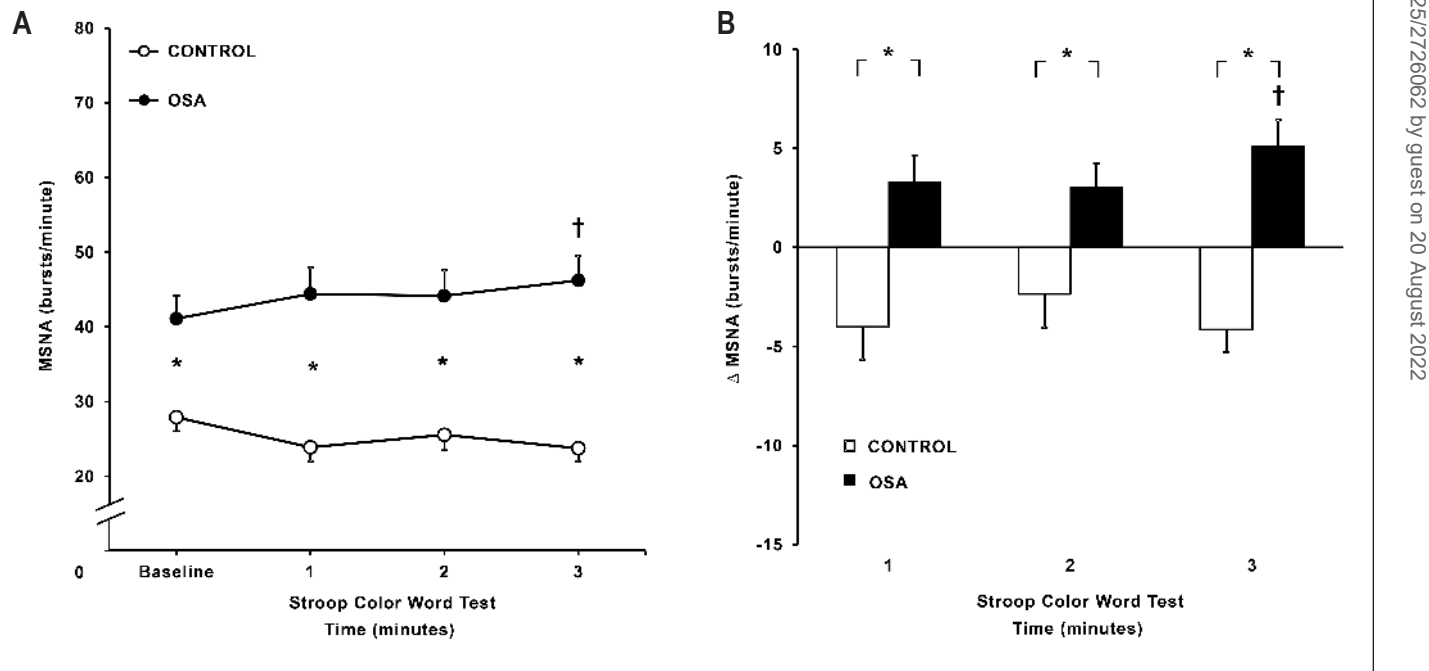

Figure 1—MSNA **(A)** and delta MSNA in bursts/min **(B)** during the SCWT. OSA indicates obstructive sleep apnea. Asterisk indicates control versus OSA, P < 0.05; dagger indicates versus baseline (time × group interaction; P < 0.05). Delta MSNA (each minute of SCWT – baseline) showed significant differences between groups with a significant increase in MSNA in patients with OSA during the third minute of the SCWT compared with baseline value (Figure 1B). MSNA, muscle sympathetic nerve activity; SCWT, Stroop Color Word Test; OSA, obstructive sleep apnea.

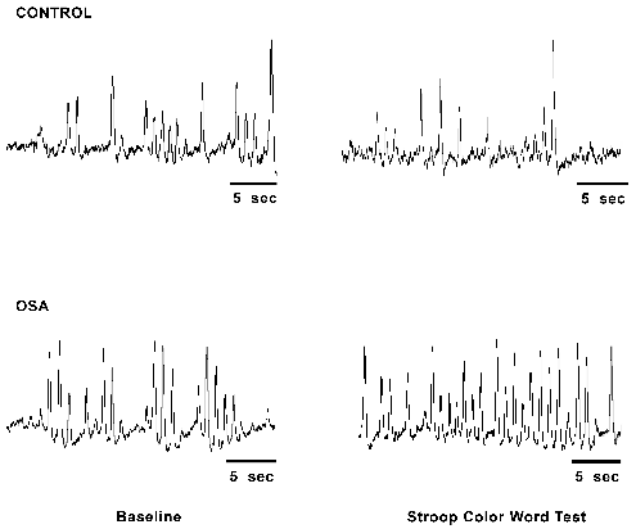

Figure 2—Sympathetic neurograms (30 sec) in controls and patients with OSA at baseline and during the third minute of the SCWT. SCWT, Stroop Color Word Test; OSA, obstructive sleep apnea.

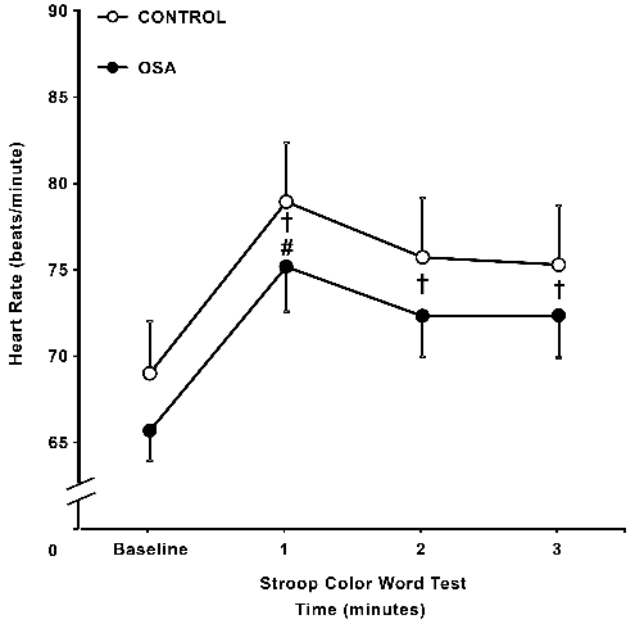

Figure 3—Heart rate at baseline and during the SCWT. Dagger stands for versus baseline, P < 0.05 (within group for control and OSA); number sign stands for versus second and third minutes of the SCWT. P < 0.05 (within group for control and OSA). SCWT, Stroop Color Word Test; OSA, obstructive sleep apnea.

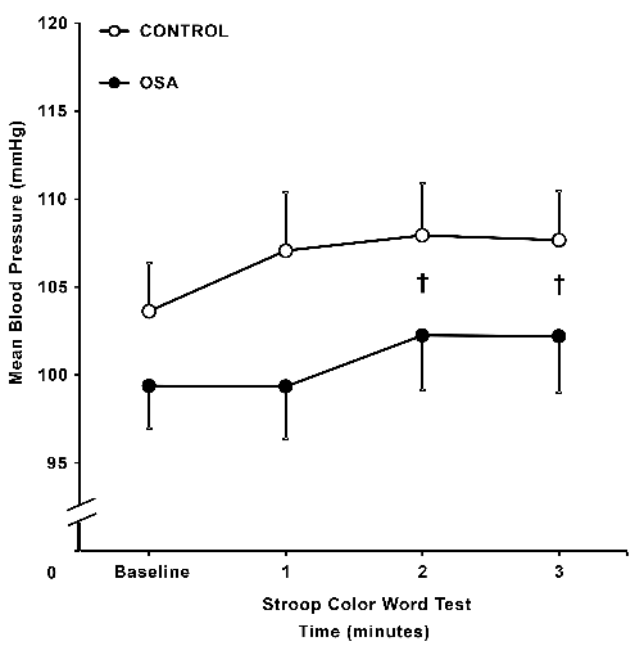

Figure 4—Ankle mean blood pressure at baseline and during SCWT. Dagger stands for versus baseline, P < 0.05 (within group for control and OSA). SCWT, Stroop Color Word Test; OSA, obstructive sleep apnea

magnitude of spontaneous arterial baroreflex control of MSNA and increases in time delay of the baroreflex response of MSNA in OSA with metabolic syndrome during resting conditions. Our study adds important information by evaluating the MSNA response during mental stress in patients with OSA compared with controls. There was a significant increase in delta MSNA (each minute of SCWT – baseline) during the third minute of SCWT compared with the baseline value only in patients with OSA (Figure 1B). The increase in MSNA in humans during SCWT is thought to reflect the balance between central nervous system arousal, which is sympathoexcitatory, and arterial baroreflex activation, which is sympathoinhibitory.[43] The time delay until impairment of MSNA during a cognitive task may suggest greater dysfunction in central autonomic regulatory regions in patients with OSA. A previous study showed a delay in functional magnetic resonance imaging signals to a physiological maneuver in patients with OSA with decreased brain activation,[44] suggesting damage to the medullary integrative circuity for arousal systems.[45] Patients with OSA may experience activation of more compensatory actions in other brain structures to perform a sustained cognitive task when compared with controls. Several recent studies are consistent with the hypothesis that patients with OSA have structural and functional changes in the brain that may also contribute to sympathetic hyperactivity.[46–49] A more recent study[50] led to the idea that higher firing rates of axons already recruited during baseline were an important mechanism by which the sympathetic nervous system is activated during reflex-mediated stress. We speculate that these factors may contribute to explaining the differences in MSNA responses between OSA and control groups. Future studies using analysis of neural coding patterns within the autonomic nervous system during SCWT in patients with OSA and control subjects may contribute to a better understand of this complex question. For instance, patients with OSA are more susceptible to the risk for cardiovascular complications. Thus, marked increases in MSNA in patients with OSA may have important implications for cardiac events during chronic situations of mental stress. Furthermore, the time delay until impairment during

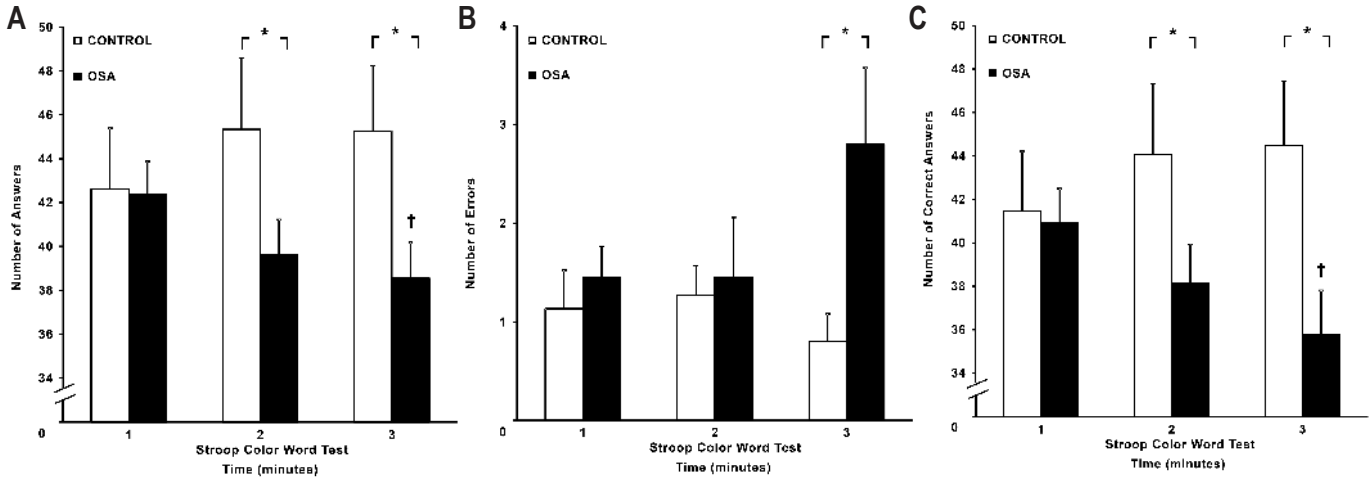

Figure 5—Results of performance indicated by the number of answers **(A)**, number of errors **(B)**, and number of correct answers **(C)** within the first to third minutes of the SCWT. Asterisk indicates control versus OSA, $P < 0.05$; dagger stands for versus first minute, $P < 0.05$ (within group). SCWT, Stroop Color Word Test; OSA, obstructive sleep apnea.

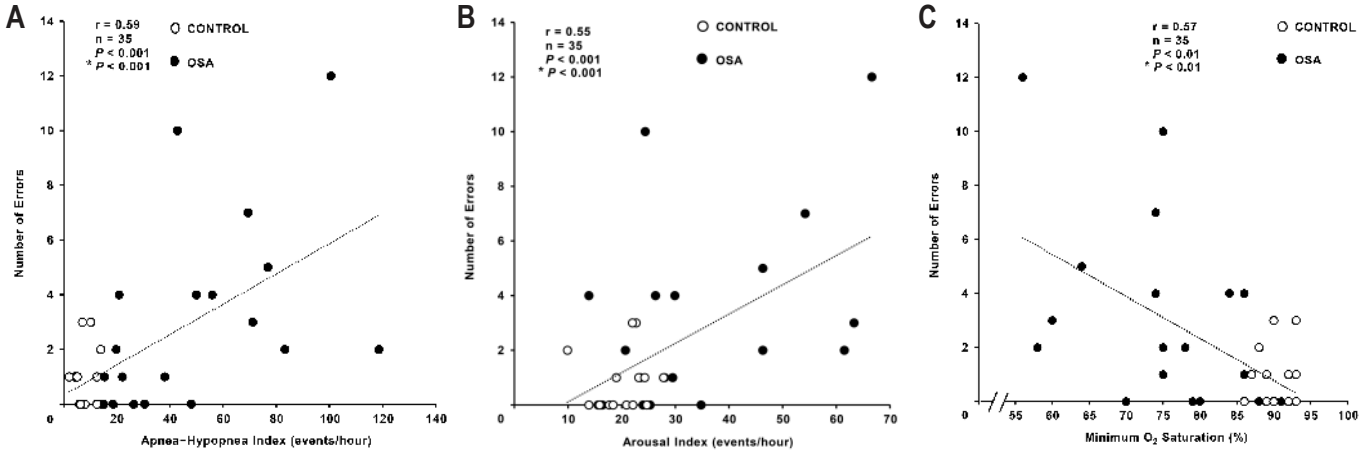

Figure 6—Group data correlations between number of errors at the third minute with apnea-hypopnea index **(A)**, arousal index **(B)**, and minimum O_2 saturation **(C)**. Open circle indicates controls and dark circle indicates obstructive sleep apnea. Asterisk indicates adjusted for sex, age, educational level, and percentage of body fat.

physiological maneuvers in patients with OSA may result in future brain tissue blood flow impairment.[45]

SCWT has been used in various modified forms.[24,25,51] For instance, mental stress has been evaluated by increasing the level of difficulty of SCWT over time. To evaluate executive performance during a continued task involving inhibitory control, we maintained the same level of task difficulty over time during SCWT as previously reported.[39,40,43] Our test elicited a moderate and similar level of subjective stress in both control patients and patients with OSA as evaluated at the end of the task (~3 in a scale from 0 to 5 points). In accordance with this subjective evaluation, HR and mean BP increased in relation to baseline similarly in control and OSA groups (Figures 3 and 4). The increase in HR and BP during mental task are consistent with results in previous studies.[25,52,53] The magnitude of increase in HR in the current study was greater in the first minute of SCWT (Figure 3). Our group data showed a significant correlation between stress perception and HR responses in the first minute of SCWT ($r = 0.36$; $P < 0.05$). In contrast to the HR and BP, MSNA tended to remain below rest value until the end of task in control group. However, delta MSNA (each minute of SCWT – baseline) showed significant increase in the OSA group (within group) during the third minute of SCWT compared with the baseline value. Tachycardia is probably due to a reduction of parasympathetic tone and/or increased cardiac sympathetic modulation[53] and is a defense reaction response at the onset of SCWT[25] that prepares the body for a fight-or-flight response. The elevation in BP may occur primarily by an increase in cardiac output mediated by elevation in HR during mental stress. Our results indicate that the sympathetic autonomic response depends on the site. Cardiac but not peripheral sympathetic activity may be increased in control subjects. The dissociation between HR and BP response to MSNA in OSA and control groups may have further implications in vascular

control. The increases in BP and MSNA during acute mental stress indicate that OSA may need adjustments to regulate vascular homeostasis under stress conditions to prevent ischemia. Future studies using direct methods to investigate blood flow changes during SCWT in patients with OSA help better explain these interactions.

The executive performance among controls and OSA was similar in the first minute. However, patients with OSA had a significantly lower number of answers, correct answers, and more errors in the second and third minute of SCWT than did controls. Additionally, the number of correct answers decreased significantly in the second and third minute of SCWT in patients with OSA. These results are consistent with results of previous investigations[4,54] that demonstrate reduced executive performance during neurocognitive tests in patients with OSA when compared with controls. In addition, we found significant correlations between the number of errors at the third minute of SCWT and sleep severity parameters (AHI, minimum O_2 saturation, and arousal index). The relationships remained significant even after controlling for age, educational level, and BMI. Several mechanisms may help to explain our findings. For instance, a study[55] reported that sleep deprivation leads to a general slowing of response speed and increased variability in performance, and measures of alertness, attention, and vigilance. Impaired executive performance in patients with OSA may be relevant to driving ability and occupational safety hazards. Our results may help to explain the increased incidence of motor vehicle crashes in patients with OSA.[56–58] Moreover, in a real situation of social stress, impaired executive performance may be associated with serious difficulties and impulsivity traits when trying to inhibit inappropriate behaviors in order to control problems related to OSA, such as excessive food consumption, leading to an increased BMI, which interferes with the quality of sleep.

Our study has several potential limitations. We used a simple cognitive screening tool (Mini-Mental State Examination) that may not be sensitive enough to detect mild cognitive impairment, which may be more prevalent in older patients with OSA than in the general population.[59] Moreover, cognitive task specificity may exist for individuals with a higher level of education or higher IQ. Higher level of education or higher IQ offers some protection against cognitive decline, possibly due to increased cognitive reserve. In this context, the groups were similar in several variables that can influence our results, including educational level, IQ, Mini-Mental State Examination, level of physical activity (functional capacity) and systolic function. In addition, other variables that may influence cognition, such as anxiety or depression symptoms, were similar between groups. In the current study, BAI and BDI scores were in the normal range and did not differ between groups. These similar results between groups can be explained by an AHI cutoff point ≥ 15 events/h of sleep for the presence of OSA. Subjects were classified as belonging to the control group if the AHI was < 15 events/h of sleep or having OSA if AHI was ≥ 15 events/h of sleep. The highest AHI in the control group was 14 events/h of sleep, which can have an effect on the symptoms of depression, and this might decrease the sensitivity for uncovering group differences.

Obesity may contribute to the sympathetic overactivity[39] associated with several mechanisms including hyperinsulinemia[60] and leptin resistance,[47,61] as well as adverse neurocognitive outcome.[62] However, in our study, the percentage of body fat, a more sensitive index for obesity, was similar between groups despite differences in BMI. In the current study, a significant correlation between the number of errors at the third minute of SCWT and OSA severity parameters remained significant after controlling for BMI, which may exclude the influence of this variable. However, the use of regression models to examine the associations between errors during SCWT and sleep parameters (AHI, arousal index, and minimum O_2 saturation) adjusted for sex, age, educational level, and BMI could miss moderately large effects given the relatively low degrees of freedom. Also, the multiple comparisons for this model using systolic BP, diastolic BP, and HR are unlikely to lead to excessive errors because the variables are closely related. Finally, the associations between the variables observed here should be interpreted with caution because of the cross-sectional nature of our study.

In summary, MSNA is increased in OSA at rest, and further significant MSNA increments and worse executive performance are seen during mental stress. The impaired executive functioning may be associated with intermittent episodes of hypoxia that negatively interferes with the prefrontal cortex, leading to poor cognitive control. Future studies are needed that perform concurrent recordings of sympathetic activities and brain imaging with a view to explore areas of brain activation, cerebral blood flow, time course of neural responses, and cognitive performance during sustained SCWT in OSA and controls without other comorbidities. Another approach is to evaluate the effect of OSA treatment to address these important issues.

REFERENCES

1. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol 2008;52:686–717.
2. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiol Rev 2010;90:47–112.
3. Marin JM , Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005;365:1046–53.
4. Beebe DW, Groesz L, Wells C, Nichols A, McGee K. The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case controlled data. Sleep 2003;3:298–307.
5. Sagaspe P, Philip P, Schwartz S. Inhibitory motor control in apneic and insomniac patients: a stop task study. J Sleep Res 2007;16:381–7.
6. Lau EY, Eskes GA, Morrison DL, Rajda M, Spurr KF. Executive function in patients with obstructive sleep apnea treated with continuous positive airway pressure. J Int Neuropsychol 2010;16:1077–88.
7. Carlson JT, Hedner J, Elam M, Ejnell H, Sellgren J, Wallin BG. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. Chest 1993;103:1763–8.
8. Narkiewicz K, Somers VK. The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. J Hypertens 1997;15:1613–9.

9. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens 2001;19:2271–7.
10. Abboud F, Kumar R. Obstructive sleep apnea and insight into mechanisms of sympathetic overactivity. J Clin Invest 2014;124:1454–7.
11. Narkiewicz K, Somers VK. Sympathetic nerve activity in obstructive sleep apnoea. Acta Physiol Scand 2003;177:385–90.
12. Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: implications for comorbidities. Chest 2015;147:266–74.
13. Smith ML, Niedermaier ON, Hardy SM, Decker MJ, Strohl KP. Role of hypoxemia in sleep apnea- induced sympathoexcitation. J Auton Nerv Syst 1996;56:184–90.
14. Morgan BJ. Acute and chronic cardiovascular responses to sleep disordered breathing. Sleep 1996;19:S206–9.
15. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med 1993;328:303–7.
16. Jelic S, Padeletti M, Kawut SM, et al. Inflammation, oxidative stress and repair capacity of the vascular endothelium in obstructive sleep apnea. Circulation 2008;117:2270–8.
17. Drager LF, Jun J, Polotsky VY. Obstructive sleep apnea and dyslipidemia: implications for atherosclerosis. Curr Opin Endocrinol Diabetes Obes 2010;17:161–5.
18. Drager LF, Jun JC, Polotsky VY. Metabolic consequences of intermittent hypoxia: relevance to obstructive sleep apnea. Best Pract Res Clin Endocrinol Metab 2010;24:843–51.
19. Jelic S, Lederer DJ, Adams T, et al. Vascular inflammation in obesity and sleep apnea. Circulation 2010;121:1014–21.
20. Ip MS, Tse HF, Lam B, Tsang KW, Lam WK. Endothelial function in obstructive sleep apnea and response to treatment. Am J Respir Crit Care Med 2004;169:348–53.
21. Atkeson A, Jelic S. Mechanisms of endothelial dysfunction in obstructive sleep apnea. Vasc Health Risk Manag 2008;4:1327–35.
22. Drager LF, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: an emerging risk factor for atherosclerosis. Chest 2011;140:534–42.
23. Kuniyoshi FH, Trombetta IC, Batalha LT, et al. Abnormal neurovascular control during sympathoexcitation in obesity. Obes Res 2003;11:1411–9.
24. Carter JR, Kupiers NT, Ray CA. Neurovascular responses to mental stress. J Physiol 2005;564:321–7.
25. Callister R, Suwarno NO, Seals DR. Sympathetic activity is influenced by task difficulty and stress perception during mental challenge in humans. J Physiol 1992;454:373–87.
26. Jensen AR, Rohwer WD Jr. The Stroop color-word test: a review. Acta Psychol (Amst) 1966;25:36–93.
27. Leung HC, Skudlarski P, Gatenby JC, Peterson BS, Gore JC. An event-related functional MRI study of the Stroop Color Word Interference Task. Cereb Cortex 2000;10:552–60.
28. Garner JK. Conceptualizing the relations between executive functions and self-regulated learning. J Psychol 2009;143:405–26.
29. Burke WH, Zencius AH, Wesolowski MD, Doubleday F. Improving executive function disorders in brain-injured clients. Brain Inj 1991;5:241–52.
30. Folstein MF, Folstein SE, McHugh PR. "Mini Mental State" A practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res 1975;12:189–98.
31. Wechsler D. Wechsler Abbreviated Scale of Intelligence (WASI). New York, NY: The Psychological Corporation: Harcourt Brace & Company, 1999.
32. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988;56:893–7.
33. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.
34. Johns, MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:540–5.
35. Ueno LM, Drager LF, Rodrigues AC, et al. Effects of exercise training in patients with chronic heart failure and sleep apnea. Sleep 2009;32:637–47.
36. Drager LF, Ueno LM, Lessa PS, Negrão CE, Lorenzi-Filho G, Krieger EM. Sleep-related changes in hemodynamic and autonomic regulation in human hypertension. J Hypertens 2009;27:1655–63.
37. Garcia CE, Drager LF, Krieger EM, et al. Arousals are frequent and associated with exacerbated blood pressure response in patients with primary hypertension. Am J Hypertens 2013;26:617–23.
38. Roveda F, Middlekauff HR, Rondon MU, et al. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. J Am Coll Cardiol 2003;42:854–60.
39. Ribeiro MM, Silva AG, Santos NS, et al. Diet and exercise training restore blood pressure and vasodilatory responses during physiological maneuvers in obese children. Circulation 2005;111:1915–23.
40. Tonacio AC, Trombetta IC, Rondon MU, et al. Effects of diet and exercise training on neurovascular control during mental stress in obese women. Braz J Med Biol Res 2006;39:53–62.
41. Durocher JJ, Klein JC, Carter JR. Attenuation of sympathetic baroreflex sensitivity during the onset of acute mental stress in humans. Am J Physiol Heart Circ Physiol 2011;300:H1788–93.
42. Toschi-Dias E, Trombetta IC, Dias da Silva VJ, et al. Time delay of baroreflex control and oscillatory pattern of sympathetic activity in patients with metabolic syndrome and obstructive sleep apnea. Am J Physiol Heart Circ Physiol 2013;304:H1038–44.
43. Middlekauff HR, Nguyen AH, Negrão CE, et al. Impact of acute mental stress on sympathetic nerve activity and regional blood flow in advanced heart failure: implications for 'triggering' adverse cardiac events. Circulation 1997;96:1835–42.
44. Henderson LA, Woo MA, Macey PM, et al. Neural responses during Valsalva maneuvers in obstructive sleep apnea syndrome. J Appl Physiol 2003;94:1063–74.
45. Macey PM, Kumar R, Woo MA, Yan-Go FL, Harper RM. Heart rate responses to autonomic challenges in obstructive sleep apnea. PLoS One 2013;8:e76631.
46. Macey PM, Kumar R, Woo MA, Walladares EM, Yan-Go FL, Harper RM. Brain structural changes in obstructive sleep apnea. Sleep 2008;31:967–77.
47. James C, Macefield VG, Henderson LA. Real-time imaging of cortical and subcortical control of muscle sympathetic nerve activity in awake human subjects. Neuroimage 2013;70:59–65.
48. Fatouleh RH, Hammam E, Lundblad LC, et al. Functional and structural changes in the brain associated with the increase in muscle sympathetic nerve activity in obstructive sleep apnoea. Neuroimage Clin 2014;27:275–83.
49. Lundblad LC, Fatouleh RH, Hammam E, McKenzie DK, Macefield VG, Henderson LA. Brainstem changes associated with increased muscle sympathetic drive in obstructive sleep apnoea. Neuroimage 2014;103:258–66.
50. Badrov MB, Usselman CW, Shoemaker JK. Sympathetic neural recruitment strategies: responses to severe chemoreflex and baroreflex stress. Am J Physiol Regul Integr Comp Physiol 2015;309:R160–8.
51. Chida Y, Steptoe A. Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: a meta-analysis of prospective evidence. Hypertension 2010;55:1026–32.
52. Schwartz CE, Durocher JJ, Carter JR. Neurovascular responses to mental stress in prehypertensive humans. J Appl Physiol 2011;110:76–82.
53. Pérusse-Lachance E, Tremblay A, Chaput Jean-Philippe, et al. Mental work stimulates cardiovascular responses through a reduction in cardiac parasympathetic modulation in men and women. Bioenergetics 2012;2:107.
54. Naëgelé B, Thouvard V, Pépin JL, et al. Deficits of cognitive executive functions in patients with sleep apnea syndrome. Sleep 1995;18:43–52.
55. Killgore WD. Effects of sleep deprivation on cognition. Prog Brain Res 2010;185:105–29.

56. Findley LJ, Unverzagt ME, Suratt PM. Automobile accidents involving patients with obstructive sleep apnea. Am Rev Respir Dis 1988;138:337–40.
57. Stoohs RA, Bingham LA, Itoi A, Guilleminault G, Dement WC. Sleep and sleep-disordered breathing in commercial long-haul truck drivers. Chest 1995;107:1275–82.
58. Kingshott RN, Cowan JO, Jones DR, et al. The role of sleep disordered breathing, day time sleepiness, and impaired performance in motor vehicle crashes-a case control study. Sleep Breath 2004;8:61–72.
59. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 2011;306:613–9.
60. Seematter G, Guenat E, Schneiter P, Cayeux C, Jéquier E, Tappy L. Effects of mental stress on insulin-mediated glucose metabolism and energy expenditure in lean and obese women. Am J Physiol Endocrinol Metab 2000;279:E799–805.
61. Carvalheira JB, Torsoni MA, Ueno M, et al. Cross-talk between the insulin and leptin signaling systems in rat hypothalamus. Obes Res 2005;13:48–57.
62. Hassing LB, Dahl AK., Pedersen NL, Johansson B. Overweight in midlife is related to lower cognitive function 30 years later: a prospective study with longitudinal assessments. Dement Geriatr Cogn Disord 2010;29:543–52.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication March, 2015
Submitted in final revised form June, 2015
Accepted for publication July, 2015
Address correspondence to: Escola de Artes, Ciências e Humanidades, Universidade de São Paulo, Av. Arlindo Béttio, 1000 Ermelino Matarazzo, CEP: 03828-000, São Paulo, Brazil; Tel: (5511) 985685530; Fax: (5511) 3069-5043; Email: lindabrz@hotmail.com, lindabrz@usp.br

DISCLOSURE STATEMENT

This was not an industry supported study. This study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP # 2010/15064-6) and in part by Pro-Reitoria de Pesquisa da Universidade de São Paulo to Dra. Linda M. Ueno Pardi. The authors have indicated no financial conflicts of interest.