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Neurocognitive Correlates of Nocturnal Oxygen Desaturation in a Memory Clinic Population

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Abstract

Previous studies suggested that sleep apnea is associated with neurocognitive impairments but did not examine populations most likely to have clinically relevant impairments. Cross-sectional, retrospective analyses were performed on 108 patients (65 with Mild Cognitive Impairment, 43 with dementia) seen in an academic medical center. Results indicated that severity of oxygen desaturation was associated with cognitive impairments in attention and executive function domains, even after controlling for age, sex, education and depressive symptoms. Strength of associations was influenced by cardiovascular disease. Screening for nocturnal oxygen desaturation may be a useful procedure to assess for a potentially reversible cause of cognitive impairment.

Keywords

Sleep Apnea; Cardiovascular Disease; Pulse Oximetry; Cognitive Disorders; Geriatrics; Neuropsychology

Introduction

Sleep apnea in adults has been associated with a wide variety of neurocognitive impairments, particularly in the domains of attention and concentration, and to a more limited degree in memory and executive function (Aloia, Arnedt, Davis, Riggs, & Byrd, 2004; Beebe, Groesz, Wells, Nichols, & McGee, 2003). Most of the studies showing such impairments have been conducted in middle-aged populations presenting with signs or symptoms of sleep apnea in Sleep Clinics. Studies examining neurobehavioral impairments in relation to polysomnographically measured sleep apnea or snoring in non-clinical populations have shown far more equivocal results (Boland et al., 2002; Foley et al., 2003; Quan et al., 2006; Tworoger, Lee, Schernhammer, & Grodstein, 2006).

Although evidence involving neuropsychological test findings is mixed, converging data from other sources suggests that pathophysiologic alterations accompanying sleep apnea can indeed affect higher order brain structure or function (Zimmerman & Aloia, 2006). Magnetic resonance imaging (MRI) indicates patients with sleep apnea show smaller mammillary body volumes relative to controls (Kumar et al., 2008), whereas diffusion tensor imaging (DTI) has shown interruptions of tracks involving anterior and posterior cingulate cortex, fornix and internal capsule (Macey et al., 2008). Functional MRI studies have demonstrated that tasks requiring attention and learning result in higher levels of

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blood-oxygen level signal (BOLD) activation in prefrontal and parietal regions in sleep apnea patients, suggestive of greater compensatory efforts in such individuals (Archbold, Borghesani, Mahurin, Kapur, & Landis, 2009; Ayalon, Ancoli-Israel, Klemfuss, Shalauta, & Drummond, 2006). Reversibility of BOLD activation in brain activity with continuous positive airway pressure treatment for sleep apnea has been reported using fMRI (Castronovo et al., 2009; Thomas, Rosen, Stern, Weiss, & Kwong, 2005). Earlier studies using magnetic resonance spectroscopy (Kamba et al., 2001) and transcranial Doppler (Hajak, Klingelhofer, Schulz-Varzegi, Sander, & Ruther, 1996) have also suggested alterations of brain metabolic and vascular flow velocity, respectively, accompanying sleep apnea. Finally, basic science studies have suggested that models of intermittent hypoxia hasten apoptosis in the CA1 layer of the hippocampus, with those effects being particularly pronounced in older, relative to younger, animals (Gozal et al., 2003).

The neuroimaging studies, in addition to epidemiologic studies establishing a strong, independent role for sleep apnea in cardiovascular disease (CVD) (Arzt, Young, Finn, Skatrud, & Bradley, 2005; Newman et al., 2001; Nieto et al., 2000; O'Connor et al., 2009; Shahar et al., 2001), prompted us to re-examine neuropsychological correlates for sleep apnea in patients enriched with both cognitive and medical comorbidities. In order to assess sleep apnea in such a population of patients seen in a geriatric memory clinic for whom overnight diagnostic polysomnography may not always be feasible, we screened for sleep apnea with ambulatory, overnight pulse oximetry (Series, Marc, Cormier, & La Forge, 1993; Yamashiro & Kryger, 1995), for which we have previously reported a high yield of usable data in such a population (Bliwise et al., 2005).

Method

Participants

Patients were consecutively recruited from the outpatient Neurology memory assessment clinics at the Wesley Woods Center on Aging. The study was approved by the Emory University Institutional Review Board. Patients underwent a routine clinical evaluation that included a physical exam, medical history and cognitive testing described in the next section. They were diagnosed by two behavioral neurologists who serve as the Principal Investigator (AIL) and Clinical Core Leader (JLL) of the National Institute on Aging supported Emory Alzheimer's Disease Research Center. Published criteria for dementia (American Psychiatric Association, 2000) or mild cognitive impairment (MCI) (Winblad et al., 2004) were used for diagnosis. The classification of MCI was not limited to those with memory impairment (MCI-amnesic) and included individuals who demonstrated impairments in other single domains or multiple domains. For those demonstrating difficulties in multiple cognitive domains, designation as either MCI or dementia was driven by an assessment of the individual's functional independence via interview and Lawton-Brody Instrumental Activities of Daily Living questionnaire (Lawton & Brody, 1969). For the current study, patients with a Mini-Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975) of less than 12, and consistent with severe dementia, were excluded to minimize floor effects on the cognitive measures. We excluded patients if they had a history of primary psychiatric (Axis I) disorders, alcohol or substance-related abuse, or co-existing neurologic conditions such as Parkinson's disease or seizure disorder. We also excluded participants with frank, large-vessel strokes based on history or neuroimaging.

The final sample included 108 outpatients (65 with dementia, 43 with MCI) who also underwent nocturnal pulse oximetry screening for sleep apnea. About a third of the sample ($n = 34$, 31.5%) had a positive cardiovascular disease (CVD) history, defined as prior cardiac surgery, myocardial infarction, atrial fibrillation, or congestive heart failure.

Elevated cholesterol and hypertension were also relatively common in this population. Table 1 presents demographic, medical history and MMSE data on the study subjects.

Neuropsychological Testing

In addition to the MMSE, patients received a battery of cognitive tests, administered by trained psychometricians, as part of their standard workup in the memory assessment clinics. Both the clinicians and the psychometrists were unaware of the pulse oximetry results, as these data were collected after the clinic visit and diagnosis had been made. Five cognitive domains were evaluated involving attention, language, episodic memory, visuomotor/visuospatial performance, and executive functioning. Two subsets of an older version of the Wechsler Memory Scale (Wechsler Memory Scale-Revised) (WMS-R) (Wechsler, 1987) were administered in order to maintain continuity with other ongoing clinical research projects. Attention was assessed by the maximum number of digits forward on the WMS-R (Wechsler, 1987), and the number of seconds needed to sequence numbers using a pencil (Trails A) (Army Individual Test Battery, 1944). Trails B was administered as well, but only 57 patients could complete this measure, which constituted a floor effect and required a different analytic approach (see below). Language was examined via the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 15 item version of the Boston Naming Test (Morris et al., 1989). Episodic memory was evaluated with the delayed recall task of the first story from the WMS-R Logical Memory test (Wechsler, 1987). Visuospatial performance was evaluated by a modified (15-item) version of the Judgment of Line Orientation test (JOLO) (Benton, Hamsher, Varney, & Spreen, 1983). Finally, executive functioning was measured via the maximum number of digits backward on the WMS-R (Wechsler, 1987), Letter Fluency ("FAS") on the Controlled Oral word Association Test (Benton & Hamsher, 1989) and the Clock Drawing test (Freedman et al., 1994). We also administered the 15-item version of the Geriatric Depression Scale (GDS) (Sheikh & Yesavage, 1986) to assess depressive symptoms. Table 1 presents test data.

Nocturnal Pulse Oximetry

Patients were sent home with a pulse oximeter (Model 2500 PalmSAT; Nonin, Plymouth, MN) and a pre-paid return mailer and asked to return this via courier mail service. We have previously reported 96% valid data on downloads of returned units as part of routine screening in our clinic (Bliwise, et al., 2005). We derived two whole-night summary measures of nocturnal desaturation: a) the average number of drops in SaO₂ of at least 4% per hour of recording (DI, Desaturation Index); and b) the percentage of recording time with SaO₂ below 90% (P90). Higher values for DI and P90 indicated more severe oxygen desaturation.

Data Analyses

We examined associations between neuropsychological measures and severity of nocturnal oxygen desaturation as continuous measures using full model linear multiple regression, simultaneously controlling for age, gender, education and depressive symptoms (GDS score) (see Appendix). The potential role of cardiovascular disease as an effect modifier was examined via stratification by performing regressions separately for those with ($n = 34$) and without ($n = 74$) such history. Because of potential overlap among cognitive test measures, we adjusted for multiple comparisons using the Hochberg correction (Norman & Steiner, 2000). We analyzed for possible floor effects in Trails B, as well as in Digit Span-Backwards, using logistic regression.

Results

Table 1 presents descriptive data. Social background characteristics were comparable across the cardiovascular disease and no cardiovascular disease groups, with the former containing a significantly higher proportion of men. There were no group differences in DI, P90 or in any of the neuropsychological tests. Noteworthy was a high occurrence of medical comorbidities, including hypertension, elevated cholesterol and diabetes, not atypical of elderly clinic patients.

Predictably, MCI and dementia patients showed statistically significant differences in all neuropsychological tests (all p 's < .01), with the latter group consistently demonstrating more impairment. Table 2 demonstrates associations between cognitive test performances and nocturnal desaturation measures. Within individuals having a positive CVD history, desaturation measures were associated with poorer performances on measures of attention/concentration and executive function, even after controlling for age, sex, education and depressive symptoms. The associations were far less apparent in patients without such history or in the group for a whole, arguing that medical comorbidity may represent an important moderator of the effect.

Because only about half of the patients were able to complete Trails B, we examined possible floor effects on this measure by performing a logistic regression predicting ability to complete this test. However, results were not statistically significant, although they approached significance for P90 ($p = .091$) for patients with CVD. Modeling floor effects on Digit Span-Backwards, examining raw scores of 3 or below (the lowest quartile of scores), yielded no statistically significant effects for either DI or P90, compatible with the results shown in Table 2.

Discussion

As noted previously by other investigators (Aloia et al., 2004; Beebe et al., 2003), these data confirm cognitive deficits associated with a measure of sleep apnea. However, unlike previous research, we have extended these findings as they apply to a population for whom impaired cognition serves as the primary focus of complaint, i.e., a memory clinic population. Sleep apnea is not assessed routinely in dementia clinics, and these data may be of importance because they imply that this possibly reversible form of cognitive impairment could be screened. Moreover, our data demonstrate that the concurrent presence of cardiovascular disease increases the likelihood of detecting such associations, whereas the absence of such medical comorbidities decreases the strength of those relationships. Sleep apnea is strongly associated with cardiovascular disease, including clinic-measured hypertension (Endeshaw, Bloom, & Bliwise, 2008; Newman, et al., 2001; Nieto et al., 2000; Shahar et al., 2001), nocturnal non-dipping of blood pressure (Endeshaw, White, Kutner, Ouslander, & Bliwise, 2009), impaired endothelial function (Nieto, Herrington, Redline, Benjamin, & Robbins, 2004), left ventricular dysfunction (Chami et al., 2008), and even incident coronary heart disease (Gottlieb et al., 2010) and stroke (Arzt et al., 2005). Given such studies, our findings are compatible with a number of epidemiologic studies (see (Qiu, Winblad, & Fratiglioni, 2005) for review) suggesting that hypertension confers risk for late life cognitive impairment. Well-known relationships between sleep apnea and glucose intolerance (Punjabi et al., 2004) also are consistent with population-based studies suggesting that diabetes and insulin resistance are associated with cognitive impairments (Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Roberts et al., 2008; Vanhanen et al., 1998). Viewed in this way, sleep apnea (defined in our study by a proxy measure, e.g., nocturnal desaturation), should be considered a correlate of cognitive impairment in a late life memory clinic population, probably equally as likely as these other medical

comorbidities. The impairments most likely to be associated with sleep apnea in this study did not involve memory, but rather were in the domains of attention and concentration.

Given the potential importance of co-morbid cardiovascular disease in these results, it is not surprising that those few studies that have examined the role of apolipoprotein epsilon (APOE) genotype as an effect modifier in the association between cognition and sleep apnea have shown that the presence of one (Cosentino et al., 2008; O'Hara et al., 2005) or two (Spira et al., 2008) E4 alleles confer risk and moderate the association. Data also suggest that sleep apnea per se may be associated with the E4 allele (Kadotani et al., 2001), though those associations may be age-dependent (Gottlieb et al., 2004). APOE genotyping was not available in our patients to test this association here. However, the poorer recovery from intracerebral and subarachnoid hemorrhage (Martinez-Gonzalez & Sudlow, 2006) and more likely cognitive impairment subsequent to cardiac bypass surgery (Tardiff et al., 1997) in E4 carriers are compatible with sleep apnea as a potential insult for decrements in higher order cognition in patients who have this vulnerability.

A limitation of our data is that we have relied exclusively on overnight ambulatory pulse oximetry for sleep apnea case identification. Nocturnal pulse oximetry is considered by the American Academy of Sleep Medicine a Level 4 measurement device for measurement of sleep apnea (Collop et al., 2007). Obviously, individuals who have sleep disordered breathing but who do not show arterial oxygen desaturation would be missed by such measurements. Such imputed high sensitivity accompanied by more modest specificity has been documented in many studies (Series et al., 1993; Yamashiro & Kryger, 1995), though a convincing case has been made for such an application as a “first tier” screening approach for initial identification of possible sleep apnea (Netzer, Eliasson, Netzer, & Kristo, 2001). As we mentioned previously, we have had success (96% usable data) adopting this procedure into the routine evaluation of our memory clinic population, who then can be followed up with a more detailed full polysomnographic evaluation, perhaps with eventual referral for nasal continuous positive airway pressure (CPAP). Although the two measures of oxygen desaturation can be differentiated (Chesson, McDowell Anderson, Walls, & Bairnsfather, 2001), our data largely suggest that both measures yielded similar associations with neurocognitive measures.

Regarding CPAP treatment for sleep apnea, although randomized clinical trials (RCTs) currently exist in patients with hypertension, congestive heart failure and diabetes, only one published RCT has been published attempting to treat dementia patients with sleep apnea with CPAP (Ancoli-Israel et al., 2008). Although the results from that trial are modestly encouraging for improving neurobehavior (improvements in mood, sleepiness and sleep architecture were clearly evident), the study was underpowered, the effects on cognition were more limited, and the role of potential effect moderators (e.g., genotype, presence of cardiovascular disease) were not considered (Bliwise, 2011). The current analyses imply that future intervention studies for sleep apnea focusing on cognition should select for patients with comorbid medical diseases.

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Appendix

For the analyses described in Table 2 of this paper, we employed the following full model linear regression:

$$\text{Test score} = a + b_1 X_{\text{age}} + b_2 X_{\text{sex}} + b_3 X_{\text{education}} + b_4 X_{\text{GDS}} + b_5 X_{\text{DI (or P90)}} ;$$

where *test score* represents the *raw score* for each of the neuropsychological measures described in the manuscript; *a* represents the *intercept*; *b* represents the *unstandardized regression coefficient*; *age* is expressed in years; *sex* is dummy coded as male = 0 and female = 1; *education* is expressed in years; *GDS* (Geriatric Depression Scale) is expressed as number of items endorsed; *DI* (Desaturation Index) is expressed as number of desaturation falls of > 4% per hour of recording; *P90* is expressed as percentage of recording time with SaO₂ below 90%. In Table 2, we report standardized regression coefficients for both DI and P90 associated with each regression performed separately for each dependent variable.

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Table 1

Demographics, Nocturnal Desaturation Measures, Medical Comorbidities and Raw Scores on Neuropsychological Tests

	Total Sample (<i>n</i> = 108)	With Cardiovascular Disease (<i>n</i> = 34)	Without Cardiovascular Disease (<i>n</i> = 74)
Variable	<i>M</i> (<i>SD</i>) or %	<i>M</i> (<i>SD</i>) or %	<i>M</i> (<i>SD</i>) or %
<u>Demographics</u>			
Age (years)	73.8 (8.5)	75.1 (8.8)	73.3 (8.4)
Education (years)	14.7 (3.3)	14.6 (3.7)	14.7 (3.1)
Gender (% Females)	54.6	41.2%	60.8%*
Race (%)			
African American	10.2	5.9%	12.2%
Caucasian	84.3	94.1%	79.7%
Other	5.5	0%	8.1%
<u>Nocturnal Desaturation</u>			
DI	7.1 (10.8)	8.0 (13.8)	6.7 (9.1)
P90	5.8 (11.5)	5.6 (10.7)	5.9 (11.9)
<u>Medical Comorbidities</u>			
Hypertension	81.5%	82.4%	81.1%
Elevated Cholesterol	55.6%	61.8%	52.7%
Diabetes	13.9%	14.7%	13.5%
<u>Depression Symptoms</u>			
GDS	2.5 (2.6)	2.6 (2.5)	2.5 (2.7)
<u>Neuropsychology</u>			
MMSE	23.1 (4.8)	22.3 (4.5)	23.4 (4.9)
Digit Span—Forward	7.7 (2.3)	8.0 (2.1)	7.5 (2.4)
Digit Span---Backwards	4.8 (2.3)	4.8 (2.1)	4.8 (2.4)
Logical Memory— Delayed	3.0 (4.0)	2.4 (4.0)	3.3 (4.0)
Trails A	81.2 (70.0)	83.1 (82.1)	80.3 (64.4)
Judgment of Line Orientation	15.6 (8.6)	14.3 (10.3)	16.2 (7.6)
FAS	27.0 (12.5)	28.9 (13.9)	26.0 (11.8)
Boston Naming Test	19.6 (7.3)	19.6 (6.8)	19.6 (7.5)
Clock Drawing	9.4 (3.6)	9.0 (3.8)	9.6 (3.5)

Note. DI = desaturation index (number of drops of oxygen saturation of 4% or greater per hour of recording); P90 = percentage of recording period with oxygen saturation less than 90%.

*
 $p < 0.05$

Table 2
Standardized Regression Coefficients of Associations between Nocturnal Desaturation Measures and Neuropsychological Tests

Test	Entire Sample (n = 108)		With Cardiovascular Disease (n = 34)		Without Cardiovascular Disease (n = 74)	
	DI	P90	DI	P90	DI	P90
MMSE	-.12	-.12	-.14	-.24	-.10	-.09
Digit Span- Forward	-.25*	-.27*	-.49*	-.53*	-.10	-.17
Digit Span- Backwards	-.14	-.20	-.28	-.39	-.05	-.11
Logical Memory- Delayed	-.08	-.10	-.12	-.15	-.09	-.10
Trails A	.17	.18	.43	.51*	-.01	.04
Judgment of Line Orientation	-.21*	-.19	-.40	-.38	-.04	-.04
FAS	-.11	-.08	-.44*	-.44*	.26*	.18
Boston Naming Test	-.15	-.10	-.14	-.19	-.16	-.08
Clock	-.27*	-.20	-.35	-.40	-.22	-.11

Note. DI = desaturation index (number of drops of oxygen saturation of 4% or greater per hour of recording); P90 = percentage of recording period with oxygen saturation less than 90%. Values represent standardized (beta) regression coefficients controlling for age, sex, education, and depression.

* $p < .05$ using Hochberg correction.