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Negative results

Do diurnal cortisol levels mediate the association between sleep disturbances and cognitive impairment?

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a b s t r a c t

Previous research found an association between sleep disturbances and cognitive deficits on the one hand, and between increased cortisol levels and poor cognitive performance on the other hand. We hypothesized that cortisol may, at least partially, mediate the link between sleep disturbances and cognitive impairment (CI). We analyzed data from 440 nondemented subjects aged _65 years (72.4 _ 4.5 years old, 55.7% women) participating at the population-based CoLaus/PsyCoLaus study, who underwent cognitive evaluation, complete polysomnography and cortisol measures during the day. Subjects with CI (N ¼ 207, 47.05% of the sample) had lower sleep efficiency, less deep sleep (stage N3) and rapid eye movement sleep, and higher apnea/hypopnea index and oxygen desaturation index. After adjustment for possible confounders, oxygen desaturation index (_4% and _6% per hour of sleep) were significantly associated with impaired cognitive performance. The results of Sobel's test for mediation using the regressions between the sleep-related variables and cortisol values, and between the cortisol and the Clinical Dementia Rating score were not significant (all p > 0.05). Our data suggest that sleepdisordered breathing is associated with CI, but that this association is not mediated by increased diurnal cortisol levels.

1. Introduction

We have recently shown that elderly subjects from the general population with cognitive impairment (CI), compared with subjects with normal cognition, had significant differences in sleep patterns.

These differences seem to be related to the occurrence of sleepdisordered breathing (SDB) (Haba-Rubio et al., 2017). SDB is highly prevalent in the general population, affecting 23.4% of women and 49.7% of men, and this prevalence rises markedly with age (Heinzer et al., 2015). SDB induces intermittent hypoxemia, and it has been associated with high cortisol levels (Vgontzas et al., 2007). High levels of cortisol could also have neurotoxic effects (Byers and Yaffe, 2011), and several studies have shown an association between increased cortisol levels and poor cognitive performances (Ouanes et al., 2017; Popp et al., 2015). The aim of our study was thus to evaluate the potential mediating effect of cortisol between sleep disturbances and CI.

2. Methods

This study is based on the subsample of 440 nondemented (Clinical Dementia Rating [CDR] < 1) subjects aged _65 years who participated in the CoLaus/PsyCoLaus study (Firmann et al., 2008; Preisig et al., 2009), and who had a complete cognitive assessment, a polysomnography (PSG), and salivary cortisol measures comprehensive neuropsychological test battery (Ouanes et al., 2017) and overall cognitive and functional status was assessed using the CDR scale (Morris, 1993). Participants were divided into 2 groups: participants with CI (CDR > 0) and participants with normal cognition (CDR ¼ 0). Four salivary samples were obtained fromeach participant: on waking, 30 minutes after waking, at 11 AM, and at 8 PM. The cortisol area under the curve was also calculated. Logistic regression models were constructed for sleep and cortisol variables according to CDR status, controlling for age, sex, alcohol and tobacco consumption, drugs influencing sleep, level of education, body mass index, metabolic syndrome, hypertension, diabetes, and depression, and Sobel's test for mediation was performed using the regression between the sleep variables and the cortisol measures, and the regression between the cortisol and the CDR status.

3. Results

CI (CDR > 0) was present in 207 participants (47.05% of the sample, Table S2). Compared with participants with normal cognition, they had lower sleep efficiency, lower slow wave and rapid eyemovement sleep, and higher apnea/hypopnea index (AHI) and oxygen desaturation index (ODI). However, no significant differences were found for cortisol measures between groups, except a trend toward higher cortisol values at 11 AM (Table S3). For each PSG-derived variable and cortisol measure, binary logistic regression models were constructed and adjusted for age, sex, body mass index, alcohol and tobacco consumption, psychotropic drugs influencing sleep, level of education, and the presence of hypertension, diabetes, metabolic syndrome, and depression. In these models, only the ODI _ 4 (regression coefficient ß for an increase of 1 unit: 0.0047, 95% confidence interval [95% CI]: 0.0002e0.0091, p = 0.037) and the ODI _ 6 (ß: 0.0075, 95% CI: 0.0010e0.0141, p = 0.023) remained significantly and independently associated with the presence of CI.

The results of Sobel's test for mediation using the regressions between either the AHI or the ODI and the cortisol measurements, and between cortisol and the CDR scorewere not significant (all p >0.05, Table S5).

4. Discussion

The main aim of this study was to evaluate increased cortisol levels as a potential pathway leading from sleep disturbances to CI. Subjects aged _65 years from the general population with CI had significant differences in sleep patterns. In the multivariate analysis, after adjustment for multiple possible confounding factors, the ODI _ 4% and ODI _ 6% remained significantly and independently associated with impaired performance on cognitive tests. However, diurnal cortisol levels were not different between groups (with or without CI), and they do not seem

to mediate the link between SDB and cognitive performance. Addressing the relationship between SDB and cortisol levels, some previous studies (Edwards et al., 2014), but not all (Dadoun et al., 2007), have identified differences in cortisol between SDB patients and controls, or before and after continuous positive airway pressure treatment (Henley et al., 2009; Schmoller et al., 2009).
A growing body of research reveals a consistent association between SDB and CI. SDB induces intermittent hypoxemia and recurrent arousals that are responsible for sudden surges of sympathetic nerve system activity and are associated with increased pulsatile cortisol release (Spath-Schwalbe et al., 1991). Increased cortisol levels have been independently associated with poor cognitive performances (Ouanes et al., 2017; Popp et al., 2015), and both SDB-related intermittent hypoxia and exposure to increased cortisol levels are thus potential mechanisms of the link between SDB and CI (Galanjauskas et al., 2017).
Our results suggest that intermittent hypoxia is likely to be the main mechanism through which SDB is associated with CI. On the contrary, measures of salivary diurnal cortisol were not different between CI and subjects with normal cognition, and the results of Sobel's test for mediation using the regressions between the AHI and the ODI indexes, and the CDR status and the cortisol measurements, were not significant. While Edwards KM et al., examining the associations between SDB, cognitive function, and cortisol levels, found that nighttime cortisol levels were a significant predictor of neurocognitive functioning (Edwards et al., 2014), our data suggest that diurnal cortisol is not a significant mediator of the link between SDB and cognitive performance in the elderly population.
Sources of inconsistency between different reports in this area include differences in study design, data collection and measurements, sample sizes, and potential confounding factors (Tomfohr et al., 2012). However, whether increased cortisol related to SDB may significantly contribute to cognitive decline in older people (Popp et al., 2015) could also depend on the presence of Alzheimer's disease pathology in brain regions particularly vulnerable to cortisol exposure such as the hippocampus. Our study has some limitations that have to be pointed out: only 28.3% of thewhole cohort had a complete evaluation (cortisol profile, the cognitive assessment, and the PSG) and our study may be underpowered to detect subtle differences between groups; the evaluations were not carried out at the same time; cortisol measure was restricted to 1 day; we do not have measures of nocturnal cortisol levels; and our analyses are based on cross-sectional data, and do not allow drawing conclusions about cause-to-effect relationships. Despite these limitations,we foundthat participants fromthegeneral population aged _65 years with CI have more disrupted sleep but similar cortisol profile during the daytime. Intermittent hypoxia related to SDB seems to be the main factor associated with cognitive deficits, and daytime cortisol levels do not seem to play a mediating role between SDB and cognitive performance.

Disclosure
The authors have no actual or potential conflicts of interest.

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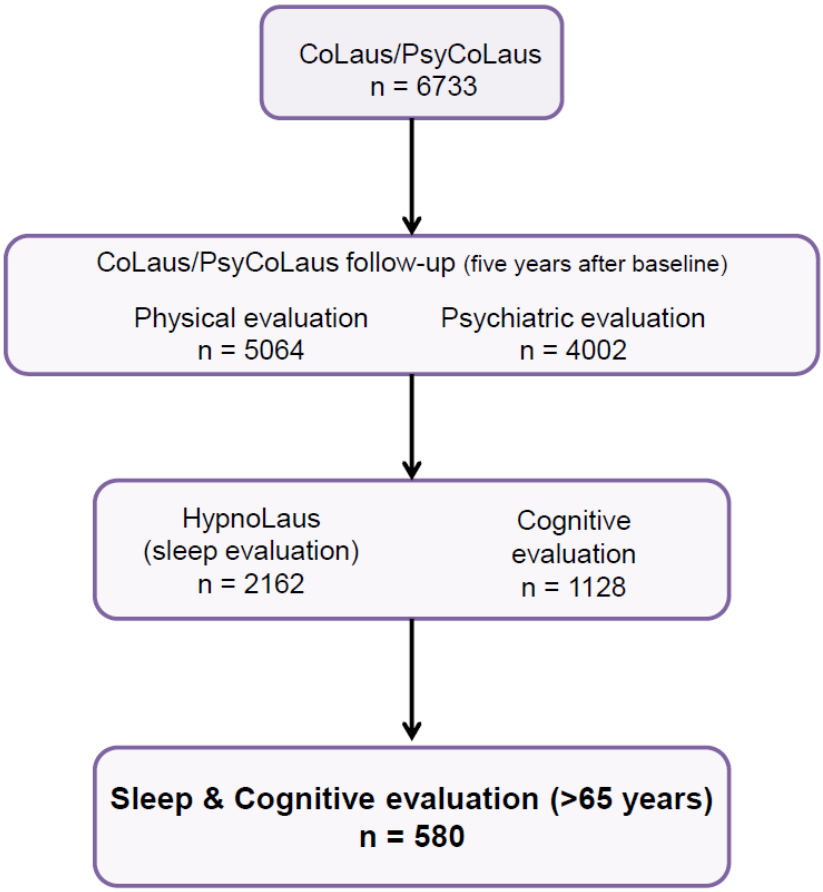
Annexes :

Supplementary Figure e-1. Studied population.



Supplementary Table e-1. Cognitive test performance of the studied population, according to CDR status.

	CDR = 0 (n=289)	CDR > 0 (n=291)	p value
Memory tasks			
(Grober and Buschke)			
Immediate recall	16.36±4.46	15.85±2.74	0.120
Total free recall	33.82±4.87	26.23±6.91	**<0.001**
Total cued recall	17.30±11.26	19.56±8.54	**0.009**
Identification	15.96±0.50	15.93±0.43	0.549
Recognition	45.61±8.21	44.85±9.04	0.322
Delayed free recall	12.82±1.90	10.38±2.81	**<0.001**
Delayed cued recall	4.60±4.31	5.73±3.57	**0.001**
Other cognitive tasks			
Mini-Mental State Examination	28.91±3.03	28.45±2.30	0.201
CERAD figures	10.52±1.01	10.42±1.14	0.307
Semantic verbal fluency	31.72±8.24	27.94±7.80	**<0.001**
Phonemic verbal fluency	22.73±7.65	19.23±7.63	**<0.001**
Stroop dots condition	23.94±0.31	23.81±0.96	**0.039**
Stroop words condition	23.96±0.22	23.92±0.60	0.303
Stroop interference condition	23.30±1.80	23.10±1.80	0.193
DO40 naming task	39.85±0.48	39.65±1.26	**0.025**

CDR: Clinical Dementia Rating Scale. Mean ± SD.

Supplementary Table e-2. Objective sleep characteristics according to CDR status.

	CDR = 0 (n=289)	CDR > 0 (n=291)	p value
Total sleep time, min[1]	392.2 ± 72.8	380.9 ± 77.4	0.070
Stage N1, min[1]	49.2 ± 28.7	55.7 ± 32.7	**0.011**
Stage N1, %[1]	12.9 ± 8.5	15.1 ± 9.5	**0.004**
Stage N2, min[1]	195.5 ± 60.3	190.4 ± 66.3	0.337
Stage N2, %[1]	49.5 ± 11.8	49.6 ± 12.4	0.914
Slow wave sleep (stage N3), min[1]	67.5 ± 32.6	61.0 ± 33.4	**0.018**
Slow wave sleep (stage N3), %[1]	17.4 ± 8.5	16.2 ± 8.9	0.097
REM sleep, min[1]	80.0 ± 31.0	73.7 ± 31.8	**0.016**
REM sleep, %[1]	20.2 ± 6.7	19.1 ± 7.0	0.054
Sleep onset latency, min[2]	12.7 [5.5-27.3]	14.3 [6.5-29.8]	0.300
Sleep efficiency, %[2]	85.0 [72.7-84.4]	78.5 [70.0-85.7]	**0.007**
Wake after sleep onset, min[2]	89.3 [55.0-141.6]	100.6 [68.3-148.0]	**0.018**
REM latency, min[2]	78.0 [59.5-128.0]	79.7 [58.0-123.5]	0.779
Number of stage shifts[2]	141 [109-172]	149 [115-190]	0.078
Apnea/hypopnea index, n/h[2]	12.9 [7.2-24.5]	18.0 [7.8-35.5]	**<0.001**
Mean SaO_2, %[2]	93.6 [92.5-94.5]	93.5 [92.4-94.4]	0.325
Lowest SaO_2, % [2]	85 [82-88]	85 [80-87]	**0.029**
Oxygen desaturation index ≥ 3%, n/h[2]	13.5 [6.9-23.7]	17.1 [7.1-32.9]	**0.007**
Oxygen desaturation index ≥ 4%, n/h[2]	6.3 [2.3-13.2]	9.0 [3.2-20.2]	**0.001**
Oxygen desaturation index ≥ 6%, n/h[2]	1.1 [0.2-4.7]	2.2 [0.5-8.0]	**<0.001**
Arousal index, n/h[2]	22.4 [15.8-29.0]	23.3 [16.4-34.2]	0.102
PLMS index, n/h[2]	10.8 [0.3-36.7]	13.4 [0.0-36.9]	0.848

CDR: Clinical Dementia Rating Scale; REM : rapid eye movement sleep ; PLMS : periodic leg movements during sleep. [1] mean ± standard deviation ; [2] percentile 50 [percentile 25-percentile75].

Supplementary Table e-3. Association of polysomnographic variables with a CDR > 0, multivariate analysis.

	Odds ratio*	[95% Conf.Interval]	p value
Total sleep time, min	1.00	0.97 - 1.02	0.884
Stage N1, min	1.04	0.97 - 1.10	0.246
Stage N2, min	0.99	0.96 - 1.02	0.576
Slow wave sleep (stage N3), min	1.01	0.95 - 1.07	0.792
REM sleep, min	0.98	0.92 - 1.04	0.548
Sleep onset latency, min	0.97	0.91 - 1.04	0.466
Sleep efficiency, %	0.97	0.82 - 1.13	0.675
Wake after sleep onset, min	1.00	0.97 - 1.03	0.832
REM latency, min	0.99	0.96 - 1.01	0.309
Number of stage shifts	1.01	0.97 - 1.04	0.720
Apnea/hypopnea index, n/h	1.15	1.00 - 1.31	**0.043**
Mean SaO2, %	0.73	0.22 - 2.38	0.602
Lowest SaO2, %	0.79	0.56 - 1.12	0.184
Oxygen desaturation index ≥ 3%, n/h	1.09	0.96 - 1.22	0.173
Oxygen desaturation index ≥ 4%, n/h	1.17	1.01 - 1.36	**0.033**
Oxygen desaturation index ≥ 6%, n/h	1.33	1.03 - 1.72	**0.029**
Arousal index, n/h	1.00	0.86 - 1.16	0.993
PLMS index, n/h	1.00	0.95 - 1.06	0.885

*Odds-ratio for an increase of 10-units. Multivariate logistic regression model adjusted for each variable for age, sex, hypertension, diabetes, metabolic syndrome, depression, lifetime depression, BMI, alcohol and tobacco consumption, drugs influencing sleep and level of education. CDR: Clinical Dementia Rating Scale; REM : rapid eye movement sleep ; AHI : apnea/hypopnea index; PLMS : periodic legs movements during sleep.